Evidence Reports of Kampo Treatment 2019:

512 Randomized Controlled Trials

(EKAT 2019)

2021.9.1

漢方治療エビデンスレポート 2019

ー 512 の RCT ー

(EKAT 2019)

1 Sep 2021

Task Force for Evidence Reports
(ER -TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Ver. 1.0 1 Sep 2021

Notes on the current version

Since 2007, the Task Force for Evidence Reports (ER -TF) of the Japan Society for Oriental Medicine EBM Committee has been exhaustively collecting randomized controlled trials (RCTs) of Kampo medicines in Japan, and then prepared and published structured abstracts (SAs) on the Japan Society for Oriental Medicine (JSOM) website as Kampo Chiryo Ebidensu Repoto (Evidence Reports of Kampo Treatment: EKAT). As indicated in the History of version upgrades on the next page, the complete version of EKAT 2016 at the time of release on 1 November 2018 listed 465 RCTs and two meta-analysis covering the period from 1986 to 2015. The current quality standard for prescribed Kampo medicines went into effect in 1986.

JSOM continued its efforts to produce EKATs, with website publication of EKAT Appendix 2017, which included only additions and revisions to EKAT 2016, in May 2020, followed by EKAT Appendix 2018, which included only additions and revisions to EKAT Appendix 2017, in June 2020. The present “Evidence Reports of Kampo Treatment 2019: 512 Randomized Controlled Trials [EKAT 2019]”, issued on 1 September 2021, is a fully updated edition of EKAT.

The present EKAT 2019 includes all SAs in EKAT 2016, 11 SAs newly included in EKAT Appendix 2017, 15 SAs newly included in EKAT Appendix 2018, and 19 SAs newly prepared this time.

The SAs based on the following articles in EKAT 2013 have been deleted from the present report because they were brief reports or news articles that were superseded by final reports. These full reports were collected and their SAs were newly prepared.

- Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto. —A study in a fasted rat model and a randomized controlled trial in postoperative patients with colorectal cancer— *Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai* (*5th Annual Meeting of the Japanese Gastroenterological Association*) 2009: 9-10. (Deleted from EKAT Appendix 2014)

- Uehara R. An evaluation of gastrointestinal symptoms and gastric mobility after endoscopic submucosal dissection (ESD) and an investigation of the usefulness of Rikkunshito (TJ-43). *Dai 8 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai Workshop 4 PROCEEDING Jobu Shokaki Shojo to Kampo* (*Workshop 4 Proceedings of the 8th Annual Meeting of the Japanese Gastroenterological Association*: *Upper Gastrointestinal Symptoms and Kampo*) 2012: 16-7. (Deleted from EKAT Appendix 2015)

- Yaegashi M. Usefulness of daikenchuto in the laparoscopic colorectal cancer perioperative period. *Progress in Medicine* 2012; 32: 616-7. (Deleted from EKAT Appendix 2015)

Also, the 1990 and 1992 reports by Chisato Hirayama et al. were previously considered as separate RCTs and thus separate SAs were prepared. However, they were found to be the same study at the time of EKAT Appendix 2014 preparation, and accordingly the two SAs were consolidated into one SA.

Consequently, the present EKAT 2019 contains the SAs of 502 RCTs and ten meta-analyses.

When one SA is prepared from multiple reports, the bibliographic information for all of the reports used to prepare the SA is listed in the order of year of publication at the top of the SA, with the main report indicated in bold face type.

History of version upgrades

1 Sep. 2021: Kampo Chiryo Ebidensu Repoto 2019 (Evidence Reports of Kampo Treatment 2019: 512 Randomized Controlled Trials)

1 June 2020: Kampo Chiryo Ebidensu Repoto Appendix 2018 (Evidence Reports of Kampo Treatment Appendix 2018)

18 May 2020: Kampo Chiryo Ebidensu Repoto Appendix 2017 (Evidence Reports of Kampo Treatment Appendix 2017)

1 Nov. 2018: Kampo Chiryo Ebidensu Repoto 2016 (Evidence Reports of Kampo Treatment 2016: 467 Randomized Controlled Trials)

31 Mar. 2017: Kampo Chiryo Ebidensu Repoto Appendix 2015 (Evidence Reports of Kampo Treatment Appendix 2015)

6 June 2015: Kampo Chiryo Ebidensu Repoto Appendix 2014 (Evidence Reports of Kampo Treatment Appendix 2014)

31 Dec. 2013: Kampo Chiryo Ebidensu Repoto 2013 – 402 no RCT (Evidence Reports of Kampo Treatment: 402 Randomized Controlled Trials)

31 Dec. 2012: Kampo Chiryo Ebidensu Repoto Appendix 2012 (Evidence Reports of Kampo Treatment Appendix 2012)

1 Oct. 2011: Kampo Chiryo Ebidensu Repoto Appendix 2011 (Evidence Reports of Kampo Treatment Appendix 2011)

1 June 2010: Kampo Chiryo Ebidensu Repoto 2010 – 345 no RCT (Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials)

1 June 2009: Kampo Chiryo Ebidensu Repoto 2009 – 320 no RCT (Evidence Reports of Kampo Treatment 2009: 320 Randomized Controlled Trials)

1 Apr. 2008: Kampo Chiryo Ebidensu Repoto Dai 2-han – RC T wo Shu ni Shite-Chukan Hokoku 2007 ver 1.1 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007 ver.1.1)

15 June 2007: Kampo Chiryo Ebidensu Repoto Dai 2-han –RC T wo Shu ni Shite-Chukan Hokoku 2007 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007)

20 July 2005: Kampo Chiryo niokeru Ebidensu Repoto (Evidence Reports of Kampo Treatment) (*Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2005: 56, EBM supplementary issue)

20 Sept. 2002: Kampo Chiryo niokeru EBM – 2002 nen Chukan Hokoku (EBM in Kampo 2002, Interim Report) (*Nihon Toyo Igaku Zasshi* [*Japanese Journal of Oriental Medicine*] 2002: 53 [5], supplementary issue)

Version/date	Title	Year of publication of target references	No. of references	No. of structured abstracts (SAs)	No. of excluded references
2021.9.1	Evidence Reports of Kampo Treatment, 2019 - 512 Randomized Controlled Trials (EKAT 2019)	1986-2018	616	512 [1)]	216
2020.6.1	Evidence Reports of Kampo Treatment, Appendix 2018 (EKAT Appendix 2018)	From EKAT 2017 2017	594 [2)]	493 [1), 2)]	203 [2)]
2020.5.18	Evidence Reports of Kampo Treatment, Appendix 2017 (EKAT Appendix 2017)	From EKAT 2016 2016	578 [3)]	478 [1), 3)]	188 [3)]
2018.11.1	Evidence Reports of Kampo Treatment, 2016 - 467 Randomized Controlled Trials (EKAT 2016)	1986-2015	567	467 [1)]	181
2017.3.31	Evidence Reports of Kampo Treatment, Appendix 2015 (EKAT Appendix 2015)	From EKAT 2014 2014	545 [4)]	447 [1), 4)]	177 [4)]
2015.6.6	Evidence Reports of Kampo Treatment, Appendix 2014 (EKAT Appendix 2014)	From EKAT 2013 2013 (First half)	513 [5)]	418 [1), 5)]	167 [5)]
2013.12.31	Evidence Reports of Kampo Treatment, 2013 - 402 Randomized Controlled Trials (EKAT 2013)	1986-2012 (First half)	494	403 [1)]	159
2012.12.31	Evidence Reports of Kampo Treatment, Appendix 2012 (EKAT Appendix 2012)	From EKAT 2011 2011 (First half)	457 [6)]	379 [1), 6)]	150 [6)]
2011.10.1	Evidence Reports of Kampo Treatment, Appendix 2011 (EKAT Appendix 2011)	From EKAT 2010 2010 (First half)	432 [7)]	360 [1), 7)]	-
2010.6.1	Evidence Reports of Kampo Treatment, 2010 - 345 Randomized Controlled Trials (EKAT 2010)	1986-2009 (First half)	416	346 [1)]	132
2009.6.1	Evidence Reports of Kampo Treatment, 2009 - 320 Randomized Controlled Trials (EKAT 2009)	1986-2008 (First half)	385	321 [1)]	111
2008.4.1	Evidence Reports of Kampo Treatment, 2nd edition - Focusing on RCTs - Interim Report 2007 ver. 1.1	1999-2005	116	98	32
2007.6.15	Evidence Reports of Kampo Treatment, 2nd edition - Focusing on RCTs - Interim Report 2007	1999-2005	104	102	42

1) Including at least 1 meta-analysis

2) Total of all references added or removed in EKAT 2016, EKAT Appendix 2017 and EKAT Appendix 2018.

3) Total of all references added or removed in EKAT 2016 and EKAT Appendix 2017.

4) Total of all references added or removed in EKAT 2013, EKAT Appendix 2014 and EKAT Appendix 2015.

5) Total of all references added or removed in EKAT 2013 and EKAT Appendix 2014.

6) Total of all references added or removed in EKAT 2010, EKAT Appendix 2011 and EKAT Appendix 2012.

7) Total of all references added in EKAT 2010 and EKAT Appendix 2011.

Executive summary

The Special Committee for Evidence Based Medicine (EBM), established in June 2001 by the Japan Society for Oriental Medicine (JSOM), issued the "EBM in Kampo 2002, Interim Report" (*Nihon Toyo Igaku Zasshi* [*Japanese Journal of Oriental Medicine*] 2002: 53 (5), supplementary issue) in 2002, followed by "Evidence Reports of Kampo Treatment" (*Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2005: 56, EBM supplementary issue) in 2005. These publications were intended to present the evidence from "good" studies, including randomized controlled trials (RCTs), of Kampo products published between 1986 and 2002. However, those studies had several methodological limitations, such as lack of clear inclusion/exclusion criteria. Thus, questions were raised by readers such as why particular existing articles had or had not been included.

Accordingly, the improvements listed below were included in the JSOM Task Force for Evidence Report (ER-TF), the second phase of the EBM Special Committee project, starting in 2005. These improvements were continued in the Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF), the third phase of the EBM Special Committee (changed to the EBM Committee in June 2012) project starting in 2009, the fourth phase of the EBM Committee's Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF) project (changed back to Task Force for Evidence Report [ER-TF] in June 2014) starting in 2013, and the fifth phase of the project starting in 2015.

(1) RCT articles with high levels of evidence were exhaustively included for review.
(2) The methods for literature search and review processes were specified to enhance accuracy and transparency.
(3) The reports were presented in the form of structured abstracts consisting of 8 items in accordance with world standards, i.e., "objectives," "design," "setting," "participants," "intervention," "main outcome measures," "main results," and "conclusions," and four additional items, i.e., "from the Kampo medicine perspective," "safety assessment in the article," "abstractor's comments," and "abstractor's name and date."
(4) Excluded references were listed along with the reasons for their exclusion.
(5) Partly because of establishment of the Task Force for Clinical Practice Guidelines in 2005, "recommendations" included in the first report compilations were excluded.
(6) A system to enable feedback from readers through the internet and other media on the current reports was established.
(7) To enhance transparency and accountability, conflicts of interests (COI) among persons concerned were disclosed.
(8) A search function was added to the website (http://www.jsom.or.jp/medical/ebm/index.html). Links to the web pages on which references are published were provided.

The inclusion criteria were RCT articles using Kampo formulations (extract and pills) approved for manufacture and sale in Japan that were published between 1986, when the quality of Kampo formulations reached present levels, and 2018. Studies of in-house formulations such as decoctions were excluded, as in the report compilations in the first phase. The phase 2 report included only RCTs of Kampo products (extract granules, tablets, and capsules, or pills, approved for sale as Kampo formulations for

prescription in Japan). It excluded studies of in-house formulations such as decoctions, since no quality control criteria have been established.

The data sources of the searches were two databases, Cochrane Library (CENTRAL) and Ichushi Web, as well as hand searches conducted at the Japan Kampo Medicines Manufacturers Association (JKMA).

Structured abstracts were arranged in the order used by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10).

Finally, out of 616 references, 502 RCTs, and ten meta-analyses were prepared as structured abstracts. The 216 references not satisfying the inclusion criteria were listed as excluded references along with their bibliographic items and the reason for exclusion.

We would appreciate your comments on compilation method, the contents of the structured abstracts, information on references not included in the report compilations, if any, and other matters. Please send your comments to ebm-er@jsom.or.jp

CONTENTS

1. Lists of Structured Abstracts

(Lists of Structured Abstracts and included references:512 abstracts, 616 references)

Note: Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (*).

Abbreviations: C: The Cochrane Library (CENTRAL), I: Igaku Chuo Zasshi(Japana Centra Revuo Medicana, Ichushi), N: Database Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)

<<Structured Abstracts Describing RCTs and the References Reporting Them>>

1. Infections (including Viral Hepatitis) (23 abstracts, 29 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
A08.0	To evaluate the efficacy of saireito (柴苓湯) for rotavirus infection.	saireito (柴苓湯)	Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection*. *Nihon Shonika Rinsho* (*Japanese Journal of Pediatrics*). 1992; 45: 1889-91 (in Japanese).	quasi-RCT	N
			Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection*. *Dai 9-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku Nihon Shoni Toyo Igakkaishi* (*Proceedings of the 9th meeting of the Japan Pediatric Society for Oriental Medicine*) 1993; 9: 20-3 (in Japanese).		N
A09	Efficacy of keihito (啓脾湯) for diarrhea in children.	keihito (啓脾湯)	Miyazaki R, Tomita H. A study of the efficacy of keihito for diarrhea in children*. *Kampo no Rinsho* (*Journal of Kampo Medicine*) 1996; 43: 217-23 (in Japanese).	quasi-RCT	N
A09.0	To evaluate the effectiveness of Kampo therapy for infectious diarrhea.	goreisan (五苓散), goreisan (五苓散) ＋ shakuyakukanzoto (芍薬甘草湯)	Miura Y, Yamagishi Y, Mikamo H, et al. Investigation into the effects of Kampo therapy for infectious diarrhea.* *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2011; 28: 102−4 (in Japanese).	RCT-envelope	I
A09.0	To compare the efficacy and safety of goreisan (五苓散) with that of probiotics in Japanese adults with acute infectious gastroenteritis.	goreisan (五苓散)	Morita F, Yokokawa H, Matsuda N, Fujibayashi K, et al. Comparative efficacy of goreisan and probiotics in Japanese adults with acute infectious gastroenteritis: Randomized controlled trial. *Traditional & Kampo Medicine* 2017; 4:89-93.	RCT	I
A16.2	Improvement effects on appetite and host defense in patients undergoing chemotherapy for pulmonary tuberculosis.	hochuekkito (補中益気湯), hochuekkito (補中益気湯) ＋ shosaikoto (小柴胡湯)	Watanabe A, Hasegawa S. Effect of combined Kampo medicines as adjuvant therapy for pulmonary tuberculosis*. *Nippon Iji Shinpo* (*Japan Medical Journal*) 1992; (3553): 76-7 (in Japanese).	RCT	N
		hochuekkito (補中益気湯)	Watanabe A, Takahashi N, Uchida Y, et al. Efficacy of hochuekkito as adjuvant therapy for pulmonary tuberculosis*. *JAMA* (*Japanese version*) 1992; 13 (6) suppl: 20-1 (in Japanese).		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
A16.2	To determine the efficacy of hochuekkito (補中益気湯) for reducing hepatic dysfunction and improving digestion and malabsorption in tuberculosis patients undergoing chemotherapy.	hochuekkito (補中益気湯)	Shijubo N, Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis – the reducing effect on hepatic dysfunction occurring as an adverse drug reaction – [*]. *Kampo Igaku* (*Kampo Medicine*) 1993; 17: 241-3 (in Japanese).	RCT	N
			Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis[*]. *Nikkei Medical* 1994; 23 (12): 24-5 (in Japanese).		N
A31.0	To evaluate the effectiveness of hochuekkito (補中益気湯) as an adjunct to conventional treatment for progressed refractory pulmonary Mycobacterium avium complex (MAC) disease.	hochuekkito (補中益気湯)	Enomoto Y, Hagiwara E, Komatsu S, et al. Pilot quasi-randomized controlled study of herbal medicine hochuekkito as an adjunct to conventional treatment for progressed pulmonary mycobacterium avium complex disease. *PLOS ONE* 2014; 9: 1-8.	quasi-RCT	C&N
A49.0	To evaluate whether hochuekkito (補中益気湯) has efficacy in preventing colonization and infection with methicillin-resistant *Staphylococcus aureus* (MRSA).	hochuekkito (補中益気湯)	Seki T, Matsumoto T, Deguchi H, et al. Evaluation of the efficacy of hochuekkito in preventing MRSA colonization and infection[*]. *Kampo Igaku* (*Kampo Medicine*) 1999; 23: 196-7 (in Japanese).	RCT-envelope	I
A49.0	To evaluate whether hochuekkito (補中益気湯) can improve immune and nutritional status in immuno-compromised hosts.	hochuekkito (補中益気湯)	Suzuki J, Arata S, Sugiyama M. Improvement of immunity and nutrition by hochuekkito in immuno-compromised hosts – for the control of MRSA – [*]. *Progress in Medicine* 2002; 22: 1362-3 (in Japanese).	RCT	I
A49.3 J20.0	To evaluate the efficacy of bakumondoto (麦門冬湯) for coughing associated with mycoplasma bronchitis.	bakumondoto (麦門冬湯)	Watanabe N, Makino S, Nakagawa T, et al. A study on the efficacy of bakumondoto for coughing associated with mycoplasma infections. *Science of Kampo Medicine* 2017; 41:116-8 (in Japanese).	RCT-envelope	I
A49.8	To evaluate the efficacy and safety of triple therapy with proton pump inhibitor, antibiotic, and goshuyuto (呉茱萸湯) for *Helicobacter pylori* (*H. pylori*) infection.	goshuyuto (呉茱萸湯)	Higuchi K, Arakawa T, Ando K, et al. Eradication of Helicobacter pylori with a Chinese Herbal medicine without emergence of resistant colonies. *American Journal of Gastroenterology* 1999; 94: 1419-20.	RCT	C
B02.2	To evaluate whether hochuekkito (補中益気湯) has a preventive effect on postherpetic neuralgia (PHN).	hochuekkito (補中益気湯)	Taniguchi S, Terai T, Kono T, et al. The effect of hochuekkito on postherpetic neuralgia[*]. *Hifu no Rinsho* (*Clinical Practice of Dermatology*) 1999; 41: 601-3 (in Japanese).	RCT	N
			Taniguchi S, Kono T, Terai T. Preventive effect of hochuekkito on postherpetic neuralgia[*]. *Progress in Medicine* 2002; 22: 863-5 (in Japanese).		I
B18.1	Therapeutic effect of shosaikoto (小柴胡湯) combined with interferon (IFN) -beta therapy on chronic active hepatitis B.	shosaikoto (小柴胡湯)	Sata M, Amagase H, Koga S, et al. Therapeutic effect of IFN-β (Feron) plus shosaikoto combination therapy on chronic active hepatitis B[*]. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1994; 71: 814-20 (in Japanese).	RCT-envelope	I
B18.1	Efficacy of shosaikoto (小柴胡湯) on chronic hepatitis B.	shosaikoto (小柴胡湯)	Sato S, Ishikawa K, Chiba T. Efficacy of sho-saiko-to on chronic type B hepatitis. *Shokakika* (*Gastroenterology*) 1991; 15: 39-49 (in Japanese).	RCT-envelope	N
B18.1	Efficacy and safety in children with HBe antigen-positive chronic hepatitis B.	shosaikoto (小柴胡湯)	Shiraki K, Tanimoto K, Togashi T, et al. A study of the efficacy of shosaikoto in children with HBe antigen-positive chronic hepatitis B[*]. *Shonika Rinsho* (*Japanese Journal of Pediatrics*) 1991; 44: 2146-51 (in Japanese).	RCT	N
			Shiraki K, Tanimoto K. Clinical Evaluation of the efficacy of TSUMURA Shosaikoto in children with chronic hepatitis B[*]. *Dai 7-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku* (*Proceedings of the 7th meeting of the Japan Pediatric Society for Oriental Medicine*) 1991; 7: 18-22 (in Japanese).		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
B18.2	Determination of efficacy and safety of shosaikoto (小柴胡湯) for type C chronic liver diseases.	shosaikoto (小柴胡湯)	Hatakeyama S, Ueki J, Ishizuka M, et al. Comparative study of ursodeoxycholic acid and shosaikoto as treatment for chronic liver diseases type C. *Yakuri to Chiryo* (*Japanese Pharmacology & Therapeutics*) 1994; 22: 3295-305 (in Japanese).	RCT-envelope	I
B18.2	Efficacy of shosaikoto (小柴胡湯) combined with interferon for reducing adverse effects in patients with chronic hepatitis C.	shosaikoto (小柴胡湯)	Nakajima O, Sone M. Interferon plus shosaikoto combination therapy for chronic hepatitis C (the first report) - effectiveness in reducing adverse effects of interferon-*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*). 1993; 70: 2994-3002 (in Japanese).	RCT-envelope	I
18.2	Efficacy and safety of shosaikoto (小柴胡湯) in chronic hepatitis C after interferon therapy.	shosaikoto (小柴胡湯)	Sone M, Nakajima O. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1995; 72: 3193-7 (in Japanese).	RCT	I
			Nakajima O, Sone M. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy - the second report-*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1998; 75: 1883-8 (in Japanese).		I
B18.2	To confirm the efficacy of shosaikoto (小柴胡湯) for interferon-resistant chronic hepatitis C.	shosaikoto (小柴胡湯)	Nakajima O, Sone M, Kurokawa K, et al. The Complemental treatment for chronic hepatitis C. *Kagaku Ryoho Kenkyusyo Kiyo* (*Bulletin of the Institute of Chemotherapy*) 2003; 34: 40-51 (in Japanese with English abstract).	RCT-envelope	I
B18.2	To confirm the efficacy of shosaikoto (小柴胡湯) for chronic hepatitis C.	shosaikoto (小柴胡湯)	Nakajima O, Sone M, Onishi H, et al. Preventive effect of shosaikoto on the progression of chronic hepatitis C to cirrhosis*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1999; 76: 1008-16 (in Japanese).	RCT	I
B18.2	Efficacy of interferon plus shosaikoto (小柴胡湯) combination therapy for chronic hepatitis C.	shosaikoto (小柴胡湯)	Tanaka N, Matsuzaki Y, Osuga T, et al. A comparative study of IFN monotherapy versus IFN plus TJ-9 Shosaikoto combination therapy in patients with chronic hepatitis C (interim report)*. *Progress in Medicine* 1993; 13: 2868-72 (in Japanese).	RCT-envelope	N
B18.2	Efficacy for reducing adverse effects of interferon therapy in patients with chronic hepatitis C.	maoto (麻黄湯) + keishito (桂枝湯) + kojinmatsu (紅参末)	Isai H. Efficacy of Kampo formulations for reducing adverse effects of interferon therapy in patients with chronic hepatitis C*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1996; 84: 1505-9 (in Japanese).	RCT	N
B24.0	Efficacy and safety shosaikoto (小柴胡湯) in the treatment of HIV infection.	shosaikoto (小柴胡湯)	Fukue H, Hagiwara T, Yoshida S, et al. Efficacy of high-dose shosaikoto for HIV infection*. *HIV Kansensha Hassho Yobo, Chiryo ni kansuru Kenkyuhan Heisei 7 Nendo Kenkyu Hokokusho* (*Research Report by the Study Group on Prevention and Treatment of HIV Infection*) 1996: 203-10 (in Japanese).	DB-RCT	N

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs) (90 abstracts, 109 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C15.9	To evaluate the efficacy of rikkunshito (六君子湯) for anorexia and nausea/vomiting occurring after cancer chemotherapy for advanced esophageal cancer.	rikkunshito (六君子湯)	Seike J. Efficacy of rikkunshito for anorexia and nausea/vomiting caused by cancer chemotherapy*. *Kampo Igaku (Science of Kampo Medicine)* 2010; 34: 12 – 3 (in Japanese).	RCT	N
			Seike J, Sawada T, Kawakita N, et al. A new candidate supporting drug, rikkunshito, for the QOL in advanced esophageal cancer patients with chemotherapy using docetaxel/5-Fu/CDDP. *International Journal of Surgical Oncology* 2011; 2011: 1-7. DOI: 10.1155/2011/715623.		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C15.9	To evaluate the efficacy of daikenchuto (大建中湯) for postoperative recovery in patients with esophageal carcinoma.	daikenchuto (大建中湯)	Nishino T, Yoshida T, Goto M, et al. The effects of the herbal medicine Daikenchuto (TJ-100) after esophageal cancer resection, open-label, randomized controlled trial. *Esophagus* 2018; 15: 75-82.	RCT	C
C15.9 K13.7	To investigate the impact of daiokanzoto (大黄甘草湯) and hangeshashinto (半夏瀉心湯) on oral mucositis, tongue coating bacteria, and gingiva condition in patients with esophageal cancer undergoing chemotherapy.	daiokanzoto (大黄甘草湯), hangeshashinto (半夏瀉心湯)	Moriyama S, Hinode D, Yoshioka M, et al. Impact of the use of Kampo medicine in patients with esophageal cancer during chemotherapy: a clinical trial for oral hygiene and oral condition. *Journal of medical investigation* 2018; 65,:184-90.	RCT-envelope	C
C16.9	To evaluate the preventive effect of rikkunshito (六君子湯) on postoperative reflux esophagitis.	rikkunshito (六君子湯)	Mizuno S, Yamagiwa K, Iwata M, et al. Effect of early treatment with TSUMURA Rikkunshito on gastrointestinal symptoms after resection of gastric cancer – focusing on reflux esophagitis -*. *Progress in Medicine* 2001; 21: 1366-7 (in Japanese).	RCT	I
C16.9	To verify the effects of rikkunshito (六君子湯) on cisplatin-induced anorexia in gastric cancer patients.	rikkunshito (六君子湯)	Ohno T, Yanai M, Ando H, et al. Rikkunshito, a traditional Japanese medicine, suppresses cisplatin-induced anorexia in humans. *Clinical and Experimental Gastroenterology* 2011; 4: 291-6.	RCT-cross over	N
C16.9	To evaluate the efficacy of rikkunshito (六君子湯) for gastrointestinal symptoms following endoscopic submucosal dissection (ESD) of early gastric cancer.	rikkunshito (六君子湯)	Uehara R, Isomoto H, Minami H, et al. Characteristics of gastrointestinal symptoms and function following endoscopic submucosal dissection and treatment of the gastrointestinal symptoms using Rikkunshito. *Experimental and Therapeutic Medicine* 2013; 6: 1083-88.	RCT	N
C16.9	Improvement effect on host-immunity in patients undergoing postoperative adjuvant chemotherapy (UFT 300 mg/day) for gastric cancer.	juzentaihoto (十全大補湯)	Konno H, Maruo Y, Baba S, et al. Improvement of host-immunity by Juzen-taiho-to in the postoperative adjuvant chemotherapy for patients with gastric cancer. *Biotherapy* 1997; 11: 193-9 (in Japanese with English abstract).	RCT-envelope	N
C16.9	Efficacy for reducing adverse effects and improving performance status in patients undergoing postoperative adjuvant chemotherapy (fluoropyrimidine anticancer drug) for gastric cancer.	ninjin'yoeito (人参養栄湯)	Sugimachi K. A study of the usefulness of ninjin'yoeito in the postoperative adjuvant chemotherapy for gastric cancer*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1995; 72: 454-8 (in Japanese).	RCT-envelope	I
C16.9	Efficacy of juzentaihoto (十全大補湯) combined with oral 5-FU as postoperative adjuvant chemotherapy in patients with surgically treated gastric cancer.	juzentaihoto (十全大補湯)	Yamada T. Randomized controlled trial of the efficacy of Juzentaihoto (TJ-48) combined with oral 5-FU for gastric cancer*. *Progress in Medicine*. 2004; 24: 2746-7 (in Japanese)	RCT-envelope	N
C16.9	To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for gastric cancer chemotherapy-induced oral mucositis.	hangeshashinto (半夏瀉心湯)	Aoyama T, Nishikawa K, Takiguchi N, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis. *Cancer chemotherapy and pharmacology* 2014; 73: 1047-54.	DB-RCT	C&N
C16.9	To evaluate the effectiveness and safety of daikenchuto (大建中湯) for postoperative bowel dysmotility after gastric cancer and total gastrectomy.	daikenchuto (大建中湯)	Omori K. Prospective randomized controlled study of daikenchuto for postoperative dysmotility after total gastrectomy*. *Progress in Medicine* 2012; 32: 614-5 (in Japanese).	RCT	N
C16.9	To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction.	daikenchuto (大建中湯)	Endo S, Nishida T, Nishikawa K, et al. Dai-kenchu-to, a Chinese herbal medicine, improves stasis of patients with total gastrectomy and jejunal pouch interposition. *American Journal of Surgery* 2006; 192: 9-13.	RCT-cross over	C

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C16.9	To evaluate the efficacy and safety of daikenchuto (大建中湯) for promoting peristalsis in patients with reduced intestinal peristalsis after total gastrectomy.	daikenchuto (大建中湯)	Akamaru Y, Takahashi T, Nishida T, et al. Effects of daikenchuto, a Japanese herb, on intestinal motility after total gastrectomy: a prospective randomized trial. *Journal of Gastrointestinal Surgery* 2015; 19: 467-72.	RCT	N
C16.9	To verify the effects of daikenchuto (大建中湯) for intestinal tract motility after total gastrectomy for gastric cancer patients.	daikenchuto (大建中湯)	Yoshikawa K, Shimada M, Wakabayashi G, et al. Effect of daikenchuto, a traditional Japanese herbal medicine, after total gastrectomy for gastric cancer: a multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Journal of American College of Surgeons* 2015; 221: 571-8.	DB-RCT	C&N
C18.9	To elucidate the mechanism by which juzentaihoto (十全大補湯) reduces the adverse reaction to treatment with 5-fluorouracil (5-FU) (hepatopathy) by determining the distribution of 5-FU in tissues of patients with colorectal cancer receiving slow-release tegafur preoperatively.	juzentaihoto (十全大補湯)	Toda T, Matsuzaki K, Kawano T, et al. Preoperative and postoperative combination therapy with slow-release tegafur capsules and juzen-taiho-to in patients with colorectal cancer - Tissue concentrations and thymidine phosphorylase activity -. *Gan no Rinsho* (*Japanese Journal of Cancer Clinics*) 1998; 44: 317-23 (in Japanese with English abstract).	RCT-envelope	N
C18.9	Immunostimulation and suppression of liver metastasis in postoperative patients with colorectal cancer.	shosaikoto (小柴胡湯)	Sasaki K, Takashima K, Kitagawa K, et al. Immunostimulation and suppression of liver metastasis by Kampo medicines in postoperative patients with colorectal cancer*. *Progress in Medicine* 1992; 12: 1652-5 (in Japanese).	RCT	N
C18.9	Immunostimulation and improvement of nutritional status in postoperative patients with colorectal cancer.	ninjin'yoeito (人参養栄湯)	Araki Y, Tanaka T, Ogata Y, et al. Immunological evaluation of the efficacy of Kampo prescription for postoperative patients with colorectal cancer*. *Shinyaku to Rinsho* (*Journal of New Remedies and Clinic*) 1992; 41: 1670-6 (in Japanese).	RCT-envelope	N
C18.9	To evaluate the clinical efficacy of juzentaihoto (十全大補湯) for the prevention of postoperative recurrence of colorectal cancer.	juzentaihoto (十全大補湯)	Sasaki K, Ezoe E, Araya J, et al. Effects of Kampo medicine on the immune Functions in gastroenteric cancer patients. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2006; 15: 9-14 (in Japanese).	RCT	N
			Sasaki K, Takasaka H, Furuhata T, et al. Effect of Kampo medicine on cancer chemotherapy. *Geka Chiryo* (*Surgical Therapy*) 2007; 97: 504-10 (in Japanese).		N
C18.9	To evaluate the efficacy of 1-week preoperative treatment with hochuekkito (補中益気湯) for improving pre- and postoperative nutritional status and immune function in patients scheduled to undergo laparotomy for large intestine carcinoma.	hochuekkito (補中益気湯)	Nishimura G. Evaluation of clinical efficacy of hochuekkito in improving nutritional/immune status in patients with surgery for large intestine carcinoma*. *Progress in Medicine* 2009; 29: 84-5.	RCT-envelope	N
C18.9	To clarify the efficacy and adverse effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by oxaliplatin therapy for advanced or recurrent colorectal cancer.	goshajinkigan (牛車腎気丸)	Nishioka M, Shimada M, Kurita N, et al. The Kampo medicine, goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen. *International Clinical Journal of Oncology* 2011; 16: 322-7.	RCT	N
			Nishioka M, Shimada M, Kurita N, et al. The significance of Kampo as needed for cancer therapy – How to put it to use in clinical settings – Goshajinkigan alleviates FOLFOX-related peripheral neuropathy*. *Sanfujinka Kanpo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2012; (29): 22–7 (in Japanese).		I
C18.9	To investigate the inhibitory effect of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules(TJ-107) on oxaliplatin-induced peripheral neuropathy (OPN).	goshajinkigan (牛車腎気丸)	Kono T, Hata T, Morita S, et al. Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE) : a phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. *Cancer Chemotherapy and Pharmacology* 2013; 72: 1283-90.	DB-RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C18.9	To evaluate the preventive effect of goshajinkigan (牛車腎気丸) for FOLFOX-induced peripheral neurotoxicity.	goshajinkigan (牛車腎気丸)	Oki E, Emi Y, Kojima H,et al. Preventive effect of goshajinkigan on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial): a placebo-controlled, double-blind, randomized phase III study. *International Journal of Clinical Oncology* 2015; 20: 767-75.	DB-RCT	C&N
C18.9	To compare the preventive effects of hangeshashinto (半夏瀉心湯) for delayed diarrhea following administration of CPT-11 for colorectal cancer.	hangeshashinto (半夏瀉心湯)	Miyauchi H. A comparative study of the preventive effects of hangeshashinto and oral alkalizer for delayed diarrhea in chemotherapy for colorectal cancer (FOLFILI)*. *Progress in Medicine* 2012; 32: 628-9 (in Japanese).	RCT	N
C18.9	To verify the clinical effects of hangeshashinto (半夏瀉心湯) for chemotherapy-induced oral mucositis.	hangeshashinto (半夏瀉心湯)	Matsuda C, Munemoto Y, Mishima H, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. *Cancer Chemotherapy Pharmacology* 2015 ;76: 97-103.	DB-RCT	C&N
C18.9	To evaluate the anti-inflammatory effects of daikenchuto (大建中湯) on patients with colorectal cancer following laparoscopic resection.	daikenchuto (大建中湯)	Yoshikawa K, Shimada M, Nishioka M, et al. The effects of the Kampo medicine (Japanese herbal medicine) ' 'Daikenchuto' ' on the surgical inflammatory response following laparoscopic colorectal resection. *Surgery Today* 2012; 42: 646-51.	RCT	I
C18.9	To evaluate the effects of daikenchuto (大建中湯) on intestinal paralysis after surgery for colorectal cancer.	daikenchuto (大建中湯)	Nagashima Y, Tanaka N, Furukawa K, et al. Effects of Daikenchuto (TJ-100) on intestinal paralysis after surgery for colorectal cancer*. *Progress in Medicine* 1998; 18: 903-5 (in Japanese).	RCT	N
C18.9	To verify inhibition of inflammatory cytokine production and post-operative enhanced reactivation of intestinal function by daikenchuto (大建中湯) in colorectal cancer patients.	daikenchuto (大建中湯)	Ota M. A Randomized controlled trial of perioperative daikenchuto for colorectal cancer surgery*. *Progress in Medicine* 2012; 32: 618–9 (in Japanese).	RCT	N
C18.9	To evaluate the effectiveness of daikenchuto (大建中湯) for perioperative intestinal paralysis following laparoscopic colon cancer surgery.	daikenchuto (大建中湯)	Yaegashi M, Otsuka K, Itabashi T, et al. Applying a Kampo medication to lower gastrointestinal tract surgery*. *Shokaki Geka* (Gastroenterological Surgery) 2013; 36: 1315-24.	RCT	C&N
			Yaegashi M, Otsuka K, Itabashi T, et al. Daikenchuto stimulates colonic motility after laparoscopic -associated colectomy. *Hepato-Gastroenterology* 2014; 61: 85-9.		N
C18.9	To evaluate the effectiveness and safety of daikenchuto (大建中湯) soon after colorectal cancer surgery.	daikenchuto (大建中湯)	Watanabe K. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* *Kampo Igaku (Science of Kampo Medicine)* 2010; 34: 346–7 (in Japanese).	quasi-RCT	N
			Fujii S. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* *Progress in Medicine* 2011; 31: 468–9 (in Japanese).		N
C18.9	To evaluate the efficacy of daikenchuto (大建中湯) for gastrointestinal dysfunction following colon surgery.	daikenchuto (大建中湯)	Katsuno H, Maeda K, Kaiho T, et al. Clinical efficacy of daikenchuto for gastrointestinal dysfunction following colon surgery: a randomized, double-blind, multicenter, placebo-controlled study (JFMC39-0902). *Japanese Journal of Clinical Oncology* 2015; 45: 650-6.	DB-RCT	N
C18.9	To verify the effects of daikenchuto (大建中湯) for gastrointestinal function recovery after laparotomy in patients with sigmoid colon cancer or rectosigmoid cancer.	daikenchuto (大建中湯)	Katsuno H, Maeda K, Ohya M, et al. Clinical pharmacology of daikenchuto assessed by transit analysis using radiopaque markers in patients with colon cancer undergoing open surgery: a multicenter double-blind randomized placebo-controlled study (JFMC39-0902 additional study). *Journal of Gastroenterology* 2016; 51: 222-9.	DB-RCT	N
C20.0	To evaluate the effects of daikenchuto (大建中湯) on intestinal obstruction following colorectal cancer surgery.	daikenchuto (大建中湯)	Takagi K, Nagata H, Horie T, et al. Effect of the preventive herbal therapy using dai-kenchu-to on intestinal obstruction following curative resection for colorectal cancer: prospective, randomized study. *Kampo Kenkyu* (*Kampo Research*) 2007; (429): 270-1 (in Japanese).	RCT	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C22.0	To evaluate the effect of juzentaihoto (十全大補湯) for reducing adverse effects of Spongel + Lipiodol + phosphatidyl choline + cisplatin treatment in transarterial embolization (TAE) for hepatocellular carcinoma.	juzentaihoto (十全大補湯)	Nagatomo H, Shigehira M. Efficacy of TSUMURA Juzentaihoto for reducing the adverse effects of the anticancer drug cisplatin*. *Kampo Igaku* (*Kampo Medicine*) 1992; 16: 116-9 (in Japanese).	RCT	N
C22.0	Preventive effect on the progression of cirrhosis to liver cancer.	shosaikoto (小柴胡湯)	Ayukawa K, Sato T, Nagase S, et al. Preventive effect of shosaikoto on liver carcinogenesis*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1994; 71: 1874-6 (in Japanese).	quasi-RCT	I
C22.0	To evaluate the efficacy of liver protectors for preventing carcinogenesis in patients with chronic hepatitis C.	shosaikoto (小柴胡湯), juzentaihoto (十全大補湯)	Tarao K, Shibuya A, Ohkawa S, et al. Prevention of hepatocarcinogenesis by anti-inflammatory therapy: is combination anti-inflammatory therapy targeting an ALT level of under 80 units effective for hepatitis C virus-related cirrhosis (Child A)?: comparison with monotherapy*. *Kanagawa Cancer Center – Nenpo (Annual Report)* 2003; 19: 92 (in Japanese).	RCT	N
			Tarao K. Persistent inflammation and hepatocarcinogenesis in chronic hepatitis C and hepatitis C virus-related cirrhosis*. *Kanagawa Igakkai Zasshi (The Journal of the Kanagawa Medical Association)* 2006; 33: 115-8 (in Japanese).		N
			Tarao K. Prevention of HCC by anti-inflammatory agents in patients with chronic hepatitis C. *Rinsho Shokaki Naika (Clinical Gastroenterology)* 2007; 22: 961-9 (in Japanese).		N
C22.0	To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.	juzentaihoto (十全大補湯)	Higuchi K, Watanabe A. Study on liver cancer-preventive effect of juzentaihoto in patients with liver cirrhosis*. *Methods in Kampo Pharmacology* 2000; 5: 29-33 (in Japanese).	RCT-envelope	N
C22.0	To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.	juzentaihoto (十全大補湯)	Higuchi K, Shimizu Y, Yasumura S, et al. Preventive effect of liver carcinogenesis by juzen-taiho-to in the patients with liver cirrhosis. *Kan-Tan-Sui* 2002; 44: 341-6 (in Japanese).	RCT-envelope	I
C22.0	To evaluate the anti-inflammatory efficacy of daikenchuto (大建中湯) in postoperative patients with liver carcinoma.	daikenchuto (大建中湯)	Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto —A study in a fasted rat model and a randomized controlled trial in postoperative patients with colorectal cancer—*. *Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai* (*5th Annual Meeting of the Japanese Gastroenterological Association*) (Workshop 5) 2009:9-10.	RCT	N
C22.0	To evaluate the usefulness of daikenchuto (大建中湯) in postoperative patients who underwent hepatectomy.	daikenchuto (大建中湯)	Nishi M, Shimada M, Uchiyama H, et al. The beneficial effects of Kampo medicine dai-ken-chu-to after hepatic resection：a prospective randomized control study. *Hepato-Gastroenterology* 2012; 59: 2290-4.	RCT	N
C22.0	To evaluate the effect of daikenchuto (大建中湯) on abdominal bloating in patients who underwent hepatectomy for liver malignancies.	daikenchuto (大建中湯)	Hanazaki K, Ichikawa K, Munekage M, et al. Effect of Daikenchuto (TJ-100) on abdominal bloating in hepatectomized patients. *World Journal of Gastrointestinal Surgery* 2013; 5: 115-22.	RCT	N
C22.0	To evaluate the safety and effectiveness of daikenchuto (大建中湯) for gastrointestinal motility after surgery for liver cancer.	daikenchuto (大建中湯)	Shimada M, Morine Y, Nagano H, et al. Effect of TU-100, a traditional Japanese medicine, administered after hepatic resection in patients with liver cancer: a multi-center, phase III trial (JFMC40-1001). *International Journal of Clinical Oncology* 2015; 20(1): 95-104.	DB-RCT	C
C22.0	To evaluate the hepatoprotection effect of inchinkoto (茵チン蒿湯) after hepatectomy with preoperative administration of inchinkoto.	inchinkoto (茵チン蒿湯)	Mizutani T, Yokoyama Y, Kokuryo T, et al. Does inchinkoto, a herbal medicine, have hepatoprotective effects in major hepatectomy? a prospective randomized study. *HPB : The Official Journal of The International Hepato Pancreato Biliary Association* 2015; 17: 461-9.	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C24.0	To evaluate the drug efficacy of inchinkoto (茵チン蒿湯) as a choleretic drug on livers of patients with biliary obstruction due to bile duct carcinoma.	inchinkoto (茵チン蒿湯)	Watanabe S, Yokoyama Y, Oda K, et al. Choleretic effect of inchinkoto, a herbal medicine, on livers of patients with biliary obstruction due to bile duct carcinoma. *Hepatology Research* 2009; 39: 247-55.	RCT	C&I
C25.9	To evaluate the effect of juzentaihoto (十全大補湯) for antigen-specific immunity and performance status of advanced pancreatic cancer patients receiving peptide vaccine therapy.	juzentaihoto (十全大補湯)	Yutani S, Komatsu N, Matsueda S, et al. Juzentaihoto failed to augment antigen-specific immunity but prevented deterioration of patients ' conditions in advanced pancreatic cancer under personalized peptide vaccine. *Evidence-Based Complementary and Alternative Medicine* 2013: 1-10. doi : 10.1155/2013/981717	RCT	N
C25.9	To evaluate the preventive efficacy of daikenchuto (大建中湯) as treatment for paralytic ileus after pancreatoduodenectomy.	daikenchuto (大建中湯)	Okada K, Kawai M, Hirono S, et al. Evaluation of the efficacy of daikenchuto (TJ-100) for the prevention of paralytic ileus after pancreaticoduodenectomy: a multicenter, double-blind, randomized, placebo-controlled trial. *Surgery* 2016; 159: 1333-41.	DB-RCT	C
			Maeda H, Okada K, Fujii T, et al. Transition of serum cytokines following pancreaticoduodenectomy: A subsidiary study of JAPAN-PD. *Oncology Letters* 2018;16: 6847-53.		C
C34.9	Preventive effect on myelosuppression in patients undergoing chemotherapy for primary lung cancer.	juzentaihoto (十全大補湯)	Yamagata T, Ajimura K, Yukawa S. Effect of juzentaihoto on myelosuppression during lung cancer chemotherapy*. *Therapeutic Research* 1998; 19: 705-8 (in Japanese).	RCT-envelope	N
C34.9	Preventive effect of hochuekkito (補中益気湯) on general malaise in patients undergoing chemotherapy for advanced primary lung cancer.	hochuekkito (補中益気湯)	Inui H, Yamagata T, Minakata Y, et al. Prevention of side effects during lung cancer chemotherapy by Hochuekki-to. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 1993; 2: 56-60 (in Japanese).	RCT-cross over	N
C34.9	To evaluate the efficacy of hochuekkito (補中益気湯) combined with clarithromycin (CAM) for improvement in the prognosis of lung cancer.	hochuekkito (補中益気湯)	Kato S, Kishiro I, Machida S, et al. Combined effects of hochu-ekki-to (bu-zhong-yi-qi-tang) and clarithromycin on Lung Carcinoma. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 1999; 13: 83-8 (in Japanese with English abstract).	RCT	N
C34.9	To evaluate the efficacy of hochuekkito (補中益気湯) for the prevention and relief of general malaise related to chemotherapy for primary lung cancer (squamous cell carcinoma, adenocarcinoma, and small cell carcinoma).	hochuekkito (補中益気湯)	Mori K, Saito Y, Tominaga K. Utility of hochu-ekki-to in general malaise accompanying lung cancer chemotherapy. *Biotherapy* 1992; 6: 624-7 (in Japanese with English abstract).	RCT	I
C34.9	To evaluate the safety and efficacy of hangeshashinto (半夏瀉心湯) (TJ-14) for CPT-11-induced diarrhea during combination chemotherapy with cisplatin (CDDP) plus irinotecan hydrochloride (CPT-11) for advanced non-small-cell lung cancer (NSCLC).	hangeshashinto (半夏瀉心湯)	Mori K, Machida S, Yoshida T, et al. Usefulness of Kampo medicine (hangeshashin-to) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Proceedings of the American Society of Clinical Oncology* 1999; 18: 518a, Abstract 1996.	RCT-envelope	C
			Mori K, Hirose T, Machida S, et al. Kampo medicines for the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)* 1998; 25: 1159-63 (in Japanese with English abstract).		C
			Mori K. Hangeshashin-to (Kampo medicined) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Progress in Medicine* 1999; 19: 886-90 (in Japanese with English abstract).		N
			Mori K, Kondo T, Kamiyama Y, et al. Preventive effect of Kampo medicine (hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. *Cancer Chemotherapy and Pharmacology* 2003; 51: 403-6.		C

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C34.9	To evaluate the efficacy of bakumondoto (麦門冬湯) on improvement in cough after lung cancer surgery.	bakumondoto (麦門冬湯)	Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery. *Kampo to Meneki Arerugi (Kampo and Immuno-Allergy)* 2008; 22: 43-55 (in Japanese with English abstract).	RCT-envelope	I
			Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery — QOL analysis with 36-Item Short Form (SF-36) v2*.. *Progress in medicine* 2010; 30: 100-1 (in Japanese).		N
C34.9	To evaluate the efficacy of rikkunshito (六君子湯) for chemotherapy-induced appetite loss.	rikkunshito (六君子湯)	Oteki T, Ishikawa A, Sasaki Y, et al. Effect of rikkunshi-to treatment on chemotherapy-induced appetite loss in patients with lung cancer: a prospective study. *Experimental and Therapeutic Medicine* 2016; 11: 243-6.	RCT	N
C34.9	To evaluate the preventive effect of shakuyakukanzoto (芍薬甘草湯) for arthralgia and myalgia following carboplatin and paclitaxel combination chemotherapy for non-small cell lung cancer.	shakuyakukanzoto (芍薬甘草湯)	Yoshida T, Sawa T, Ishiguro T, et al. The efficacy of prophylaetic shakuyaku-kanzo-to for myalgia and arthralgia following carboplatin and paclitaxel combination chemotherapy for non-small cell lung cancer. *Support Care Cancer* 2009; 17: 315-20.	RCT	N
C50.9	To verify the effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy during chemotherapy for breast cancer.	goshajinkigan (牛車腎気丸)	Abe H, Kawai Y, Mori T, et al. The kampo medicine Goshajinkigan prevents neuropathy in breast cancer patients treated with Docetaxel. *Asian Pacific Journal of Cancer Prevention* . 2014; 14: 6351-6.	RCT	N
C50.9	To evaluate the efficacy of the carbonate spring foot bath and goshajinkigan (牛車腎気丸) for lower-extremity peripheral neuropathy due to cancer chemotherapy.	goshajinkigan (牛車腎気丸)	Kawabata K, Nakano T, Tsutsumi J, et al. Evaluation of alleviation for lower-extremity peripheral neuropathy due to cancer chemotherapy. Effectiveness of the carbonate spring foot bath and goshajinkigan*. *Journal of the Japanese Society of Footcare* . 2014; 12: 145-50 (in Japanese).	RCT-envelope	I
C50.9	To evaluate the efficacy of hochuekkito (補中益気湯) or ninjin'yoeito (人参養栄湯) for reducing adverse drug reactions and improving quality of life (QOL) in breast cancer patients undergoing postoperative (after curative resection or initial treatment) Sunfral S (800 mg/day).	ninjin'yoeito (人参養栄湯) or hochuekkito (補中益気湯)	Nagao K, Nishimura R, Matsuda M, et al. Clinical evaluation of the combined effect of tegafur and hozai (traditional Chinese medicine)*. *Toho Igaku* (*Eastern Medicine*) 1998; 14: 63-71 (in Japanese with English abstract).	RCT-envelope	N
C50.9	To evaluate effects of ninjin′ yoeito (人参養栄湯) prophylaxis dosing on the postoperative immune status in breast cancer patients.	ninjin'yoeito (人参養栄湯)	Takanami I, Ohnishi H. Clinical effects of ninzin-yoei-to as the immunopotentiator. *Kiso to Rinsho (The Clinical Report)* 1988;22: 1835-46 (in Japanese).	RCT	N
C50.9	Efficacy of supportive therapy for advanced breast cancer patients.	juzentaihoto (十全大補湯)	Adachi I. Supporting therapy with shi quan da bu tang in advanced breast cancer patients. *Biomedical Research* 1990; 11 suppl: 25-31.	RCT-envelope	N
			Adachi I, Watanabe T, Chen JY, et al. Supportive therapy of oriental medicine for patients with advanced breast cancer. *Gan to Kagaku Ryoho* (*Japanese Journal of Cancer and Chemotherapy*) 1989; 16: 1538-43 (in Japanese with English abstract).		C&I
			Adachi I. Juzen-taiho-to as a supporting therapy in advanced breast cancer. *Biotherapy* 1989; 3: 782-8 (in Japanese with English abstract).		I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C57.7	To evaluate the efficacy of using juzentaihoto (十全大補湯) to augment preoperative autologous blood donation in cancer patients.	juzentaihoto (十全大補湯)	Aoe H, Matsuo T, Ebisutani M, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation in cancer patients*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2000; 17: 67-71 (in Japanese).	RCT	N
			Aoe H, Ota M, Kawahara N, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation*. *Rinsho Kensa (Journal of Medical Technology)* 2003; 47: 395-9 (in Japanese).		I
			Aoe H. Effect of Juzen-taiho-to on haematological recovery from predeposit autologous blood donation. *Pharma Medica* 2007; 25: 11-4.		I
C57.7	To evaluate the effects of preoperative administration of shosaikoto (小柴胡湯) on thrombocytopenia in gynecologic cancer patients receiving anti-cancer drugs.	shosaikoto (小柴胡湯)	Mori T, Tauchi K, Yokoyama S, et al. Effects of sho-saiko-to (xiao-chai-hu-tang) on thrombocytopenia bei therapy with anti-cancer drugs. *Sanfujinka Chiryo (Obstetrical and Gynecological Therapy)* 1992; 65: 102–5 (in Japanese).	RCT	N
C57.7	To evaluate the effect of kamikihito (加味帰脾湯) on thrombocytopenia and leukopenia in patients receiving anti-cancer drugs.	kamikihito (加味帰脾湯)	Inoue S, Kuwahara H, Kato Y, et al. Thrombopoietic and leukopoietic effects of a traditional Chinese herbal medicine, formula reverti lienalis compositae (Japanese name: *Kami-kihi-to TJ-137*) in cancer patients. *Biotherapy* 1998; 12: 1071-6 (in Japanese with English abstract).	RCT-cross over	N
C57.7	To evaluate the effect of combined juzentaihoto (十全大補湯) on myelosuppression during chemotherapy in patients with gynecologic cancers.	juzentaihoto (十全大補湯)	Fujiwara M, Koumoto Y. Effect of juzentaihoto on myelosuppression due to chemotherapy for gynecologic malignant tumor*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 1998; 15: 86-9 (in Japanese).	RCT-cross over	N
C57.7	To evaluate the potential use of sokeikakketsuto (疎経活血湯) and shakuyakukanzoto (芍薬甘草湯) in preventing peripheral nerve disorder in patients receiving taxol.	sokeikakketsuto (疎経活血湯)	Miyabe Y, Taniguchi C, Kawashima M, et al. Effect of Kampo medicines (sokeikakketsuto, shakuyakukanzoto) for taxol-caused peripheral nerve disorder – evaluation by current perception threshold measured by Neurometer□*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2006; 23: 65-8 (in Japanese).	RCT-cross over	N
C57.7	To evaluate the efficacy of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by chemotherapy (paclitaxel and carboplatin) for uterine and ovarian cancer.	goshajinkigan (牛車腎気丸)	Kaku H, Kumagai S, Onoue H, et al. Objective evaluation of the alleviating effects of goshajinkigan on peripheral neuropathy induced by paclitaxel/carboplatin therapy: A multicenter collaborative study. *Experimental and Therapeutic Medicine* 2012; 3: 60-5.	RCT	N
C57.7	To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) and L-glutamine for paclitaxel-induced myalgia and arthralgia.	shakuyakukanzoto (芍薬甘草湯)	Hasegawa K, Mizutani Y, Kuramoto H, et al. The Effect of L-glutamine and shakuyaku-kanzo-to for paclitaxel-induced myalgia/arthralgia. *Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)* 2002; 29: 569-74 (in Japanese with English abstract).	RCT-cross over	I
C57.7 R11.0	To evaluate the efficacy and safety of rikkunshito (六君子湯) added to antiemetics for nausea, vomiting, and anorexia in patients treated with cisplatin and paclitaxel for cervical and endometrial cancers.	rikkunshito (六君子湯)	Ohnishi S, Watari H, Sakuragi N, et al. Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: results of a randomized phase II study (JORTC KMP-02). *Journal of Gynecologic Oncology* 2017; 28: 1-10. doi: 10.3802/jgo.2017.28.e44	RCT	C
C57.7 N95.1	To evaluate the effect of Kampo medicines kamikihito (加味帰脾湯) and kamishoyosan (加味逍遙散) on menopausal symptoms in gynecological cancer patients.	kamishoyosan (加味逍遙散), kamikihito (加味帰脾湯)	Yoshimura A, Sawada K, Sasano T, et al. Effect of Japanese Kampo medicine therapy for menopausal symptoms after treatment of gynecological malignancy. *Obstetrics and Gynecology International* 2018: 1-6.	RCT-envelope	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C57.9	Efficacy for relieving subjective symptoms and improving activities of daily living in patients following gynecologic cancer surgery.	ninjin'yoeito (人参養栄湯)	Mizuno M, Yoshikawa H, Taketani Y, et al. Clinical effects of ninjin'yoeito on performance status (PS) and recovery of physical strength in patients following gynecologic cancer treatment – comparison with no-treatment controls–*. *Sanka to Fujinka* (*Obstetrics and Gynecology*) 1993; 60: 1533-45 (in Japanese).	RCT	I
C57.9	To evaluate the efficacy of combination of ninjin'yoeito (人参養栄湯) and juzentaihoto (十全大補湯) for reducing adverse effects of cyclophosphamide, adriamycin, cisplatin (CAP) chemotherapy including myelosuppression, renal impairment, and gastrointestinal symptoms.	ninjin'yoeito (人参養栄湯) + juzentaihoto (十全大補湯)	Hasegawa K, Fukunishi H, Kiyoshige K, et al. Clinical usefulness of Kampo medicines (ninjin-yoei-to, juzen-taiho-to) for side effects in gynecologic cancer chemotherapy – Effects on reducing side effects by CDDP in CAP therapy–. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 181-7 (in Japanese with English abstract).	RCT	N
C57.9	Efficacy of ninjin'yoeito (人参養栄湯) on subjective and objective symptoms and bone-marrow function during postoperative chemotherapy or radiotherapy in female patients with genital cancer.	ninjin'yoeito (人参養栄湯)	Yamamoto T, Fujita H, Okada H, et al. Clinical evaluation of the effects of ninjin'yoeito on subjective and objective symptoms and bone-marrow function during chemotherapy or radiotherapy in female patients with genital cancer*. *Oncology & Chemotherapy* 1994; 10: 126-34 (in Japanese).	RCT-envelope	N
C57.9	To evaluate the efficacy of ninjin'yoeito (人参養栄湯) for reducing myelosuppression due to chemotherapy for gynecologic cancer.	ninjin'yoeito (人参養栄湯)	Oda T. My prescription – clinical application of ninjin'yoeito in gynecologic cancer – a preventive effect on bone marrow suppression–*. *WE* 2004; 9: 5-6.	quasi-RCT	I
			Oda T, Ohnuki T, Kihara K, et al. A clinical study of a traditional Chinese herbal medicine, ninjin-youei-to in bone marrow suppression due to chemotherapy in gynecologic cancer. *Yamagata Kenritsu Byoin Igaku Zasshi* (*The Yamagata Journal of Medicine*) 2004; 38; 6-9 (in Japanese).		I
C57.9	To evaluate the efficacy of juzentaihoto (十全大補湯) and ninjin'yoeito (人参養栄湯) combined with an erythropoietin (EPO) preparation in preoperative autologous blood donation in cancer patients.	juzentaihoto (十全大補湯), ninjin'yoeito (人参養栄湯)	Aoe H, Sumida Y, Kawahara N, et al. Efficacy of an erythropoietin preparation and Kampo medicines in preoperative autologous blood donation in cancer patients*. *Jikoketsu Yuketsu (Journal of Japanese Society of Autologous Blood Transfusion)* 1999; 12: 100-4 (in Japanese).	RCT	N
C57.9	To evaluate the efficacy of goshajinkigan (牛車腎気丸) and keishikajutsubuto (桂枝加朮附湯) as treatment for chemotherapy-induced myalgia, arthralgia, and numbness in ovarian cancer.	goshajinkigan (牛車腎気丸), keishikajutsubuto (桂枝加朮附湯)	Sato Y, Yamamoto S, Tanoue K, et al. Evaluation of the effects of herbal medicines on the side effects of TC therapy (muscle pain, arthralgia, numbness). A cross-over study between goshajinkigan and keishikajutsubuto. *Sanfujinka Kampo Kenkyu no Ayumi* 2015; 32:68-71 (in Japanese).	RCT-cross over	N
C61 N42.8	To evaluate the efficacy and safety of Kampo medicines (hochuekkito [補中益気湯] and keishibukuryogan [桂枝茯苓丸]) for enhancing the immune response to tailor-made cancer peptide vaccine therapy (PPV) in men with castration-resistant prostate cancer (CRPC).	hochuekkito (補中益気湯) + keishibukuryogan (桂枝茯苓丸)	Koga N, Moriya F, Waki K, et al. Immunological efficacy of herbal medicines in prostate cancer patients treated by personalized peptide vaccine. *Cancer Science* 2017; 108: 2326-32.	RCT	N
C64 K12.3	To evaluate the clinical usefulness of gargling with hangeshashinto (半夏瀉心湯) for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer.	hangeshashinto (半夏瀉心湯)	Oh-oka H. The clinical usefulness of gargling with hangeshashinto for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer. *Kampo Medicine* 2018;69: 1-6 (in Japanese with English abstract).	RCT	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C67.9	To evaluate the effect of postoperative adjuvant chemotherapy for bladder cancer on survival (the efficacy of the combination with juzentaihoto (十全大補湯) was assessed in patients stratified into 3 groups).	juzentaihoto (十全大補湯)	Fukui I, Gotoh S, Kihara K, et al. Adjuvant chemotherapy for invasive bladder cancer: multicenter study. *Nippon Hinyokika Gakkai Zasshi* (*Japanese Journal of Urology*) 1992; 83: 1633-9 (in Japanese with English abstract).	RCT	N
68.9	Efficacy and safety of saireito (柴苓湯) for relieving the adverse urological effects of anticancer drugs.	saireito (柴苓湯)	Ohkawa T, Ebisuno S, Watanabe T, et al. Clinical evaluations of saireito, a herbal drug, for the side-effects of cancer chemotherapy in urological field. *Biotherapy* 1990; 4: 1445-60 (in Japanese with English abstract).	RCT-envelope	I
C80.0	To evaluate the efficacy of juzentaihoto (十全大補湯) for reducing adverse effects and improving quality of life (QOL) in postoperative patients undergoing chemotherapy (tegafur-uracil [UFT] 4 capsules/day) for gastric, colorectal, or breast cancer (curative resection/non-curative resection).	juzentaihoto (十全大補湯)	Kosaka A, Hojyo M, Osaku M, et al. The value of TSUMURA Juzentaihoto (TJ-48) in reducing adverse effects of anticancer drugs from the perspective of QOL improvement*. *Progress in Medicine* 1993; 13: 1072-9 (in Japanese).	RCT-envelope	N
			Kosaka A, Kamiya T, Sumiyama M, et al. Usefulness of TSUMURA Juzentaihoto (TJ-48) for reducing adverse effects of anticancer drugs and improving QOL*. *Progress in Medicine* 1994; 14: 2259-64 (in Japanese).		N
C80.0	Efficacy and safety for reducing adverse reactions during cancer radiotherapy.	juzentaihoto (十全大補湯)	Tanaka Y, Hashimoto S. Effects of TSUMURA Juzentaihoto on various complaints occurring as adverse reactions during radiotherapy*. *JAMA* (*Japanese version*) 1988; (6) suppl: 70-1 (in Japanese).	RCT-envelope	N
			Hashimoto S, Tanaka Y. Adverse reactions to cancer radiotherapy*. *Sanfujinka no Sekai* (*World of Obstetrics and Gynecology*) 1990; 42 suppl: 176-84 (in Japanese).		N
C80.0	Effect on the cell-mediated immunity of postoperative patients with esophageal, gastric, or colorectal cancer.	juzentaihoto (十全大補湯)	Yamada T. Clinical study of Juzen-taiho-to administration for postoperative esophageal carcinoma, gastric carcinoma, and colorectal carcinoma – Influence of surgical intervention and postoperative chemotherapy on cell mediated immunity – . *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1992; 9: 157-64 (in Japanese with English abstract).	RCT-envelope	N
C80.0	To evaluate the effects of juzentaihoto (十全大補湯) on leukopenia in patients receiving cancer chemotherapy.	十全大補湯	Suzuki S, Abe R, Nomizu T, et al. Effect of Juzentaihoto (TJ-48) on leukopenia in patients receiving cancer chemotherapy*. *Progress in Medicine* 1995; 15: 1968-71 (in Japanese).	RCT-envelope	I
C80.0	Clinical effects in patients undergoing chemotherapy (tegafur).	hochuekkito (補中益気湯), ninjin'yoeito (人参養栄湯)	Ohara T, Onda M, Futagawa S, et al. Clinical evaluation of the combined effect of bu-zhong-yi-qi-tang (Japanese name, hochu-ekki-to) or ren-shen-yang-rong-tang (Japanese name, ninjin-youei-to) and the anticancer drug tegafur. *Yakuri to Chiryo* (*Japanese Phamacology & Therapeutics*) 1993; 21: 4423-34 (in Japanese).	RCT-envelope	C&I
C80.0	To evaluate whether preoperative administration of hochuekkito (補中益気湯) relieves surgical stress in patients with gastric or colorectal cancer.	hochuekkito (補中益気湯)	Saito S, Iwagaki H, Kobayashi N, et al. Effects of a Japanese herbal medicine (TJ-41) on surgical stress of patients with gastric and colorectal cancer*. *Nihon Rinsho Geka Gakkai Zasshi* (*Journal of Japan Surgical Association*) 2006; 67: 568-74 (in Japanese).	RCT	I
C80.0	To evaluate the effectiveness of hochuekkito (補中益気湯) for cancer-related fatigue.	hochuekkito (補中益気湯)	Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: A pilot randomized clinical trial. *Integrative Cancer Therapies* 2010; 9: 331-8.	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C80.0	To evaluate the efficacy of preoperative administration of hochuekkito (補中益気湯) for postoperative systemic inflammatory response syndrome (SIRS) in gastric/colon cancer.	hochuekkito (補中益気湯)	Iwagaki H, Saito S. Regulation of post-operative systemic inflammatory response syndrome (SIRS) by preoperative administration of hochuekkito (a Japanese herbal medicine). *Nihon Toyo Igaku Zasshi (Kampo Medicine)* 2010; 61: 78–83 (in Japanese with English abstract).	RCT	I
C80.0	To evaluate the improvement in subjective symptoms and leukopenia after ninjin'yoeito (人参養栄湯) administration in patients undergoing radiotherapy for thoracoabdominal tumors.	ninjin'yoeito (人参養栄湯)	Okawa T, Hashimoto S, Sakamoto S, et al. Ninjin-yoei-to in the treatment of leukopenia and symptoms associated with radiotherapy of malignant tumors. *Gan no Rinsho (Japanese Journal of Cancer Clinics)* 1995; 41: 41–51 (in Japanese with English abstract).	RCT	I
C80.0	To evaluate the healing effect of TSUMURA Saibokuto (柴朴湯) on mucositis induced by head-and-neck and mediastinal irradiation.	saibokuto (柴朴湯)	Saito Y, Mitsuhashi N, Takahashi I, et al. Effect of TSUMURA Saiboku-to as an agent for healing damage in treatment of radiomucositis due to irradiation of the head and neck area and mediastinum. *Biotherapy* 1992; 6: 1899–906 (in Japanese with English abstract).	RCT	N
C80.0	To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for delayed diarrhea induced by irinotecan (CPT-11) in patients with metastatic gastric and colorectal cancer.	hangeshashinto (半夏瀉心湯)	Hibi S, Ina K, Furuta R, et al. Clinical effects of hange-shashin-to on combination therapy of S-1/irinotecan for patients with metastatic gastric and colorectal cancer*. *Gan to Kagaku Ryoho* (*Japanese Journal of Cancer Chemotherapy*) 2009; 36: 1485–8 (in Japanese with English abstract).	RCT-envelope	C&I
C80.0 F05.9	To evaluate the efficacy and safety of yokukansan (抑肝散) for postoperative delirium in patients with gastrointestinal and lung cancers.	yokukansan (抑肝散)	Sugano N, Aoyama T, Sato T, et al. Randomized phase II study of TJ-54 (Yokukansan) for postoperative delirium in gastrointestinal and lung malignancy patients. *Molecular and Clinical Oncolog* y 2017; 7: 569-73.	RCT	C&N
D25.9	To evaluate the anti-tumor effect of keishibukuryogan (桂枝茯苓丸) in patients with hysteromyoma/uterine adenomyosis.	keishibukuryogan (桂枝茯苓丸)	Yamamoto K, Hirano F, Ikoma N, et al. Efficacy of keishibukuryogan for hysteromyoma/uterine adenomyosis. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 135-7 (in Japanese).	RCT	I

3. Blood Diseases including Anaemia (8abstracts, 9 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
D50.0	To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for hypochromic anemia in patients with uterine myoma.	tokishakuyakusan (当帰芍薬散)	Akase T, Akase T, Onodera S, et al. A comparative study of the usefulness of toki-shakuyaku-san and an oral iron preparation in the treatment of hypochromic anemia in cases of uterine myoma. *Yakugaku Zasshi* (*Journal of the Pharmaceutical Society of Japan*) 2003; 123: 817-24.	RCT	C&I
D50.8	Efficacy of ninjin'yoeito (人参養栄湯) for iron deficiency anemia due to menorrhagia.	ninjin'yoeito (人参養栄湯)	Yanagihori A, Miyagi M, Hori M, et al. Efficacy of ninjin'yoeito for iron deficiency anemia*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1995; 72: 2605-8 (in Japanese).	RCT-envelope	I
D50.8	Combined effect of erythropoietin and ninjin'yoeito (人参養栄湯) on anemia after autologous blood donation.	ninjin'yoeito (人参養栄湯)	Aoe H, Takada K, Kawahara N, et al. Effectiveness of erythropoietin and ninjin'yoeito in preoperative autologous blood donation*. *Jikoketsu Yuketsu* (*Journal of Japanese Society of Autologous Blood Transfusion*) 1997; 10: 145-51 (in Japanese).	RCT	N
D64.8	To evaluate the efficacy and safety of ninjin'yoeito (人参養栄湯) for ribavirin-induced anemia.	ninjin'yoeito (人参養栄湯)	Motoo Y, Mouri H, Ohtsubo K, et al. Herbal medicine ninjinyoeito ameliorates ribavirin-induced anemia in chronic hepatitis C: A randomized controlled trial. *World Journal of Gastroenterology* 2005; 11: 4013-7.	RCT	C
D64.8	To evaluate the efficacy and safety of juzentaihoto (十全大補湯) for erythropoietin-resistant anemia in patients on hemodialysis.	juzentaihoto (十全大補湯)	Nakamoto H, Mimura T, Honda N. Orally administrated Juzen-taiho-to/TJ-48 ameliorates erythropoietin (rHuEPO)-resistant anemia in patients on hemodialysis. *Hemodialysis International* 2008; 12: S9-14.	RCT	C

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
D69.6	Efficacy of goreisan (五苓散) for thrombocytopenia after cholecystectomy.	goreisan (五苓散), shosaikoto (小柴胡湯)	Seki M. Efficacy of goreisan for preventing thrombocytopenia and activating vascular endothelial cells after cholecystectomy*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1990; 7: 510-1 (in Japanese).	RCT	N
D72.8	Preventive effect of preoperative administration of shosaikoto (小柴胡湯) on postoperative lymphopenia in female patients.	shosaikoto (小柴胡湯)	Hatano T. Mitigation of postoperative lymphopenia and protection of T cells by preoperative administration of xial-chai-hu-tang. *Saitama Ika Daigaku Zasshi* (*Journal of Saitama Medical School*) 1990; 17: 357-63 (in Japanese with English abstract).	RCT	N
D86.0	Effects of keishikajutsubuto (桂枝加朮附湯) on the levels of angiotensin-converting enzyme and lysozyme in sarcoidosis patients.	keishikajutsubuto (桂枝加朮附湯)	Inagaki M, Nakazawa T, Michimata H, et al. Treatment experience with TSUMURA Keishikajutsubuto for pulmonary sarcoidosis*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1990; 7: 316-7 (in Japanese).	RCT	N
			Inagaki M. Effectiveness of Kampo medicine in relieving complaints associated with chronic intractable diseases*. *Kampo Shinryo* 1993; 12: 1-3 (in Japanese).		N

4. Metabolism and Endocrine Diseases (13 abstracts, 17 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
E11.9	Efficacy and safety of seishinrenshiin (清心蓮子飲) on improvement in glucose tolerance.	seishinrenshiin (清心蓮子飲)	Azuma M, Motomiya M, Toyota T. Effects of Seishin-renshi-in (TJ-111) on blood sugar levels of patients with non-insulin-dependent diabetes mellitus. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1994; 45: 339-44 (in Japanese with English abstract).	RCT-envelope	N
E14	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for treatment of diabetic complications.	goshajinkigan (牛車腎気丸)	Watanabe K, Shimada A, Miyaki K, et al. Long-term effects of goshajinkigan in prevention of diabetic complications: A randomized open-labeled clinical trial. *Evidence-Based Complementary and Alternative Medicine* 2014 :1-8. doi：10.1155/2014/128726	RCT	C&N
E22.9	To evaluate the efficacy of unkeito (温経湯) for reducing high luteinizing hormone (LH) levels and improving ovulation disorder.	unkeito (温経湯)	Ushiroyama T, Ikeda A, Sakai M, et al. Effects of unkei-to, an herbal medicine, on endocrine function and ovulation in women with high basal level of luteinizing hormone secretion. *The Journal of Reproductive Medicine* 2001; 46: 451-6.	RCT-envelope	C
E28.2	To evaluate the efficacy of switching to unkeito (温経湯) from treatment based on the traditional diagnostic criterion “eight-principle pattern identification” in women with polycystic ovary syndrome (PCOS).	unkeito (温経湯), tokisyakuyakusan (当帰芍薬散), keishibukuryogan (桂枝茯苓丸)	Ushiroyama T, Hosotani T, Mori K, et al. Effects of switching to wen-jing-tang (unkei-to) from preceding herbal preparations selected by eight-principle pattern identification on endocrinological status and ovulatory induction in women with polycystic ovary syndrome. *The American Journal of Chinese Medicine* 2006; 34: 177-87.	RCT-envelope	C
E28.3	To evaluate the efficacy of unkeito (温経湯) for luteal phase deficiency.	unkeito (温経湯)	Ushiroyama T, Ikeda A, Higashio S, et al. Unkei-to for correcting luteal phase defects. *The Journal of Reproductive Medicine* 2003; 48: 729-34.	RCT-envelope	C
E66.9	To evaluate the anti-obesity effect of bofutsushosan (防風通聖散) extract granules in obese patients and the course of high-sensitivity C-reactive protein (HS-CRP) as an arteriosclerosis-promoting factor.	bofutsushosan (防風通聖散)	Namiki T. Basic and clinical investigation of the effect of Kampo medicines on arteriosclerosis*. *Uehara Kinen Seimei Kagaku Zaidan Kenkyu Hokokushu* (*Research Reports of Uehara Memorial Foundation*) 2007; 21: 60-3 (in Japanese).	RCT-envelope	I
E78.5	Efficacy and safety of daisaikoto (大柴胡湯) combined with probucol in patients with hyperlipidemia.	daisaikoto (大柴胡湯)	Takashima T, Ohmori K, Higuchi N, et al. Combination therapy with probucol and daisaikoto (a Kampo medicine) - Effects of daisaikoto on HDL metabolism -. *Domyaku Koka* (*The Journal of Japan Atherosclerosis Society*) 1993; 21: 47-52 (in Japanese with English abstract).	RCT-envelope	N
			Yamamoto K. A study of the hepatic triglyceride (TG)-lowering effects and antioxidant capacity of various Kampo preparations*. *Proceedings of the 4th Kampo Treatment Seminar at Kyoto University* 1995: 48-56 (in Japanese).		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
E78.5	Efficacy and safety of daisaikoto (大柴胡湯) in patients with hyperlipidemia.	daisaikoto (大柴胡湯)	Sasaki J, Matsunaga A, Handa K, et al. Effect of daisaikoto on hyperlipidemia - comparison with clinofibrate -*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1991; 68: 3861-71 (in Japanese).	RCT	I
E78.5	Efficacy and safety of daisaikoto (大柴胡湯) combined with bezafibrate in patients with hyperlipidemia.	daisaikoto (大柴胡湯)	Muramatsu N, Okayasu M. Clinical study on hyperlipidemia at bezafibrate and da-chai-hu-tang (dai-saiko-to) for the combination therapy. *Shigaku* (*Odontology*) 1993; 81: 94-9 (in Japanese with English abstract).	RCT	N
E78.5	Effects of daisaikoto (大柴胡湯) on serum lipid level and cerebral circulation.	daisaikoto (大柴胡湯)	Yamano S, Sawai F, Hashimoto T, et al. Comparative effects between dai-saiko-to and elastase on lipid metabolism and cerebral circulation in patients with hyperlipidemia. *Kampo to Saishin-chiryo* (*Kampo & The Newest Therapy*) 1995; 4: 309-13 (in Japanese).	RCT-envelope	N
E87.8	Efficacy and safety of goreisan (五苓散) in the treatment of hyponatremia after surgery for cholelithiasis or gallbladder polyps.	goreisan (五苓散), shosaikoto (小柴胡湯)	Takagi S. Mitigation of hyponatremia after operation for cholelithiasis or gallbladder polyp by preoperative administration of wu-ling-san. *Journal of Saitama Medical School* 1990; 17: 145-50 (in Japanese with English abstract).	RCT	N
			Seki M, Fujioka M, Hatano T, et al. Analysis of regulatory effects of gorei-san on circulatory, metabolic and diuretic function - especially in relation to endothelial activation and increase of urinary 6-keto-prostaglandin $F_1\alpha$ level-. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1992; 42: 313-22 (in Japanese with English abstract).		N
E88.9	To evaluate whether bofutsushosan (防風通聖散) reduces obesity.	bofutsushosan (防風通聖散)	Uebaba K, Xu F. Association between the SNP in sympathetic b3-adrenergic receptor gene and the efficacy of bofutsushosan*. *Nihon Toyo Igaku Zasshi* (*Kampo medicine*) 2003; 54: S225.	DB-RCT	N
			Kamohara S, Kawakami T, Uebaba K, et al. A study on the development of individualized medicine for the prevention, diagnosis, and treatment of metabolic syndrome using an integrative approach*. *Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku* (*Research Papers of the Suzuken Memorial Foundation*) 2009; 26: 399–403.		N
			Xu FH, Uebaba K, Ogawa H, et al. Personalized effects of a Kampo herbal formulation on metabolism — A randomized, double-blind, placebo controlled study of bohutusei-san — — *Toho Igaku* (*Eastern Medicine*) 2012; 28: 37-59 (in Japanese).		I
E88.9	To evaluate the effects of co-administration of probiotics with bofutsushosan (防風通聖散) on obesity.	bofutsushosan (防風通聖散)	Lee S J, Bose S, Seo J-G, et al. The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis：A randomized double-blind controlled clinical trial. *Clinical Nutrition* 2014; 33: 973-81.	DB-RCT	N

5. Psychiatric/Behavioral Disorders (21abstracts,25 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
F01.9	Efficacy of chotosan (釣藤散) in the treatment of vascular dementia.	chotosan (釣藤散)	Shimada Y, Terasawa K, Yamamoto T, et al. A well-controlled study of choto-san and placebo in the treatment of vascular dementia. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 246-55.	RCT-envelope	I
			Shimada Y, Terasawa K, Yamamoto T, et al. Efficacy of choto-san on vascular dementia: A well, placebo-controlled study. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 370-1 (in Japanese).		I
F01.9	Efficacy of chotosan (釣藤散) in the treatment of vascular dementia.	chotosan (釣藤散)	Terasawa K, Shimada Y, Kita T, et al. Choto-san in the treatment of vascular dementia: A double blind, placebo-controlled study. *Phytomedicine* 1997; 4: 15-22.	DB-RCT	N
			Terasawa K. Chotosan in the treatment of vascular dementia. *Pharma Medica* 2007; 25: 57-9 (in Japanese).		I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
F03	To evaluate the efficacy of hachimijiogan (八味地黄丸) for dementia.	hachimijiogan (八味地黄丸)	Iwasaki K, Kanbayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "ba wei di huang wan" in the treatment of dementia. *Journal of the American Geriatrics Society* 2004; 52: 1518-21.	DB-RCT	C
F03	To evaluate the efficacy of chotosan (釣藤散) for improvement of cognitive function and activities of daily living in dementia patients.	chotosan (釣藤散), goshajinkigan (牛車腎気丸)	Suzuki T, Futami S, Igari Y, et al. A Chinese herbal medicine, choto-san, improves cognititive function and activities of daily living of patients with dementia: A double-blind, randomized, placebo-controlled study. *Journal of the American Geriatrics Society* 2005; 53: 2238-40.	DB-RCT	C
F03	To evaluate the efficacy and safety of yokukansan (抑肝散) for treating behavioral disorders and improving activities of daily living in dementia patients.	yokukansan (抑肝散)	Iwasaki K, Satoh-Nakagawa T, Maruyama M, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine yi-gan san for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. *Journal of Clinical Psychiatry* 2005; 66: 248-52.	RCT	C
F03	To evaluate the efficacy and safety of yokukansan (抑肝散) in the treatment of behavioural and psychological symptoms of dementia.	yokukansan (抑肝散)	Mizukami K, Asada T, Kinoshita T, et al. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. *The International Journal of Neuropsychopharmacology* 2009; 12: 191-9.	RCT-cross over	C
F03	To evaluate the efficacy and safety of yokukansankachimpihange (抑肝散加陳皮半夏) on cognitive function.	yokukansankachimpihange (抑肝散加陳皮半夏)	Fujita H, Yoshida M, Yomoda S. Effects of Yokukansankachimpihange on cognitive ability, an open randomized controlled trial. *Psychiatry* 2013; 23: 130-8 (in Japanese with English abstract).	quasi-RCT	N
F03	To evaluate the effectiveness of yokukansan (抑肝散) for cognitive dysfunction after surgery for fracture of the proximal femur/ in the elderly.	yokukansan (抑肝散)	Egawa H, Hamaguchi S. Clinical applications of Kampo medications – Clinical applications of Kampo medications for Postoperative Cognitive Dysfunction (POCD) – Yokukansan and perioperative management of fracture of the proximal femur in the elderly.* *Nou 21* (*Brain 21*) 2015; 18: 271-4.	RCT	I&N
F05.9	To evaluate the efficacy of yokukansan (抑肝散) for postoperative delirium after cardiovascular surgery in the elderly.	yokukansan (抑肝散)	Takase S. The efficacy of Yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 132–4 (in Japanese).	RCT-envelope	N
			Takase S, Yokoyama H. Using a Kampo medication in the perioperative period – The preventative effects of yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly*. *Kampo to Saishin-chiryo (Kampo & the Newest Therapy)* 2013; 22: 113–19 (in Japanese).		N
C80.0 F05.9	To evaluate the efficacy and safety of yokukansan (抑肝散) for postoperative delirium in patients with gastrointestinal and lung cancers.	yokukansan (抑肝散)	Sugano N, Aoyama T, Sato T, et al. Randomized phase II study of TJ-54 (Yokukansan) for postoperative delirium in gastrointestinal and lung malignancy patients. *Molecular and Clinical Oncolog* y 2017; 7: 569-73.	RCT	C&N
F20.9	To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.	yokukansan (抑肝散)	Miyaoka T, Furuya M, Yasuda H, et al. Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia: an open-label study. *Clinical Neuropharmacology* 2009; 32: 6-9.	RCT	N
F20.9	To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.	yokukansan (抑肝散)	Miyaoka T, Furuya M, Horiguchi J, et al. Efficacy and safety of yokukansan in treatment-resistant schizophrenia: a randomized, multicenter, double-blind, placebo-controlled trial. 2015 *Evidence-Based Complementary and Alternative Medicine* 2015; 1-11. doi: 10.1155/2015/201592.	DB-RCT	C&N
			Miyaoka T, Furuya M, Horiguchi J, et al. Efficacy and safety of yokukansan in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled trial (a positive and negative syndrome scale, five-factor analysis). *Psychopharmacology* 2015; 232: 155-64.		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
F41.1	To evaluate the effectiveness and safety of yokukansan (抑肝散) in preoperative sedation.	yokukansan (抑肝散)	Arai YC, Kawanishi J， Sakakima Y, et al. The effect of the kampo medicine Yokukansan on preoperative anxiety and sedation levels. *Evidence-Based Complementary and Alternative Medicine*. 2014: 1-4. doi：10.1155/2014/965045	RCT	N
F41.9	To evaluate the efficacy of saibokuto (柴朴湯) as a potentiator of the anxiolytic and antidepressant effects of diazepam.	saibokuto (柴朴湯)	Ishida H, Otake T, Kurihara H, et al. Clinical study on augmentative effect of Saiboku-to for anxiolytic and antidepressive action of diazepam. *Pain Clinic*, 1999; 20: 395-9 (in Japanese).	RCT	N
F43.1	To evaluate the efficacy and safety of saikokeishikankyoto (柴胡桂枝乾姜湯) for posttraumatic stress disorder (PTSD).	saikokeishikankyoto (柴胡桂枝乾姜湯)	Numata T, Gunfan S, Takayama S, et al. Treatment of posttraumatic stress disorder using the traditional Japanese Herbal Medicine saikokeishikankyoto: A randomized observer-blinded controlled trial in survivors of the Great East Japan earthquake and tsunami. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-6. doi:10.1155/2014/683293	RCT	C&N
F45.3	Efficacy for relieving discomfort in the throat.	saibokuto (柴朴湯)	Yamagiwa M, Sakakura Y, Harada T, et al. Therapeutic response to various drugs in patients with continuous or periodic discomfort in the throat. *Jibiinkoka Rinsho* (*Practica otologica*) 1990; 83: 1687-92 (in Japanese with English abstract).	RCT	N
F45.3	To evaluate the efficacy of lansoprazole in patients with pharyngolaryngeal paresthesia and acid reflux symptoms (compared with rikkunshito (六君子湯) as a control).	rikkunshito (六君子湯)	Yamagiwa M, Fujita K. Effect of treatment using lansoprazole on patients with an abnormal sensation in the throat and concomitant heart burn. *Jibi to Rinsho* (*Otologia Fukuoka*) 2007; 53: 109-15 (in Japanese with English abstract).	quasi-RCT	I
F45.9	Symptom-relieving effects in elderly patients with underlying chronic disease.	hachimijiogan (八味地黄丸) ＋ kojinmatsu (紅参末)	Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of combination treatment of hatimi-zio-gan and Red Ginseng powder on unidentified clinical complaints - estimation of double blind comparative study in many hospitals -. *Therapeutic Research* 1989; 10: 4951-65 (in Japanese).	DB-RCT-envelope	I
F45.9	To evaluate the efficacy and safety of kamikihito (加味帰脾湯) and kamishoyosan (加味逍遙散) for otorhinolaryngological symptoms with a strong psychosomatic element.	kamikihito (加味帰脾湯)	Tanaka H. Problems and approaches to treatment of psychosomatic disease by an otorhinolaryngologist, and Kampo treatment for psychosomatic cases with depressive tendency – Focusing on kamikihito (加味帰脾湯) –. *Phil Kampo* 2014; 47: 20-2.	RCT-cross over	I
F52.2	Efficacy and safety of oral prostaglandin E1 in the treatment of erectile dysfunction.	goshajinkigan (牛車腎気丸)	Sato Y, Horita H, Adachi N, et al. Effect of oral administration of prostaglandin E1 on erectile dysfunction. *British Journal of Urology* 1997; 80: 772-5.	quasi-RCT	N
F52.2	To compare the efficacy of LEOPIN ROYAL with that of Kampo medicines for aging in males.	kamishoyosan (加味逍遙散), hangekobokuto (半夏厚朴湯), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯), hochuekkito (補中益気湯), goshajinkigan (牛車腎気丸), hachimijiogan (八味地黄丸)	Nishimatsu H, Kitamura T, Yamada D, et al. Improvement of symptoms of aging in males by a preparation LEOPIN ROYAL containing aged garlic extract and other five of natural medicines-comparison with traditional herbal medicines (Kampo). *Aging male* 2014; 17: 112-6.	RCT	C&N

6. Nervous System Diseases (including Alzheimer's Disease) (18 abstracts, 21 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
G10	Efficacy and safety of yokukansan (抑肝散) in patients with Huntington’s disease.	yokukansan (抑肝散), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)	Satoh T, Takahashi T, Iwasaki K, et al. Traditional Chinese Medicine on four patients with Huntington's disease. *Movement Disorders* 2009; 24: 453-5.	RCT-cross over	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
G20.0	To evaluate the efficacy and safety of rikkunshito (六君子湯) for anorexia and indigestion in patients with Parkinson's disease.	rikkunshito (六君子湯)	Yakabi K, Yamaguchi N, Ono S, et al. Open label trial of the efficacy and safety profile of rikkunshito used for the treatment of gastrointestinal symptoms in patients with Parkinson's disease: a pilot study. *Current Therapeutic Research* 2017; 87: 1-8.	RCT-cross over	N
G25.9	To evaluate the effectiveness and safety of shakuyakukanzoto (芍薬甘草湯) on extrapyramidal symptoms during antipsychotic treatment.	shakuyakukanzoto (芍薬甘草湯)	Ota T, Miura I, Kanno-Nozaki K, et al. Effects of shakuyaku-kanzo-to on extrapyramidal symptoms during antipsychotic treatment: a randomized, open-label study. *Journal of Clinical Psychopharmacology* 2015; 35: 304-7.	RCT	C&N
G30.1	Efficacy and safety of yokukansan (抑肝散) in the treatment of behavioral and psychological symptoms of dementia (BPSD) in elderly patients with Alzheimer's disease.	yokukansan (抑肝散)	Monji A, Takita M, Samejima T, et al. Effect of yokukansan on the behavioral and psychological symptoms of dementia in elderly patients with Aizheimer's disease. *Progress in Neuro-Psychopharmacology & Bioiogical Psychiatry* 2009; 33: 308-11.	RCT	N
			Monji A, Kanba S. Effectiveness of yokukansan (抑肝散) on BPSD in Alzheimer ' s disease — Results of a long-term antipsychotic combination trial at a department of neuropsychiatry in Kyushu*. *No 21* (*Brain 21*) 2009; 12: 446-51 (in Japanese).		I
G30.1	To investigate the efficacy and safety of yokukansan (抑肝散) as a common treatment for behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD).	yokukansan (抑肝散)	Okahara K, Ishida Y, Hayashi Y, et al. Effects of yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 2010; 34: 532-6.	RCT	C
G30.1	To evaluate the efficacy of yokukansan (抑肝散) and risperidone in the treatment of behavioral and psychological symptoms of dementia (BPSD).	yokukansan (抑肝散)	Furuhashi Y. Comparative efficacy of risperidone versus yokukansan (抑 肝 散) on behavioral and psychological symptoms of dementia in patients with Alzheimer ' s disease*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 120–1 (in Japanese).	RCT	N
G30.1	To evaluate the efficacy and safety of yokukansan (抑肝散) for behavioral and psychological symptoms of dementia (BPSD).	yokukansan (抑肝散)	Teranishi M, Kurita M, Nisiho S, et al. Efficacy and tolerability of risperidone, yokukansan, and fluvoxamine for the treatment of behavioral and psychological symptoms of dementia: A blinded, randomized trial. *Journal of Clinical Psychopharmacology* 2014; 33: 600-7.	RCT	N
			Kurita M, Efficacy and tolerability of yakukansan for behavioral and psychological symptoms of dementia (BPSD) – A 3-way comparative trial of risperidone and fluvoxamine. *Brain 21* 2015; 18: 249-52.	RCT	I&N
G30.1	To evaluate the efficacy and safety of yokukansan (抑肝散) for behavioral and psychological symptoms of dementia due to Alzheimer's disease.	yokukansan (抑肝散)	Furukawa, K, Tomita N, Une K, et al. Randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's disease. *Geriatrics and Gerontology International* 2017; 17: 211-8.	DB-RCT	C
G30.9	To evaluate the efficacy and safety of kihito (帰脾湯) for Alzheimer-type dementia.	kihito (帰脾湯), goshajinkigan (牛車腎気丸)	Higashi K, Rakugi H, Yu H, et al. Effect of kihito extract granules on cognitive function in patients with Alzheimer's-type dementia. *Geriatrics & Gerontology International* 2007; 7: 245-51.	RCT	I
G43.9	To evaluate the efficacy and safety of goshuyuto (呉茱萸湯) for treatment of migraine.	goshuyuto (呉茱萸湯)	Maruyama T. Goshuyu-to versus lomerizine hydrochloride in the prophylactic treatment of migraine headaches: an open crossover trial. *Itami to Kampo* (*Pain and Kampo Medicine*) 2006; 16: 30-9 (in Japanese with English abstract).	RCT-cross over	I
G47.0	To evaluate the efficacy and safety of DS-4773 for sedation versus sansoninto (酸棗仁湯) used as control.	sansoninto (酸棗仁湯)	Matsushita M, Saito M, Katayama S, et al. Clinical evaluation of DS-4773 on sedative effect: a cross-over trial. *Yakuri to Chiryo* (*Japanese Pharmacology & Therapeutics*) 1994; 22: 2371-82 (in Japanese).	RCT-cross over	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
G47.1	Effect of kakkonto (葛根湯) on sleepiness after sleep deprivation.	kakkonto (葛根湯)	Zhuang H.Y., Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation of normal young adults. *Shinkei Seishin Yakuri* (*Japanese journal of neuropsychopharmacology*) 1992; 14: 319-25 (in Japanese with English abstract).	DB-RCT-cross over	I
			Hagino H, Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation with quantitative EEG method. *Noha to Kindenzu* (*Japanese Journal of Electroencephalography and Electromyography*) 1995; 23: 361-7 (in Japanese with English abstract).		N
G47.3	To evaluate the lipid lowering and antihypertensive effects of bofutsushosan (防風通聖散) and daisaikoto (大柴胡湯) for patients with obstructive sleep apnea as a complication of obesity and hypertension.	bofutsushosan (防風通聖散), daisaikoto (大柴胡湯)	Murase K, Toyama Y, Harada Y, et al. Evaluation and comparison of the effect of two Chinese herbal medicines (Bofu-tsusho-san and Dai-saiko-to) on metabolic disorders in obstructive sleep apnea patients. *American journal of respiratory and critical care medicine* 2013; 187: A5694.	RCT	C
G47.9	Effectiveness of orengedokuto (黄連解毒湯) on sleep disorder in patients in the acute phase of psychotic disorders.	orengedokuto (黄連解毒湯)	Yamada K, Kanba S, Ohnishi K, et al. Clinical effectiveness of oren-gedoku-to for sleep disorder associated with acute schizophrenia and other psychotic disorders. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1997; 47: 827-31 (in Japanese with English abstract).	RCT-envelope	N
G47.9	To evaluate the efficacy of yokukansankachimpihange (抑肝散加陳皮半夏) for sleep disorders.	yokukansankachimpihange (抑肝散加陳皮半夏), anchusan (安中散)	Aizawa R, Kanbayashi T, Saito Y, et al. Effects of yoku-kan-san ka chimpi-hange on the sleep of normal healthy adult subjects. *Psychiatry and Clinical Neurosciences* 2002; 56: 303-4.	RCT-cross over	C&I
G51.3	Efficacy of shakuyakukanzoto (芍薬甘草湯) for relieving facial spasm.	shakuyakukanzoto (芍薬甘草湯)	Kimura H, Otake T, Ishikura H. Efficacy of shakuyakukanzoto for relieving facial spasm*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1991; 79: 2505-8 (in Japanese).	RCT	N
G54.4	To evaluate the efficacy of goshajinkigan (牛車腎気丸) for treatment of lumbar (low back) and leg pain.	goshajinkigan (牛車腎気丸)	Sekine R, Watanabe H, Mimura M, et al. The effects of Gosha-jinki-gan on the low back pain and lower limb pain caused by the lumbar spine: A comparison of Gosha-jinki-gan with Benfotiamine. *Itami to Kampo* (*Pain and Kampo Medicine*) 2003; 13: 84-7 (in Japanese)	RCT-cross over	I
G81.9	To evaluate the efficacy and safety of hochuekkito (補中益気湯) for decreased ADL, nutrition, and immune state in patients with hemiplegia due to sequelae of cerebrovascular disorders who are undergoing rehabilitation.	hochuekkito (補中益気湯)	Fukumura N, Yamamoto H, Kitahara M, et al. Hochuekkito suppresses the incidence of inflammatory complications in patients with sequelae of cerebrovascular disorders in the convalescent rehabilitation ward – Study in a multicenter randomized controlled trial. *Japanese Journal of Rehabilitation Medicine* 2017; 54: 303-14 (in Japanese with English abstract).	RCT	I

7. Eye Diseases (4 abstracts, 5 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
H00.0	To evaluate the efficacy of hainosankyuto (排膿散及湯) for internal hordeolum in the acute phase.	hainosankyuto (排膿散及湯)	Takama N, Fujiwara T. The Efficacy of hainou-san-kyu-to for internal hordeolum. *Ganka Rinsho Iho* (*Japanese Review of Clinical Ophthalmology*) 2006; 100: 9-11 (in Japanese).	RCT	I
H18.9	To evaluate the efficacy of goshajinkigan (牛車腎気丸) for corneal sensitivity, superficial keratitis, and tear secretion in patients with insulin-dependent (type 1) diabetes mellitus.	goshajinkigan (牛車腎気丸)	Nagaki Y, Hayasaka S, Hayasaka Y, et al. Effects of goshajinkigan on corneal sensitivity, superficial punctate keratopathy and tear secretion in patients with insulin-dependent diabetes mellitus. *American Journal of Chinese Medicine* 2003; 31: 103-9.	DB-RCT	C
			Nagaki Y. Effects of goshajinkigan on diabetic keratopathy*. *Kampo Igaku* (*Kampo Medicine*) 2004; 28: 63-5 (in Japanese).		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
H25.9	To evaluate the efficacy of Kampo medicines for aqueous flare elevation after small-incision cataract surgery.	orengedokuto (黄連解毒湯), kakkonto (葛根湯), saireito (柴苓湯)	Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of traditional Sino-Japanese herbal medicines on aqueous flare elevation after small-incision cataract surgery. *Journal of Ocular Pharmacology and Therapeutics* 2001; 17: 59-65.	RCT	C
H25.9	To evaluate the efficacy of Kampo medicines for aqueous flare elevation after complicated cataract surgery.	kakkonto (葛根湯), saireito (柴苓湯)	Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of kakkon-to and sairei-to on aqueous flare elevation after complicated cataract surgery. *American Journal of Chinese Medicine* 2002; 30: 347-53.	RCT	C

8. Ear Diseases (9 abstracts, 10 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
H65.0	To evaluate the efficacy of shoseiryuto (小青竜湯) combined with eppikajutsuto (越婢加朮湯) for otitis media with effusion (OME) in adults.	shoseiryuto (小青竜湯) + eppikajutsuto (越婢加朮湯)	Inoue H. Rapid effect of combination therapy with shoseiryuto and eppikajutsuto for acute otitis media with effusion in adults. *Jibi to Rinsho* (*Otologia Fukuoka*) 2001; 47: 361-6 (in Japanese).	quasi-RCT	I
H65.9	Efficacy of saireito (柴苓湯) for otitis media with effusion.	saireito (柴苓湯)	Machii K, Ikezono T, Utasato S, et al. Comparative study of the efficacy of saireito monotherapy versus antiallergic agent plus carbocysteine combination therapy for otitis media with effusion*. *Kampo Igaku* (*Kampo Medicine*) 1992; 16: 200-3 (in Japanese).	RCT	N
H65.9	Efficacy of saireito (柴苓湯) for otitis media with effusion.	saireito (柴苓湯)	Sato H, Nakamura H, Honjo I, et al. Clinical evaluation of Tsumura-Saireito in children with otitis media with effusion - A comparative randomized controlled study of cepharanthine -. *Jibiinkoka Rinsho* (*Practica otologica*) 1988; 81: 1383-7 (in Japanese with English abstract).	RCT	N
H66.9	To evaluate the efficacy and safety of juzentaihoto (十全大補湯) in children with recurrent otitis media.	juzentaihoto (十全大補湯)	Yoshizaki T. A multicenter, double-blind, randomized controlled trial on the usefulness of juzentaihoto in children with recurrent otitis media* (2009—clinical study—general—007) *Chozai to Joho (Dispensing and Information)* Health Labour Sciences Research Grant, General Research Program for Practical Application of Medical Technology, 2009, General Research Report in 2011. 2012: 1-23 (in Japanese).	DB-RCT	N
			Ito M, Maruyama Y, Kitamura K, et al. Randomized controlled trial of juzen-taiho-to in children with recurrent acute otitis media *Auris Nasus Larynx* 2017; 44: 390-7.		I
H90.5	To compare the effectiveness of saireito (柴苓湯) and isosorbide for low-frequency sensorineural hearing loss.	saireito (柴苓湯)	Kaneko T. Comparison of saireito and isosorbide in efficacy against low-frequency sensorineural hearing loss. *Kampo to Saishin Chiryo (Kampo and the Newest Therapy)* 2010; 19: 233–9 (in Japanese with English abstract).	quasi-RCT	I
H93.1	Efficacy of saireito (柴苓湯) for tinnitus.	saireito (柴苓湯)	Tanaka H. Efficacy of a Kampo preparation combined with tranquilizers in patients with tinnitus. *Jibiinkoka Rinsho* (*Practica otologica*) 1996; suppl 89: 8 (in Japanese).	RCT-cross over	N
H93.1	To evaluate the efficacy of chotosan (釣藤散) for tinnitus.	chotosan (釣藤散)	Suzuki T. *Clinical efficacy of chotosan for tinnitus. Pathology and treatment of tinnitus and dizziness*. The 28th Chiba Symposium of Japanese Traditional Medicine Tokyo: Kudansha; 2001:8-20 (in Japanese).	RCT-cross over	I
H93.1	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for tinnitus.	goshajinkigan (牛車腎気丸), chotosan (釣藤散)	Onishi S. Kampo treatment for tinnitus and hearing impairment*. *JOHNS* 1990; 6: 535-9 (in Japanese).	quasi-RCT	N
H93.1	To evaluate the effects of hangekobokuto (半夏厚朴湯) on chronic tinnitus.	hangekobokuto (半夏厚朴湯)	Ino T, Odaguchi H, Wakasugi A, et al. A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of hangekobokuto in adult patients with chronic tinnitus. *Journal of Traditional Medicines* 2013; 30: 72-81.	DB-RCT	I

9. Cardiovascular Diseases (19 abstracts, 22 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
I10	To evaluate the efficacy of chotosan (釣藤散) and orengedokuto (黄連解毒湯) for hypertension using ambulatory blood pressure monitoring.	chotosan (釣藤散), orengedokuto (黄連解毒湯)	Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitor. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 282-3 (in Japanese).	RCT	N
			Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitoring*. *Kampo Shinryo* 1996; 15: 34-5 (in Japanese).		N
I10	Efficacy and safety of daisaikoto (大柴胡湯) and chotosan (釣藤散) in patients with essential hypertension.	daisaikoto (大柴胡湯), chotosan (釣藤散)	Sasaki J, Matsunaga A, Kusuda M, et al. Efficacy of daisaikoto and chotosan in patients with essential hypertension*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1993; 70: 1965-75 (in Japanese).	RCT-envelope	I
I10	Effects of daisaikoto (大柴胡湯) and saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) on serum lipid levels in patients with mild to moderate hypertension.	daisaikoto (大柴胡湯), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)	Saku K, Hirata K, Zhang B, et al. Effects of Chinese herbal drugs on serum lipids, lipoproteins and apolipoproteins in mild to moderate essential hypertensive patients. *Journal of Human Hypertension* 1992; 6: 393-5.	RCT	C
I10	To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) in patients with hypertension symptoms.	orengedokuto (黄連解毒湯)	Arakawa K, Saruta T, Abe K, et al. Double-blind placebo-controlled trial of TSUMURA Orengedokuto (TJ-15) for the treatment of accessory symptoms of hypertension*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Study*) 2003; 80: 354-72 (in Japanese)	DB-RCT	I
			Arakawa K, Saruta T, Abe K, et al. Improvement of accessory symptoms of hypertension by TSUMURA Orengedokuto Extract, a four herbal drugs containing Kampo-Medicine Granules for ethical use: a double-blind, placebo-controlled study. *Phytomedicine* 2006; 13: 1-10.		C
I10	To verify the effectiveness of the combined use of bofutsushosan (防風通聖散) with Western medical treatments for obesity hypertension patients using Ambulatory Blood Pressure Monitoring (ABPM).	bofutsushosan (防風通聖散)	Azushima K, Tamura K, Haku S, et al. Effects of the oriental herbal medicine Bofu-tsusho-san in obesity hypertension: a multicenter, randomized, parallel-group controlled trial (ATH-D-14-01021.R2). *Atherosclerosis* 2015; 240(1): 297-304.	RCT	C
I50.9	To investigate combined effect of goreisan (五苓散) in elderly tolvaptan-responder patients with heart failure.	goreisan (五苓散)	Tamano M, Toyoda S, Kato S, et al. Clinical investigation of the combined effect of goreisan and tolvaptan in tolvaptan-responder elderly patients with heart failure. *Progress in Medicine* 2018; 38: 751-6 (in Japanese).	RCT	I
I51.9	Efficacy and safety of orengedokuto (黄連解毒湯) plus red ginseng combination therapy for relieving symptoms associated with hypertension.	orengedokuto (黄連解毒湯), orengedokuto (黄連解毒湯) + kojinmatsu (紅参末)	Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of the effect of ohrengedoku-toh and ohrengedoku-toh - Red Ginseng mixture on chronic cardiovascular disorders in middle and aged patients. *The Ginseng Review* 1991; 12: 89-93 (in Japanese with English abstract).	DB-RCT	N
I62.0	To evaluate the effectiveness and safety of goreisan (五苓散) after chronic subdural hematoma surgery in elderly people.	goreisan (五苓散)	Yoshikawa T, Munakata S, Okuma H. Effectiveness of goreisan for recurrence prevention in elderly cases of chronic subdural hematoma surgery— Interim report on a comparative trial.* *Noshinkei Geka to Kampo (Neurosurgery and Kampo)* 2010: 16 (in Japanese).	RCT	N
I62.0	To investigate the preventative effect of goreisan (五苓散) on post-operative recurrence of chronic subdural hematoma.	goreisan (五苓散)	Katayama K, Matsuda N, Kakuta K, et al. The effect of goreisan on the prevention of chronic subdural hematoma recurrence: multi-center randomized controlled study. *Journal of Neurotrauma* 2018; 35: 1537-42.	RCT	C
I63.9	Efficacy and safety of orengedokuto (黄連解毒湯) in the treatment of cerebral infarction.	orengedokuto (黄連解毒湯)	Ito E, Takahashi A, Kuzuya F. Clinical effectiveness of TSUMURA Orengedokuto in the treatment of cerebral infarction*. *Geriatric Medicine* 1991; 29: 303-13 (in Japanese).	RCT-envelope	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
I63.9	To evaluate the effectiveness of saireito (柴苓湯) for acute ischemic stroke.	saireito (柴苓湯)	Nakae Y. Effectiveness of saireito in acute ischemic stroke. *Kampo to Saishin Chiryo (Kampo & the Newest Therapy)* 2013; 22: 329-32.	RCT	I&N
I67.9	Efficacy and safety of orengedokuto (黄連解毒湯) for relieving psychiatric symptoms in patients with late effects of cerebrovascular disease.	orengedokuto (黄連解毒湯)	Otomo E, Togi H, Kogure K, et al. Clinical usefulness of TSUMURA Orengedokuto for the treatment of cerebrovascular disease: a well-controlled study comparing TSUMURA Orengedokuto versus Ca hopantenate, using sealed envelopes for allocation*. *Geriatric Medicine* 1991; 29: 121-51 (in Japanese).	RCT-envelope	I
I69.4	To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for treatment of hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder.	tokishakuyakusan (当帰芍薬散)	Shimada Y. Efficacy of tokishakuyakusan for hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder*. *Kosei Rodo Kagaku Kenkyuhi Hojokin Choju Kagaku Kenkyu Jigyo: Koreisha no Nokekkan Shogai no Shinten Yobo wo Mokuteki to Shita Kampoyaku niyoru Tailor-made Iryo no Kaihatsu, Heisei 18 Nendo Buntan Kenkyu Hokokusho* (*Ministry of Health, Labour and Welfare, Science Research Grant, Comprehensive Studies on Science of Aging, Development of Personalized Medicine using Kampo Medicines to Prevent Progression of Cerebrovascular Disorders in the Elderly, Working-group Research Report Fiscal Year 2006*) 2007: 22-30 (in Japanese)	RCT	N
I69.4	To evaluate the effectiveness of tokishakuyakusan (当帰芍薬散) in reducing impairment and increasing independence in post-stroke patients.	tokishakuyakusan (当帰芍薬散)	Goto H, Satoh N, Hayashi Y, et al. A Chinese herbal medicine, tokishakuyakusan, reduces the worsening of impairmenis and independence after stroke: A 1-year randomized, controlled trial. *Evidence-based complementary and Alternative Medicine* 2009: 1-6. (2011: 1-6. doi: 10.1093/ecam/nep026)	RCT	N
I73.0	To evaluate the effectiveness of orengedokuto (黄連解毒湯) in improving peripheral circulation in Raynaud's phenomenon.	tokishakuyakusan (当帰芍薬散), orengedokuto (黄連解毒湯)	Akiyama Y, Ohno S, Asaoka T, et al. The combination therapy with sarpogrelate hydrochloride and Kampo medicine (oren-gedoku-to or toki-shakuyaku-san) for Raynaud's phenomenon. *Japanese Journal of Oriental Medicine* 2001; 51: 1101-8 (in Japanese with English abstract).	quasi-RCT	N
I80.3	To evaluate the effect of keishibukuryogan (桂枝茯苓丸) on swelling in patients with deep vein thrombosis (DVT) of the lower limb.	keishibukuryogan (桂枝茯苓丸)	Uchida N. A Randomized controlled trial of the Chinese herbal medicine keisi-bukuryo-gan (gui-zhi-fu-ling-wan) in the treatment of deep vein thrombosis. *Jomyakugaku* (*The Japanese Journal of Phlebology*) 2009; 20:1-6 (in Japanese with English abstract).	RCT	I
I84.9	To evaluate the clinical efficacy of otsujito (乙字湯) combined with aluminum potassium sulfate/tannic acid (ALTA) sclerotherapy, the latest treatment for hemorrhoids.	otsujito (乙字湯)	Kato N, Kato K, Hosoi Y. Effects of Otsuji-to in patients with hemorrhoid using ALTA and LE combined therapy*. *Igaku to Yakugaku* (*Journal of Medicine and Pharmaceutical Science*) 2008; 60:747-53 (in Japanese).	RCT	I
I89.0	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in the treatment of lymphedema.	goshajinkigan (牛車腎気丸)	Abe Y. The efficacy of goshajinkigan against lymphedema*. *Kampo Igaku* (*Kampo Medicine*) 2002; 25: 284-7 (in Japanese).	RCT	I
			Abe Y, Kosugi I, Kasashima F, et al. Lymphedema and Kampo*. *Progress in Medicine* 2003; 23: 1538-9 (in Japanese).		N
I95.1	To evaluate the safety and efficacy of goreisan (五苓散) in the treatment of orthostatic hypotension in patients with diabetes mellitus.	goreisan (五苓散)	Nakamura H, Nakamura T, Nakagawa S et al. Efficacy of goreisan in treatment of orthostatic hypotension in patients with diabetes mellitus*. *Diabetes Frontier* 2000; 11: 561-3 (in Japanese).	RCT-cross over	I

10. Respiratory Diseases (including Influenza and Rhinitis) (58 abstracts, 74 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
J00	To compare the efficacy of Kampo treatment and fenoprofen as antipyretics in patients with common cold syndrome associated with fever.	kakkonto (葛根湯), maoto (麻黄湯), keimakakuhanto (桂麻各半湯), chikujountanto (竹ジョ温胆湯), shoseiryuto (小青竜湯), keishikashakuyakuto (桂枝加芍薬湯), kososan (香蘇散)	Homma Y. Kampo treatment of patients with common cold syndrome associated with fever. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1995; 46: 285-91 (in Japanese with English abstract).	RCT-envelope	N
J00	Effect on the duration and resolution of symptoms and treatment efficacy in patients with common cold syndrome.	maobushisaishinto (麻黄附子細辛湯)	Homma Y, Takaoka K, Yozawa H, et al. Effectiveness of mao-bushi-saishin-to in treating common cold syndrome - controlled comparative study using the sealed envelope method -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1996; 47: 245-52 (in Japanese with English abstract).	RCT-envelope	I
			Homma Y. Treatment of common cold by a Kampo medicine - maobushisaishin-tou-. *Pharma Medica* 2007; 25: 19-21 (in Japanese).		
J00	To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in patients with common cold.	shosaikoto (小柴胡湯)	Kaji M, Kashiwagi S, Yamakido M, et al. A double-blind, placebo-controlled study of TSUMURA Shosaikoto (TJ-9) for common cold*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Study*) 2001; 78: 2252-68 (in Japanese).	DB-RCT	I
J00	To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for postinfectious cough.	bakumondoto (麦門冬湯)	Fujimori K, Suzuki E, Simojo F. Comparison between bakumondoto (mai men dong tang) and dextromethorphan hydrobromide in terms of effect on postinfectious cough: a pilot study. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 2000; 51: 725-32	RCT	I
J00	To compare the cough-improvement effect of maobushisaishinto (麻黄附子細辛湯) and western drugs in patients with the common cold.	maobushisaishinto (麻黄附子細辛湯)	Nishizawa Y, Nagano F, Yamada M, et al. A randomized comparison of cough-improvement effects between mao-bushi-saishin-to and western drugs for cold in common patients with allergic cold syndrome. *Kampo to Meneki Arerugi* (*Kampo and Immuno-Allergy*) 2005; 18: 56-67 (in Japanese with English abstract).	RCT	N
J00	To compare the effects of treatment (Kampo medicine vs. Western medicine) for upper airway inflammation in children.	Kampo medicine (maoto [麻黄湯], keimakakuhanto [桂麻各半湯], etc.)	Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku* (*Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine*) 1993; 10: 19–23 (in Japanese).	quasi-RCT	N
			Abe K, Takagi K, Comparison of treatment results between Kampo medicine-treated group and Western medicine-treated group for upper respiratory tract inflammation in children, *Kampo medicine* 1993; 43: 509-15.		N
J00	To compare the effects of two different treatments, Western medicine and byakkokaninjinto (白虎加人参湯), on summertime cold.	byakkokaninjinto (白虎加人参湯)	Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. *Nihon Shoni Toyo Igakkaishi* (*Journal of the Japan Pediatric Society for Oriental Medicine*) 2003; 19: 46–52 (in Japanese).	quasi-RCT	N
J00	To evaluate the efficacy of Kakkonto (葛根湯) for alleviating early cold symptoms.	Kakkonto (葛根湯)	Okabayashi S, Goto M, Kawamura T, et al. Non-superiority of Kakkonto, a japanese herbal medicine, to a representative multiple cold medicine with respect to anti-aggravation effects on the common cold: a randomized controlled trial. 2014 *Internal Medicine* 2014; 53: 949-56.	RCT	N
J00	To evaluate the efficacy and safety of shimpito (神秘湯) for treatment of cough associated with cold syndrome.	shimpito (神秘湯)	Itagaki K, Efficacy of shimpito for treatment of cough associated with cold syndrome.* *Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)* 2013; 70: 813-6 (in Japanese).	quasi-RCT	I&N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
J00	To verify the effectiveness of Kampo medications for the prevention of common cold syndrome in the elderly.	rikkunshito (六君子湯), hochuekkito (補中益気湯), juzentaihoto (十全大補湯), ninjin'yoeito (人参養栄湯), rokumigan (六味丸), hachimijiogan (八味地黄丸), goshajinkigan (牛車腎気丸)	Kato S, Tamano M, Okamura A, et al. Clinical Research The preventive effects of Kampo medications for common cold syndrome in the elderly*.*Kampo Igaku (Science of Kampo Medicine)* 2015; 39: 183-6.	RCT	I&N
J02.9	To evaluate the efficacy of kikyoto (桔梗湯) for treatment of postoperative sore throat.	kikyoto (桔梗湯)	Kuwamura A, Komasawa N, Takahashi R, et al. Preoperative oral administration of kikyo-to, a Kampo medicine, alleviates postoperative score throat: a prospective, double-blind, randomized study. *Journal of Alternative and Complementary Medicine* 2016; 22: 294-7.	DB-RCT	C
J10.1	To evaluate the effect of maoto (麻黄湯) in combination with oseltamivir on the duration of fever.	maoto (麻黄湯)	Kubo T. Effect of maoto for treatment of influenza in children (from The 56th General Meeting of The Japan Society for Oriental Medicine, presentation C-41)*. *Medicament News* 2005 Sep 5; 1846: 15.	RCT	N
			Kubo T, Nishimura H. Antipyretic effect of mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children. *Phytomedicine* 2007; 14: 96-101.		C
J10.1	To evaluate the efficacy of maoto (麻黄湯) in combination with oseltamivir phosphate in treating pediatric influenza.	maoto (麻黄湯)	Kimoto H, Kuroki H. Efficacy of combined administration of oseltamivir phosphate and maoto in treating influenza. *Kampo Igaku (Kampo Medicine)* 2005; 29: 166-9 (in Japanese).	quasi-RCT	I
J10.1	To evaluate the efficacy of combined oseltamivir phosphate and maoto (麻黄湯) for the treatment of pediatric influenza.	maoto (麻黄湯)	Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and mao-to for influenza – 3rd report-. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 2006; 19: 17-25 (in Japanese with English abstract).	quasi-RCT	N
J10.1	To evaluate the efficacy and safety of maobushisaishinto (麻黄附子細辛湯) as an adjuvant for influenza vaccination in the elderly.	maobushisaishinto (麻黄附子細辛湯)	Iwasaki K, Taguchi M, Cyong JC, et al. Effects of mao-bushi-saishin-to on influenza vaccination in elderly subjects; a randomized control study. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2004; 17: 97-103 (in Japanese with English abstract).	RCT-envelope	N
			Iwasaki K. Influenza and Kampo in the elderly*. *TSUMURA Mail Magazine* 2008; Suppl: 22-3 (in Japanese).		N
J10.1	To evaluate the efficacy of coadministration of maoto (麻黄湯) and shosaikoto (小柴胡湯) for the treatment of influenza A infection, in comparison to oseltamivir.	maoto (麻黄湯) + shosaikoto (小柴胡湯)	Yaegashi H. Efficacy of coadministration of maoto and shosaikoto, a Japanese traditional herbal medicine (Kampo medicine), for the treatment of influenza A infection, in comparison to oseltamivir. *Nihon Hokan Daitai Iryo Gakkaishi* (*Japanese Journal of Complementary and Alternative Medicine*). 2010; 7: 59 – 62 (in English with Japanese summary).	RCT	N
J10.1	To evaluate the efficacy of maoto (麻黄湯) against influenza A in adults.	maoto (麻黄湯)	Saita M, Naito T, Boku S, et al. The efficacy of ma-huang-tang (maoto) against influenza. *Kampo to Meneki Arerugi* (*Kampo and Immuno-allergy*). 2010; 23: 17 – 26 (in Japanese with English abstract).	RCT	N
			Saita M, Naito T, Boku S, et al. The efficacy of ma-huang-tang (maoto) against influenza. *Health* 2011; 3: 300-3.		N
J10.1	To compare the effectiveness of oseltamivir, zanamivir, and maoto (麻黄湯) in adult influenza patients.	maoto (麻黄湯)	Nabeshima S, Kashiwagi K, Ajisaka K, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. *Journal of Infection and Chemotherapy* 2012; 18: 534-43.	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
J10.1	To compare the effects of two different treatments (a Kampo medicine treatment and a Western medicine treatment) on influenza.	Kampo medicine (maoto [麻黄湯], keimakakuhanto [桂麻各半湯], etc.)	Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku* (*Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine*) 1993; 10: 19–23 (in Japanese).	quasi-RCT	N
J10.1	To compare the effects on influenza of treatment with byakkokaninjinto (白虎加人参湯), maoto (麻黄湯), antibiotics, and amantadine.	byakkokaninjinto (白虎加人参湯), maoto (麻黄湯)	Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. *Nihon Shoni Toyo Igakkaishi* (*Journal of the Japan Pediatric Society for Oriental Medicine*) 2003; 19: 46–52 (in Japanese).	quasi-RCT	N
J10.1	To evaluate the effectiveness of two brands of maoto (麻黄湯) and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients.	maoto (麻黄湯)	Kawamura K. No difference between two brands of maoto and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients*. *Nihon Shonika Rinsho* (*Japanese Journal of Pediatrics*) 2009; 62: 1855-61 (in Japanese).	quasi-RCT	N
J10.1	To compare the effect the combination of oseltamivir phosphate and Western medications with that of oseltamivir phosphate and maoto (麻黄湯) for pediatric influenza.	maoto (麻黄湯)	Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and mao-to for influenza. *Kampo to Meneki-Allergy* (*Kampo and Immunoallergy*) 2005; 18: 47-55 (in Japanese with English abstract).	quasi-RCT	N
J10.1	To evaluate the long-term effects of juzentaihoto (十全大補湯) on maintenance of the anti-influenza antibody titer in elderly people after influenza vaccination.	juzentaihoto (十全大補湯)	Saiki I, Koizumi K, Goto H, et al. The long-term effects of a kampo medicine, Juzentaihoto, on maintenance of antibody titer in elderly people after influenza vaccination. *Evidence-Based Complementary and Alternative Medicine* 2013: 1-8. doi: 10.1155/2013/568074	RCT	N
J20.0	To compare the efficacy of bakumondoto (麦門冬湯) and tipepidine hibenzate as antitussive agents in patients with mycoplasmal bronchitis.	bakumondoto (麦門冬湯)	Watanabe N, Miyazawa T. Comparative study of the effect of bakumondoto and tipepidine hebinzate on cough in patients with mycoplasmal bronchitis. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2007; 21: 31-6 (in Japanese).	RCT-envelope	N
			Watanabe N, Nakagawa T, Miyazawa T. Examination of effective antitussive against cough caused by mycoplasma bronchitis. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2008; 22: 63-8 (in Japanese with English abstract).		I
A49.3 J20.0	To evaluate the efficacy of bakumondoto (麦門冬湯) for coughing associated with mycoplasma bronchitis.	bakumondoto (麦門冬湯)	Watanabe N, Makino S, Nakagawa T, et al. A study on the efficacy of bakumondoto for coughing associated with mycoplasma infections. *Science of Kampo Medicine* 2017; 41:116-8 (in Japanese).	RCT-envelope	I
J30.1	Preventive effect and safety of preseasonal administration of shoseiryuto (小青竜湯) in patients with cedar pollen allergy (hay fever).	shoseiryuto (小青竜湯)	Ohya Y. Kampo treatment for allergic diseases: from the perspective of a general hospital*. *Progress in Medicine* 1988; 8: 604-12 (in Japanese).	RCT	N
			Ohya Y. Efficacy of preseasonal administration of shoseiryuto for cedar pollen alergy*. *Kampo Shinryo* 1991; 10: 42-8 (in Japanese).		N
J30.1	Effects of shoseiryuto (小青竜湯) and ryokankyomishingeninto (苓甘姜味辛夏仁湯) on springtime nasal allergy.	shoseiryuto (小青竜湯), ryokankyomishingeninto (苓甘姜味辛夏仁湯)	Mori H. Comparative study of Kampo preparations sho-seiryu-to and ryokankyomishingenin-to for nasal allergy. *Therapeutic Research* 1996; 17: 3691-6 (in Japanese with English abstract).	quasi-RCT	N
J30.1	Effects of shoseiryuto (小青竜湯) and eppikajutsuto (越婢加朮湯) on springtime nasal allergy.	shoseiryuto (小青竜湯), eppikajutsuto (越婢加朮湯)	Mori H, Shimazaki Y, Kurata H, et al. Comparative study of Kampo preparations sho-seiryu-to and eppika-jutsu-to for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1997; 18: 3093-9 (in Japanese with English abstract).	quasi-RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
J30.1	Effects of shoseiryuto (小青竜湯) and daiseiryuto (大青竜湯) on springtime nasal allergy.	shoseiryuto (小青竜湯), daiseiryuto (大青竜湯) [keishitogo-makyokansekito (桂枝湯合麻杏甘石湯)]	Mori H. Comparative study of Kampo preparations sho-seiryu-to and dai-seiryu-to for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1998; 19: 3299-307 (in Japanese with English abstract).	quasi-RCT	N
J30.1	To compare the efficacy of shoseiryuto (小青竜湯) and keimakakuhanto (桂麻各半湯) in treating springtime nasal allergy and allergic conjunctivitis.	shoseiryuto (小青竜湯), keimakakuhanto (桂麻各半湯) [keisito+maoto (桂枝湯+麻黄湯)]	Mori H, Kurata H, Shimazaki Y, et al. Comparative study of Kampo preparations sho-sei-ryu-to and kei-ma-kakuhan-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 1999; 20: 2941-7 (in Japanese with English abstract).	quasi-RCT	N
J30.1	To compare the effects of shoseiryuto (小青竜湯) and maobushisaishinto (麻黄附子細辛湯) in treating springtime nasal allergy and allergic conjunctivitis.	shoseiryuto (小青竜湯), maobushisaishinto (麻黄附子細辛湯)	Yoshimoto T, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and maoh-bushi-saisin-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 2002; 23: 2253-9 (in Japanese with English abstract).	quasi-RCT	I
J30.1	To compare the effects of shoseiryuto (小青竜湯) and gokoto (五虎湯) in subjects with nasal allergy and allergic conjunctivitis in spring.	shoseiryuto (小青竜湯), gokoto (五虎湯)	Shimazaki Y, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and go-ko-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 2001; 22: 2385-91 (in Japanese with English abstract).	quasi-RCT	I
J30.3	Efficacy and safety of shoseiryuto (小青竜湯) in the treatment of perennial nasal allergy.	shoseiryuto (小青竜湯)	Baba S, Takasaka T, Inamura N, et al. Double-blind clinical trial of Sho-seiryu-to (TJ-19) for perennial nasal allergy. *Jibiinkoka Rinsho* (*Practica otologica*) 1995; 88: 389-405 (in Japanese with English abstract).	DB-RCT	C&I
J303	To evaluate the efficacy and safety of maobushisaishinto (麻黄附子細辛湯) extract granules prepared based on Shanghanlun (傷寒論, Treatise on Cold Damage Diseases) and conventionally-prepared maobushisaishinto extract powder in the treatment of perennial nasal allergy.	maobushisaishinto (麻黄附子細辛湯)	Nakai Y, Ohashi Y, Esaki Y, et al. Clinical evaluation of maobushisaishinto for nasal allergy*. *Jibi-inkouka Tenbou* (*Oto-Rhino-Laryngology, Tokyo*) 1990; 33: 655-73 (in Japanese).	quasi-RCT	N
J32.9	Effectiveness of shin'iseihaito (辛夷清肺湯) and shigyakusan (四逆散) for chronic rhinitis and sinusitis.	shin'iseihaito (辛夷清肺湯), shigyakusan (四逆散)	Sakurada T, Ikeda K, Takasaka T, et al. Clinical effectiveness of Kampo medicine for chronic rhinitis and sinusitis. *Jibiinkoka Rinsho* (*Practica otologica*) 1992; 85: 1341-6 (in Japanese with English abstract).	RCT-envelope	N
J39.2	Efficacy of saibokuto (柴朴湯) for relieving complaints after thyroid or parathyroid surgery.	saibokuto (柴朴湯)	Suzuki S, Furukawa H, Ami H, et al. Experience with TSUMURA Saibokuto (TJ-96) in patients who underwent thyroid or parathyroid surgery*. *Progress in Medicine* 1994; 14: 2254-8 (in Japanese).	RCT-envelope	I
J40	To evaluate the efficacy and safety of shoseiryuto (小青竜湯) in the treatment of bronchitis.	shoseiryuto (小青竜湯)	Miyamoto T, Inoue H, Kitamura S, et al. Effect of TSUMURA Sho-seiryu-to (TJ-19) on bronchitis in a double-blind placebo-controlled study. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicine*) 2001; 17: 1189-214 (in Japanese with English abstract).	DB-RCT	I
			Miyamoto T. Clinical effectiveness of shosei-ryuto in bronchitis. *Pharma Medica* 2007; 25: 23-5 (in Japanese).		I
J44.9	Effectiveness of bakumondoto (麦門冬湯) as an expectorant.	bakumondoto (麦門冬湯)	Sasaki H, Satou K, Sasaki M, et al. Usefulness of bakumondo-to in senile chronic respiratory disease patients having difficulty in expectoration: comparison with bromhexine hydrochloride preparations. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1993; 7: 139-45 (in Japanese with English abstract).	RCT-envelope	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
J44.9	To determine the efficacy of smoking cessation combined with administration of seihaito (清肺湯) for chronic obstructive pulmonary disease (COPD).	seihaito (清肺湯)	Kato S, Matsuda T, Nakajima T, et al. Clinical significance of the combination therapy of smoking cessation and seihaito for chronic obstructive pulmonary disease. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2005; 14: 260-5 (in Japanese).	RCT-envelope	I
			Kato S, Oda K, Hasumi H, et al. The combined effect of smoking cessation and seihai-to on airway clearance on COPD patients. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2006; 19: 26-35 (in Japanese with English abstract).		N
J44.9	To investigate the effect of hochuekkito (補中益気湯) on systemic inflammation in subjects with chronic obstructive pulmonary disease (COPD).	hochuekkito (補中益気湯)	Shinozuka N, Tatsumi K, Nakamura A, et al. Evaluation of systemic inflammation and utility of hochuekkito administration in subjects with COPD*. *Kosei Rodosho Kagaku Kenkyu Kenkyuhi Hojokin Nanchisei Shikkan Kokufuku Kenkyu Jigyo Kokyufuzen ni Kansuru Chosa Kenkyu Heisei 18 Nendo Buntan Kenkyu Hokokusho* (*Ministry of Health, Labour and Welfare, Science Research Grant: The Intractable Disease Treatment Research Project, Research on Respiratory Failure, Working-group Research Report Fiscal Year 2006*) 2007:94-9 (in Japanese).	RCT-envelope	N
			Shinozuka N, Tatsumi K, Nakamura A, et al. A traditional herbal medicine hochuekkito improves systemic inflammation in patients with COPD. *American Journal of Respiratory and Critical Care Medicine* 2007; 175: A638.		C
			Shinozuka N, Tatsumi K, Nakamura A, et al. The traditional herbal medicine Hochuekkito improves systemic inflammation in patients with chronic obstructive pulmonary disease. *Journal of the American Geriatrics Society* 2007; 55: 313-4.		C
			Fukuchi Y, Tatsumi K. Utility evaluation of Kampo in the treatment of chronic obstructive pulmonary disease*. *Kosei Rodosho Kagaku Kenkyuhi Hojokin Choju Kagaku Sogo Kenkyu Jigyo: Mansei Heisokusei Shikkan ni Taisuru Kampochiryo no Yuyosei Hyoka ni Kansuru Kenkyu, Heisei 18 Nendo Sokatsu Kenkyusyo Hokokusho* (*Ministry of Health, Labour and Welfare, Science Research Grant: Comprehensive Studies on Science of Aging, Study on Evaluation of Usefulness of Kampo Treatment for Chronic Obstructive Pulmonary Disease, Summary Report Fiscal Year 2006),* 2007:1-31 (in Japanese).		N
			Tatsumi K, Shinozuka N, Nakayama K, et al. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. *The American Geriatrics Society* 2009; 57: 169-70.		N
J44.9	To evaluate the effect of bakumondoto (麦門冬湯) on cough in patients with chronic obstructive pulmonary disease (COPD).	bakumondoto (麦門冬湯)	Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. *Phytomedicine* 2011; 18: 625-9.	RCT-cross over	N
			Hattori N, Mukaida K, Haruta Y, et al. A pilot study of the effects of Bakumondoto (TJ-29) on cough in chronic obstructive pulmonary disease (COPD)*. *Kampo to Meneki – Arerugi* (*Kampo and Immuno-Allergy*) 2011; 24: 38–45 (in Japanese with English abstract).		N
J44.9	To investigate the efficacy and safety of adding hochuekkito (補中益気湯) to pulmonary rehabilitation for patients with chronic obstructive pulmonary disease (COPD).	hochuekkito (補中益気湯)	Hamada H, Sekikawa K, Murakami I, et al. Effects of Hochuekkito combined with pulmonary rehabilitation in patients with COPD. *Experimental and Therapeutic Medicine* 2018; 16 :5236-42.	RCT	C
J45.0	Development of saibokuto (柴朴湯) inhalation therapy, and to evaluate its efficacy in preventing attacks of aspirin-induced asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive Effect of Japanese Herbal Medicine, saiboku-to (cai-pu-tang) on brochospasms in aspirin-induced bronchial asthmatic patients. A randomized, double-blind test. *Jibi-inkoka Tenbo* (*Oto-Rhino-Laryngology Tokyo*) 2001; 44: 5-13 (in Japanese with English abstract).	DB-RCT	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
J45.0	To evaluate the efficacy of short-term inhaled saibokuto (柴朴湯) in suppressing airway constriction, and long-term inhaled saibokuto in alleviating psychological suffering.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Kampo medicine, Cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on brochospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain. *Itami to Kampo* (*Pain and Kampo Medicine*) 2001; 11: 14-21 (in Japanese with English abstract).	RCT-cross over	I
J45.0	To investigate the clinical effect of saibokuto (柴朴湯) for the treatment of atopic asthma.	saibokuto (柴朴湯)	Urata Y, Yoshida S, Irie Y, et al. Treatment of asthma patients with herbal medicine TJ-96: a randamized controlled trial. *Respiratory Medicine* 2002; 96: 469-74.	RCT-cross over	C
J45.0	To evaluate the efficacy and safety of inhaled shimpito (神秘湯) for the control of aspirin-induced asthma.	shinpito (神秘湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Chinese traditional medicine, she-bi-tang (shinpi to) on bronchospasm in aspirin-indolerant bronchial asthmatic patients – a randomized, group-paralleled comparative trial – . *Jibi-inkoka Tenbo* (*Oto-rhino-laryngology Tokyo*) 2003; 46: 3-14 (in Japanese with English abstract).	RCT	C&I
J45.0	To evaluate the efficacy and safety of inhaled shimpito (神秘湯) therapy for improving asthma symptoms in patients with aspirin-induced asthma.	shinpito (神秘湯)	Nishizawa Y, Nishizawa Y, Goto GH, et al.A randomized, group-parallel comparative trial of the suppressiveeffect of Chinese traditional medicine, shen-mi-tang (shin-pi-to), compared to sodium oramolycate inhalation in improving subjective and objective symptoms in bronchial asthmatics. *Jibi-inkoka Tenbo* (*Oto-rhino-laryngology Tokyo*) 2004; 47: 20-7 (in Japanese with English abstract).	RCT	C&I
J45.0	To investigate the effect of saibokuto (柴朴湯) inhalation therapy in improving quality of life (QOL) in patients with aspirin-intolerant asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Goto HG. Chronic pain in intractable and chronic medical conditions -*. *Mansei Totsu* (*The Journal of the Japanese Society for the Study of Chronic Pain*) 2002; 21: 67-77 (in Japanese with English abstract).	RCT	I
J45.9	Efficacy and safety of saibokuto (柴朴湯) in patients with steroid-dependent bronchial asthma.	saibokuto (柴朴湯)	Egashira Y, Nagano H, et al. Results of a comparative clinical study of the effect of "TSUMURA Saiboku-to" (TJ-96) against steroid dependent bronchial asthma in 2 groups, a Saiboku-to administration group and a non-administration group, divided by the envelope method. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1990; 4: 128-44 (in Japanese with English abstract).	RCT-envelope	N
			Egashira Y, Nagano H. A multicenter clinical trial of TJ-96 in patients with steroid-dependent bronchial asthema. A comparison of groups allocated by the envelope method. *Annals of the New York Academy of Science* 1993; 685: 580-3.		C
J45.9	Efficacy and safety of saibokuto (柴朴湯) in the treatment of bronchial asthma in children.	saibokuto (柴朴湯)	Ito S, Mikawa H. Effect of "TSUMURA Saiboku-to" (TJ-96) on bronchial asthma in children. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1990; 4: 115-25 (in Japanese with English abstract).	RCT-envelope	N
			Ito S, Mikawa H. Clinical evaluation of saibokutou in the treatment of children with bronchial asthma. *Kiso to Rinsho* (*The Clinical Report*) 1992; 26: 3993-8 (in Japanese).		I
J45.9	Efficacy of shinpito (神秘湯) for inhibiting exercise-induced asthma and relieving clinical symptoms in patients with moderate or worse bronchial asthma.	shinpito (神秘湯)	Tubaki T, Ebisawa M, Akimoto K, et al. Effects of shinpi-to (*shenbi-tang*) on bronchial asthma. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1994; 8: 65-71 (in Japanese with English abstract).	RCT	N
J45.9	To assess the efficacy and safety of inhaled saibokuto (柴朴湯) while reducing the amount of inhaled beclomethasone during the course of treatment for bronchial asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Nagano F, et al. Sparing effect of saibokuto inhalation on inhaled beclomethasone dipropionate to halved of reduction of inhaled beclomethasone dipropinate-dose: well-controlled comparative study of saiboku-to-inhalation and sodium cromoglycate-inhalation. *Jibi-inkoka Tenbo* (*Oto-rhino-laryngology Tokyo*) 2002; 45: 8-15 (in Japanese with English abstract).	RCT	C&I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
J45.9	To compare the efficacy of the anxiolytic-like agent saibokuto (柴朴湯) with that of shoseiryuto (小青竜湯) in patients with bronchial asthma.	saibokuto (柴朴湯), shoseiryuto (小青竜湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Kampo medicine, chai-po-tang (Japanese name: saiboku-to) compared with xiao-quing-long tang (Japanese name: shoseiryu-to) in asthmatics with anxiety and depression due to asthmatic attacks. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2003; 18: 11-7 (in Japanese with English abstract).	RCT	I
J45.9	To assess the efficacy of the anxiolytic-like agent, saibokuto (柴朴湯), in treating bronchial asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Chinese tracitional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clotiazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine)* 2002; 17: 20-7 (in Japanese with English abstract).	RCT	I
J45.9	To evaluate the efficacy and safety of saibokuto (柴朴湯) in patients with asthma exacerbations based on anticipatory anxiety.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of chai-po-tang (Japanese name: saiboku-to), a Chinese tracitional herbal medicine, in patients with bronchial asthma and autonomic nerve dysfunction: a multicenter, randomized, double-blined, placebo-controlled study. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental and Psychosomatic Medicine*) 2004; 19:37-41 (in Japanese with English abstract).	RCT	I
J69.0	To investigate whether hangekobokuto (banxia houp tang) (半夏厚朴湯) improves cough reflex in elderly patients likely to have aspiration pneumonia.	hangekobokuto (半夏厚朴湯)	Iwasaki K, Cyong JC, Kitada S, et al. A traditional Chinese herbal medicine, banxia houp tang, improves cough reflex of patients with aspiration pneumonia. *Journal of the American Geriatrics Society* 2002; 50: 1751-2.	RCT	C
J69.0	To evaluate whether hangekobokuto (半夏厚朴湯) prevents aspiration pneumonia and pneumonia-related mortality in elderly people with dementia.	hangekobokuto (半夏厚朴湯)	Iwasaki K, Kato S, Monma Y, et al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in older adults with dementia. *Journal of the American Geriatrics Society* 2007; 55: 2035-40.	RCT	C
			Iwasaki K, Kato S, Monma Y, et.al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in brain-damaged elderly. *International Journal of Stroke* 2010; 5 suppl 2: 38-9.		C
J98.8	To evaluate the efficacy, impact on recurrence rate, and medical cost efficiency of antibiotics plus Kampo combination therapy for bacterial respiratory infections.	juzentaihoto (十全大補湯), kakkonto (葛根湯), keishito (桂枝湯), kososan (香蘇散), shosaikoto (小柴胡湯), hochuekkito (補中益気湯)	Mikamo H, Tamaya T. Usefulness of Kampo medicine for the treatment of infections from the perspective of medical economics*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2007; 24: 105-8 (in Japanese).	RCT	I

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases (71 abstracts, 90 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K11.7	Efficacy of ninjin'yoeito (人参養栄湯) for improvement of xerostomia induced by oxybutynin hydrochloride.	ninjin'yoeito (人参養栄湯)	Miyazaki Y, Yamada A, Saitou M. Effect of ninjin-youei-tou on xerostomia induced by oxybutynin hydrochloride. *Shinyaku to Rinsho* (*Journal of New Remedies and Clinics*) 1994; 43: 2613-7 (in Japanese).	RCT	N
K11.7	To compare the efficacy of bakumondoto (麦門冬湯) versus cevimeline hydrochloride hydrate (Evoxac) or nizatidine (Acinon) for treating dry mouth.	bakumondoto (麦門冬湯)	Umemoto M, Nin T, Miuchi S, et al. Treatment of human dry mouth using various medicines. *Jibiinkoka Rinsho* (*Practica otologica*) 2007; 100: 145-52 (in Japanese with English abstract).	RCT	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K11.7	To evaluate the effects of bakumondoto (麦門冬湯) on neuropeptide levels in human plasma and saliva.	bakumondoto (麦門冬湯)	Satoh Y, Itoh H, Takeyama M. Effects of bakumondoto on neuropeptide levels in human saliva and plasma. *Journal of Traditional Medicines* 2009; 26: 122-30.	RCT-cross over	I
K11.7	To evaluate the effects of daikenchuto (大建中湯) on salivary secretion and salivary neuropeptide levels in humans after a single oral dose.	daikenchuto (大建中湯)	Suzuki Y, Itoh H, Yamamura R, et al. Significant increase in salivary substance P level after a single oral dose of Japanese herbal medicine Dai-kenchu-to in humans. *Biomedicine & Aging Pathology* 2012; 2: 81-4.	RCT-cross over	N
K12.1	Efficacy and safety of orento (黄連湯) for treating stomatitis.	orento (黄連湯)	Oka S. The effects of Oren-to on stomatitis. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1995; 46: 439-45 (in Japanese with English abstract).	RCT	N
C64 K12.3	To evaluate the clinical usefulness of gargling with hangeshashinto (半夏瀉心湯) for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer.	hangeshashinto (半夏瀉心湯)	Oh-oka H. The clinical usefulness of gargling with hangeshashinto for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer. *Kampo Medicine* 2018;69: 1-6 (in Japanese with English abstract).	RCT	I
C15.9 K13.7	To investigate the impact of daiokanzoto (大黄甘草湯) and hangeshashinto (半夏瀉心湯) on oral mucositis, tongue coating bacteria, and gingiva condition in patients with esophageal cancer undergoing chemotherapy.	daiokanzoto (大黄甘草湯), hangeshashinto (半夏瀉心湯)	Moriyama S, Hinode D, Yoshioka M, et al. Impact of the use of Kampo medicine in patients with esophageal cancer during chemotherapy: a clinical trial for oral hygiene and oral condition. *Journal of medical investigation* 2018; 65,:184-90.	RCT-envelope	C
K14.6	To evaluate the efficacy of saibokuto (柴朴湯) compared with tranquilizer plus vitamin B complex combination therapy for patients with glossodynia.	saibokuto (柴朴湯)	Bessho K, Okubo Y, Hori S, et al. Effectiveness of Kampo medicine (Sai-Boku-To) in treatment of patients with glossdynia. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 1998; 86: 682-6.	RCT	C
			Yamada T, Bessho K, Murakami K, et al. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. *Shika Yakubutsu Ryoho* (*Oral Therapeutics and Pharmacology*) 1998; 17: 18-22 (in Japanese with English abstract).		N
			Yamada T, Bessho K. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 1999; 8: 261-5 (in Japanese).		I
K21.0	To evaluate the efficacy of rikkunshito (六君子湯) combined with a proton pump inhibitor (PPI) for treating gastroesophageal reflux disease (GERD).	rikkunshito (六君子湯)	Koide A. Effect and role of TJ-43: rikkun-shi-to from the aspects of endoscopic findings and QOL improvement in GERD patients. *Medical Tribune Online* (*Digestive Disease Week: DDW*) 2005: 6-7 (in Japanese).	RCT	N
K21.0	To evaluate the efficacy of hangekobokuto (半夏厚朴湯) - combined treatment in patients with respiratory symptoms associated with refractory gastroesophageal reflux disease (GERD).	hangekobokuto (半夏厚朴湯)	Kato S, Nakajima T, Matsuda T, et al. The effectiveness of the traditional Kampo medicine, " banxia houpu tang (hangekobokuto) " to respiratory disturbance by esophageal reflux disease. *Kampo to Saishin-Chiryo* (*Kampo & the Newest Therapy*) 2005; 14: 333-8 (in Japanese).	RCT-envelope	I
K21.9	To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) Extract Granules for treatment of non-erosive reflux disease (NERD) unresponsive to proton pump inhibitors (PPIs).	rikkunshito (六君子湯)	Koide A. Establishment of new treatment strategy for non-erosive reflux disease (endoscopy-negative gastroesophageal reflux disease) – potential of rikkunshito*. *MedicalQ* 2006; 187 (in Japanese).	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K21.9	To evaluate the effectiveness of rikkunshito (六君子湯) for patients with proton pump inhibitor (PPI)–resistant gastroesophageal reflux disease (GERD, and especially non-erosive reflux disease [NERD]).	rikkunshito (六君子湯)	Tominaga K, Fujiwara Y, Shimoyama Y, et al.Rikkunshito improves PPI-refractory NERD: a prospective randomized multi-center trial in Japan. *Gastroenterology* 2010; 138: S655-6.	RCT	N
			Tominaga K, Fujiwara Y, Arakawa T, et al. GERD — Rikkunshito*. *Shindan to Chiryo (Diagnosis and Treatment)* 2011; 99: 771–6 (in Japanese).		N
			Tominaga K, Iwakiri R, Fujimoto K, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multicenter trial in Japan. *Journal of Gastroenterology* 2012; 47: 284-92.		N
K21.9	To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.	rikkunshito (六君子湯)	Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. *Nikkei Medical* (*Supplement*) 2010; 8: 27 (in Japanese).	DB-RCT-cross over	N
			Morita T, Furuta K, Adachi K, et al. Effects of Rikkunshito (TJ-43) on esophageal motor function and gastroesophageal reflux. *Journal of Neurogastroenterology and Motility* 2012; 18: 181-6.		N
K21.9	To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.	rikkunshito (六君子湯)	Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. *Nikkei Medical* (*Supplement*) 2010; 8: 27 (in Japanese).	DB-RCT-cross over	N
K21.9	To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton-pump inhibitor (PPI)-refractory laryngopharyngeal reflux (LPR).	rikkunshito (六君子湯)	Tokashiki R,Okamoto I,Funato N, et al. Rikkunshito improves globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. *World Journal of Gastroenterology*. 2013; 19: 5118-24.	RCT	N
K21.9	To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton pump inhibitor-refractory non-erosive reflux disease.	rikkunshito (六君子湯)	Tominaga K, Kato M, Takeda H, et al. A randomized, placebo-controlled , double-blind clinical trial of Rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor : The G-Pride study. *Journal of Gastroenterology* 2014; 49: 1392-1405.	DB-RCT	N
			Sakata Y, Tominaga K, Kato M, et al. Clinical characteristics of elderly patients with proton pump inhibitor-refractory non-erosive reflux disease from theG-PRIDE study who responded to Rikkunshito. *BMC Gastroenterology* 2014; 14: 1-10.	RCT	N
K21.9	To determine the efficacy and safety of hangeshashinto (半夏瀉心湯) in treating patients with proton pump inhibitor (PPI)-refractory gastroesophageal reflux disease (GERD).	hangeshashinto (半夏瀉心湯)	Takeuchi T, Hongo H, Kimura T, et al. Efficacy and safety of hangeshashinto for treatment of GERD refractory to proton pump inhibitors : Usual dose proton pump inhibitors plus hangeshashinto versus double-dose proton pump inhibitors: randomized. *Journal of Gastroenterology* 2019; 1-12.	RCT	N
K25.9	To compare the efficacy of saikokeishito (柴胡桂枝湯), H2 receptor antagonist, or their combination for preventing recurrence of gastric ulcer.	saikokeishito (柴胡桂枝湯)	Nakahara A, Kashimura H, Fukutomi H. Gastric ulcer - saikokeishito or shigyakusan monotherapy -*. *Nikkei Medical* (separate-volume supplement) 1988; 17: 20-1 (in Japanese).	RCT-envelope	N
			Fukutomi H, Nakahara A. Traditional oriental therapy of the gastric ulcer. *Shokakika* (*Gastroenterology*) 1990; 12: 159-65 (in Japanese).		N
K27.9	To evaluate the usefulness of H2-blocker (cimetidine) combined with Kampo medicine (shigyakusan (四逆散), saikokeishito (柴胡桂枝湯)) as a maintenance therapy for peptic ulcer.	shigyakusan (四逆散), saikokeishito (柴胡桂枝湯)	Watanabe H. A study of peptic ulcer maintenance therapy combined with Kampo medicines*. *Kampo Igaku* (*Kampo Medicine*) 1995; 19: 18-21 (in Japanese).	RCT	N
K29.7	Efficacy and safety of rikkunshito (六君子湯) and hangeshashinto (半夏瀉心湯) for treating acute gastritis and acute exacerbation of chronic gastritis.	rikkunshito (六君子湯), hangeshashinto (半夏瀉心湯)	Ohta Y, Nishioka M, Yamamoto Y, et al. Multicenter clinical evaluation of Kampo preparations for medical use in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - comparison with gefarnate as a control -*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1990; 78: 2935-46 (in Japanese).	RCT-envelope	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K29.7	Efficacy and safety of rikkunshito (六君子湯) for treating gastritis (acute gastritis and acute exacerbation of chronic gastritis).	rikkunshito (六君子湯)	Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - multicenter comparative study using sodium azulene sulfonate as a control -*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1991; 79: 789-810 (in Japanese).	RCT-envelope	N
K29.7	To evaluate the efficacy and safety of TSUMURA Rikkunshito (六君子湯) for treating gastritis in a comparison with cetraxate as a control.	rikkunshito (六君子湯)	Takemoto T, Matsuda K, Tada M, et al. Clinical evaluation of the efficacy of TJ-43 Tsumura Rikkunshi-To on gastritis with abdominal symptom - multicenter group study in comparison with cetraxate -. *Shokakika* (*Gastroenterology*) 1990; 12: 223-34 (in Japanese with English abstract).	RCT-envelope	N
K30	Efficacy and safety of rikkunshito (六君子湯) for treating epigastric indefinite complaints complicated by depression.	rikkunshito (六君子湯)	Kawamura S, Okita K, Tada M, et al. Clinical comparison of TSUMURA Rikkunshito and sulpiride in the treatment of indefinite complaints of epigastric distress - mainly the antidepressive effect and the improvement of gastric emptying -*. *Progress in Medicine* 1992; 12: 1156-62 (in Japanese).	RCT-envelope	N
K30	Efficacy of rikkunshito (六君子湯) for treating indefinite complaints of epigastric distress.	rikkunshito (六君子湯)	Komatsuzaki O. Clinical effect of TSUMURA Rikkunshito on indefinite epigastric distress - comparison with a control agent, and assessment mainly based on the endoscopic findings and the histology of gastric mucosal biopsy specimens before and after the treatment -*. *Kampo Igaku* (*Kampo Medicine*) 1993; 17: 120-31 (in Japanese).	RCT-envelope	N
K30	Efficacy of saireito (柴苓湯) for post-infectious dyspepsia in infants.	saireito (柴苓湯)	Ito J, Ito Y, Asai M, et al. Efficacy of Saireito (TSUMURA) for post-infectious dyspepsia in infants: comparison with intestinal regulators*. *Shonika Shinryo* (*Journal of Pediatric Practice*) 1992; 55: 2089-92 (in Japanese).	RCT	I
K30	Efficacy of rikkunshito (六君子湯) in dyspeptic patients.	rikkunshito (六君子湯)	Tatsuta M, Iishi H. Effect of treatment with Liu-jun-zi-tang (TJ-43) on gastric emptying and gastrointestinal symptoms in dyspeptic patients. *Alimentary Pharmacology and Therapeutics* 1993; 7: 459-62.	RCT	C
K30	Efficacy and safety of rikkunshito (六君子湯) for treating complaints of gastrointestinal disorders including chronic gastritis.	rikkunshito (六君子湯)	Miyoshi A, Yachi A, Masamune O, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis - a multicenter comparative study using cisapride as a control -*. *Progress in Medicine* 1991; 11: 1605-31 (in Japanese).	RCT-envelope	N
K30	To evaluate the efficacy of rikkunshito (六君子湯) as an agent to improve symptoms before endoscopy in patients with upper abdominal symptoms and need for endoscopy of the upper gastrointestinal tract.	rikkunshito (六君子湯)	Koide A. Adoption of rikkunshito before endoscopy in patients with upper abdominal symptoms*. *Nikkei Medical* 2002; 31: 22-3 (in Japanese).	RCT-envelope	N
			Koide A. The improvement of QOL by rikkunshito in patients with need for endoscopy*. *Medical Tribune* 2004: 45 (in Japanese).		N
			Yamaguchi T, Koide A. Usefulness of Rikkun-shi-to (TJ-43), a Chinese herbal medicine, for the treatment of gastro-esophageal reflux disease (GERD). *Medical Science Digest* 2007; 33: 748-52 (in Japanese).		N
K30	To evaluate the efficacy and safety of TJ-43 TSUMURA Rikkunshi-to (六君子湯) in patients with dyspepsia caused by dysfunction of the upper gastrointestinal tract.	rikkunshito (六君子湯)	Harasawa S, Miyoshi A, Miwa T, et al. Double-blind multicenter post-marketing clinical trial of TJ-43 TSUMURA Rikkunshi-to for the treatment of dysmotility-like dyspepsia. *Igaku no Ayumi* (*Journal of Clinical and Experimental Medicine*) 1998; 187: 207-29 (in Japanese).	DB-RCT	I
			Harasawa S. The role of rikkunshito against NUD (non-ulcer dyspepsia) – especially its efficacy in dysmotility-like NUD*. *Progress in Medicine* 1999; 19: 843-8 (in Japanese).		N
			Harasawa S. Evidence from an RCT of rikkunshito (六君子湯) for epigastric complaints*. *Kampo Igaku* (*Science of Kampo Medicine*) 2011; 35: 113-7 (in Japanese).		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K30	To clarify the effect of rikkunshito (六君子湯) on increasing ghrelin secretion and improving symptoms and its mechanism of action in patients with functional dyspepsia (FD).	rikkunshito (六君子湯)	Arai M. Rikkunshito significantly enhances the secretion of ghrelin in patients with functional dyspepsia*. *Kampo Igaku* (*Kampo Medicine*) 2009; 33: 405-6.	RCT	N
			Matsumura T, Arai M, Suzuki T, et al. The traditional japanese medicine rikkunshito improves upper gastrointestinal symptoms in patients with functional dyspepsia. *Gastroenterology* 2010; 138: S471.		C
			Arai M, Matsumura T, Yoshikawa M, et al. Analysis of the Rikkunshito efficacy on patients with functional dyspepsia*. *Nihon Yakurigaku Zasshi* (*Folia Pharmacologica Japonica*) 2011; 137: 18–21. (in Japanese).		N
			Arai M, Matsumura T, Tsuchiya N, et al. Rikkunshito improves the symptoms in patients with functional dyspepsia, accompanied by an increase in the level of plasma ghrelin. *Hepato-Gastroenterology* 2012; 59: 62-6.		N
K30	To evaluate the efficacy and safety of rikkunshito (六君子湯) in patients with functional dyspepsia.	rikkunshito (六君子湯)	Tominaga K, Sakata Y, Kusunoki H, et al. Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: A randomized clinical trial (the DREAM study). *Neurogastroenterology and Motility* 2018; 1-12. doi: 10.1111/nmo.13319	DB-RCT	N
K30.0	To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) Extract Granules for stimulating gastrointestinal emptying in patients after pylorus-preserving gastrectomy (PPG).	rikkunshito (六君子湯)	Nishida T. Effect of rikkunshito on gastrointestinal function in patients after gastrectomy*. *Progress in Medicine* 2006; 26: 3224-5 (in Japanese).	RCT-cross over	N
			Takahashi T, Endo S, Nakajima K, et al. Effect of rikkunshito, a Chinese herbal medicine, on stasis in patients after pylorus-preserving gastrectomy. *World Journal of Surgery* 2009; 33: 296-302.		C
K30.0	To evaluate the effects of rikkunshito (六君子湯) on gastric contraction and expansion.	rikkunshito (六君子湯)	Shiratori M, Shoji T, Kanazawa M, et al.Effect of rikkunshito on gastric sensorimotor function under distention. *Neurogastroenterology & Motility* 2011; 23: 323-9, e155-6.	RCT-cross over	N
K30.0	To evaluate the treatment effects of rikkunshito (六君子湯) on functional dyspepsia.	rikkunshito (六君子湯)	Suzuki H, Matsuzaki J, Fukushima Y, et al. Randomized clinical trial: rikkunshito in the treatment of functional dyspepsia-a multicenter, double-blind, randomized, placebo-controlled study. *Neurogastroenterology and Motility* 2014; 26: 950-61.	DB-RCT	C&N
K31.9	To evaluate the effects of daikenchuto (大建中湯) and orengedokuto (黄連解毒湯) on cardiac output (CO) and superior mesenteric artery (SMA) blood flow.	daikenchuto (大建中湯), orengedokuto (黄連解毒湯)	Takayama S, Seki T, Watanabe M, et al. The herbal medicine Daikenchuto increases blood flow in the superior mesenteric artery. *The Tohoku Journal of Experimental Medicine* 2009; 219: 319-30.	RCT-cross over	C&I
K31.9	Comparative evaluation of the regulatory effects of thermal stimulation to the abdomen and Daikenchuto (大建中湯) on superior mesenteric artery (SMA) blood flow in healthy people.	daikenchuto (大建中湯)	Takayama S, Seki T, Watanabe M, et al. The effect of warming of the abdomen and of herbal medicine on superior mesenteric artery blood flow - a pilot study. *Forschende Komplementrmedizin* 2010; 17: 195-201.	RCT	N
K31.9	To verify the effectiveness of rikkunshito (六君子湯) on gastrointestinal motility function in critically ill patients.	rikkunshito (六君子湯)	Hayakawa M, Ono Y, Wada T, et al. Effects of rikkunshito (traditional Japanese medicine) on enteral feeding and the plasma ghrelin level in critically ill patients: a pilot study. *Journal of Intensive Care* 2014; 2: 53.	DB-RCT	C&I
K56.0	To evaluate the efficacy and safety of daikenchuto (大建中湯) for improving intestinal peristalsis in patients with intestinal paralysis after surgery for abdominal aortic aneurysm (AAA).	daikenchuto (大建中湯)	Takagaki Y, Kawasaki S, Komai H, et al. The effect of Chinese hearb medicine (dai-kenchu-to) on paralytic ileus after repair of abdominal aortic aneurysm. *Nihon Rinsho Geka Gakkai Zasshi (Journal of Japan Surgical Association)* 2000; 61: 325-8 (in Japanese with English abstract).	RCT	N
K56.5	Efficacy of daikenchuto (大建中湯) in patients with adhesive ileus.	daikenchuto (大建中湯)	Ohyabu H, Matsuda S, Kurisu S, et al. Evaluation of daikenchuto in patients with adhesive ileus in a randomized trial*. *Progress in Medicine* 1995; 15: 1954-8 (in Japanese).	RCT-envelope	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K58.9	Efficacy of saikokeishito (柴胡桂枝湯) and keishikashakuyakuto (桂枝加芍薬湯) for irritable bowel syndrome (IBS).	saikokeishito (柴胡桂枝湯), keishikashakuyakuto (桂枝加芍薬湯)	Ishii F, Iizuka B, Nagasako K, et al. Evaluations of the therapeutic efficacy of Saikokeishito (TJ-10) versus Keishikashakuyakuto (TJ-60) for irritable bowel syndrome and Saireito (TJ-114) for ulcerative colitis*. *Progress in Medicine* 1993; 13: 2893-900 (in Japanese).	RCT	N
K58.9	Efficacy and safety of keishikashakuyakuto (桂枝加芍薬湯) for irritable bowel syndrome.	keishikashakuyakuto (桂枝加芍薬湯)	Sasaki D, Uehara A, Hiwatashi N, et al. Clinical efficacy of keishikashakuyakuto for irritable bowel syndrome - a multicenter, randomized, parallel-group clinical trial -*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine)* 1998; 75: 1136-52 (in Japanese).	DB-RCT	I
K58.9	To evaluate the efficacy and safety of keihito (啓脾湯) in patients with irritable bowel syndrome.	keihito (啓脾湯)	Mori H, Iwamoto M. Comparison study of keihito and trimebutine maleate for irritable bowel syndrome. *Therapeutic Research* 1999; 20: 2179-85 (in Japanese).	quasi-RCT	I
K58.9	To evaluate the effect of daikenchuto (大建中湯) on rectal sensation in patients with irritable bowel syndrome.	daikenchuto (大建中湯)	Acosta A, Camilleri M, Linker-Nord S, et al. A pilot study of the effect of daikenchuto on rectal sensation in patients with irritable bowel syndrome. *Journal of Neurogastroenterological Motility* 2016; 22: 69-77.	DB-RCT	N
K59.0	Efficacy of junchoto (潤腸湯) and mashiningan (麻子仁丸) for atonic constipation in the elderly.	junchoto (潤腸湯), mashiningan (麻子仁丸)	Ishioka T. Comparison of the efficacy of junchoto and mashiningan for atonic constipation in the elderly stratified by physical strength*. *Kampo no Rinsho* (*Journal of Kampo Medicine*) 1996; 43: 1431-7 (in Japanese).	RCT-cross over	N
K59.0	A preceding double-blinded controlled trial of daiokanzoto (大黄甘草湯), compared with placebo, in the treatment of constipation found it was effective against constipation, but not useful (no details available). The objective of this study was to reexamine the effects of daiokanzoto (大黄甘草湯) on constipation using a newly-defined assessment standard and the same results mentioned above.	daiokanzoto (大黄甘草湯)	Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-To Extract Granules for ethical use (TJ-84) on constipation using double blind test. *Shokakika* (*Gastroenterology*) 1994; 18: 299-312 (in Japanese with English abstract).	DB-RCT	I
			Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-to Extract Granules for ethical use (TJ-84) against the constipation based on the new standard. *Shokakika* (*Gastroenterology*) 1996; 22: 314-28 (in Japanese with English abstract).		I
			Harasawa S, Miyoshi A. Reevaluation of Kampo medicine in patients with constipation - efficacy of Daio-kanzo-to -. *Shokakigan* (*Japanese Journal of Cancer of the Digestive Organs*) 1996; 6: 271-7 (in Japanese with English abstract).		I
K59.0	To evaluate the efficacy and safety of kumibinroto (九味檳榔湯) for chronic constipation in elderly dialysis patients.	kumibinroto (九味檳榔湯)	Nishizawa Y, Nishizawa Y, Goto HG, et al. Prospective multicenter randomized group-parallelled study: effect of Chinese traditional herb medicine, jiu-wei-bing-lang-tang (Japanese name: kumi-binro-to) on constipation in elderly patients with renol dialysis. *Kampo Kenkyu* (*Kampo Research*) 2004; 388: 132-8 (in Japanese).	RCT	I
K59.0	To evaluate the effects of daikenchuto (大建中湯) in combination for chronic constipation patients taking sennoside.	daikenchuto (大建中湯)	Horiuchi A, Nakayama Y, Tanaka N. Effect of traditional Japanese medicine, Daikenchuto (TJ-100) in patients with chronic constipation. *Gastroenterology Research* 2010; 3: 151-5.	RCT	N
K59.0	To evaluate the efficacy and safety of daikenchuto (大建中湯) in the treatment of functional constipation.	daikenchuto (大建中湯)	Iturrino J, Camilleri M, Wong BS, et al. Randomised clinical trial： the effects of daikenchuto, TU-100, on gastrointestinal and colonic transit, anorectal and bowel function in female patients with functional constipation. *Alimentary Pharmacology and Therapeutics* 2013; 37: 776-85.	DB-RCT	C
K59.0	To evaluate the efficacy and safety of daikenchuto (大建中湯) as treatment for functional constipation in poststroke patients.	daikenchuto (大建中湯)	Numata T, Takayama S, Tobita M, et al. Traditional Japanese medicine Daikenchuto improves functional constipation in poststroke patients. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-8. doi：10.1155/2014/231258	RCT	C&N
			Numata T, Takayama S, Iwasaki K, et al. A prospective comparative trial using the Kampo medicine, daikenchuto (大建中湯) for constipation in poststroke patients. *Kampo & the Newest Therapy* 2015; 24:145-152	RCT-envelope	I&N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K59.8	To verify the anti-inflammatory effects of daikenchuto (大建中湯) on intestinal distress in the aftermath of gastrointestinal surgery.	daikenchuto (大建中湯)	Ikemoto T. The role of Kampo in gastrointestinal surgery and the effectiveness of daikenchuto (大建中湯) for intestinal stress - From bacterial translocation to microbiome*. *Progress in Medicine* 2011; 31: 466-7 (in Japanese).	RCT	N
K70.9	Efficacy of Kampo medicines for alcoholic liver disease.	shosaikoto (小柴胡湯), shosaikoto (小柴胡湯) ＋ inchingoreisan (茵チン五苓散)	Takahashi H, Maruyama K. Clinical aspects of Kampo treatment for alcoholic liver disease. *Igaku no Ayumi* (*Journal of Clinical and Experimental Medicine*) 1993; 167: 811-4 (in Japanese).	RCT	N
K73.2	Effiacy and safety of shosaikoto (小柴胡湯) for chronic active hepatitis.	shosaikoto (小柴胡湯)	Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of sho-saiko-to in chronic active hepatitis. *Gastroenterologia Japonica* 1989; 24: 715-9.	DB-RCT	C&I
			Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis. *Kan-Tan-Sui* 1990; 20: 751-9 (in Japanese).		I
			Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis – Variation in serum enzyme activity*. *Kan-Tan-Sui* 1992; 25: 551–8 (in Japanese).		I
K73.9	Efficacy and safety of saireito (柴苓湯) for chronic hepatitis.	saireito (柴苓湯)	Sasaki D, Sudoh T, Kunikane M, et al. Usefulness of Kanebo Saireito Extract Fine Granules for chronic hepatitis - a comparative study (with randomization carried out using the sealed-envelope method) -*. *Progress in Medicine* 1989; 9: 2923-37 (in Japanese).	RCT-envelope	I
K73.9	To evaluate whether use of Kampo medicines (Shimbuto [真武湯] and Ninjinto [人参湯]) in combination with pegylated interferon a plus ribavirin promotes therapeutic responses in patients with chronic hepatitis C.	Shimbuto (真武湯), Ninjinto (人参湯)	Kainuma M, Furusyo N, Murata M, et al. The effectiveness of traditional Japanese medicine(Kampo), in combination with pegylated interferon α plus ribavirin for patients with chronic hepatitis C: A pilot study. *Journal of Traditional Medicines* 2013; 30: 132-9.	RCT	I
K75.9	Efficacy of shosaikoto (小柴胡湯) for chronic non-A, non-B hepatitis in children.	shosaikoto (小柴胡湯)	Tajiri H, Kozaiwa K, Sawada A, et al. Efficacy of shosaikoto for chronic non-A, non-B hepatitis in children (non-A, non-B hepatitis in children and shosaikoto)*. *Nihon Shoni Toyo Igaku Kenkyukai Kaishi*（*Journal of the Japan pediatric society for oriental medicine*） 1996; 12: 12-7 (in Japanese).	RCT-envelope	N
K76.9	Efficacy of saikokeishito (柴胡桂枝湯) for liver dysfunction induced by chemotherapy for pulmonary tuberculosis.	saikokeishito (柴胡桂枝湯)	Mizutani Y, Imai S, Watanabe H, et al. Saiko-Keishi-To on patients with pulmonary tuberculosis: effect on liver disfunction. *Donan Igakkaishi* (*Journal of the Medical Association of South Hokkaido*) 1994; 29: 247-9 (in Japanese).	RCT-envelope	N
K76.9 Z94.4	To evaluate the efficacy and safety of daikenchuto (大建中湯) on the reinforcing effect of oral/tubal caloric intake in patients undergoing liver transplantation.	daikenchuto (大建中湯)	Kaido T, Shinoda M, Inomata Y,et al. Effect of herbal medicine daikenchuto on oral and enteral caloric intake after liver transplantation: a multicenter, randomized controlled trial. *Nutrition* 2018; 54: 68-75.	DB-RCT	N
K80.2	Effects of shosaikoto (小柴胡湯), goreisan (五苓散), and tokishakuyakusan (当帰芍薬散) on the sphincter of Oddi.	goreisan (五苓散), tokishakuyakusan (当帰芍薬散), shosaikoto (小柴胡湯)	Seki M, Fujioka M, Hatano T, et al. Differences between the effects of sho-saiko-to, gorei-san, and toki-shakuyaku-san on the sphincter of Oddi - An intraoperative cholangiomanometric study -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1993; 43: 395-402 (in Japanese with English abstract).	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
K82.8	Efficacy of goreisan (五苓散) and tokishakuyakusan (当帰芍薬散) on urinary 6-keto-prostaglandin F1a level in patients with gallbladder stones or polyps.	goreisan (五苓散), tokishakuyakusan (当帰芍薬散), shosaikoto (小柴胡湯)	Takagi S. Increase of urinary 6-keto-prostaglandin F1α level by preoperative administration of gorei-san or toki-shakuyaku-san to the patients of gallbladder stones or polyps. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1992; 9: 32-9 (in Japanese with English abstract).	RCT	N
K83.1	Efficacy of inchinkoto (茵チン蒿湯) for improving the bilirubin reduction rate after biliary drainage in patients with obstructive jaundice.	inchinkoto (茵チン蒿湯)	Okabayashi T, Tanaka N, Orita K. The effect of a Kanpo medicine, inchinko-to for the bilirubin reduction rate after biliary drainage on the patients with obstructive jaundice. *Nihon Rinsho Geka Gakkaishi* (*Journal of Japan Surgical Association*) 1998; 59: 2495-500 (in Japanese with English abstract).	RCT-envelope	I
K91.0	To evaluate the effect of rikkunshito (六君子湯) on postoperative nausea and vomiting.	rikkunshito (六君子湯)	Okuno S, Hirayama K, Inoue J, et al. Effects of rikkunshito on the postoperative nausea and vomiting (PONV) after laparoscopic gynecological surgery. *Masui* (*Japanese Journal of Anesthesiology*) 2008; 57: 1502-9 (in Japanese with English abstract).	RCT	C
K91.0	To verify the inhibitory effect of goreisan (五苓散) on nausea and vomiting after surgery under general anesthesia.	goreisan (五苓散)	Kori K, Oikawa T, Odaguchi H, et al. Go-rei-San，a Kampo medicine，reduces postoperative nausea and vomiting：a prospective，single-blind，randomized trial. *The Journal of Alternative and Complementary Medicine*. 2013; 19: 946-50.	RCT	N
K91.0	To evaluate the efficacy and safety of goreisan (五苓散) for nausea and vomiting after gynecological surgery under general anesthesia.	goreisan (五苓散)	Kume K, Kasuya Y, Ozaki M. Effect of Goreisan，a traditional Japanese Kampo medicine，on postoperative nausea and vomiting in gynecological patients. *JA Clinical Reports* 2017; 3: 552: 1-6. doi: 10.1186/s40981-017-0122-5	DB-RCT	N
K91.3	Efficacy and safety of daikenchuto (大建中湯) for ileus.	daikenchuto (大建中湯)	Kubo N, Uchida Y, Akiyoshi T, et al. Efficacy of daikenchuto for ileus - a multicenter study -*. *Progress in Medicine* 1995; 15: 1962-7 (in Japanese).	RCT-envelope	I
K91.3	To evaluate the efficacy of daikenchuto (大建中湯) for the treatment of postoperative ileus and the improvement of postoperative conditions.	daikenchuto (大建中湯)	Itoh T, Yamakawa J, Mai M, et al. The effect of the herbal medicine dai-kenchu-to on post-operative ileus. *The Journal of International Medical Research* 2002; 30: 428-32.	RCT	C
K91.8	Efficacy and safety of shosaikoto (小柴胡湯) for postoperative liver dysfunction.	shosaikoto (小柴胡湯)	Okabayashi T, Mimura H, Orita K. Usefulness of Shosaikoto (TJ-9) in the treatment of postoperative liver dysfunction*. *Progress in Medicine* 1989; 9: 851-5 (in Japanese).	RCT-envelope	N
K91.8	Effect of shosaikoto (小柴胡湯) on postoperative liver dysfunction.	shosaikoto (小柴胡湯)	Usuba A, Gao L. S., Motoki R. Effect of sho-saiko-to (xao-chai-hu-tang) on liver dysfunctions after surgery - the benefits of preoperative administration and the importance of diagnosis according to traditional Chinese logic -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1992; 43: 1-12 (in Japanese).	RCT	N
K91.9	To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal and colonic transit and bowel function in healthy humans.	daikenchuto (大建中湯)	Manabe N., Camilleri M, Rao A, et. al. Effect of Daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2010; 298: G970-5.	DB-RCT	C
K92.9	Efficacy and safety of keishikashakuyakuto (桂枝加芍薬湯) combined with acarbose.	keishikashakuyakuto (桂枝加芍薬湯)	Hasebe K, Machida M, Yada M, et al. Clinical application of keishi-ka-syakuyaku-to for abdominal symptoms caused by α-glucosidase inhibitor acarbose. *Kiso to Rinsho* (*The Clinical Report*) 1997; 31: 3179-86 (in Japanese with English abstract).	quasi-RCT	I
K92.9	To evaluate the clinical effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by fluvoxamine, an antidepressant.	rikkunshito (六君子湯)	Oka T, Tamagawa Y, Hayashida S, et al. Rikkunshi-to atenuates adverse gastrointestinal symptoms induced by fluvoxamine. *Biopsychosocial Medicine* 2007; 1: 21.	RCT	I
K92.9	To evaluate the effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by milnacipran, an antidepressant.	rikkunshito (六君子湯)	Oka T. Rikkunshito attenuates milnacipran – induced adverse gastrointestinal symptoms and potentiates its antidepressant effect. *Medical Tribune* 2008;41:82 (in Japanese).	RCT	N

12. Skin Diseases (19 abstracts, 22 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
L20.8	Efficacy and safety of shosaikoto (小柴胡湯) for treating atopic dermatitis and for withdrawing or tapering topical corticosteroids.	shosaikoto (小柴胡湯)	Shimoda S, Hashizume S, Morita M, et al. Efficacy of TSUMURA Shosaikoto for atopic dermatitis*. *Hifuka ni okeru Kampo Chiryo no Genkyo* 1991; 2: 15-24 (in Japanese).	RCT	N
L20.9	To evaluate the efficacy and safety of hochuekkito (補中益気湯) in patients with *kikyo* (気虚, delicate constitution) associated with atopic dermatitis (AD).	hochuekkito (補中益気湯)	Furue M, Tanaka Y, Kobayashi H, et al. Efficacy of Kanebo Hochuekkito in patients with atopic dermatitis with "qi-kyo" – a multicenter, double-blind trial*. *Arerugi* (*Japanese Journal of Allergology*). 2005; 54: 1020 (in Japanese).	DB-RCT	N
			Kobayashi H, Ishii M, Takeuchi S, et al. Efficacy and safety of a traditional herbal medicine, hochu-ekki-to in the long-term management of kikyo (delicate constitution) patients with atopic dermatitis: A 6-month, multicenter, double-blind, randomized, placebo-controlled study. *Evidence-based Complementary and Alternative Medicine* 2008: 1-7. (2010; 7: 367-73.)		N
			Kobayashi H, Ishii M, Furue M. Efficacy of hochuekkito for skin symptoms in patients with atopic dermatitis associated with qikyo – An investigation by rash element – *. *Nishinihon Hifuka (the Nishinihon Journal of Dermatology)* 2012; 74: 642-7 (in Japanese).		I
L20.9	To evaluate the efficacy and safety of byakkokaninjinto (白虎加人参湯) used concomitantly in the treatment of atopic dermatitis.	byakkokaninjinto (白虎加人参湯)	Wadabayashi M. Kampo Clinical Report: Study on benefits of byakkokaninjinto in treating atopic dermatitis. *Phil Kampo* 2017; 73: 14-5 (in Japanese).	quasi-RCT	I
L20.9	To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) and goreisan (五苓散) for dampness-heat pattern in atopic dermatitis (AD) patients.	orengedokuto (黄連解毒湯) + goreisan (五苓散), goreisan (五苓散)	Choi I, Kim S, Kim Y, et al. The effect of TJ-15 plus TJ-17 on atopic dermatitis: a pilot study based on the principle of pattern identification. *The Jornal of Alternative and Complementary Medicine* 2012; 18: 576-82.	DB-RCT	N
L20.9	To evaluate the efficacy of unseiin (温清飲) or shimotsuto (四物湯) for the subjective and objective symptoms of atopic dermatitis.	unseiin (温清飲), shimotsuto (四物湯)	Kobayashi H, Yanagihara S, Tamiya H, et al. Combined effects of herbal medicines on the subjective and objective symptoms of patients with atopic dermatitis - a comparison study of unseiin or shimotsuto -. *The Nishinihon Journal of Dermatology* 2016; 78:171-6 (in Japanese).	RCT-envelope	I
L29.8	Efficacy and safety of orengedokuto (黄連解毒湯) and goshajinkigan (牛車腎気丸) for the treatment of senile pruritus.	orengedokuto (黄連解毒湯), goshajinkigan (牛車腎気丸)	Ohkawara A, Furuya K, Kurisu Y, et al. Experience with Orengedokuto (TJ-15) and Goshajinkigan (TJ-107) for the treatment of senile pruritus*. *Nishinihon Hifuka* (*The Nishinihon Journal of Dermatology*) 1991; 53: 1234-41 (in Japanese).	RCT-envelope	I
L29.8	Efficacy of tokiinshi (当帰飲子) combined with a bath preparation containing licorice extract in patients with senile xerosis.	tokiinshi (当帰飲子)	Iida T, Nishiyama C, Suzuki H. The effects of toki-inshi and a bath preparation containing licorice extract on patients with senile pruritus. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1996; 47: 35-41 (in Japanese with English abstract).	RCT	N
L29.8	Efficacy of hachimijiogan (八味地黄丸) for the treatment of senile pruritus.	hachimijiogan (八味地黄丸)	Ishioka T, Aoi R. Comparative evaluation of hachimijiogan and ketotifen fumarate on senile pruritus*. *Shinyaku to Rinsho* (*Journal of New Remedies and Clinics*) 1992; 41: 2603-8 (in Japanese).	RCT-cross over	N
L29.8	Efficacy of rokumigan (六味丸) and hachimijiogan (八味地黄丸) for the treatment of senile pruritus.	hachimijiogan (八味地黄丸), rokumigan (六味丸)	Ishioka T. Comparative evaluation of rokumigan and hachimi-jiogan on senile pruritus. *Therapeutic Research* 1995; 16: 1497-504 (in Japanese with English abstract).	RCT-cross over	N
L29.9	Effect on itching due to eczema and other skin disorders.	unseiin (温清飲)	Kusumoto M, Fujimura Y, Yamada H, et al. Evaluation of the effectiveness of various drugs for relieving itching due to eczema carried out by personnel in inpatient pharmacy practice: assessment based on "itching" score -*. *Iyaku Journal* (*Medicine and Drug Journal*) 1993; 29: 973-6 (in Japanese).	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
L29.9	Efficacy of orengedokuto (黄連解毒湯) and tokiinshi (当帰飲子) for the treatment of pruritus.	orengedokuto (黄連解毒湯) + tokiinshi (当帰飲子)	Ohkuma M. Treatment of pruritus by Chinese drugs. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1993; 10: 126-30 (in Japanese with English abstract).	RCT	N
L29.9	Efficacy of orengedokuto (黄連解毒湯), tokiinshi (当帰飲子), external application, and oral antihistamine monotherapy or combination therapy for the treatment of pruritus.	orengedokuto (黄連解毒湯) + tokiinshi (当帰飲子)	Ohkuma M. Treatment of pruritus by Chinese drugs with external application and oral antihistamine. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 302-3 (in Japanese).	RCT	N
L30.9	Efficacy and safety of jumihaidokuto (十味敗毒湯) for the treatment of chronic eczema and atopic dermatitis.	jumihaidokuto (十味敗毒湯)	Kobayashi K, Ohkawara A. Therapeutic effect of jumihaidokuto on chronic eczema and atopic dermatitis*. *Hifuka ni okeru Kampo Chiryo no Genkyo* (*Current Situation of Kampo Therapy in Dermatology*) 1994; 5: 25-34 (in Japanese).	RCT-envelope	N
L40.9	Efficacy of saireito (柴苓湯) combined with topical steroid therapy for psoriasis.	saireito (柴苓湯)	Kukita A, Harada S, Fujisawa R, et al. The clinical efficacy of the herb medicine, TJ-114 (Sairei-to), on the topical steroid therapy of psoriasis vulgaris. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicines*) 1991; 7: 927-36 (in Japanese with English abstract).	RCT-envelope	C&I
L50.8	To evaluate the efficacy of jumihaidokuto (十味敗毒湯) in urticaria.	jumihaidokuto (十味敗毒湯)	Murota H, Azukizawa H, Katayama I. Impact of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) on treatment of chronic spontaneous urticaria: a randomized controlled study. *Chinese Journal of Integrative Medicine* 2017; 1-5. doi: 10.1007/s11655-017-2950-6. (2019; 25: 820-4.)	RCT	C
L50.9	Efficacy of kakkonto (葛根湯) as an adjuvant for reducing adverse reactions to oxatomide.	kakkonto (葛根湯)	Tanaka M. Effects of oxatomide on urticaria. *Yakuri to Chiryo (Japanese Pharmacology and Therapeutics)* 1991; 19:5029-31 (in Japanese).	RCT	N
L70.0	Efficacy of jumihaidokuto (十味敗毒湯) and orengedokuto (黄連解毒湯) for the treatment of acne vulgaris.	jumihaidokuto (十味敗毒湯), orengedokuto (黄連解毒湯)	Ohkuma M. Treatment of acne by Chinese drugs and external application. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1993; 10: 131-4 (in Japanese with English abstract).	RCT	N
			Ohkuma M. Treatment of acne by Chinese drugs and external application - comparison with oral antibiotics -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1993; 44: 173-7 (in Japanese).		N
L70.0	To examine the effectiveness and safety of keigairengyoto (荊芥連翹湯) in treating acne vulgaris.	keigairengyoto (荊芥連翹湯)	Ito K, Masaki S, Hamada M, et al.Efficacy and safety of the traditional Japanese medicine keigairengyoto in the treatment of acne vulgaris. *Dermatology Research and Practice* 2018: 1-7.	RCT	C
L89	Effects of juzentaihoto (十全大補湯) on pressure ulcers.	juzentaihoto (十全大補湯)	Nagai Y, Hasegawa M, Tago O, et al. Assessment of the therapeutic effect of juzentaihoto on pressure ulcer. *Kampo to Saishin-chiryo* (*Kampo & The Newest Therapy*) 2009; 18: 143-9.	RCT-envelope	I

13. Diseases of the Musculoskeletal System and Connective Tissue (21 abstracts, 20 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
M06.90	To evaluate the efficacy of saireito (柴苓湯) in the management of chronic rheumatoid arthritis in a controlled trial using lobenzarit, a western medicine with the established efficacy, as control.	saireito (柴苓湯)	Matsuura M. Efficacy of saireito in the management of chronic rheumatoid arthritis (RA)*. *Modern Physician* 1994; 14: 403-8 (in Japanese).	RCT-envelope	I
M06.90	Efficacy for reducing adverse effects of steroids in patients with chronic rheumatoid arthritis.	jiinkokato (滋陰降火湯)	Matsuta K, Gu XP, Ito K, et al. Evaluation of jiinkokato and steroid combination therapy for chronic rheumatoid arthritis*. *Kampo Igaku* (*Kampo Medicine*) 1995; 19: 50-2 (in Japanese).	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
M17.9	To compare the efficacy of Kampo medicines (boiogito (防已黄耆湯) and shuchibushimatsu (修治附子末) with NSAIDs for improving analgesia, quality of life (QOL), and exercise capacity in patients with knee osteoarthritis.	boiogito (防已黄耆湯) + shuchibushimatsu (修治附子末)	Nishizawa Y, Nishizawa Y, Amenomori Y, et al. A comparison of the analgesic effect of non-steroid anti-inflammatory drugs (NSAIDs alminoprofen) and those of a Chinese traditional herbal medicine, boi-ogi-to and shuchi-bushi-powder on osteoarthropathy of the knee joint in middle-aged and elderly patients with knee-joint osteoarthropathy. *Itami to Kampo* (*Pain and Kampo Medicine*) *1998; 8: 17-32* (in Japanese with English abstract).	RCT	I
M17.9	To evaluate the efficacy of boiogitokashuchibushimatsu (防已黄耆湯加修治附子末) for gonarthrosis.	boiogitoka-shuchibushimatsu (防已黄耆湯加修治附子末)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Therapeutic effect of boiogitokashuchibushimatsu on gonarthrosis: a 10-year prospective randomized controlled trial with loxoprofen sodium*. *Pharma Medica* 2007; 25: 15-21 (in Japanese).	RCT	I
M17.9	To evaluate the efficacy and safety of boiogito (防已黄耆湯), a Kampo medicine for gonarthrosis with joint effusion.	boiogito (防已黄耆湯)	Majima T, Inoue M, Kasahara Y, et al. Effect of the Japanese herbal medicine, boiogito, on the osteoarthritis of the knee with joint effusion. *Sports Medicine Arthroscopy Rehabilitation Therapy & Technology* 2012; 4: 1-6.	RCT	N
M35.0	To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for dryness associated with primary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effects of traditional Chinese herbal medicine, mai-men-dong-tang (Japanese name: bakumondo-to) compared with bromhexine, hydrochloride on sicca syndrome, especially, salivary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group parallel comparative trial study with bromhexine. *Nihon Daekisen Gakkaishi* (*Journal of the Japan Salivary Gland Society*) 2002; 43: 62-6.	RCT	I
M35.0	To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for salivary hyposecretion associated with primary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effect of traditional Chinese herbal medicine, mai-men-don-tang on sicca syndrome, especially, salicary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group-pararell double-blined study. *Nihon Daekisen Gakkaishi* (*Journal of the Japan Salivary Gland Society*) 2004; 45: 66-74.	DB-RCT	N
M35.0	To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for treatment of secondary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Goto GH, et al. The Multicenter randomized comparative study of kampo herbal medicine, mai-men-dong-tang (Japanese name Bakumondo-to) compared with bromhexine on salivary secretion in secondary Sjögren's syndrome. *Itami to Kampo* (*Pain and Kampo Medicine*) 2004; 14: 10-7 (in Japanese with English abstract).	RCT	I
M35.0	To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for treatment of dryness associated with secondary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Improving effect of Chinese herb medicine mai-men-dong- tang (Japanese name: bakumondo-to) comparative with sicca syndrome in especial salivary patients with secondary Sjögren's syndrome in multicenter, well controlled, long-term comparative study. *Nihon Daekisen Gakkaishi* (*Journal of the Japan Salivary Gland Society*) 2003; 44: 65-70.	RCT	N
M35.0	To evaluate the efficacy for Sjögren's syndrome.	bakumondoto (麦門冬湯), rokumigan (六味丸), hachimijiogan (八味地黄丸), hochuekkito (補中益気湯)	Ohno S. The effect of Kampo medicine on salivary secretion in Sjögren's syndrome. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2006; 15: 134-40 (in Japanese).	quasi-RCT	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
M48.02	To evaluate the efficacy of hachimijiogan (八味地黄丸), goshajinkigan (牛車腎気丸), and shuchibushi (修治附子) powder for relief of residual symptoms after surgical treatment of cervical spinal stenosis.	hachimijiogan (八味地黄丸), goshajinkigan (牛車腎気丸), goshajinkigan (牛車腎気丸) + shuchibushimatsu (修治附子末)	Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. *Kampo to Saishin-Chiryo* (*Kampo & the Newest Therapy*) 2004; 13: 232-6 (in Japanese).	RCT	I
M48.06	Efficacy and safety of hachimijiogan (八味地黄丸) for lumbar spinal stenosis.	hachimijiogan (八味地黄丸)	Hayashi Y, Saito E, Takahashi O. Usefulness of hachimijiogan for lumbar spinal stenosis*. *Geriatric Medicine* 1994; 32: 585-91 (in Japanese).	quasi-RCT	N
M48.06	To evaluate the efficacy of goshajinkigan (牛車腎気丸)and shuchibushi (修治附子末) powder for relief of chronic low back pain associated with lumbar spinal stenosis.	goshajinkigan (牛車腎気丸), oshajinkigan (牛車腎気丸) + shuchibushimatsu (修治附子末)	Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. *Kampo to Saishin-Chiryo* (*Kampo & the Newest Therapy*) 2004; 13: 232-6 (in Japanese).	RCT	I
M54.56	To evaluate the clinical effect of shakuyakukanzoto (芍薬甘草湯) on acute lumbago (so-called strained back).	shakuyakukanzoto (芍薬甘草湯)	Tamakawa S, Ogawa H. The effect of shakuyaku-kanzo-to and goshakusan on lumbago. *Itami to Kampo* (*Pain and Kampo Medicine*) 1997; 7: 83-5 (in Japanese with English abstract).	RCT	N
M54.56	To clinically evaluate the effects of keishibukuryogan (桂枝茯苓丸) and its combination with bushi (附子) on nonspecific lumbago in women during menopause.	keishibukuryogan (桂枝茯苓丸), keishibukuryogan (桂枝茯苓丸) + shuchibushimatsu (修治附子末)	Ohta H, Makita K. Lumbago - with emphasis on nonspecific lumbago, which obstetricians and gynecologists think is the most common form in women -*. *Chiryo* (*The Journal of Therapy*) 1995; 77: 1646-57 (in Japanese).	RCT	N
M54.56	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in comparison with that of tiaramide hydrochloride for lumbago in the elderly.	goshajinkigan (牛車腎気丸)	Nakamura T, Souza ACA, Ouchi Y, et al. Effects of goshajinkigan on lumbago*. *Dai 4 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu* 1989; 4: 24-9 (in Japanese).	RCT-envelope	N
M62.59	To evaluate the efficacy of juzentaihoto (十全大補湯) combined with hachimijiogan (八味地黄丸) in patients with disuse syndrome.	juzentaihoto (十全大補湯), hachimijiogan (八味地黄丸)	Wang XD, Yoshida K, Honda K, et al. Study of the immunoregulatory activity of the combination therapy with juzentaihoto and hachimijiogan in patients with disuse syndrome*. *Kampo Igaku* (*Kampo Medicine*) 2006; 30: 65-7 (in Japanese).	RCT-envelope	I
M79.2	To evaluate the efficacy of maobushisaishinto (麻黄附子細辛湯) for treatment of occipital neuralgia.	maobushisaishinto (麻黄附子細辛湯)	Nakajima K, Sato H, Ooyama K, Is maobushisaishinto effective for neuropathic pain? Effect of maobushisaishinto on occipital neuralgia* *Itami to Kampo (Pain and Kampo Medicine)* 2014: 24: 31-7 (in Japanese with English abstract).	RCT-envelope	I&N
M81.1	Combined effect of keishibukuryogan (桂枝茯苓丸) and vitamin D3 on osteopenia in women during menopause.	keishibukuryogan (桂枝茯苓丸)	Ohta H, Nemoto K. Effect of concurrent administration of active vitamin D_3 and TSUMURA Keishibukuryogan on osteopenia following oophorectomy*. *Kampo Igaku* (*Kampo Medicine*) 1989; 13: 173-9 (in Japanese).	RCT	N
M81.1	Combined effect of keishibukuryogan (桂枝茯苓丸) or tokishakuyakusan (当帰芍薬散) and vitamin D3 on osteopenia in women during menopause.	keishibukuryogan (桂枝茯苓丸), tokishakuyakusan (当帰芍薬散)	Ohta H, Nemoto K. Preventive effect of 1α-hydroxyvitamin D_3 plus Kampo medicine combination therapy on osteopenia following oophorectomy - comparison between keishibukuryogan and tokishakuyakusan -*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 1990; 7: 65-70 (in Japanese).	RCT	N
M81.9	Positive effects on menopause index, bone mass, and anemia in postmenopausal women with osteoporosis.	kamikihito (加味帰脾湯)	Kanai S. The effect of kami-kihi-to on the maintenance of bone mass in patients with osteoporosis. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1998; 49: 59-66 (in Japanese with English abstract).	quasi-RCT	N

14. Genitourinary Tract Disorders (including Climacteric Disorders)(43 abstracts, 50 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
N02.8	Efficacy and safety of saireito (柴苓湯) in childhood IgA nephropathy with focal/minimal mesangial proliferation.	saireito (柴苓湯)	Yoshikawa N, Ito H, Sakai T, et al. A prospective controlled study of sairei-to in childhood IgA nephropathy with focal/minimal mesangial proliferation. *Nihon Jinzo Gakkaishi* (*The Japanese Journal of Nephrology*) 1997; 39: 503-6 (in Japanese with English abstract).	RCT-envelope	C
N02.8	Efficacy and safety of Kampo medicines for IgA nephropathy in adults.	saireito (柴苓湯)	Saruta T, Konishi K. Efficacy of Kampo medicines for renal diseases - with emphasis on saireito -*. *21 Seiki no Iryo to Kampo* (*Medical Care and Kampo in the 21st Century*) 1994: 157-65 (in Japanese).	RCT-envelope	N
N04.9	Efficacy of initial steroid therapy with saireito (柴苓湯) for preventing relapses in childhood steroid-responsive nephrotic syndrome.	saireito (柴苓湯)	Yoshikawa N, Ito H, Takekoshi Y, et al. Standard versus long-term prednisolone with sairei-to for initial therapy in childhood steroid-responsive nephrotic syndrome: A prospective controlled study. *Nihon Jinzo Gakkaishi* (*The Japanese Journal of Nephrology*) 1998; 40: 587-90 (in Japanese with English abstract).	RCT-envelope	C&I
N20.9	Efficacy for promoting the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy.	choreitogoshimotsuto (猪苓湯合四物湯) ＋ shakuyakukanzoto (芍薬甘草湯)	Kinoshita H, Kanaya H, Yamamoto S, et al. Effects of Chinese herbal medicine in promoting the spontaneous discharge of upper urinary tract stones after ESWL. *Nishinihon Hinyokika* (*The Nishinihon Journal of Urology*) 1993; 55: 61-6 (in Japanese with English abstract).	RCT	N
N20.9	To evaluate the efficacy of low-dose tamsulosin and choreito (猪苓湯) for stone expulsion after extracorporeal shock wave lithotripsy (ESWL) in patients with ureteral stones.	choreito (猪苓湯)	Kobayashi M, Naya Y, Kino M, et al. Low dose tamsulosin for stone expulsion after extracorporeal shock wave lithotripsy: Efficacy in Japanese male patients with ureteral stone. *International Journal of Urology* 2008; 15: 495-8.	RCT	I
N32.8	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) and propiverine hydrochloride for overactive bladder.	goshajinkigan (牛車腎気丸)	Nishizawa Y., Nishizawa Y, Yoshioka H., et al. Efficacy and safety of Chinese traditional medicine, niu-che-shwn-qi-wan (Japanese name: goshajinki-gan) versus propiverine hydrochloride on health-related quality of life in patients with overactive bladder in prospective randomized comparative study. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2007; 16: 131-42 (in Japanese).	RCT	I
N35.9	To evaluate the protective effect of saireito (柴苓湯) on postoperative urethral stricture.	saireito (柴苓湯)	Oh-oka H. Effect of Saireito for Prevention and Improvement of Urethral Stricture after Transurethral Resection of the Prostate. *Kampo Medicine* 2016; 67: 244-50. (in Japanese with English abstract).	RCT	I
N39.0	Efficacy of shosaikoto (小柴胡湯) for improving immunity in the elderly.	shosaikoto (小柴胡湯)	Toba K. Role in host defense mechanisms and effect on prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation. *Taisha* (*Metabolism and Disease*) 1992; 29 suppl: 350-4 (in Japanese).	RCT-envelope	N
			Toba K. Role in host defense mechanisms and effect on the prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation*. *Dai 8 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu* (*Proceedings of the 8th Meeting of the Tokyo Society for Internal Kampo Medicine*) 1993; 8: 31-42 (in Japanese).		N
N39.9	Efficacy of choreito (猪苓湯) and choreitogoshimotsuto (猪苓湯合四物湯) for relieving nonspecific lower urinary tract complaints.	choreito (猪苓湯), choreitogoshimotsuto (猪苓湯合四物湯)	Ohkawa T, Ebisuno S, Watanabe T. Urological diseases and Kampo medicine*. *Dai 23 Kai Nihon Igakkai Sokai Sateraito Shinpojiumu Nihon Toyo Igakkai Rinsho Kampo Kenkyukai Koen Naiyo Shu* (*Proceedings of the Meeting for Clinical Kampo Medicine of the Japan Society for Oriental Medicine, the Satellite Symposium of the 23rd General Assembly of the Japan Medical Congress*) 1992: 22-39 (in Japanese).	RCT-envelope	N
N39.9	Efficacy of choreito (猪苓湯) and hachimijiogan (八味地黄丸) for relieving urinary frequency, voiding pain, and incomplete emptying in patients without organic urinary tract disease.	hachimijiogan (八味地黄丸), choreito (猪苓湯)	Fuse H, Sakamoto M, Iwasaki M, et al. Effect of chorei-to and hachimi-jio-gan on unidentified complatints on urinary tract. *Hinyoki Geka* (*Japanese Journal of Urological Surgery*) 1995; 8: 603-9 (in Japanese).	RCT-envelope	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
N39.9	To evaluate the effect of single-dose administration of maobushisaishinto (麻黄附子細辛湯) on urine flow.	maobushisaishinto (麻黄附子細辛湯)	Aoki Y, Ueda K, Tsutani K, et al. The influence of formula ma-huang-fu-zi-xi-xin-tang (mao-bushi-saishin-to; Mbst) on the results of urodynamic studies. *Journal of Traditional Medicine* 2001; 18: 203-9.	RCT-cross over	I
N40	Efficacy and safety for treating atopic dermatitis and for withdrawing or tapering topical corticosteroids.	hachimijiogan (八味地黄丸), choreito (猪苓湯)	Sakamoto Y, Iwasaki M, Kazama T, et al. Study of effects hachimi-jio-gan and chorei-to on prostatic hypertrophy. *Dai 13 Kai Hinyokika Kampo Kenkyukai Koen Shu* (*Proceedings of the 13th Meeting of the Urological Society for Kampo Medicine*)1996: 7-14 (in Japanese with English abstract).	RCT-envelope	N
N41.1	Efficacy and safety of goshajinkigan (牛車腎気丸) in the treatment of chronic prostatitis.	goshajinkigan (牛車腎気丸)	Horiba M, Kato S, Tanaka T, et al. Clinical validity of gosha-jinki-gan in the treatment of chronic prostatitis - open comparative study with gosha-jinki-gan vs ciprofloxacin -. *Gendai Toyo Igaku* (*The Journal of Traditional Sino-Japanese Medicine*) 1994; 15: 37-44 (in Japanese).	RCT-envelope	N
N41.1	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for relieving lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH) and concomitant overactive bladder (OAB).	goshajinkigan (牛車腎気丸)	Ishizuka O, Yamanishi T, Gotoh M, et al. LUTS: new evidence – clinical efficacy of Kampo formulations focusing on goshajinkigan -*. *Urology View* 2009; 7: 81-4.	RCT-cross over	I
C61 N42.8	To evaluate the efficacy and safety of Kampo medicines (hochuekkito [補中益気湯] and keishibukuryogan [桂枝茯苓丸]) for enhancing the immune response to tailor-made cancer peptide vaccine therapy (PPV) in men with castration-resistant prostate cancer (CRPC).	hochuekkito (補中益気湯) + keishibukuryogan (桂枝茯苓丸)	Koga N, Moriya F, Waki K, et al. Immunological efficacy of herbal medicines in prostate cancer patients treated by personalized peptide vaccine. *Cancer Science* 2017; 108: 2326-32.	RCT	N
N46	Positive effect on sperm profiles of male infertility patients.	saikokaryukotsuboreito (柴胡加竜骨牡蛎湯), hochuekkito (補中益気湯)	Hiramatsu M, Maehara I, Takahashi M, et al. Treatment experience with saikokaryukotsuboreito and hochuekkito in male infertility patients*. *Kampo Igaku* (*Kampo Medicine*) 1993; 17: 246-8 (in Japanese).	RCT	N
N46	Efficacy and safety of hochuekkito (補中益気湯) in the treatment of male infertility.	hochuekkito (補中益気湯)	Kazama T. Male infertility*. *Current Therapy* 1988; 6: 1683-6 (in Japanese).	RCT-envelope	N
N50.8	To evaluate the efficacy of androgen replacement therapy (ART) combined with saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) for late-onset hypogonadism (LOH) syndrome.	saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)	Sugimoto K, Shigehara K, Izumi K, et al. Effect of combination of saiko-ka-ryukotsu-borei-to with androgen replacement therapy for LOH syndrome. *Nihon Sei Kino Gakkai Zasshi (Japanese Journal of Sexual Medicine)* 2009; 24: 349–53 (in Japanese).	RCT	I
N64.9	Efficacy of kamishoyosan (加味逍遙散) in the treatment of mastitis.	kamishoyosan (加味逍遙散), keishibukuryogan (桂枝茯苓丸)	Inoue M. Kampo treatment for mastitis - kamishoyosan -*. *Kampo Igaku* (*Kampo Medicine*) 1994; 18: 238-41 (in Japanese).	RCT-envelope	N
N64.9	Efficacy of shigyakusan (四逆散) in the treatment of mastitis.	shigyakusan (四逆散), keishibukuryogan (桂枝茯苓丸)	Inoue M. Kampo therapy for mastitis - shigyakusan -*. *Kampo Igaku* (*Kampo Medicine*) 1990; 14: 132-6 (in Japanese).	RCT-envelope	N
N64.9	Efficacy of tsudosan (通導散) in the treatment of mastitis.	tsudosan (通導散), keishibukuryogan (桂枝茯苓丸)	Inoue M. Clinical study of effects of tsu-do-san on mastitis. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1993; 43: 517-21 (in Japanese).	RCT-envelope	N
N64.9	Efficacy of tokakujokito (桃核承気湯) in the treatment of mastitis.	tokakujokito (桃核承気湯), keishibukuryogan (桂枝茯苓丸)	Inoue M. Clinical studies on effects of tokakujoki-to for fibro-cystic disease of the breast. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1992; 42: 415-8 (in Japanese).	RCT-envelope	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
N81.4	To evaluate the hachimijiogan (八味地黄丸)-induced improvement in postoperative discomfort associated with surgery for uterine prolapse and quality of life (QOL).	hachimijiogan (八味地黄丸)	Oribe K, Nishida Y. Efficacy of hachimijiogan for discomfort after surgery for uterine prolapse. *Gekkan Kampo Ryoho* (*Monthly Journal of Kampo Medicine and Herbs*) 2006; 10: 282-8 (in Japanese).	RCT	N
N93.9	To evaluate the efficacy and safety of kyukikyogaito (キュウ帰膠艾湯) for menometrorrhagia.	kyukikyogaito (キュウ帰膠艾湯)	Iwabuchi S. Effect of kyuki-kyogai-to on stopping dysfunctional uterine bleeding – comparison with occidental hemostatic drugs -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 2000; 50: 883-903 (in Japanese with English abstract).	quasi-RCT	I
N94.6	Double-blind study on pain-relieving effect of tokishakuyakusan (当帰芍薬散) on dysmenorrheal.	tokishakuyakusan (当帰芍薬散)	Kotani N, Oyama T, Sakai I, et al. Analgesic effect of a herbal medicine for treatment of primary dysmenorrhea - a double-blind study. *The American Journal of Chinese Medicine* 1997; 25: 205-12.	DB-RCT	C
N95.1	To compare the clinical effects of keishibukuryogan (桂枝茯苓丸) monotherapy with combined therapy (keishibukuryogan plus autonomic modulator).	keishibukuryogan (桂枝茯苓丸)	Tanaka E, Saito H, Hiroi M. Kampo treatment for nonspecific complaints in climacteric women - comparison of clinical efficacy of Kampo medicine alone versus Kampo medicine combined with tofisopam -*. *Kampo Shinryo* 1997; 16: 22-4 (in Japanese).	RCT	N
N95.1	Clinical effect on climacteric disorders.	tokishakuyakusan (当帰芍薬散), kojinmatsu (紅参末)	Samukawa K, Ogita S. Climacteric disorders and medicinal ginseng*. *Chiryogaku* (*Biomedicine & Therapeutics*) 1994; 28: 57-62 (in Japanese).	RCT-envelope	N
N95.1	To compare hormone replacement therapy (HRT) and Kampo therapy as treatment of climacteric disorders.	Kampo therapy（keishibukuryogan (桂枝茯苓丸), kamishoyosan (加味逍遙散), goshajinkigan (牛車腎気丸), etc.）	Ota H. Positioning of Kampo therapy and hormone replacement therapy in treatment of climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2001; 18: 21-9 (in Japanese).	RCT	I
N95.1	To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-*sho* -based (非随証) Kampo medicines for gynecological disease.	kamishoyosan (加味逍遙散), tokishakuyakusan (当帰芍薬散), keishibukuryogan (桂枝茯苓丸), juzentaihoto (十全大補湯)	Takamatsu K, Musha C, Okano H, et al. Study of usefulness of Kampo therapy for climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2002; 19: 111-6 (in Japanese).	quasi-RCT	I
		tokishakuyakusan (当帰芍薬散), kamishoyosan (加味逍遙散), keishibukuryogan (桂枝茯苓丸)	Takamatsu K. HRT and Kampo medicine*. *Nippon Konenki Igakkai Zasshi* (*The Journal of the Japan Menopause Society*) 2004; 12:155-7 (in Japanese).		N
			Takamatsu K, Makita K, Tanabe K, et al. HRT and Kampo medicine*. *Rinsho Kensa* (*Journal of Medical Technology*) 2004; 48: 877-84 (in Japanese).		N
			Takamatsu K, Tanabe K. Efficacy of Kampo medicine against climacteric disorders*. *Sanfujinka Chiryo* (*Obstetrical and Gynecological Therapy*) 2004; 89: 408-15 (in Japanese).		N
			Takamatsu K. Study of the usefulness of Kampo therapy for climacteric disorders – a randomized trial of three major Kampo medicines for treatment of gynecological disease – *. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2006; 23: 35-42 (in Japanese).		I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
N95.1	To investigate the equivalence between non-extracted keishibukuryogan (桂枝茯苓丸) and keishibukuryogan (桂枝茯苓丸) extract.	keishibukuryogan (桂枝茯苓丸)	Ogita Y, Fujimoto S, Ushiroyama T, et al. Efficacy of formulation TK-061 for various climacteric symptoms – comparison with Teikoku Keishibukuryogan Extract Granules*. *Rinsho Fujinka Sanka* (*Clinical Gynecology and Obstetrics*) 2002; 56: 799-810 (in Japanese).	RCT	I
			Ogita Y, Fujimoto S, Ushiroyama T, et al. Keishibukuryogan formulation TK-061 prepared with crude drug – verification of efficacy for various climacteric symptoms*. *Sanka to Fujinka* (*Obstetrics and Gynecology*) 2002; 69: 953-62 (in Japanese).		I
N95.1	To evaluate the efficacy of unkeito (温経湯) for climacteric disorders with depressive symptoms.	unkeito (温経湯), tokishakuyakusan (当帰芍薬散)	Koike K, Ohno S, Takahashi N, et al. Efficacy of the herbal medicine unkei-to as an adjunctive treatment to hormone replacement therapy for postmenopausal women with depressive symptoms. *Clinical Neuropharmacology* 2004; 27: 157-62.	RCT-cross over	C
N95.1	To evaluate effects of hormone replacement therapy (HRT) alone and in combination with kamishoyosan (加味逍遙散) on climacteric disorders.	kamishoyosan (加味逍遙散)	Higuchi T, Tarakida A, Abe K, et al. Comparing the effects of hormone replacement therapy and kamishoyosan treatment on climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2009; 26: 18-23.	RCT-envelope	I
			Higuchi T, Iino K, Tarakida A, et al. A comparing the effects of kamishoyosan or HRT on climactericdisorders in postmenopausal women: results from a randomized controlled trial. *Nihon Josei Igaku Gakkai Zasshi* (*The Journal of Japan Society for Menopause and Women's Health*) 2012; 20: 305-12 (in Japanese).		N
N95.1	To evaluate the clinical effects of keishibukuryogan (桂枝茯苓丸) for hot flashes in menopausal American women.	keishibukuryogan (桂枝茯苓丸)	Plotnikoff GA, Watanabe K, Torkelson C, et al. The TU-025 Keishibukuryogan clinical trial for hot flash management in postmenopausal women: result and lessons for future research. *Menopause* 2011; 18: 886-92.	RCT	N
C57.7 N95.1	To evaluate the effect of Kampo medicines kamikihito (加味帰脾湯) and kamishoyosan (加味逍遙散) on menopausal symptoms in gynecological cancer patients.	kamishoyosan (加味逍遙散), kamikihito (加味帰脾湯)	Yoshimura A, Sawada K, Sasano T, et al. Effect of Japanese Kampo medicine therapy for menopausal symptoms after treatment of gynecological malignancy. *Obstetrics and Gynecology International* 2018: 1-6.	RCT-envelope	N
N95.1	To evaluate the effects of keishibukuryogan (桂枝茯苓丸) and kamishoyosan (加味逍遙散) on levels of circulating cytokines in patients with hot flashes.	keishibukuryogan (桂枝茯苓丸), kamishoyosan (加味逍遙散)	Yasui T, Matsui S, Yamamoto S, et al. Effects of Japanese traditional medicines on circulating cytokine levels in women with hot flashes. *Menopause* 2011; 18: 85-92	quasi-RCT	N
N95.1	To verify the efficacy of nyoshinsan (女神散) for female climacteric disorder.	nyoshinsan (女神散), tokishakuyakusan (当帰芍薬散), kamishoyosan (加味逍遙散), keishibukuryogan (桂枝茯苓丸)	Takamatsu K, Fujii E, Mizuno H, et al. An investigation of the usefulness of nyoshinsan for climacteric disorder*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 95-100 (in Japanese).	quasi-RCT	N
N95.1	To verify the clinical efficacy of porcine placental extract on shoulder stiffness in climacteric women.	tokishakuyakusan (当帰芍薬散)	Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on shoulder stiffness in climacteric women. *Climacteric* 2013; 16: 447-52.	RCT	N
N95.1	To verify the clinical efficacy of porcine placental extract on shoulder stiffness in postmenopausal women taking hormone replacement therapy.	tokishakuyakusan (当帰芍薬散)	Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on shoulder stiffness in climacteric women. *Climacteric* 2013; 16: 447-52.	RCT	N
N95.1	To evaluate clinical effects of porcine placental extract on climacteric symptoms in peri-postmenopausal women.	tokishakuyakusan (当帰芍薬散)	Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on climacteric symptoms in peri-and postmenopausal women. *Climacteric* 2013; 16: 28-35.	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
N95.8	To compare the efficacy of keishibukuryogan (桂枝茯苓丸) and hormone replacement therapy (HRT) for relief of hot flashes and chills.	keishibukuryogan (桂枝茯苓丸)	Ushiroyama T, Ikeda A, Sakuma K, et al. Comparing the effects of estrogen and an herbal medicine on peripheral blood flow in post-menopausal women with hot flashes: hormone replacement therapy and gui-zhi-fu-ling-wan, a Kampo medicine. *American Journal of Chinese Medicine* 2005; 33: 259-67.	RCT	C
N95.8	To evaluate the usefulness of Kampo medicine for treatment of depressive patients refractory to hormone replacement therapy (HRT).	unkeito (温経湯), tokishakuyakusan (当帰芍薬散)	Matsuo A, Koike K, Hoshina Y, et al. Study of the efficacy of unkeito for depressive and anxiety symptoms during menopause that are refractory to hormone replacement therapy.* *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2005; 22: 70-4 (in Japanese).	RCT-cross over	I
			Koike K. A slight advantage of Kampo treatment for gynecological disease 4: Menopausal depressed mood and the herbal medicine unkei-to. *Sanfujinka Chiryo* (*Obstetrical and Gynecological Therapy*) 2006; 92: 784-6 (in Japanese).		N
N95.8	To compare the effects of unkeito (温経湯) and vitamin E on peripheral blood flow.	unkeito (温経湯)	Ushiroyama T, Sakuma K, Nosaka S. Comparison of effects of vitamin E and wen-jing-tang (unkei-to), an herbal medicine, on peripheral blood flow in post-menopausal women with chilly sensation in the lower extremities: a randomized prospective study. *The American Journal of Chinese Medicine* 2006; 34: 969-79.	RCT	C
N97.0	To compare the effects of clomiphene monotherapy with tokishakuyakusan (当帰芍薬散) and clomiphene combination therapy infrequent menses, anovular menstrual cycle, and amenorrhea.	tokishakuyakusan (当帰芍薬散)	Yasui T, Irahara M, Aono T. Studies on treatment with the combination clomiphene citrate and toki-shakuyaku-san. *Nippon Funin Gakkai Zasshi* (*Japanese Journal of Fertility and Sterility*) 1995; 40: 83-91 (in Japanese).	RCT-envelope	N

15. Ante/Post-partum Diseases (11 abstracts, 13 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
O12.0	To evaluate the effectiveness of saireito (柴苓湯) combined with either sojutsu (蒼朮, Atractylodes Lancea Rhizome) or byakujutsu (白朮, Atractylodes Rhizome) as constituent crude drugs for lower limb edema and functional dyspepsia-like gastrointestinal symptoms.	saireito (柴苓湯)	Takushima Y, Michigami F. Clinical study of saireito on gestational edema and upper gastrointestinal symptoms. *Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)* 2010; 64: 709–15 (in Japanese).	quasi-RCT	I
O20.0	To evaluate the efficacy of kyukikyogaito (キュウ帰膠艾湯) as a therapeutic drug for imminent abortion in patients with uterine hemorrhage.	kyukikyogaito (キュウ帰膠艾湯)	Ushiroyama T, Araki R, Sakuma K, et al. Efficacy of the kampo medicine xiong-gui-jiao-ai-tang, a traditional herbal medicine, in the treatment of threatened abortion in early pregnancy. *American Journal of Chinese Medicine* 2006; 34: 731-40.	RCT	C
			Ushiroyama T, Sakuma K, Nosaka S, et al. Clinical efficacy of kyukikyogaito for imminent abortion with uterine hemorrhage*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2006; 23: 100-3 (in Japanese).		I
O47.0	Usefulness of tokishakuyakusan (当帰芍薬散) combined with ritodrine hydrochloride in the management of threatened premature delivery.	tokishakuyakusan (当帰芍薬散)	Mizuno M, Sato K, Mori T, et al. Clinical evaluation of TSUMURA Tokishakuyakusan and ritodrine hydrochloride combination therapy in the management of threatened premature delivery*. *Sanka to Fujinka* (*Obstetrics and Gynecology*) 1992; 59: 469-80 (in Japanese).	RCT-envelope	N
O90.9	To evaluate the usefulness of kyukichoketsuin (キュウ帰調血飲) for control of puerperium.	kyukichoketsuin (キュウ帰調血飲)	Takushima Y, Inoguchi H, Study on usefulness of kyukichoketsuin for control of puerperium – comparison with methylergometrine maleate (1st report) -*. *Progress in Medicine* 2001; 21: 1535-42 (in Japanese).	quasi-RCT	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
O90.9	To evaluate the efficacy and safety of kyukichoketsuin (キュウ帰調血飲) for puerperal psychosomatic disorder.	kyukichoketsuin (キュウ帰調血飲)	Sakuma K, Ushiroyama T, Akise D, et al. Clinical efficacy of kyukichoketsuin for regulation of puerperal psychosomatic functions. *Sanfujinka no Shinpo* (*Advances in Obstetrics and Gynecology*) 2002; 54: 80-6 (in Japanese with English abstract).	RCT-envelope	I
			Ushiroyama T, Sakuma K, Souen H, et al. Therapeutic effects of kyuki-chouketsu-in in restoring postpartum physical condition. *American Journal of Chinese Medicine* 2003; 31: 437-44.		C
O90.9	To evaluate the clinical usefulness of kyukichoketsuin (キュウ帰調血飲) for "postpartum restoration".	kyukichoketsuin (キュウ帰調血飲)	Wada H, Wada K, Motoyama K. Usefulness in postpartum control by kyukichoketsuin. *Sanfujinka no Sekai* (*World of Obstetrics and Gynecology*) 2003; 55: 1057-61.	RCT	I
O90.9	To evaluate the clinical usefulness of kyukichoketsuin (キュウ帰調血飲) during puerperium.	kyukichoketsuin (キュウ帰調血飲)	Narimatsu A., Ito A., Usefulness of kyukichoketsuin during puerperium. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicine*) 2001; 17: 1329-35 (in Japanese with English abstract).	RCT	I
O92.3	To evaluate the postpartum lactation-promoting effect and safety of kyukichoketsuin (キュウ帰調血飲).	kyukichoketsuin (キュウ帰調血飲)	Ushiroyama T, Sakuma K, Souen H, et al. xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, stimulates lactation with increase in secretion of prolactin but not oxytocin in the postpartum period. *The American Journal of Chinese Medicine* 2007; 35: 195-202.	RCT-envelope	C
O92.5	To evaluate a Kampo medicine effective for relieving the feeling of lactation deficiency.	kakkonto (葛根湯), Juzentaihoto (十全大補湯), kyukichoketsuin (キュウ帰調血飲), and combination of these Kampo formulations	Kawakami S, Nishimura J, Umeki M, et al. Kampo therapy for feeling of lactation deficiency*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 140-3.	RCT	I
O99.0	To evaluate whether rikkunshito (六君子湯) combined with oral iron can improve hemoglobin level and reduce adverse reactions associated with the administration of iron for anemia in pregnant women.	rikkunshito (六君子湯)	Fushiki H, Saeki A, Shiozaki A. Attempt to reduce adverse reactions associated with oral iron preparation for anemia in pregnancy by combination with Rikkunshito (TJ-43)*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 138-9 (in Japanese).	RCT	I
O99.3	To confirm the efficacy of kyukichoketsuin (キュウ帰調血飲) for the "maternity blues."	kyukichoketsuin (キュウ帰調血飲)	Ushiroyama T, Sakuma K, Ueki M. Efficacy of the Kampo medicine xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, in the treatment of maternity blues syndrome in the postpartum period. *The American Journal of Chinese Medicine* 2005; 33: 117-26.	RCT-envelope	C

18. Symptoms and Signs (27 abstracts, 36 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
R05	To evaluate the efficacy of bakumondoto (麦門冬湯) for persistent cough after infection in the elderly.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Beneficial effect of Chinese traditional herbal medicine, mai-men-don-tang (Japanese name: bakumondo-to) on acute pain in patients with acute internalmedical disease: antitussive effect on elderly patients with post infectious persistent coughs, prospective, multicenter, randomized comparative trial between mai-men-dong-tang and forminoben hydrochloride. *Itami to Kampo* (*Pain and Kampo Medicine*) 2003; 13: 12-21 (in Japanese with English abstract).	RCT	I
R05.0	To evaluate the combined effects of bakumondoto (麦門冬湯) and a bronchodilator for prolonged cough following common cold.	bakumondoto (麦門冬湯)	Irifune K, Hamada H, Ito R, et al. Antitussive effect of bakumondoto a fixed kampo medicine (six herbal components) for treatment of post-infectious prolonged cough: controlled clinical pilot study with 19 patients. *Phytomedicine* 2011; 18: 630-3.	RCT-envelope	C
R11	Effects of a Kampo suppository preparation on vomiting in children.	goreisan (五苓散)	Nishi K, Takata K, Asano S, et al. Effects of goreisan suppository on vomiting in children - comparison with domperidone suppository -*. *Nihon Byoin Yakuzaishikai Zasshi* (*Journal of Japanese Society of Hospital Pharmacists*) 1998; 34: 1173-6 (in Japanese).	quasi-RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
R11	To evaluate the efficacy and safety of goreisan (五苓散) for vomiting in young children.	goreisan (五苓散), hochuekkito (補中益気湯)	Yoshida M, Mizuno T, Mizoguchi F, et al. Efficacy of goreisan suppositories for vomiting in young children (2nd report) – a double-blind study of the hochuekkito suppository–*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1991; 7: 506-7 (in Japanese).	DB-RCT	I
			Yoshida M. Efficacy of goreisan suppository for vomiting in young children*. *Toyoigaku* (*Japanese Journal of Oriental Medicine*) 2000; 28: 36-8 (in Japanese).		N
			Yoshida M. Efficacy of goreisan suppository*. *Nihon Syoni Toyo Igakkaishi* (*The Japan Pediatric Society for Oriental Medicine*) 2003; 19: 13-7 (in Japanese).		I
C57.7 R11.0	To evaluate the efficacy and safety of rikkunshito (六君子湯) added to antiemetics for nausea, vomiting, and anorexia in patients treated with cisplatin and paclitaxel for cervical and endometrial cancers.	rikkunshito (六君子湯)	Ohnishi S, Watari H, Sakuragi N, et al. Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: results of a randomized phase II study (JORTC KMP-02). *Journal of Gynecologic Oncology* 2017; 28: 1-10. doi: 10.3802/jgo.2017.28.e44	RCT	C
R11.0	To evaluate the effectiveness and safety of goreisan (五苓散) suppository on vomiting in pediatric infectious diseases.	goreisan (五苓散)	Sakiyama T, Wada E, Inoue M, et al. Study of effectiveness of goreisan suppository. *Journal of Japan Pediatric Oriental Medicine Society* . 2017; 30: 33-42 (in Japanese).	DB-RCT	I
R13.0	To evaluate the nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding.	hochuekkito (補中益気湯)	Sasaki S, Oumi A, Kumeda M, et al. Evaluation of nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding. *Science of Kampo Medicine 2014 (in Japanese)*, 38: 263-6.	RCT	I
R22.4	Efficacy and safety of saireito (柴苓湯) for posttraumatic or postoperative swelling in the lower extremities.	saireito (柴苓湯)	Igarashi I. Clinical study of traditional Chinese medicine therapy for post-operative or post-traumatic swelling in lower extremities. *Seikeigeka* (*Orthopedic Surgery*) 1993; 44: 127-31 (in Japanese).	RCT	N
R25.2	Efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for preventing muscle cramps in diabetic patients.	shakuyakukanzoto (芍薬甘草湯)	Yoshida M, Kitaoka H, Masui Y, et al. Effects of shakuyaku-kanzo-to on muscle cramp in diabetics. *Shinkei Chiryogaku* (*Neurological Therapeutics*) 1995; 12: 529-34 (in Japanese).	RCT-envelope	N
R25.2	To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for relief of muscle cramp.	shakuyakukanzoto (芍薬甘草湯)	Kumada T, Kumada H, Yoshiba M, et al. Effects of Shakuyaku-kanzo-to (Tsumura TJ-68) on muscle cramps accompanying cirrhosis in a placebo-controlled double-blined parallel study. *Rinsho Iyaku* (*Journal of Clinical Therapeutics and Medicine*) 1999; 15: 499-523 (in Japanese with English abstract).	DB-RCT	I
			Kumada T, Kiriyama I, Sone Y, et al. EBM-based Kampo therapy for gastrointestinal diseases 3. Efficacy of shakuyakukanzoto for “muscle cramps in the calves” associated with hepatic cirrhosis*. *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) 2003; 54: 536-8 (in Japanese).		N
R25.2	To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for muscle cramps in the calves.	goshajinkigan (牛車腎気丸), shakuyakukanzoto (芍薬甘草湯)	Nishizawa Y, Nishizawa Y, Amemori Y, et al. A randomized paralleled group comparison in multicenter cooperation: analgesic effect and safety with gosha-jinki-gan and shakuyaku-kanzo-to in the treatment of painful muscle cramps in patients with cirrhosis. *Itami to Kamp* o (*Pain and Kampo Medicine*) 2000; 10: 13-8 (in Japanese with English abstract).	RCT	I
R25.2	To evaluate the preventive effect and safety of shakuyakukanzoto (芍薬甘草湯) for gastrocnemius muscle hardness in knee osteoarthritis patients doing exercises at home.	shakuyakukanzoto (芍薬甘草湯)	Toda Y, Effect of peony and licorice decoction on muscle hardness of gastrocnemius in patients with osteoarthritis of the knee* *Seikei Igaku (Orthopedic Surgery)* 2015; 66: 521-4.	quasi-RCT	I&N
R25.2	To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) for muscle spasms in lumbar spinal stenosis.	shakuyakukanzoto (芍薬甘草湯)	Takao Y, Takaoka Y, Sugano A,et al. Shakuyaku-kanzo-to (Shao-Yao-Gan-Cao-Tang) as Treatment of Painful Muscle Cramps in Patients with Lumbar Spinal Stenosis and Its Minimum Effective Dose. *Kobe Journal of Medical Sciences* 2015; 61: E132-7.	RCT	C

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
R31	Efficacy and safety of kyukikyogaito (キュウ帰膠艾湯) and saireito (柴苓湯) for essential microscopic hematuria.	kyukikyogaito (キュウ帰膠艾湯), saireito (柴苓湯)	Yoshikawa H, Ikeuchi T, Kai Y. Clinical effects of kyuki-kyogai-to and Sairei-to for essential microscopic hematuria. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 1997; 6: 55-8 (in Japanese).	RCT	N
R31	Clinical efficacy of saireito (柴苓湯) for essential hematuria.	saireito (柴苓湯)	Suzuki Y, Machida T, Onodera S, et al. Clinical effects of sairei-to for essential hematuria. *Hinyoki Geka* (*Japanese Journal of Urological Surgery*) 1994; 7: 325-7 (in Japanese).	RCT	I
R35.0	To evaluate the effectiveness of goshajinkigan (牛車腎気丸) for nocturnal polyuria with elevated B-type natriuretic peptide.	goshajinkigan (牛車腎気丸)	Shimizu Y, Yoshimura K, Soda T, et al. The effects of gosha-jinki-gan, a blended herbal medicine, and furosemide for nocturnal polyuria with elevated B-type natriuretic peptide: a crossover trial. *Neurourology and Urodynamics* 2010; 29: 833-4.	RCT-cross over	C
			Yoshimura K, Shimizu Y, Masui K, et al. Furosemide versus gosha-jinki-gan, a blended herbal medicine, for nocturnal polyuria: a randomized crossover trial. *Lower Urinary Tract Symptoms* 2012; 4: 77-81.		N
R39.8	Effects of hachimijiogan (八味地黄丸) and seishinrenshiin (清心レン子飲) on anti-heat shock protein (HSP) 60 antibodies.	hachimijiogan (八味地黄丸), seishinrenshiin (清心レン子飲)	Sekiguchi Y, Miyai K, Noguchi K, et al. Study of effects of anti-heat shock protein 60 antibody by ba wei di huang wan and qing xin lian zi yin (II). *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1998; 15: 326-7 (in Japanese).	RCT-cross over	N
R51	Efficacy and safety of chotosan (釣藤散) for relieving the accompanying symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension.	chotosan (釣藤散)	Matsushita S, Ueda S, Ouchi Y, et al. Usefulness of Chotosan (TJ-47) for relieving the accompanying symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension*. *Geriatric Medicine* 1995; 33: 1333-41 (in Japanese).	RCT-envelope	I
R51	Efficacy and safety of chotosan (釣藤散) for relieving headache in patients with spinal cord injury.	chotosan (釣藤散)	Nishizawa Y, Nishizawa Y, Fushiki S. Analgesic effects on headache in patients with spinal cord injury. *Nippon Zutsu Gakkaishi* (*Japanese Journal of Headache*) 1997; 25: 23-6.	DB-RCT	I
R51	To evaluate the efficacy and safety of goshuyuto (呉茱萸湯) for relieving chronic headache using keishininjinto (桂枝人参湯) as a control.	goshuyuto (呉茱萸湯), keishininjinto (桂枝人参湯)	Seki H, Tateyama M, Sahara M, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization using the sealed-envelope method)*. *Shinryo to Shinyaku* (*Medical Consultation & New Remedies*) 1991; 28: 573-6 (in Japanese).	RCT-envelope	I
			Seki H, Okita N, Takase S, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization carried out using the sealed-envelope method)*. *Pharma Medica* 1993; 11: 288-91 (in Japanese).		I
R51	To evaluate the efficacy of goshuyuto (呉茱萸湯) for relief of chronic headache and to evaluate the associated adverse drug reactions.	goshuyuto (呉茱萸湯)	Odaguchi H, Hanawa Y. Complementary alternative medicine in headache treatment*. *Igaku no Ayumi* (*Journal of Clinical and Experimental Medicine*) 2005; 215: 1137-40 (in Japanese).	DB-RCT	N
			Odaguchi H, Wakasugi A, Ito H, et al. The efficacy of goshuyuto, a typical Kampo (Japanese herbal medicine) formula, in preventing episodes of headache. *Current Medical Research and Opinion* 2006; 22: 1587-97.		C
R53	To evaluate the efficacy of hochuekkito (補中益気湯) for the elderly with weakness.	hochuekkito (補中益気湯)	Satoh N, Sakai S, Kogure T, et al. A randomized double blind placebo-controlled clinical trial of hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness N of one and responder restricted design. *Phytomedicine* 2005; 12: 549-54.	DB-RCT	C
R53.0	To evaluate the effect of hochuekkito (補中益気湯) on lymphocytes.	hochuekkito (補中益気湯), hachimijiogan (八味地黄丸)	Ohno S, Suzuki T, Asaoka T, et al. Effects of Oriental medicine on lymphoid cells. *Kampo to Meneki-Allergy* (*Kampo and Immunoallergy*) 1995; 9: 78-86 (in Japanese with English abstract).	quasi-RCT	N
R60.0	Efficacy of goreisan (五苓散) and saireito (柴苓湯) for mild edema of the dorsum of the foot in the elderly.	saireito (柴苓湯)	Ishioka T. Comparison of the efficacy of goreisan and saireito for mild edema of the dorsum of the foot in elderly subjects stratified by physical strength*. *Kampo no Rinsho* (*Journal of Kampo Medicine*) 1997; 44: 1091-5 (in Japanese).	RCT-cross over	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
R60.9	To investigate the efficacy and safety of saireito (柴苓湯) on postoperative edema and inflammation after total hip arthroplasty (THA).	saireito (柴苓湯)	Kishida Y, Miki H, Nishii T, et al. Therapeutic effects of Saireito (TJ-114), a traditional Japanese herbal medicine, on postoperative edema and inflammation after total hip arthroplasty. *Phytomedicine* 2007; 14: 581-6.	RCT	C
R68.8	To evaluate the clinical effects of tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯) for peripheral coldness in women.	tokishigyakukagoshuyu-shokyoto (当帰四逆加呉茱萸生姜湯)	Nishida S, Eguchi E, Ohira T, et al. Effects of a traditional herbal medicine on peripheral blood flow in women experiencing peripheral coldness: a randomized controlled trial. *BMC Complementary Alternative Medicine* 2015; 15: 105.	RCT	C&N
R73.0	To evaluate the efficacy and safety of bofutsushosan (防風通聖散) in obese Japanese women with impaired glucose tolerance.	bofutsushosan (防風通聖散)	Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san, an oriental herbal medicine, in obese Japanese women with impaired glucose tolerance. *Clinical and Experimental Pharmacology and Physiology* 2004; 31: 614-9.	DB-RCT	C
			Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san in obese Japanese women with IGT. *Rinsho Kampo Yakuri Kenkyukai Kaishi* (*Journal of the Society for Clinical Kampo Pharmacology*), 2004; 100th Memorial Issue: 19-22.		I
			Hioki C. Efficacy of bofutsushosan in obese women with IGT*. *Pharma Medica* 2007; 25: 43-8.		I
			Hioki C, Arai M. Bofutsushosan use for obesity with IGT: search for scientific basis and development of effective therapy with Kampo medicine. *Journal of Traditional Medicines* 2007; 24: 115-27.		N

19. Injury, Poisoning, and Postoperative Pain (11 abstracts, 11 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
S22.3	Comparison of the efficacy of jidabokuippo (治打撲一方) and non-steroidal anti-inflammatory drugs for fracture of ribs	jidabokuippo (治打撲一方)	Nakae H, Yokoi A, Kodama H, et al. Comparison of the Effects on Rib Fracture between the Traditional Japanese Medicine Jidabokuippo and Nonsteroidal Anti-Inflammatory Drugs: A Randomized Controlled Trial. *Evidence Based-Complementary and Alternative Medicine* 2012: 1-7. doi: 10.1155/2012/837958.	RCT-envelope	N
S93.4	To evaluate the efficacy of a Western medicine and a Kampo medicine (jidabokuippo [治打撲一方]) for pain and swelling after a fresh and isolated anterior talofibular ligament (ATFL) grade III injury.	jidabokuippo (治打撲一方)	Takeda N. Conservative therapy for fresh lateral ligament injury of the ankle joint – Comparison of a Western medicine and a Kampo medicine for pain and swelling*. *Kampo to Rinsho* (*Journal of Kampo Medicine*) 2010; 1: 128–32 (in Japanese).	RCT	I
T67.8	To evaluate the efficacy of Kampo therapy in patients with heat illness requiring hospitalization.	hochuekkito (補中益気湯), rikkunshito (六君子湯), daikenchuto (大建中湯), yokukansan (抑肝散)	Nimura T, Yamada S, Ohwaki T, et al. Evaluation of the efficacy of Kampo therapy in patients with heat illness requiring hospitalization*. *Kampo Igaku (Kampo Medicine)* 2014: 38; 178-81 (in Japanese).	quasi-RCT	I&N
T67.8	To evaluate the effect of Kampo extract preparations as an adjunct to the standard therapy to shorten the symptom resolution time in patients with heat illness.	shakuyakukanzoto (芍薬甘草湯)	Takamura M, Effectiveness of Kampo extract preparations for the treatment of heat illness.* *Kampo to Saishinchiryo (Kampo & the Newest Therapy)* 2014; 23: 121-4 (in Japanese).	RCT	N
T88.5	Efficacy of goshuyuto (呉茱萸湯) and goreisan (五苓散) for post-spinal headache.	goshuyuto (呉茱萸湯), goreisan (五苓散)	Otake T, Kato I, Saito S, et al. The prophylactic effect of "gosyuyu-to" and "gorei-san" for post-spinal headache. *Pain Clinic* 1991; 12: 648-52 (in Japanese).	RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
T88.8	Effects on pain and hyperhidrosis after thoracotomy.	keishikajutsubuto (桂枝加朮附湯), keishikajutsubuto (桂枝加朮附湯) ＋ shakuyakukanzoto (芍薬甘草湯)	Isai H. Successful control of postoperative pain and hyperidrosis by Kampo medicine after thoracotomy for pulmonary disease. *Itami to Kampo* (*Pain and Kampo Medicine*) 1997; 7: 29-32 (in Japanese with English abstract).	RCT	N
T88.8	To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) for pain after hemorrhoidectomy	shakuyakukanzoto (芍薬甘草湯)	Miyazaki M, Yasui M, Ikenaga M, et al. The effect of Shakuyaku-kanzo-to (Tsumura TJ-68) on pain after hemorrhoidectomy – a prospective randomized study –. *Journal of the Japan Society of Coloproctology* 2012; 65: 313–7 (in Japanese with English abstract).	RCT	I
T88.8	To evaluate pre-and post-operative analgesic effects of shakuyakukanzoto (芍薬甘草湯) for treatment of pain after hemorrhoidectomy.	shakuyakukanzoto (芍薬甘草湯)	Fukuda Y, Azuma M, Novel pain reliever shakuyaku-kanzo-to after hemorrhoidectomy, *Journal of the Japan Society of Coloproctology*, 2014; 67: 324-9.	RCT	I&N
T88.8	To evaluate the efficacy and safety of hangeshashinto (半夏瀉心湯) on postoperative sore throat and nausea.	hangeshashinto (半夏瀉心湯)	Kuwamura A, Komasawa N, Kori K,et al. Preventive effect of preoperative administration of hange-shashin-to on postoperative sore throat: a prospective, double-blind, randomized trial. *Journal of Alternative Complementary Medicine* 2015; 21: 485-8.	DB-RCT	C&N
T88.8	To determine the efficacy and safety of preoperative administration of jidabokuippo (治打撲一方) in treating postoperative pain after tooth extraction with mandible bone removal under general anesthesia.	jidabokuippo (治打撲一方)	Komasawa N, Yamamoto K, Ito Y, et al.Preoperative administration of jidabokuippo, a Kampo medicine, alleviates postoperative pain after tooth extraction with mandible bone removal under general anesthesia : a prospective, single-blind, randomized controlled Trial. *Journal of Alternative and Complementary Medicine* 2018 ;24:1214-8.	RCT-envelope	C
T94.1	To evaluate the effectiveness and safety of saireito (柴苓湯) for keloid and hypertrophic scars following surgery, burn injury, and wound injury.	saireito (柴苓湯)	Watanabe Y, Asai S, Hida A, et al. Regarding the utility of saireito against keloid and hypertrophic scars following surgery and injury. *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2012; 67: 245–9 (in Japanese).	quasi-RCT	I

21. Others (44 abstracts, 51 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
Z01.0	To evaluate the ability of tokishakuyakusan (当帰芍薬散) to increase ocular blood flow.	tokishakuyakusan (当帰芍薬散)	Takayama S, Shiga Y, Kokubun T, et al. The traditional kampo medicine Tokishakuyakusan increases ocular blood flow in healthy subjects. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-8. doi: 10.1155/2014/586857	RCT-cross over	C&N
Z01.8	To evaluate the effect of bakumondoto (麦門冬湯) on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities.	bakumondoto (麦門冬湯)	Saruwatari J, Hisaeda S, Higa Y, et al. The in-vivo effect of Bakumondo-to (TJ-29), a traditional Japanese medicine used for treatment of chronic airway disease, on cytochrome P450 1A2, xanthine oxidase and N-acetyltransferase 2 activity in man. *Journal of Pharmacy and Pharmacology* 2004; 56: 1171-7.	RCT-cross over	C
Z01.8	To evaluate the effect of shoseiryuto (小青竜湯) on blood carbamazepine concentration.	shoseiryuto (小青竜湯)	Ohnishi N, Yonekawa Y, Fumihara T. et al. Studies on interactions between traditional herbal and Western medicines, II. Lack of pharmacokinetic interaction between shoseiryu-to and carbamazepine in healthy volunteers. *TDM Kenkyu (Japanese Journal of Therapeutic Drug Monitoring)* 1999; 16: 399-404.	RCT-cross over	I
			Yonekawa Y, Ohnishi N, Kitano N, et al. Drug interaction with Kampo medicines (2): kinetic characteristics of carbamazepine combined with shoseiryuto in healthy volunteers. *TDM Kenkyu* (*Japanese Journal of Therapeutic Drug Monitoring*) 1999; 16: 191-2.		N
Z01.8	To evaluate the effect of hachimijiogan (八味地黄丸) on human central retinal artery.	hachimijiogan (八味地黄丸)	Isobe H, Yamamoto K, Cyong JC. Effects of hachimi-jio-gan (ba-wei-di-huang-wan) on blood flow in the human central retinal artery. *The American Journal of Chinese Medicine* 2003; 31: 425-35.	RCT-cross over	C

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
Z01.8	To assess the efficacy and safety of hochuekkito (補中益気湯) on antibody production after influenza vaccination.	hochuekkito (補中益気湯)	Hamazaki K, Sawazaki S, Itomura M, et al. No effect of a traditional Chinese medicine, hochu-ekki-to, on antibody titer after influenza vaccination in man: a randomized, placebo-controlled, double-blind trial. *Phytomedicine* 2007; 14: 11-4.	DB-RCT	C
Z01.8	To evaluate the effect of maobushisaishinto (麻黄附子細辛湯) on antibody titer after influenza vaccination.	maobushisaishinto (麻黄附子細辛湯)	Terashima Y, Hamazaki K, Itomura M, et al. Effect of a traditional Chinese medicine, maobushisaishinto, on the antibody titer after influenza vaccination: A randomized, placebo-controlled, double-blind trial. *Journal of Traditional Medicines* 2007; 24: 59-66.	DB-RCT	I
Z01.8	To elucidate the mechanism of bushirichuto (附子理中湯) activity in raising gut-regulated peptide levels.	bushirichuto (附子理中湯)	Sato Y, Katagiri F, Itoh H, et al. Bushi-richu-to raises calcitonin gene-related peptide, substance P, somatostatin, and vasoactive intestinal polypeptides levels in human plasma. *Journal of Health Science* 2007; 53: 615-21.	RCT-cross over	I
Z01.8	To evaluate effects of rokumigan (六味丸) on serum amino acid concentrations.	rokumigan (六味丸)	Takahashi H, Nakao R, Hirasaka K, et al. Effects of single administration of Rokumi-gan (TJ-87) on serum amino acid concentration of 6 healthy Japanese male volunteers. *Journal of Medical Investigation* 2007; 54: 91-8.	RCT-cross over	I
Z01.8	Interaction with the pharmacokinetics of acetaminophen.	kakkonto (葛根湯)	Qi J, Toyoshima A, Honda Y, et al. Pharmacokinetic study on acetaminophen: interaction with a Chinese medicine.*Journal of Medical and Dental Sciences* 1997; 44: 31-5.	RCT-cross over	C
Z01.8	Effects of kakkonto (葛根湯) on the pharmacokinetics of phenacetin.	kakkonto (葛根湯)	Shimakura K, Mineshita S, Sanaka M, et al. Effects of kakkonto on the pharmacokinetics of phenacetin in human serum and saliva*. *Rinsho Yakuri* (*Japanese Joournal of Clinical Phamacology and Therapeutics*) 1994; 25: 229-30 (in Japanese).	RCT-cross over	N
Z01.8	Effects of saibokuto (柴朴湯) and saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) on central nervous systems in humans.	saibokuto (柴朴湯), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)	Fukushima M. Profiles of effects of traditional oriental herbal medicines on central nervous system in humans - assessment of Saiboku-to and Saiko-ka-ryukotsu-borei-to using EEG and pharmacokinetics of herbal medicine-derived ingredients as indices -. *Seishin Shinkeigaku Zasshi* (*Psychiatria et Neurologia Japonica*) 1997; 99: 355-69 (in Japanese with English abstract).	RCT	N
Z01.8	Effects on bioavailability of ofloxacin (OFLX) in healthy volunteers.	Shosaikoto (小柴胡湯), rikkunshito (六君子湯), saireito (柴苓湯)	Hasegawa T, Yamaki K, Nadai M, et al. Lack of effect of Chinese medicines on bioavailability of ofloxacin in healthy volunteers. *International Journal of Clinical Pharmacology and Therapeutics* 1994; 31: 57-61.	RCT-cross over	C
Z01.8	To evaluate the effects of shosaikoto (小柴胡湯), saibokuto (柴朴湯), and saireito (柴苓湯) on prednisolone metabolism.	shosaikoto (小柴胡湯), saibokuto (柴朴湯), saireito (柴苓湯)	Niitsuma T, Fukuda T, Yamamoto S, et al. Effects of saibokuto and other *saiko-zai* (saiko-drugs) on prednisolone metabolism*. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1993; 7: 43-52 (in Japanese).	RCT-cross over	N
			Homma M, Oka K, Ikeshima K, et al. Different effects of traditional Chinese medicines containing similar herbal constituents on prednisolone pharmacokinetics. *Journal of Pharmacy and Pharmacology* 1995; 47: 687-92.		C
Z01.8	Effect of coadministered Kampo medicine on the pharmacokinetics of levofloxacin (Cravit).	hochuekkito (補中益気湯), rikkunshito (六君子湯), juzentaihoto (十全大補湯)	Hasegawa T, Yamaki K, Muraoka I, et al. Effects of traditional Chinese medicines on pharmacokinetics of levofloxacin. *Antimicrobial Agents and Chemotherapy* 1995; 39: 2135-37.	RCT-cross over	C
Z01.8	To evaluate the effects of co-administered byakkokaninjinto (白虎加人参湯) on pharmacokinetics and renal excretion of antibiotics (tetracycline or ciprofloxacin).	byakkokaninjinto (白虎加人参湯)	Ohnishi M, Hitoshi K, Katoh M, et al. Effect of a Kampo preparation, byakkokaninjinto, on pharmacokinetics of ciprofloxacin and tetracycline. *Biological & Pharmaceutical Bulletin* 2009; 32: 1080-4.	RCT-cross over	C&I
Z01.8	To evaluate the antioxidative effect of bofutsushosan (防風通聖散) in healthy adults using the lag time of low-density lipoprotein (LDL) oxidation as the main yardstick.	bofutsushosan (防風通聖散)	Ogawa H, Xu F, Uebaba K, et al. Antioxidative potentiality of a Kampo formulation measured by an ex vivo study. *The Journal of Alternative and Complementary Medicine* 2009; 15: 267-74.	DB-RCT	N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
Z01.8	To compare the effects of kamishoyosan (加味逍遙散) and paroxetine in improving anxiety and depression as menopausal symptoms.	kamishoyosan (加味逍遙散)	Yasui T, Yamada M, Uemura H, et al. Changes in circulating cytokine levels in midlife women with psychological symptoms with selective serotonin reuptake inhibitor and Japanese traditional medicine. *Maturitas* 2009; 62: 146-52.	RCT	N
Z01.8	To evaluate the pharmacokinetic profiles of serum ephedrine and pseudoephedrine after oral administration of kakkonto (葛根湯), and changes in biokinetics after different administered doses.	kakkonto (葛根湯)	Inotsume N, Fukushima S, Hayakawa T, et al. Pharmacokinetics of ephedrine and pseudoephedrine after oral administration of kakkonto to healthy male volunteers. *Rinsho Yakuri* (*Japanese Journal of Clinical Pharmacology and Therapeutics*) 2009; 40: 79-83.	RCT-cross over	I
Z01.8	To analyze the blood kinetics of indicator components in daikenchuto (大建中湯).	daikenchuto (大建中湯)	Munekage M, Kitagawa H, Ichikawa K, et al. Pharmacokinetics of daikenchuto, a traditional Japanese medicine (Kampo) after single oral administration to healthy Japanese volunteers. *Drug Metabolism and Disposition* 2011; 39: 1784-8.	RCT	N
Z01.8	To analyze the blood kinetics of indicator ingredients in daikenchuto (大建中湯).	daikenchuto (大建中湯)	Munekage M, Ichikawa K, Kitagawa H, et al. Population pharmacokinetic analysis of daikenchuto , a traditional Japanese medicine (Kampo) in Japanese and US health volunteers. *Drug Metabolism and Disposition* 2013; 41: 1256-63.	RCT-cross over	N
Z01.8	To evaluate the effect of daikenchuto (大建中湯) and abdominal thermotherapy on blood flow through the superior mesenteric artery.	daikenchuto (大建中湯)	Takayama S, Okitsu R, Iwasaki K, et al. The effect of warming the abdomen with herbal medicine or thermal therapy on superior mesenteric artery blood flow. *Kampo to Saishin Chiryo* (*Kampo & the Newest Therapy*) 2011; 20: 253-8 (in Japanese with English abstract).	RCT	I
Z01.8	Pharmacokinetics of the blood concentration of active ingredients of yokukansan (抑肝散) in healthy subjects.	yokukansan (抑肝散)	Kitagawa H, Munekage M, Ichikawa K. et al. Pharmacokinetics of active components of yokukansan, a traditional Japanese herbal medicine after a single oral administration to healthy Japanese volunteers: a cross-over, randomized study. *PloS One* 2015 7; 1-14.	RCT-cross over	C&N
Z01.8	To analyze the pharmacokinetics of the active ingredients of rikkunshito (六君子湯) in healthy volunteers.	rikkunshito (六君子湯)	Kitagawa H, Munekage M, Matsumoto T, et al. Pharmacokinetic profiles of active ingredients and its metabolites derived from rikkunshito, a ghrelin enhancer, in healthy Japanese volunteers: a cross-over, randomized study. *PloS One* 2015 10; 1-19.	RCT-cross over	C&N
Z01.8	Comparative analysis of the plasma concentrations of components of shakuyakukanzoto (芍薬甘草湯) after administration of different doses.	shakuyakukanzoto (芍薬甘草湯)	Sadakane C, Watanabe J, Fukutake M, et al. Pharmacokinetic profiles of active components after oral administration of a Kampo medicine, shakuyakukanzoto, to healthy adult Japanese volunteers. *Journal of Pharmaceutical Sciences* 2015; 104(11): 3952-9.	RCT-cross over	C&N
Z01.8	To evaluate the interaction of daijyokito (大承気湯) on the pharmacokinetics of ranitidine.	daijyokito (大承気湯)	Endo Y, Ishihara Y, Tsuno S , et al. Pharmacokinetic interaction study of ranitidine and daijokito in healthy volunteers. *Yonago Acta Medica* 2016; 59: 111-7.	RCT-cross over	C
Z03.8	Efficacy of shakuyakukanzoto (芍薬甘草湯) for relieving pain during colonoscopy.	shakuyakukanzoto (芍薬甘草湯)	Arai M, Sato H, Shirota F. An investigation into the relief of colonscopy pain provided by shakuyaku-kanzo-to. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1994; 44: 385-90 (in Japanese with English abstract).	RCT	N
Z03.8	Efficacy of shakuyakukanzoto (芍薬甘草湯) for relieving pain and complaints during preparation for barium enema.	shakuyakukanzoto (芍薬甘草湯)	Imazato S, Kai S, Koizumi K, et al. A clinical study of shakuyaku-kanzo-to (Kampo) as a preparation for double contrast barium enema. *Therapeutic Research* 1997; 18: 5505-10 (in Japanese with English abstract).	RCT	N
			Imazato S, Kai S, Koizumi K, et al. A Clinical Study of shakuyaku-kanzo-to (Kampo) as a Preparation for Double Contrast Barium Enema. *Science of Kampo Medicine* 1998; 22: 87–92 (in Japanese).		N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
Z03.8	Efficacy of a new colon preparation using daiokanzoto (大黄甘草湯).	daiokanzoto (大黄甘草湯)	Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). *Therapeutic Research* 1989; 10: 1637-43 (in Japanese with English abstract). Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). *Current Therapy* 1989; 7: 749-54 (in Japanese). Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). *Current Therapy* 1990; 8: 805-10 (in Japanese).	RCT	N
Z03.8	To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) combined with polyethylene glycol solution (PEG) in pretreatment for large bowel endoscopy.	shakuyakukanzoto (芍薬甘草湯)	Saida Y, Takase M, Okumura C, et al. Efficacy of combined use of shakuyakukanzoto in pretreatment for large bowel endoscopy – prospective randomized trial*. *Nihon Daicho Kensa Gakkai Zasshi* (*Journal of the Japan Society of Colon Examination*) 2003; 20: 34-7 (in Japanese).	RCT-envelope	I
Z03.8	To evaluate the efficacy of directly sprayed shakuyakukanzoto (芍薬甘草湯) on large bowel spasm.	shakuyakukanzoto (芍薬甘草湯)	Ai M. Assessment of the antipasmodic effect of peppermint oil and shakuyaku-kanzon-to (TJ-68); a Chinese herbal medicine on the clonic wall. *Medical Tribune Online* (*Digestive Disease Week: DDW*) 2005: 10-1 (in Japanese).	RCT	N
Z03.8	To evaluate the efficacy of pretreatment with shakuyakukanzoto (芍薬甘草湯) for upper gastrointestinal tract endoscopy.	shakuyakukanzoto (芍薬甘草湯)	Sugihara N. Effectiveness of shakuyaku-kanzo-to as a pretreatment for upper digestive tract endoscopic examination*. *Kampo Shinryo* 1999; 18: 17-9 (in Japanese).	quasi-RCT	N
Z03.8	To evaluate the efficacy of daikenchuto (大建中湯) combined with polyethylene glycol solution (PG solution) in pretreatment for large bowel endoscopy.	daikenchuto (大建中湯)	Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, a herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Digestive Endoscopy* 2005; 17: 50-3.	RCT-envelope	C&I
Z03.8	To evaluate the efficacy and safety of direct spraying of shakuyakukanzoto (芍薬甘草湯) on the colonic mucosa for suppression of bowel movement during colonoscopy.	shakuyakukanzoto (芍薬甘草湯)	Ai M, Yamaguchi T, Odaka T, et al. Objective assessment of the antispasmodic effect of Shakuyaku-kanzo-to (TJ-68), a Chinese herbal medicine, on the colonic wall by direct spraying during colonoscopy. *World Journal of Gastroenterology* 2006; 12: 760-4.	RCT	C
Z03.8	To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) solution in preparation for colonoscopy used with the water method of distension.	shakuyakukanzoto (芍薬甘草湯)	Mizukami T, Maruyama K, Yamauchi H, et al. Assessment of antispasmodic effect of herbal medicine, shyakuyakukanzoto (TJ-68) on colonoscopy – Using colonoscopy insertion technique "collapsing method" –. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2006; 15: 69-76 (in Japanese).	quasi-RCT	I
Z03.8	To evaluate the bowel cleansing effect of precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage solution (PG solution) combined with daikenchuto (大建中湯) and mosapride.	daikenchuto (大建中湯)	Saida Y, Nagao J, Nakamura Y, et al. Dai-kenchu-to and mosapride in combination with precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Nihon Daicho Kensa Gakkai Zasshi* (*Journal of the Japan Society of Colon Examination*) 2005; 22: 145-8 (in Japanese).	RCT	I
Z03.8	To evaluate the effectiveness of daikenchuto (大建中湯) in bowel preparation for barium enema X-ray study.	daikenchuto (大建中湯)	Arai J, Nakajima S, Fujinuma S, et al. A Comparative study of bowel preparation for barium enema using divided administrations of powdered magnesium citrate with mosapride or DAIKEN CHUTOU. *Nihon Daicho Kensa Gakkai Zasshi* (*Journal of the Japan Society of Colon Examination*) 2002; 19: 170-3 (in Japanese).	RCT	I

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
Z03.8	To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) as premedication for ERCP in suppressing duodenal peristalsis.	shakuyakukanzoto (芍薬甘草湯)	Fujinami H. Assessment of diminished persistalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): randomized placebo-controlled trial. *Nikkei Medical* (*Supplement*) 2010; 8: 34 (in Japanese).	RCT	N
			Fujinami H, Kudo T, Nakayama Y, et al. Assessment of diminished peristalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): a randomized, placebo-controlled trial. *Gastrointestinal Endoscopy* 2010; 71: AB227.		N
Z03.8	To evaluate the efficacy of intraduodenal administration of shakuyakukanzoto (芍薬甘草湯) on duodenal peristalsis during endoscopic retrograde cholangiopancreatography (ERCP).	shakuyakukanzoto (芍薬甘草湯)	Fujinami H, Kajiura S, Nishikawa J, et al. The influence of duodenally-delivered Shakuyakukanzoto (Shao Yao Gan Cao Tang) on duodenal peristalsis during endoscopic retrograde cholangiopancreatography: a randomised controlled trial. *Chinese Medicine* 2017; 12: 3 : 1-6. doi: 10.1186/s13020-016-0125-6	RCT	N
Z04.8	To assess whether differences in ethical Kampo extract formulation dosage and dosing frequency have an effect on compliance and patient satisfaction.	Not described	Kita T, Sumino M. The effect of dosage frequency of ethical Kampo extract formulations on drug compliance – a comparison of twice a day and three times a day prescriptions. *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2011; 66: 117–22 (in Japanese).	RCT-cross over	I
Z04.8	To select the Pharmacopeia indicator components for evaluation of the equivalence of kakkonto (葛根湯) extract formulation and decoction.	kakkonto (葛根湯)	Horii C, Okonogi A, Okubo T, et al. Studies on bioequivalence of kakkonto decoction and its extract preparation (I)*. *Shoyakugaku zasshi* 2014; 68: 9-12.	RCT-cross over	N
			Horii C, Okonogi A, Okubo T, et al. Study of the equivalence of kakkonto (葛根湯) extract formulation and decoction (II). *Natural Medicines* 2015; 69: 59-65.	RCT-cross over	I&N
Z04.8	To evaluate the bioequivalence of shoseiryuto (小青竜湯) extract and its decoction.	shoseiryuto (小青竜湯)	Horii C, Okonogi A, Studies on bioequivalence of shoseiryuto decoction and its extract preparation (I), *Shoyakugaku zasshi (Journal of Natural Medicines)* 2014; 68: 65-9.	RCT-cross over	I&N
Z22.8	To evaluate the effects of hochuekkito (補中益気湯) on prevention of MRSA carriage, prevention of Pseudomonas aeruginosa carriage, prevention of infection development, neutrophil count, and C-reactive protein (CRP) value.	hochuekkito (補中益気湯)	Ueda T, Yamashita K, Nakamori Y, et al. Study of the MRSA carriage-preventing effect of hochuekkito (TJ-41): 1st report*. *Progress in Medicine* 1999; 19: 1000-3 (in Japanese).	RCT	N
Z31.1	Effect of ovarian stimulation by tokishakuyakusan (当帰芍薬散) (used during in vitro fertilization and embryo transfer (IVF-ET) cycles) on follicular growth, luteal function, pregnancy rate, and abortion rate.	tokishakuyakusan (当帰芍薬散)	Fujii S, Fukushi Y, Yamaguchi E, et al. A study of the addition of tokishakuyakusan during in-vitro fertilization cycles*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 1997; 14: 121-5 (in Japanese).	RCT	N
K76.9 Z94.4	To evaluate the efficacy and safety of daikenchuto (大建中湯) on the reinforcing effect of oral/tubal caloric intake in patients undergoing liver transplantation.	daikenchuto (大建中湯)	Kaido T, Shinoda M, Inomata Y,et al. Effect of herbal medicine daikenchuto on oral and enteral caloric intake after liver transplantation: a multicenter, randomized controlled trial. *Nutrition* 2018; 54: 68-75.	DB-RCT	N

<<Structured Abstracts describing Meta-analysis and the Reference Reporting Them>>

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs) (5 abstracts, 5 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C26.9 K91.9	To assess the efficacy of daikenchuto (大建中湯) in improving intestinal dysfunction after abdominal surgery.	daikenchuto (大建中湯)	Zhang L, Cheng Y, Li H, et al. Meta-analysis of randomized controlled trials on the efficacy of daikenchuto on improving intestinal dysfunction after abdominal surgery. *Annual of Surgical and Treatment Reseach* 2018; 95: 7–15.	meta-analysis	N
C26.9 K91.3	To analyze whether daikenchuto (大建中湯) accelerates the recovery from prolonged postoperative ileus after open abdominal surgery.	daikenchuto (大建中湯)	Kono T, Shimada M, Nishi M, et al. Daikenchuto accelerates the recovery from prolonged postoperative ileus after open abdominal surgery: a subgroup analysis of three randomized controlled trials. *Surgery Today* 2019: 1-8.	meta-analysis	N
C78.8 K91.3	A meta-analysis of to evaluate the efficacy of perioperative daikenchuto (DKT)(大建中湯) treatment for postoperative bowel obstruction (postoperative ileus) in gastrointestinal cancer.	daikenchuto (大建中湯)	Ishizuka M, Shibuya N, Nagata H, et al. Perioperative administration of traditional Japanese medicine daikenchuto relieves postoperative ileus in patients undergoing surgery for gastrointestinal cancer: a systemic review and meta-analysis. *Anticancer Research* 2017; 37: 5967-74.	meta-analysis	N
C80.0	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in peripheral neuropathy during chemotherapy.	goshajinkigan (牛車腎気丸)	Hoshino N, Ganeko R, Hida K, et al. Goshajinkigan for reducing chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *International Journal of Clinical Oncology* 2018; 23: 434–42.	meta-analysis	N
C97.0 G62.0	To examine whether goshajinkigan (牛車腎気丸) prevents chemotherapy-induced peripheral neuropathy (CIPN) in patients receiving neurotoxic chemotherapy.	goshajinkigan (牛車腎気丸)	Kuriyama A, Endo K. Goshajinkigan for reducing chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Supportive Care in Cancer* 2018 ;26: 1051-9.	meta-analysis	N

5. Psychiatric/Behavioral Disorders (3 abstracts, 3 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
F03	A systematic review of yokukansan (抑肝散) for behavioral psychological symptoms of dementia (BPSD).	yokukansan (抑肝散)	Matsunaga S, Kishi T, Iwata N. Yokukansan in the treatment of behavioral and psychological symptoms of dementia: an updated meta-analysis of randomized controlled trials. *Journal of Alzheimer's Disease* 2016; 54: 635-43.	meta-analysis	N
F03	To assess the effectiveness and acceptability of choto-san (釣藤散) in the treatment of adults with cognitive impairment.	chotosan (釣藤散)	Imai H, Takeshima N, Oda H,et al. Choto-san versus placebo for patients with dementia: systematic review and meta-analysis. *Psychogeriatrics* 2017; 17: 466-78.	meta-analysis	I
F03	To determine the most efficacious and acceptable treatments of agitation (including yokukansan (抑肝散) in dementia.	yokukansan (抑肝散)	Kongpakwattana K, Sawangjit R, Tawankanjanachot ,et al. Pharmacological treatments for alleviating agitation in dementia : a systematic review and network meta-analysis. *British Journal of Clinical Pharmacology* 2018; 84: 1445-56.	meta-analysis	N

6. Nervous System Diseases (including Alzheimer's Disease) (2 abstract, 2 reference)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
G30.1	To perform a systematic review of the efficacy and tolerability of yokukansan (抑肝散) in the treatment of behavioral and psychological symptoms of dementia (BPSD).	yokukansan (抑肝散)	Matsuda Y, Kishi T, Shibayama H, et al. Yokukansan in the treatment of behavioral and psychological symptoms of dementia ： a systematic review and meta － analysis of randomized controlled trials. *Human Psychopharmacology* 2013; 28: 80-6.	meta-analysis	N
C97.0 G62.0	To examine whether goshajinkigan (牛車腎気丸) prevents chemotherapy-induced peripheral neuropathy (CIPN) in patients receiving neurotoxic chemotherapy.	goshajinkigan (牛車腎気丸)	Kuriyama A, Endo K. Goshajinkigan for reducing chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Supportive Care in Cancer* 2018 ;26: 1051-9.	meta-analysis	N

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases (3 abstracts, 3 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
C78.8 K91.3	A meta-analysis of to evaluate the efficacy of perioperative daikenchuto (DKT)(大建中湯) treatment for postoperative bowel obstruction (postoperative ileus) in gastrointestinal cancer.	daikenchuto (大建中湯)	Ishizuka M, Shibuya N, Nagata H, et al. Perioperative administration of traditional Japanese medicine daikenchuto relieves postoperative ileus in patients undergoing surgery for gastrointestinal cancer: a systemic review and meta-analysis. *Anticancer Research* 2017; 37: 5967-74.	meta-analysis	N
C26.9 K91.3	To analyze whether daikenchuto (大建中湯) accelerates the recovery from prolonged postoperative ileus after open abdominal surgery.	daikenchuto (大建中湯)	Kono T, Shimada M, Nishi M, et al. Daikenchuto accelerates the recovery from prolonged postoperative ileus after open abdominal surgery: a subgroup analysis of three randomized controlled trials. *Surgery Today* 2019: 1-8.	meta-analysis	N
C26.9 K91.9	To assess the efficacy of daikenchuto (大建中湯) in improving intestinal dysfunction after abdominal surgery.	daikenchuto (大建中湯)	Zhang L, Cheng Y, Li H, et al. Meta-analysis of randomized controlled trials on the efficacy of daikenchuto on improving intestinal dysfunction after abdominal surgery. *Annual of Surgical and Treatment Reseach* 2018; 95: 7–15.	meta-analysis	N

15. Ante/Post-partum Diseases (1 abstract, 1 reference)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source
O90.8	To evaluate the efficacy of kyukichoketsuin (キュウ帰調血飲) in puerperal care in comparison with methylergometrine maleate by conducting a meta-analysis.	kyukichoketsuin (キュウ帰調血飲)	Koinuma M, Narikawa H, Kamei M, et al. Meta-analysis on the usefulness in postpartum control by kyukichoketsuin with methylergometrine maleate as control. *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) 2006; 57: 45-55 (in English with Japanese abstract).	meta-analysis	I

2. Background

In an effort to disseminate evidence-based medicine (EBM) in oriental medicine, the Japan Society for Oriental Medicine (JSOM) established the Special Committee for Evidence Based medicine (EBM) in June 2001. In the Committee, led by Chairman Tetsuo Akiba, experts worked to organize clinical evidence of Kampo treatment. The achievements were the "EBM in Kampo 2002, Interim Report" (*Nihon Toyo Igaku Zasshi* [*Japanese Journal of Oriental Medicine*] 2002: 53(5), supplementary issue) issued in 2002, and "Evidence Reports of Kampo Treatment" (*Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2005: 56, EMB supplementary issue) in 2005 (in Japanese).

These reports covered the studies of Kampo formulations for prescription satisfying the new standards for Kampo formulations implemented in 1986, using the same prescription from the start through the end of the observation period in at least 10 subjects, and published between 1986 and 2002, including not only controlled trials but also case series (including records of academic or study meetings). References that satisfied the above criteria were selected from among the original database gathered and enumerated by the Japan Kampo Medicines Manufacturers Association (JKMA) and offered by the JKMA. In the final report, "Evidence Reports of Kampo Treatment," 93 of 905 references offered by the JKMA were selected by the EBM Special Committee and compiled as structured abstracts consisting of five items, as follows: "participants," "design (methods, period, and others)," "main results," "from Kampo medicine perspective," and "safety assessment in the article." In addition, reference appraisal and recommendation ratings were made.

Preparation of this report was an epoch-making activity at that time, in terms of its basic procedures. However, some defects were pointed out; for example, whether a certain reference was not included because it was not found or because it was excluded in the selection process could not be distinguished

Okabe T. How much has the Kampo evidence been established to date? – the current state and future challenges based on the Evidence Reports. *Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] –2007; 58(3): 435-41 [in Japanese].

Building on the achievements of its predecessors, the second phase of the JSOM EBM Special Committee project starting in 2005 under its second chairperson, Kiichiro Tsutani, adopted the systematic review approach, focusing on exhaustibility and transparency, to prepare structured abstracts limited to randomized controlled trials (RCTs) published in or after 1986 in accordance with worldwide standards.

Furthermore, in consideration of how the results could best be utilized, the results were to be published on the Japan Society for Oriental Medicine (JSOM) web site to improve

accessibility, for the following reasons:

In a flood of medical information, it is not easy to make a right decision on which information would profit the patient. Dissemination of evidence-based medicine usually involves four steps, as follows: step 1, identification of issues; step 2, information gathering; step 3, information review; and step 4, administration to patients. For busy clinicians, however, it is difficult to search various databases for available references, review all these references, and decide which reliable and appropriate medicines are. Especially for physicians not specialized in Kampo, it is even more difficult to judge which Kampo medicine should be used based on a search of general databases such as Medline.

In this context, it is desirable to develop a system that entrusts implementation of step 2 and step 3 procedures to a third party in advance so that information may be gathered and reviewed exhaustively and offered in an easy, accessible manner. Therefore, the second phase activity more clearly employed pre-appraisal and IT technology.

The outcomes of the activities after the second phase were sequentially published on the Society's website (http://www.jsom.or.jp/medical/ebm/er/index.html) according to version, as shown on page ii. The summary of the activities during the first 4-year period was reported in the Japan Society for Oriental Medicine 60th Annual Meeting (Tokyo) Forum "Transfer Kampo evidence," along with the activities of the Task Force for Clinical Practice Guidelines (CPG-TF) and the Task Force for Best Cases (BC-TF) (Abstracts of the Speeches in the Japan Society for Oriental Medicine 60th Annual Meeting, *Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2009; 60 suppl.: 157-72) (in Japanese).

The slides used by all ten speakers in the Forum were all published in book form along with the above abstracts of the speeches, and on the Society's website: http://www.jsom.or.jp/medical/ebm/doc/Forum2009.html

The activities were continued in the third and fourth phases by the Committee for EBM (changed from Special Committee for EBM in June 2012), chaired by Kiichiro TSUTANI, starting from April 2009, and then in the fifth phase by the Committee, chaired by Yoshiharu MOTOO, starting from September 2015, and in the sixth phase by Toshiaki KOGURE, starting from June 2019. Since the activities and outcomes of the second phase of the Task Force for Evidence Reports (ER-TF) project were naturally strongly associated with those of the Task Force for Clinical Practice Guidelines (CPG-TF) project, they were combined into the Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF) for 5 years beginning in 2009. From June 2014, however, because of differences in the activities between evidence reports and guidelines task forces, the Task Force for Evidence Reports (ER-TF) resumed updating the Evidence Reports and preparing their English versions. The members of the committees etc. are listed by phase in "9. Japan Society for Oriental Medicine EBM Committee members (participants)", beginning on page 101.

3. Purpose

The purpose was to exhaustively gather and review reports of randomized controlled trials of Kampo formulations, compile structured abstracts of them, and publish them on the website or in book form along with comments of third parties.

4. Steps for development of structured abstracts

(1) Criteria for reference selection

References that satisfied all of the following 3 criteria were included:

1) References using Kampo formulations approved for manufacture and sale in Japan
   (excluding in-house formulations such as decoctions, because of unknown quality of the medicines used)
2) Randomized controlled trials (RCTs), quasi-randomized controlled trials (quasi-RCTs), crossover trials, and meta-analyses
   (including some with randomization procedure not fully indicated. Crossover trials are regarded as RCT)
3) References published in or after 1986
   Those published in or after 1986 obviously using formulations of 1985 or previous quality, which differs from the current quality levels, were excluded throughout the study period.

(2) Search and screening

Searches were performed using the two databases listed below, with additional reports collected by hand searches. Screening was performed in 2 steps: first, the references that obviously did not satisfy the criteria were excluded by the search staff; then, the remaining references were reviewed to finally select the ones to undergo the process of structured abstract preparation as described below.

1) The Cochrane CENTRAL (C)

   The Cochrane Central Register of Controlled Trials (CENTRAL), which is the world's largest database of RCTs, was used to search for RCTs of Kampo medicines. Cochrane was formerly known as the Cochrane Collaboration, founded in 1992, and the name was changed as of 30 January 2015.

   https://www.cochrane.org/news/announcing-cochranes-new-brand-identity

   CENTRAL is a database dedicated to RCTs, identified from searches of the PubMed and Embase databases, and from hand searches of journals.

https://www.cochranelibrary.com/central

For this reason, no direct search of PubMed has been conducted in this project since its beginning.

On 1 April 2019, searches were performed by using the following search formula and limited to articles published in and after 1986:

#1 MeSH descriptor Medicine, East Asian Traditional explode all trees
#2 MeSH descriptor Medicine, Kampo explode all trees
#3 MeSH descriptor Medicine, Chinese Traditional explode all trees
#4 MeSH descriptor Drugs, Chinese Herbal explode all trees
#5 MeSH descriptor Herb-Drug Interactions explode all trees
#6 MeSH descriptor Herbal Medicine explode all trees
#7 MeSH descriptor Plants, Medicinal explode all trees
#8 MeSH descriptor Plant Structures explode all trees
#9 MeSH descriptor Plant Extracts explode all trees
#10 MeSH descriptor Materia Medica explode all trees
#11 MeSH descriptor Phytotherapy explode all trees
#12 (Kampo):ti,ab,kw
#13 (Kanpo):ti,ab,kw
#14 (Japanese):ti,ab,kw
#15 (Oriental):ti,ab,kw
#16 (Traditional):ti,ab,kw
#17 (East Asia):ti,ab,kw
#18 (East-Asia):ti,ab,kw
#19 (Herb*):ti,ab,kw
#20 (Chinese):ti,ab,kw
#21 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20), from 1986 to 2018
#22 (HS-EKAT)
#23 (#21 AND NOT #22)

In October 2011, of the RCT papers on Kampo formulations appearing EKAT 2010 under the “Reference(s)” of structured abstracts, those that had not been previously listed in CENTRAL were so listed and after HS-EKAT tagging, were linked to the EKAT SAs on the JSOM website. The present search excludes 352 papers with “HS-EKAT” in the search formula, so as to exclude those papers related SAs.

Out of 59,229 search hits, 176 Kampo references were visually confirmed. Among the Kampo references identified by searching the CENTRAL database, 20 references were also found in the Ichushi Web database.

Kampo-related reports accounted for approx. 0.3% of the total hits.

Finally, of the 176 references, 113 satisfying the inclusion criteria were compiled as structured abstracts; the remaining 63 were cited as excluded references along with bibliographic items and the reason for exclusion.

2) Ichushi Web (I)

Ichushi Web, the Japan Medical Abstracts Society's database available on the Internet, was used to search for RCTs of Kampo medicines on 1 April 2019, using the following search formula:

Search formula:

(漢方薬 [Kampo medicine]/TH or 漢方 [Kampo]/AL) and (メタアナリシス [meta-analysis]/RD or ランダム化比較試験 [randomized controlled trial]/RD or 準ランダム化比較試験 [quasi-randomized controlled trial]/RD) and (DT=1986: 2018)

Since the Ichushi Web tags meta-analyses, randomized controlled trials, and quasi-randomized controlled trials, the present search targeted references that were tagged (メタアナリシス [meta-analysis]/RD or ランダム化比較試験 [randomized controlled trial]/RD or 準ランダム化比較試験 [quasi-randomized controlled trial]/RD), had "漢方薬 [Kampo medicine]" as a keyword (control term) (漢方薬 [Kampo medicine]/TH), or a title or abstract including the term "Kampo [漢方]" (漢方 [Kampo]/AL), and were published between 1986 and 2018 (DT=1986:2018).

As a result, 345 references were identified (20 of them were also CENTRAL hits). Of these references, 206 satisfying the inclusion criteria were selected and compiled as structured abstracts (204 RCTs and two meta-analysis). Of the references compiled as structured abstracts, one included two RCTs, for which separate structured abstracts were prepared.

The Ichushi Web assigns the keyword "漢方 [Kampo]" to traditional Chinese medicines and food and Indian medicines as well. These references, in addition to references to randomized studies not evaluating Kampo medicine, non-clinical articles, and citations of existing references, totaled 94 and were not compiled as structured abstracts. They were listed as excluded references along with bibliographic items and the reason for exclusion.

3) Hand searches conducted at the Japan Kampo Medicines Manufacturers Association (N)

Hand searches were conducted at the Japan Kampo Medicines Manufacturers Association (JKMA) on 1 April 2019 to identify articles published in or after 1986 about Kampo or crude drugs collected by member companies of JKMA. The following key terms were used in the search strategy.

Keywords: the search terms are given in their original form (words in parentheses indicate search terms or hits in Roman characters, and the corresponding meanings in English):

メタアナリシス (meta-anarisisu, meta-analysis); メタ解析（meta-kaiseki, meta-analysis); メタ分析 (meta-bunseki, meta-analysis); RCT; ランダム (randamu, random); 無作為, 無作意(musakui, random); 封筒(futo, envelope); 来院順 (raiinjun, order of presentation); 受診順 (jushinjun, order of presentation); 診断順 (shindanjun, order of diagnosis); 割付, 割り付け, 割つけ, わりつけ (;waritsuke, allocation); ブラインド (buraindo, blind); 盲検, 盲験(mouken, blind), 遮蔽, 遮へい, しゃへい (shahei, mask), マスク (masuku, mask); マスキング (masukingu, masking); クロスオーバー (kurosuoba, crossover), 交叉, 交差 (kosa, crossover), 比較臨床 (hikaku rinsho, controlled clinical); random; cross over; meta analysis; envelope

SAs were prepared for 314 hand-searched articles that did not duplicate articles obtained in CENTRAL or Ichushi Web searches. Among the source articles of SAs, three articles respectively contained two RCTs, and thus separate SAs were prepared for each RCT. No SAs were prepared for 62 hand-searched articles that failed to meet the inclusion criteria. For these excluded articles, the bibliographic information and the reasons for exclusion are provided in the list of excluded references.

Overall, from the two databases and hand searches, 832 articles were identified, as shown in **Table 1**. SAs were prepared for 616 of these articles, and the remaining 216 appear in the excluded references list along with bibliographic information.

Table 1 Number of references compiled as structured abstracts / excluded by database

Database	No. of hits	Visual refinement	Preparation of structured abstract	Exclusion
The Cochrane CENTRAL (C)	59,229 [1)]	176 [5)]	113 [6)]	63 [7)]
Igaku Chuo Zasshi (I)	345 [1)]	300 [5)]	206 [2), 6)]	94 [7)]
Hand search conducted at the Japan Kampo Medicines Manufacturers Association (N)	-	412 [8)]	314 [3)]	62
Total, excluding overlapped references		832	616 [4)]	216

[1)] Total number of search hits, [2)] including 2 meta-analysis, [3)] including 8 meta-analyses, [4)] including 10 meta-analyses,
[5)] 20 references overlapped between (C) and (I), [6)]17 references overlapped between (C) and (I), [7)] 3 references overlapped between (C) and (I),
[8)] 21 references overlapped between (C) and (N), and 15 references overlapped between (I) and (N)

(3) Preparation of structured abstracts

The references satisfying the inclusion criteria were compiled as structured abstracts (SA). Studies on SA started in the 1980s. Here, an 8-item structured abstract format of RCTs, as proposed by Altman, et al. and currently used worldwide, was employed.

Altman DG, Gardner MJ. More informative abstracts. *Ann Inter Med* 1987; 107(5): 790-1.

Aoki T. Kozoka shoroku no kisochisiki (Basic understanding in structured abstracts). In: Tsutani K, Yamazaki S, Sakamaki H (eds). *EBM no tameno joho senryaku – ebidensu wo tsukuru, tsutaeru, tsukau* – (*Information strategies for EBM – generate, transfer and use evidence*–). Tokyo: Chugai-igakusha; 2000: 82-93 (in Japanese).

Here, 8 items are referred to as, (1) objectives, (2) design, (3) setting, (4) participants, (5) intervention, (6) main outcome measures, (7) main results, and (8) conclusions.

These 8 items are widely used in medical journals such as JAMA and secondary information journals such as Evidence Based Medicine, ACP Journal Club, as well as in secondary information journals on traditional medicine and complementary and alternative medicine, represented by *Focus on Alternative and Complementary Therapies* (*FACT*). The acupuncture part of the journal is available in Japanese (Tsutani K [supervise-trans]. *Hari no ebidensu* [*Evidence for acupuncture – abstracts of articles on clinical evaluation of acupuncture*–]. Yokosuka: Ido-no-Nippon-sha; 2003 [in Japanese]. Thereafter, serialized in the journal "*IDO-NO NIPPON* [*The Japanese Journal of Acupuncture & Manual Therapies*]" [in Japanese]).

If one SA has been based on multiple references, all the bibliographic information for references used for the SA appears at the top of the SA, in order of publication, with the principle reference appearing in bold type.

Regarding (5) intervention, since the quality may differ among manufacturers, the brand name indicated in the original article was to be used as a rule. When the brand name was changed after the issue of the article for such reason as a change in manufacturer name, the brand name indicated in the article was used.

In the structured abstracts in the "Evidence Reports of Kampo Treatment", in addition to the above-mentioned 8 worldwide standard items, the following 4 items are included: (9) from the Kampo medicine perspective; (10) safety assessment in the article; (11) abstractor's comments; and (12) abstractor and date. These are described below:

(9) "From the Kampo medicine perspective" means how the unique diagnosis

system of Kampo medicine is used. This is applied to 2 processes: design of a clinical trial and analysis after completion of the study. With RCT, this can be referred to as pre-randomization and post-randomization. In the former process of designing clinical trial design, "*sho* (証, pattern)" of Kampo medicine is indicated in the entry criteria and exclusion criteria of participants in the protocol in a manner that participating investigators can understand. The latter process involves stratified analysis, in which participants are stratified by "*sho*" (with *sho* or without *sho*), as well as by age and sex, etc. However, the stratified analysis is associated with "inference multiplicity"; that is, repeated testing of many strata produces false positive results, which indicates a difference when actually there is no difference. Among post-hoc approaches are adjustment for covariates.

(10) Safety assessment in the article" was incorporated since not only efficacy but also safety should always be considered in Kampo medicine as well. Here, the expression of "safety assessment in the article" was used rather than mere "safety assessment" because "safety assessment" is frequently misunderstood. RCTs usually use efficacy-related endpoints to determine appropriate sample sizes, and are not intended to assess safety. For instance, when no adverse drug reactions occurred among 100 subjects receiving a Kampo medicine, the Kampo medicine is apt to be considered "safe because there are no adverse drug reactions when used in as many as 100 subjects." Certainly, point estimation yields an incidence of 0%; however, interval estimation yields a 95% confidence interval (CI) for the incidence of 0-3%. Especially when a serious adverse drug reaction may infrequently occur, safety should be judged in consideration of the number of participants in the clinical trial in the article. From this perspective, the expression of "safety assessment in the article" was used.

Reports on Kampo medicines sometime use expressions such as "30 patients received the treatment, and had no adverse reactions". However, caution is required here in two respects.

First, an adverse drug reaction is different from an adverse event. An adverse event (AE) means "any untoward medical occurrence, whether or not related to the medical product," and an adverse drug reaction (ADR) means an AE with "causal relationship to the medical product that cannot be ruled out".

Second, for probabilistic reasons, a confidence interval (CI) is necessary, and usually a 95% CI is used. Its upper and lower limits are referred to as confidence limits. For example, if 10 patients are treated and no adverse events occur, the 95% CI is 0–26%; if 20 patients are treated, the 95% CI is 0–14%; if 50 patients, 0–6%; if 100 patients, 0–3%; and if 500 patients, 0–0.6%. When the sample size is greater than 50, the rule of three can be used to give approximate results. The lower confidence limit is always zero, while the upper confidence limit is $[1-0.05^{1/n}]$. A detailed explanation of the above can be found in the reference cited below.

Tsutani K. Kenkyu dezain no kiso (Research design basics). In: Tsutani K et al. (eds).

EBM no tameno joho senryaku – ebidensu wo tsukuru, tsutaeru, tsukau – (*Information strategies for EBM – generate, transfer, and use evidence –*). Tokyo: Chugai-igakusha; 2000: 26-47. (in Japanese)

The above example assumed no occurrence of adverse events in any patients. Generally, however, when "adverse events occurred in m of n patients", the 95% CI can be calculated based on binomial distribution using the equation below. This equation, which utilizes normal approximation of binominal distribution, produces larger error with smaller sample size ($n < 25$).

95% confidence interval for event incidence $=p \pm 1.96\sqrt{(p(1-p)/n)}$, where $p=m/n$.

Although normal approximation was used for calculating the confidence interval in the above equation, there are other calculation systems readily available on the Internet.

In this evidence report, the description in "safety assessment included in the article" is standardized as follows:

1) Without indication

   When safety assessment was not performed or indicated, "none" was indicated.

2) With indication

   When safety assessment was performed, even if only slightly, and revealed no adverse drug reactions, that effect was indicated. When adverse drug reactions were specifically indicated, the abstractor in charge indicated this according to the expression used in the reference. When the number of patients with adverse drug reactions was specified in the reference, it was indicated. Note that some indications of adverse drug reactions are not unified.

(11) Abstractor's comments" refers to objective comments on a reference presented as a structured abstract. This helps busy readers not used to critical appraisal correctly and easily judge the value of the article. Abstractors were selected such that the abstractor did not belong to the same group of the authors concerned or have a master-student relationship, in consideration of conflict of interest (COI). How comments should be made was most actively discussed among members of the task force. With the aim of improving and standardizing comments, the 2nd Workshop of the Task Force for Evidence Report "To prepare appropriate comments" was held in conjunction with the Japan Society for Oriental Medicine 58th Annual Meeting held in Hiroshima on 17 Jun. 17, 2007.

Tsuruoka H, Okabe T, Tsutani K. Kampoyaku RCT no kozokashoroku niokeru komento kisai no kaizen － Dai 2-kai ebidensu repoto tasuku fosu wakushoppu hokoku － (Improvement of indication of comments in structured abstracts of RCTs on Kampo medicine－the Report of the 2nd Workshop of the Task Force for Evidence Report－. *Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2009: 60: 177-84 (in Japanese).

(12) Abstractor and date" is intended to clarify the responsibility, which also concerns the abovementioned conflict of interest, and to show the temporary relationship between the comments and related studies and in consideration of the possibility of correction at a later date. When a structured abstract was revised, the date of revision was added.

Structured abstract preparation tasks were assigned to Task Force members in consideration of their specialties. However, since the specialties of members did not cover the whole field, some abstracts were prepared by non-specialized members.

Bibliographic items were indicated in the Vancouver style as a rule, with some modifications, including that the number of authors listed shall be up to 3 and that the name of a journal shall not be abbreviated.

Structured abstracts were arranged in the order of ICD10 (Version 2003) code of diseases. Those with the same code were arranged by date of publication of the main reference evaluated. When more than one ICD code was possible, the one seeming to be generally more understandable was selected. Similarly, excluded references were arranged in the order of ICD10 code. The names of Kampo formulae, etc. that could not be written in Chinese characters for daily use in Japan were written in Katakana. The names of ICD code diseases differ from general names and were therefore read as shown in **Table 2** to indicate them in this report.

Table 2 Expression of the disease classification in this report

In preparing structured abstracts, to maintain the quality, a Structured Abstract Preparation Manual was prepared, distributed to Task Force members, and updated as appropriate.

	ICD10	Chapter title of ICD 10	Disease name in the reports
1	A00-B99	Certain infectious and parasitic diseases	Infections (including viral hepatitis)
2	C00-D48	Neoplasms	Cancer (condition after cancer surgery and unspecified adverse drug reactions of anti-cancer drugs)
3	D50-D89	Diseases of the blood and blood-forming organs, and certain disorders involving the immune mechanism	Blood diseases including anaemia
4	E00-E90	Endocrine, nutritional and metabolic diseases	Metabolism and endocrine diseases
5	F00-F99	Mental and behavioural disorders	Psychiatric/behavioral disorders
6	G00-G99	Diseases of the nervous system	Nervous system diseases (including Alzheimer's disease)
7	H00-H59	Diseases of the eye and adnexa	Eye diseases
8	H60-H95	Diseases of the ear and mastoid process	Ear diseases
9	I00-I99	Diseases of the circulatory system	Cardiovascular diseases
10	J00-J99	Diseases of the respiratory system	Respiratory diseases (including influenza and rhinitis)
11	K00-K93	Diseases of the digestive system	Gastrointestinal, hepato-biliary-pancreatic diseases
12	L00-L99	Diseases of the skin and subcutaneous tissue	Skin diseases
13	M00-M99	Diseases of the musculoskeletal system and connective tissue	Diseases of the musculo skeletal system and connective tissue
14	N00-N99	Diseases of the genitourinary system	Genitourinary tract disorders (including climacteric disorders)
15	O00-O99	Pregnancy, childbirth and the puerperium	Ante/post-partum diseases
18	R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	Symptoms and signs
19	S00-T98	Injury, poisoning and certain other consequences of external causes	Injury, poisoning, and postoperative pain
21	Z00-Z99	Factors influencing health status and contact with health services	Others

5. Included and excluded references

(1) Relations among included references, included studies, and excluded references

SAs were prepared for the 832 selected references including 65 cases of “2 papers for 1 study,” 13 cases of “3 papers for 1 study,” 3 cases of “4 papers for 1 study,” 2 cases of “5 papers for 1 study,” and also 4 cases of “1 paper for 2 studies,” and resulted in the preparation of 512 SAs (corresponding to 502 RCTs and ten meta-analyses). The number of excluded references deviating from the inclusion criteria was 216 (**Table 3**).

Table 3 Relation between included references, included studies, and excluded references

No. of included references	832
1 study 2 papers	65
1 study 3 papers	13
1 study 4 papers	3
1 study 5 papers	2
2 studies 1 paper	4
No. of SAs (No. of studies)	512
No. of excluded references	216

The International Committee of Medical Journal Editors (ICMJE) developed the manuscript guidelines initially called “Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM)” in 1979, which were updated and renamed in accord with ICMJE Recommendations in 2013, with subsequent revisions almost annually.

http://www.icmje.org/recommendations/archives/

Worldwide, more than 5000 journals follow the ICMJE Recommendations.

http://www.icmje.org/journals-following-the-icmje-recommendations/

The revisions in and after 1984 mention duplicate publication and require that submission of already published study contents be approved by the editorial committee. The ICMJE Recommendations permits secondary publication for the following cases: editors of both journals concerned have accepted; the second publication targets different readers from those of the first publication; the second publication faithfully reflects the data and interpretations in the first publication; and the second publication specifies that it is a "secondary publication."

As shown in Table 3, it was unclear whether the considerable number of duplicate publications about clinical studies on Kampo medicines were secondary publications or versions. Submitting already published contents without permission of the editorial committee constitutes not only ethical but also copyright issues. With rising interests in publication-related ethics at home and abroad, consideration should be given to duplicate publication in papers on Kampo as well. These findings were published as study results in the following reference:

Kitagawa M, Tsutani K. Duplicate publication cases in the field of Kampo (Japanese herbal medicine) in Japan. *Zhong Xi Yi Jie He Xue Bao (Journal of Chinese Integrative Medicine; 中西医結合学報)* 2011; 9(10): 1055-60.

In the following symposium, the issue of duplicate publication was addressed from the perspective of the above study:

Tsutani K. Publish or perish: Tajusyuppan ni tsuite (Publish or perish: duplicate publication). The Japanese Association of Medical Journal Editors (JAMJE) 2nd symposium (7 Jul. 2009, Tokyo) (in Japanese)

(2) Studies compiled as structured abstracts

For the studies shown in **Table 4**, structured abstracts were prepared.

Table 4 Studies prepared as structured abstracts

Meta-Analysis		10
Randomized Controlled Trial [1)]		454
Double blinded RCT: DB-RCT	58 [2)]	
Envelope method: RCT-envelope	111	
Randomized Controlled Trial: RCT	227	
RCT-cross over	58	
Quasi-RCT: Controlled Clinical Trial (CCT) [3)]		48
Total		512

[1)] Although it is possible to further sort RCTs using finer classifications, they have been sorted here into four classifications for convenience.

[2)] Including 1 DB-RCT-envelope and 3 DB-RCT-cross over.

[3)] Quasi-RCT: Quasi-RCT refers to randomization that is not complete, such as alternate assignment and assignment in the order of visit.

It is referred to as "Controlled Clinical Trial (CCT) " in MeSH of Medline

For studies compiled as structured abstracts, the following items were indicated in the structured abstract and included the reference list: 1) SA No.; 2) ICD10 (2003 revision) code of disease; 3) research question; 4) name of Kampo formula; 5) bibliographic items of the reference; 6) study design; and 7) search source.

Research questions were supposed to be formulated with four items of patient, intervention, control, and outcome (PICO), but were simplified here.

(3) Preparation of excluded references list

The references not compiled as structured abstracts but listed as excluded references along with bibliographic items and the reason for exclusion were:

1) Clinical articles but not RCTs or meta-analyses
2) Those using formulations not approved for manufacture and sale in Japan as Kampo extract formulations (ex. Kampo decoctions, Chinese formulations)
3) Those using Kampo formulations in or before 1985 (with different quality from the current standards)
4) Citations of existing RCT articles.
5) Indicated with insufficient clarity to prepare the structured abstract
6) Others

Furthermore, when the SA of a brief report or news article was prepared and subsequently its final report was collected, then the previous SA and its source report or article were removed because of “6) Others” above, and transferred to the list of excluded references with statement of justification. Although EKAT initially emphasized comprehensiveness and contained a broad range of articles including medical society

interview columns, this led to issues such as sample size or result inconsistencies between earlier and final reports of the same study, or to link errors between the RCTs and their reports. For this reason, starting with EKAT Appendix 2014, brief reports or news articles obviously written by study report authors are excluded, and previously prepared SAs are reviewed upon collection of the final reports. Consequently, one report in EKAT Appendix 2014 and two reports in EKAT Appendix 2015 have been transferred to the list of excluded references.

Finally, 216 references appear on the excluded references list.

6. Relation to other projects

The relation of this project to some other projects is described below.

(1) Development in Japan and Korea of universal-style structured abstracts of RCTs in the fields of traditional medicine and complementary and alternative medicine

The first initiative to deliver SAs to people who require them was the *ACP Journal Club* in 1991. A further, similar initiative was taken by the *Evidence-Based Medicine*.

In the field of Complementary and Alternative Medicine (CAM), the quarterly journal *FACT (Focus on Alternative and Complementary Therapies)* was published from 1996 to 2016. For acupuncture articles, in particular, the Japanese translation project was started in 2001, with translation of articles published since 1996. As the total number of translated articles reached 150, they were compiled with comments of Japanese experts into a book published in 2009.

Hari no ebidensu: Shinkyu rinsho hyoka ronbun no abusutorakuto zokyo kaiteiban (*Evidence for acupuncture: abstracts of articles on clinical evaluation of acupuncture. Enlarged and revised edition*). Ido no Nippon, 2009.

Several other initiatives have followed in Japan that are modeled on the EKAT initiative. In terms of Oriental medicine, in 2012, the fiscal 2010-2011 Ministry of Health, Labour and Welfare (MHLW) scientific research grant project, entitled “Higashi Ajia Dento Igaku no Yukosei, Anzensei, Keizaisei no Shisutematic Rebu” (Systematic Review of the Effectiveness, Safety, and Economy of East Asian Traditional Medicine [Principal Researcher: Kiichiro Tsutani]), prepared reports entitled “Shinkyu Ebidensu Repoto 2011” (Evidence Reports of Japanese Acupuncture and Moxibustion 2011), “Anma Massagi Shiatsu (Amashi) Ebidensu Repoto 2011” (Evidence Reports of Anma-Massage-Shiatsu 2011), and “Kampoyaku no Keizaihyoukaryoiki no Ebidensu Repoto 2011” (Evidence Report of Economic Evaluation of Kampo Treatment 2011).

In Korea, the Special Committee for EBM of the Korean Oriental Medicine Society (KOMS), with which JSOM has established an exchange agreement in 2009, published the Korean translation (근거중심의 한방처방 : 임상 근거를 만들고, 전달하며, 사용하는)

of Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials (EKAT 2010) on 15 July 2011.

The Committee also used the same methods as for EKAT to prepare an evidence report on traditional Korean medicine, which was published on 20 January 2012 as 근거중심의 한의치료. The Committee prepared SAs in Korean after gathering and selecting 306 papers (including 134 RCTs), which include trials using designs other than RCT designs and were found by searching The Cochrane Library (CENTRAL), PubMed, the Korea Institute of Oriental Medicine (KIOM) database, and the websites of 17 sub-committees in the field of traditional Korean medicine. The SAs for the 134 RCTs were translated into English in "Heisei 22-23 nendo Kosei Rodo Kagakukenkyu Chiikiiryo Kibankaihatsu Suishin Kenkyujigyo －Higashiajia Dentoigaku no Yukosei Anzensei Keizaisei no Shisutematikku Rebyu" (Systematic Review of the Effectiveness, Safety, and Economy of East Asian Traditional Medicine, a Research on Region Medical under the 2010/2011 Ministry of Health, Labour and Welfare Scientific Research grants) (Principal Researcher: Kiichiro Tsutani). The report is entitled "Evidence Reports of Korean Medicine Treatment 2010: 132 Randomized Clinical Trials (EKOM 2010)". This evidence report contains 77 RCTs on acupuncture and moxibustion, 27 RCTS on herbal medicines, one RCT on both, and 27 RCTs on other traditional Korean medicine.

Of the above, SAs on Japanese acupuncture and moxibustion (in Japanese and English), Amashi (Japanese and English), traditional Korean medicine (English), economic evaluation of Kampo treatment (Japanese) can be accessed on the website of the Evidence Reports of Traditional East Asian Medicine (ETEAM).

Furthermore, SAs of evidence reports on acupuncture, moxibustion, and massage in sport were prepared in 2016, and also on yoga in 2017, and can be accessed on the website of the integrative medicine information project subsidized by the Ministry of Health, Labour and Welfare known as:
Information site for evidence-based Japanese Integrative Medicine (eJIM)

(2) CONSORT Statement

With the aim of improving the quality of references of RCTs, the CONSORT statement was published in 1996 and revised in 2001 and 2010 (http://www.consort-statement.org/).

The 2010 version consists of a total of 25 items, and authors are requested to attach a checklist showing on which page the information on each item can be found. They are also requested to attach a flowchart representing subject disposition in case results might differ depending on the analysis population. These requirements not only control the quality of RCT articles but also improve the quality RCT themselves. The JSOM has added the statement that

“RCT papers shall conform to revised CONSORT statement (2001)” to the instructions to authors its March 2008 revision (*Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2008; 59: 580-89). Use of the CONSORT statement 2010 has been required since 2010.

Two herbal extensions of the CONSORT statement have been published:

Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, et al. Reporting randomized controlled trials of herbal interventions: An elaborated CONSORT statement. *Annals of Internal Medicine* 2006; 144(5): 364-7. (Available in Japanese: Okabe T, Tsutani K [trans], Habu kainyu no randamuka hikakusiken hokoku: shosai na CONSORT seimei. In: Nakayama T, Tsutani K [supervise-eds] *Rinshokenkyu to Ekigakukenkyu notameno Kokusairuru-shu* (*International Rulebook for Clinical and Epidemiological Studies*. Tokyo: Life Science Publishing Co., Ltd.; 2008: 156-63).

Chen CW, et,al CONSORT-CHM Formulas 2017 Group.CONSORT Extension for Chinese Herbal Medicine Formulas 2017: Recommendations, Explanation, and Elaboration. *Ann Intern Med*, 167 (2), 112-21

The former extension applies to single herbs, while the latter to Chinese herbal formulas. These extensions explain in detail how to describe the “intervention”, taking into consideration the nature of crude drugs. The latter extension also gives consideration to the diagnostic system used in Chinese traditional medicine and the number of years of clinical experience. Following the 2006 and 2007 editions and laborious efforts over 11 years, as the edition known as the “CONSORT Extension for Chinese Herbal Medicine Formulas” was released in 2017.

In the third phase of the Special Committee for EBM starting 2009, the Task Force for KCONSORT (KC-TF) was established. A survey of the references compiled as structured abstracts in EKAT 2009 for compliance with the CONSORT statement demonstrated that few were good in quality. Particularly, the following defects were commonly noted: no indication that the study is an RCT in title/abstract; no indication of the study site or period; no indication of the name of the manufacturer of Kampo formulation or the daily dosing frequency; no indication of the methods and assurance of randomization; unclear numbers of enrolled patients, assigned patients, and analyzed patients; no indication of adverse events in the control group. In the future, Kampo RCTs will also be required to be reported in compliance with the CONSORT statement. These findings were presented in the following meeting and published in *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) as study results.

Okabe T, Arai I, Tsutani K. Ebidensu repoto purojekuto: autorain to Kampo RCT no shitsu hyoka (Evidence Report Project [1] Outline and evaluation of Kampo RCTs). The Japan Society for Oriental Medicine 60th Annual Meeting Forum "Kampo no ebidensu wo tsutaeru (Transfer Kampo evidence)," 21 Jun. 2009, Tokyo. *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) 2009; 60 suppl.: 160 (in Japanese).

While it is recommended that RCTs be published in accordance with the CONSORT statement, the existing CONSORT statement and its extensions made it clear that it was not possible to correctly describe Kampo formulation interventions. To resolve that problem and to enable completion of the necessary information in the RCT paper methods field without needing to have a high degree of familiarity with Kampo formulations, the KCONSORT webpage was published in English in August 2011 by the Department of Pharmacognosy, Phytochemistry and Narcotics (DPPN), National Institute of Health Sciences (NIHS) of Japan, and the Research Center for Medicinal Plant Resources (RCMPR), National Institute of Biomedical Innovation (NIBIO) of Japan under work collaboration of KC-TF and Japan Kampo Medicines Manufacturers Association (JKMA). The website is intended to replace the need for authors writing RCTs on Kampo preparations to complete detailed information in their papers relating to the Kampo preparations used in research, by including the web address of this website, which contains detailed information on Kampo preparations. KCONSORT was then renamed STORK in May 2017, in part because it employs only one of the 25-item CONSORT Checklist, i.e., "Interventions". STORK is available at the link below.

STORK (Standards of Reporting Kampo Products)

The CONSORT statement was extended to include various study designs such as epidemiological studies and systematic reviews, and further studies on above-mentioned complementary and alternative medicine (CAM). In this context, the "Equator Network" was established in June 2008 to cover the publication guidelines for all these studies for enhanced accessibility and to help prepare such guidelines in future.

The Japanese version of these guidelines is included in the following:

Nakayama T, Tsutani K (eds). *Rinsho kenkyu to ekigaku kenkyu notameno kokusai ruru-shu* (*International Rulebook for Clinical and Epidemiological Studies*). Tokyo: Life Science Publishing Co., Ltd.; 2008 (in Japanese).

Nakayama T, Tsutani K (eds). *Rinsho kenkyu to ekigaku kenkyu notameno kokusai ruru-shu Part 2* (*International Rulebook for Clinical and Epidemiological Studies Part 2*). Tokyo: Life Science Publishing Co., Ltd.; 2016 (in Japanese).

The above and other related publications are also available at the link below:

Reporting guidelines at JPT Online

(3) Clinical trial registry

In the Declaration of Helsinki revised in October 2008, a sentence “Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject” was added in section 19. However, this requirement is not well known. Therefore, the discussion here includes the historical background underlying the implementation of this requirement.

Awareness of the clinical trial registry (CTR) has increased since the 1990s, when evidence-based medicine (EBM) emerged. In particular, the problems became clearer after the Cochrane Collaboration, which plays a role in the EBM information infrastructure, was established in 1992 to fully implement systematic review (SR). SR is almost synonymous with meta-analysis (MA).

However, no matter how exhaustive the survey or search, how careful the assessment of quality, and how sophisticated the statistical method used for data consolidation, a problem of bias ("publication bias") arises when studies are not reported. This leads to flaws in decision making by health care providers, policy makers, medical consumers, etc. As a result, ineffective therapies, hazardous therapies, and therapies with poor cost-effectiveness are “used”.

Table 5 gives an example of publication bias in the area of acupuncture. Search for papers with an abstract published between 1966 and 1995 by the Medline identified 108 of 109 papers published in China (99%) that have shown favorable results, that is, demonstrated the efficacy of acupuncture compared with control. The efficacy rate was 75% in England and similar to that in China in other countries including Japan. This has been attributed to failure to publish studies that do not show efficacy.

Table 5 Favorable results of controlled clinical trials of acupuncture interventions by country

Country of publication	Abstracts screened	Abstracts included	Favoring test treatment	
			Number	Percent
China	196	109	108	99
England	329	107	80	75
Japan	317	120	107	89
Russia/USSR	150	29	28	97
Taiwan	78	40	38	95
Total	1100	405	361	89

Vickers A, et al. Do certain countries produce only positive results? A systematic review of controlled trials. *Controlled Clinical Trials* 1998; 19: 159-66

This situation was widely acknowledged by those involved in systematic review of these studies. Although some measures might avoid this bias, such as encouraging researchers to publish all studies, passing legislation mandating registry of all trials, and establishing a website to register planned or ongoing clinical trials, no specific measures were fully established.

In 2003, the National Library of Medicine (NLM) of the National Institutes of Health (NIH) established "Clinical Trials.gov" (https://clinicaltrials.gov/) with the aim of encouraging patients to access information on clinical trials of new drugs (therapies) intended for life-threatening disease. This is also an aim of the 1997 US-FDA Modernization Act. This system was not intended to avoid publication bias, but partially did a limited number of diseases including cancer, AIDS, and Alzheimer's disease.

The Glaxo SmithKline fraud scandal reported on the front page of the New York Times dated 3 June 2004 triggered a worldwide reaction. In a clinical trial of an anti-depressant in children, the company failed to properly report attempted suicide as an adverse event. The scandal prompted worldwide support for legislation requiring clinical trial registration and raised ethical issues such as the risk adverse events in similar clinical trials and abuse of the altruistic goodwill of participants.

In September 2004, the International Committee of Medical Journal Editors (ICMJE) issued a statement that no manuscript would be accepted in advance of registration of the clinical trial. Trials already in progress were given additional time to comply. The Cochran Colloquium in October 2004 issued the "Ottawa Statement." The WHO also supported these statements by holding the “WHO Technical Consultation on Clinical Trial Registration Standard Meeting” in its headquarters in Geneva in April 2005 to determine 20 items to be registered, etc.

This trend continued between 2004 and 2005 as indicated below:

(1) Rinshoshiken no toroku to kekka no kokai (Clinical trial registry and publication of the results [regardless of whether or not results are positive or negative]). The 25th Annual Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics Symposium 12 (18 Sept. 2004, Shizuoka). *Rinsho Iyaku* (*Journal of Clinical Therapeutics Medicine*) 2005; 21(1): 3-62 (in Japanese).

(2) Rinshoshiken toroku nikansuru “Otawa seimei” to “Junebu kaigi” no doko (“Trend toward clinical trial registry as advocated by the "Ottawa Statement" and "Geneva Conference."). *Yakuri to Chiryo* (*Japanese Pharmacology & Therapeutics*) 2005; 33(6): 543-66 (in Japanese).
http://www.lifescience.co.jp/yk/jpt_online/ottawa/index_ottawa.html

(3) UMIN Clinical Trial Registry System Symposium (2 Feb. 2005)
https://upload.umin.ac.jp/ctr/symposium20050202.htm

In Japan, the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (June 2005-), the Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC-CTI) (July 2005-), and Japan Medical Association Center for Clinical Trials (JMA CCT) system (December 2005-) were launched. In April 2007, interventional clinical studies supported by Health and Labour Sciences Research Grants were required to be registered. Registration is also required for clinical trials by the “Ethical Guidelines for Clinical Research” issued by the Ministry of Health, Labour, and Welfare in April 2009, and also for specific clinical trials by the Clinical Trials Act (Act No. 16 of 2017). On the basis of this Act, the Japan Registry of Clinical Trials (jRCT) was created.

Since 2008, these data have been sent through the Japan Primary Registries Network (JPRN) (since October 2008) of the National Institute of Public Health to the WHO International Clinical Trials Registry Platform (ICTRP), and one-click access to the data is available worldwide. Currently, all clinical trials registered in Japan, including those on Kampo, can be searched at this website.

(4) The Cochrane Library (CENTRAL)

The Cochrane Library (CENTRAL) is a global RCT database platform, but includes only 67 of the 345 RCTs on Kampo formulations in EKAT 2010. The Center for Integrative Medicine, University of Maryland Medical School manages the compilation of RCTs on complementary therapies in CENTRAL. We have made contact with the Center and negotiated for the RCT papers compiled in EKAT to be added to CENTRAL. As a result, the Kampo RCT papers in EKAT 2010 will be included in CENTRAL, and it will have links to

the English versions of JSOM's EKAT SAs. When CENTRAL was updated in October 2011, additional EKAT papers were included. However, due to copyright issues, there are no links from the RCT papers on Kampo formulations that were originally included in CENTRAL. Nevertheless, it is now possible to access RCTs of 352 Kampo formulations from the Cochrane Library (CENTRAL), the worldwide database of RCTs. When evidence-based clinical practice guidelines (CPG) are produced, CENTRAL will be used most often to search for RCT papers. It is expected that this will facilitate Kampo formulation RCT searches, and that there will be no gaps in the evaluation of Kampo formulations for such CPGs.

The following paper describes the above in detail.

Wieland LS, Manheimer E, Sampson M, et al. Bibliometric and content analysis of the Cochrane Complementary Medicine Field specialized register of controlled trials. *Systematic Reviews* 2013, 2: 51

(5) Clinical practice guidelines

Traditional medicines are already international commodities. From this perspective, Japan's Kampo formulations have fallen a little behind. If high quality SAs are prepared for Chinese and Korean traditional medicines, then it may become possible to reduce confusion in the debate through the publication of clinical practice guidelines (CPG) for traditional medicines, something that the WHO Office for the Western Pacific (WPRO) attempted to do in 2005 and 2006.

Motoo Y, Arai I, Hyodo I, Tsutani K. Current status of Kampo (Japanese herbal) medicines in Japanese clinical practice guidelines. *Complementary Therapies in Medicine* 2009; 17: 147-54.

Motoo Y, Tsutani K. Dento Igaku no Gurobaru Shinryo Gaidorain wa Kano ka? (Is it Possible to Realize Global Clinical Guidelines for Traditional Medicines?) *Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2006; 57 (4): 465-75 (in Japanese).

Furthermore, the WHO/WPRO traditional medicine CPG project was discontinued at the 5th meeting in Hong Kong (2007) due to strong opposition from Japan and others. However, work was continued in China and the following three volumes were published in 2011.

China Academy of Chinese Medical Sciences ed. Chinese medicine evidence-based clinical practice guidelines: TCM Internal Medicine (Chinese Edition) (中医循証臨床実践指南 - 中医内科). Beijing. China Press of Traditional Chinese Medicine, 2011

China Academy of Chinese Medical Sciences ed. Chinese medicine evidence-based clinical practice guidelines: Special disease (Chinese Edition) (中医循証臨床実践指南 - 専科専病), Beijing. China Press of Traditional Chinese Medicine, 2011

China Academy of Chinese Medical Sciences ed. Chinese medicine evidence-based clinical practice guidelines: Acupuncture (Chinese Edition) (中医循証臨床実践指南 - 鍼灸). Beijing. China Press of Traditional Chinese Medicine, 2011

The following paper includes details of the above.

Yanagawa T, Tsutani K. Chuyaku no Kokusaika to Hyojunka ni Kansuru Chugoku no Seisaku. Dai 5 kai Chui Shinryo ni Kansuru Gyokai Hyojun to Shinryo Gaidorain. (Chinese Policies on Internationalization and Standardization of Chinese Medicines. 5th Industry Standard and Clinical Practice Guidelines for Traditional Chinese Medicine Therapy) *Wakan'yaku* 2013; No.720: 3-10 (in Japanese).

7. Lists of Excluded References
(216 references)

Note: **Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (*).**

Abbreviations: **C, The Cochrane Library (CENTRAL); I, Igaku Chuo Zasshi (Japana Centra Revuo Medicana, Ichushi); N, Database Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)**

Reasons for exclusion were classified as follows:

1) Clinical studies that were not RCTs or meta-analyses.
2) Studies using medicines that were not approved as Kampo preparations in Japan (Kampo tozai [decoctions], Chinese preparations, and others).
3) Studies using Kampo preparations manufactured before 1985 (their quality being different from that currently available).
4) Studies citing existing RCT papers.
5) Studies with unclear content.
6) Others (reasons are described in the list)

1. Infections (including Viral Hepatitis) (5 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
A09	Effects of Kampo prescriptions on inflammatory bowel disease (IBD)	Various prescriptions	Okumi H. An EBM evaluation of Kampo prescriptions related to inflammatory bowel disease (IBD). *Nihon Toyo Shinshin Igaku Keknkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*). 2010; 25: 95-9 (in Japanese with English abstract).	4) RCT review	I
A09	To evaluate the efficacy of goreisan for treatment of acute vomiting and diarrhea in pediatric patients with acute gastroenteritis	goreisan (五苓散)	AHMED S, Uchida R. Children's water metabolism and goreisan: Effects of goreisan extract on acute vomiting and diarrhea mainly in the digestive system in Bangladeshi pediatric patients with acute gastroenteritis: a randomized, double-blind, placebo-controlled study. *Accessible Chinese Medicines for Pediatric Diseases* 2016; 14:38-43.	5)	N
B08.1	Clinical efficacy for molluscum contagiosum	yokuinin extract powder	Clinical research group for coix seed (yokuinin) extract powder. Therapeutic effect of coix seed (yokuinin) extract powder on molluscum contagiosum – well-controlled double blind trials by multi-institutes compared with placebo- . *Hifu* (*Skin Research*) 1987; 29: 762-73.	2)	N
B18.2	Clinical evaluation for chronic hepatitis C	shosaikoto (小柴胡湯)	Gibo Y. Clinical evaluation of shosaikoto for chronic hepatitis C - long term comparison with no treatment group*. *Kampo Igaku* (*Kampo Medicine*) 1994; 18: 396-9.	1)	N
B34.9	Effects on immunocompetence in the elderly	hachimijiogan (八味地黄丸)	Yamamoto T, Tei M. Effects of Kampo medicine on immunocompetence in the elderly (III) - effects on the activity of the alternative complement pathway*. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)* 1986; 3: 270-1.	3)	N

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs) (26 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
C16.9	To evaluate the effectiveness of rikkunshito for gastrointestinal symptoms after endoscopic submucosal dissection (ESD) for early gastric cancer.	rikkunshito (六君子湯)	Uehara R. An evaluation of gastrointestinal symptoms and gastric mobility after endoscopic submucosal dissection (ESD) and an investigation of the usefulness of Rikkunshito (TJ-43). *Dai 8 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai Workshop 4 PROCEEDING Jobu Shokaki Shojo to Kampo* (*Workshop 4 Proceedings of the 8th Annual Meeting of the Japanese Gastroenterological Association: Upper Gastrointestinal Symptoms and Kampo*) 2012: 16-7 (in Japanese).	6) Report in article form Was included in structured abstracts up to EKAT 2014 but has been deleted following publication of a new paper.	N
C18.9	Efficacy of oxaliplatin combined with hydroxycamptothecin as an adjuvant therapy for colorectal cancer	Hydroxy-camptothecin	Yao Y, Zhao H, Sun Y, et al. Combined chemotherapy of hydroxycampothecin with oxaliplatin as an adjuvant treatment for human colorectal cancer. *The Tohoku Journal of Experimental Medicine* 2008; 215: 267-78.	2)	I
C18.9	To evaluate the reduction in the number of days to postoperative flatulence and the anti-inflammatory efficacy of daikenchuto in patients who underwent laparotomy for large intestine carcinoma.	daikenchuto (大建中湯)	Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto —A study in a fasted rat model and a randomized controlled trial in postoperative patients with colorectal cancer—. *Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai* (*5th Annual Meeting of the Japanese Gastroenterological Association*) 2009:9-10.	6) Report in article form Was included in structured abstracts up to EKAT 2014 but has been deleted following publication of a new paper.	N
C18.9	Effectiveness of hangeshashinto for colorectal cancer chemotherapy-induced oral mucositis	hangeshashinto (半夏瀉心湯)	Matsuda C, Kono T, Munemoto Y. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. *Annals of Cancer Research and Therapy* 2013; 21: 26-30.	5) Publication only includes protocols.	N
C18.9	To evaluate the efficacy and safety of daikenchuto for postoperative bowel dysmotility after laparoscopic surgery.	daikenchuto (大建中湯)	Yaegashi M. Usefulness of daikenchuto in the laparoscopic colorectal cancer perioperative period. *Progress in Medicine* 2012; 32: 616-7 (in Japanese).	6) Report in article form Was included in structured abstracts up to EKAT 2014 but has been deleted following publication of a new paper.	N
C18.9 K91.9	Evaluation of the efficacy of daikenchuto for gastrointestinal symptoms after laparoscopic colon cancer resection	daikenchuto (大建中湯)	Hoshino N, Kawada K, Hida K, et al. Effect of Daikenchuto (TJ-100) on gastrointestinal symptoms following laparoscopic colectomy in patients with colon cancer: study protocol for a randomized controlled trial. *Trials* 2017; 18: 1-6.	5) Reference had only a protocol	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
C22.0	Preventive effect on hepatoma in patients with hepatic cirrhosis	shosaikoto (小柴胡湯)	Yamamto S, Oka H, Kanno T, et al. Controlled prospective trial to evaluate syo-saiko-to for the prevention of hepatocellular carcinoma in patients with cirrhosis of the liver. *Gan to Kagaku Ryoho* (*Japanese Journal of Cancer and Chemotherapy*) 1989; 16: 1519-24.	1)	C
C22.0		shosaikoto (小柴胡湯)	Oka H. Chemoprevention of hepatocellular carcinoma with sho-saiko-to. *Rinsho Shokaki Naika* (*Clinical Gastroenterology*) 1998; 13: 1525-30.		I
C22.0		shosaikoto (小柴胡湯)	Oka H, Kobayashi K, Yamamoto S. Prevention of hepatoma with shosaikoto*. *Progress in Medicine* 1992; 12: 1196-200.		I
C22.0		shosaikoto (小柴胡湯)	Oka H, Yamamoto S. Controlled prospective study of prevention of hepatocellular carcinoma in patients with cirrhosis of the liver. *Biotherapy* 1991; 5: 1867-73.		I
C22.0		shosaikoto (小柴胡湯)	Oka H, Yamamoto S, Kuroki T, et al. Prospective study on chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). *Cancer* 1995; 76: 743-9.		C
C22.0		shosaikoto (小柴胡湯)	Oka H, Yamamoto S, Kanno T, et al. Controlled prospective evaluation of sho-saiko-to in prevention of hepatocellular carcinoma in patients with chirrosis of the liver. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1989; 6: 40-4.		I
C22.0	Effects on hepatic cirrhosis and hepatoma	shosaikoto (小柴胡湯)	Yamauchi H, Nakayama S, Sato S, et al. Hepatic cirrhosis and hepatoma*. *Current Therapy* 1986; 4: 599-607.	3)	N
C22.0	Protective effect of juzentaihoto on hepatocarcinogenesis	juzentaihoto (十全大補湯)	Tsuchiya M, Kono H, Matsuda M, et al. Protective effect of juzen-taiho-to on hepatocarcinogenesis is mediated through the inhibition of Kupffer cell-induced oxidative stress. *International Journal of Cancer* 2008; 123: 2503-11.	6) This was a basic study.	C
C26.9 K91.3	Meta-analysis evaluation of the efficacy of daikenchuto for prolonged ileus after open surgery	daikenchuto (大建中湯)	Kono T, Shimada M, Nishi M, et al. Daikenchuto administration for intestinal hypomotility after open abdominal surgery: a pooled analysis of three randomized controlled trials. *Annals of Cancer Research and Therapy* 2017; 25: 41-3.	5) Reference had only a protocol	C
C26.9 K12.1	Clinical impact of Hangeshashinto in the treatment of chemotherapy-induced oral mucositis in gastric cancer and colorectal cancer	hangeshashinto (半夏瀉心湯)	Nishikawa K, Aoyama T, Oba MS, et al.The clinical impact of Hangeshashinto (TJ-14) in the treatment of chemotherapy-induced oral mucositis in gastric cancer and colorectal cancer： Analyses of pooled data from two phase II randomized clinical trials (HANGESHA-G and HANGESHA-C). *Journal of Cancer* 2018; 9: 1725-30.	1)	N
C34.9	Effects on the adverse effects of chemotherapy for lung cancer	juzentaihoto (十全大補湯)	Okimoto N, Yoshida K, Tamada S, et al. Effects of TSUMURA Juzentaihoto on myelosuppression by anticancer agents*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1993; 81: 2040-3.	1)	N
C34.9 R63.0	Effect of rikkunshito on loss of appetite due to cancer chemotherapy	rikkunshito (六君子湯)	Inoue T, Takagi H, Owada Y, et al. The efficacy of the Kampo medicine rikkunshito for chemotherapy-induced anorexia (RICH trial) : study protocol for a randomized controlled trial. *Trials* 2017; 18 :1-8.	5) Reference had only a protocol	C
C56	Effects on the adverse effects of anticancer agents in patients with ovarian cancer	kamikihito (加味帰脾湯)	Ikeda A, Higashio S, Ushiroyama T, et al. Experience with administration of kamikihito with chemotherapy and palliative care in patients with gynecologic cancer. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 152-5.	1) Although this was a randomized study, Kampo medicine use was not randomized.	I
C57.9	Effects of juzentaihoto on the adverse effects of chemotherapy for gynecologic cancer	juzentaihoto (十全大補湯)	Matsui H, Takamizawa H. Effects of juzentaihoto on adverse effects of chemotherapy for gynecologic cancer. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 1993; 10: 104-9.	1)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
C57.9	Evaluation of goshajinkigan on myalgia and arthralgia concurrent with chemotherapy for gynecological cancer	goshajinkigan (牛車腎気丸), keishikajutsubuto (桂枝加朮附湯)	Sato Y, Yamamoto S, Tagami K, et al. The effects of Kampo medicines on the adverse effects (myalgia, arthralgia, numbness) of TC therapy - A crossover study of goshajinkigan and keishikajutsubuto. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2015; 32: 68-71.	1)	I&N
C80	Effects on gastrointestinal complaints in postoperative patients with esophageal and lung cancer	Kampo medicines (rikkunshito [六君子湯], ninjin'yoeito [人参養栄湯], bakumondoto [麦門冬湯], and saireito [柴苓湯])	Shikama T, Abo S. Usefulness of Kampo medicines in postoperative patients with esophageal and lung cancer - especially for gastrointestinal complaints*. *Roka to Shikkan* (*Ageing and Diseases*) 1996; 9: 103-6.	1)	N
C80	Effects in postoperative patients with esophageal cancer	rikkunshito (六君子湯)	Li S, Nabeya K, Yamada T, et al. Experience with postoperative administration of rikkunshito*. *Dai-3-kai Rinsho WAKAN-YAKU Kenkyukai Koen Kirokusyu* (*Proceedings of the 3rd Meeting of the WAKAN-YAKU Medical and Pharmaceutical Society*) 1986: 4-6.	3)	N
C80.0	Usefulness for fatigue associated with cancer chemotherapy.	hochuekkito (補中益気湯)	Motoo Y, Nakatani N, Shimasaki T, et al. Usefulness of hochuekkito for fatigue associated with cancer chemotherapy*. *Gan Chiryo no Ayumi* (*Advances in Cancer Treatment*) 2009; 28: 39-43.	5)	N
C90.0	Effect of ninjin'yoeito on patients with multiple myeloma	ninjin'yoeito (人参養栄湯)	Nomura S, Ishii K, Fujita Y, et al. Immunotherapeutic effects of Ninjin-youei-to on patients with multiple myeloma. *Current Trends in Immunology* 2014; 15: 19-27.	1)	C&N
D25.9	Effects of kampo treatment and gonadotropin-releasing hormone on uterine leiomyoma in perimenopausal women	shakuyakukanzoto (芍薬甘草湯), keishibukuryogan (桂枝茯苓丸)	Sakamoto S, Mitamura T, Iwasawa M, et al. Conservative management for perimenopausal women with uterine leiomyomas using Chinese herbal medicines and synthetic analogs of gonadotropin-releasing hormone*. *In Vivo* 1998; 12: 333-8.	1)	C

3. Blood diseases including anaemia (2 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
D64.9	Influence of juzentaihoto on hemoglobin recovery during preoperative autologous blood donation and after hip surgery	juzentaihoto (十全大補湯)	Kishida Y, Nishii T, Inoue T, et al. Juzentaihoto (TJ-48), a traditional Japanese herbal medicine, influences hemoglobin recovery during preoperative autologous blood donation and after hip surgery. *International Journal of Clinical Pharmacology and Therapeutics* 2009; 47: 716-21.	1)	C
D64.9	Evaluation of the relation between the clinical effects of tokishakuyakusan and *Paeonia lactiflora* raw materials	tokishakuyakusan (当帰芍薬散)	Shimada K, Kawase M, Shibahara N, et al. The relation between clinical effects of tokishakuyakusan and the identity of *Paeonia lactiflora* materials. *Journal of Ethnopharmacology* 2010; 132: 438-42.	2)	C

4. Metabolism and Endocrine Diseases (14 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
E10.4	Therapeutic effect on numbness caused by diabetic neuropathy	goshajinkigan (牛車腎気丸)	Sato Y. Diabetic complications and Kampo 1. Clinical effects of gosha-jinkigan for diabetic neuropathy. *Nihon Toyo Igaku Zasshi* (*Kampo medicine*) 2003; 54: 500-3.	4)	I
E11.0	Efficacy for insulin resistance in patients with type 2 diabetes	goshajinkigan (牛車腎気丸)	Uno T, Ohsawa I, Tokudome M, et al. Effect of goshajinkigan on insulin resistance in patients with type 2 diabetes. *Diabetes Research and Clinical Practice* 2005; 69: 129-35.	1)	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
E11.6	Improvement effect of yidiyin on erectile dysfunction in diabetic patients	yindin	Feng X, Qin C, Leng J, et al. Yidiyin, a Chinese herbal decoction, improves erectile dysfunction in diabetic patients and rats through the NO-cGMP pathway. *Bioscience, Biotechnology, and Biochemistry* 2012; 76: 257-63.	2) Chinese decoction	I
E11.9	The anti-HSP antibody-reducing effect of rokumijiogan and goshajinkigan in patients with noninsulin-dependent diabetes	rokumigan (六味丸), goshajinkigan (牛車腎気丸)	Tomii M, Kobayashi T, Sekiguchi Y, et al. The effects of Kampo formulations on anti-hsp antibody titer of the non insulin depended diabetes mellitus (NIDDM) patients. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1998; 15: 274-5.	1)	N
E13.6	Effects on diabetic complications	goshajinkigan (牛車腎気丸)	Sato Y. Measures and treatments for diabetic complications*. *Fukuoka Ishi Kampo Kenkyukai Kaiho* 1988; 9: 1-36.	4)	I
E14.4	Effects on diabetic neuropathy	goshajinkigan (牛車腎気丸)	Tawata M, Kurihara A, Nitta K, et al. The effects of goshajinkigan, an herbal medicine, on subjective symptoms and vibratory threshold in patients with diabetic neuropathy. *Diabetes Research and Clinical Practice* 1994; 26: 121-8.	1)	C
E28.3	Effects on luteal phase deficiency	tokishakuyakusan (当帰芍薬散)	Usuki S, Nakauchi T, Higa S, et al. The improvement of luteal insufficiency in fecund women by tokishakuyakusan treatment. *American Journal of Chinese Medicine* 2002; 30: 327-38.	1)	C
E28.9	Effects on FSH, LH, and estradiol levels in women with amenorrhea	unkeito (温経湯)	Ushiroyama T, Hosotani T, Yamashita Y, et al. Effects of unkei-to on FSH, LH and estradiol in anovulatory young women with hyper- or hypo-functioning conditions. *American Journal of Chinese Medicine* 2003; 31: 763-71.	1)	C
E34.8	Effect of ninjin'yoeito on Werner's syndrome skin fibroblasts	ninjin'yoeito (人参養栄湯)	Uchiyama Y, Nakajima S, Ohno T, et al. The effect of ninjinyoeito on Werner's syndrome skin fibroblasts. *American Journal of Chinese Medicine*. 1992; 20: 295-305.	6) This was a basic study.	C
E66.9	Effect on body fat mass or distribution.	-	Goto T, Matsushita D, Takasuka Y, et al. Evaluation of improvement effect on obesity for the uptake of the tea product "Gokusen Shanhai Koucha". *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2004; 52: 349-58.	2)	I
E78.5	Combined effect of daisaikoto and probucol on hyperlipidemia associated with non-insulin-dependent diabetes mellitus (NIDDM)	daisaikoto (大柴胡湯)	Murakami T, Oku J, Kimura Y, et al. The effect of Oriental medicine (dai-sai-ko-to) with probucol on lipoprotein metabolism in non-insulin dependent diabetics with hypercholesterolemia. *Domyaku Koka* (*The Journal of Japan Atherosclerosis Society*) 1991; 19: 839-46.	1)	N
E78.5	Effect of seiryu on dyslipidemia and alcoholic liver disease	herbal products (seiryu [青流])	Sou S, Shu G. A study of dyslipidemia and alcoholic liver disease diagnosed based on the Chinese medicine concept. The *Journal of Comparative Integrative Medicine/Japan* 2017; 25:21-6.	2), 6) Basic study	I
E88.9	Effect of keishibukuryogan on endothelial function in patients with metabolic syndrome	keishibukuryogan (桂枝茯苓丸)	Nagata Y, Goto H, Hikiami H, et al. Effect of keishibukuryogan on endothelial function in patients with at least one component of the diagnostic criteria for metabolic syndrome: a controlled clinical trial with crossover design. *Evidence-Based Complementary and Alternative Medicine* 2012; 2012: 1-10. doi: 10.1155/2012/359282	2) Homemade preparation	N
E88.9	Effect of bofutsushosan on metabolic syndrome	bofutsushosan (防風通聖散)	Wakasugi A. Clinical study of Kampo medicine on metabolic syndrome. *Research Reports of Uehara Memorial Foundation* [A1] 2012; 26: 105.	5)	I

5. Psychiatric/Behavioral Disorders (24 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
F01.9	Efficacy for vascular dementia	chotosan (釣藤散)	Itoh T, Shimada Y, Terasawa K. Efficacy of choto-san on vascular dementia and the protective effect of the hooks and stems of Uncaria sinensis on glutamate-induced neuronal death. *Mechanisms of Ageing and Development* 1999; 111: 155-73.	4)	C
F03	Effects on senile dementia	yokukansanka-chimpihange (抑肝散加陳皮半夏)	Hayano T, Majima M, Kadomae S, et al. Effects of TSUMURA Yokukansankachimpihange extracts for various dementias (II)*. *Kampo Igaku* (*Kampo Medicine*) 1987; 11: 16-25.	1) ,3)	I
		yokukansanka-chimpihange (抑肝散加陳皮半夏)	Hayano T. Effects of yokukansankachimpihange in the treatment of senile dementia*. *Gendai Iryogaku* 1989; 5: 109-13.		I
F03	Effects of Kampo preparations in the treatment of senile dementia	hachimijiogan (八味地黄丸), shosaikoto (小柴胡湯), yokukansan (抑肝散)	Tei M, Yamamoto T. Effects of hachimijiogan on mental activity and performance status in elderly*. *Gendai Iryogaku* 1989; 5: 122-8.	3)	N
F03	Efficacy of ninjinyoeito for cognitive and depressive disorders in patients with Alzheimer's disease	ninjin'yoeito (人参養栄湯)	Kudoh C, Arita R, Honda M, et al. Effect of ninjin'yoeito, a Kampo (traditional Japanese) medicine, on cognitive impairment and depression in patients with Alzheimer's disease: 2 years of observation. *Psychogeriatrics* 2016; 16: 85-92.	1)	C
F03	Meta-analysis evaluation of the efficacy of herbal medications on the management of behavioral and psychological symptoms (BPSD) associated with dementia	yokukansan (抑肝散), ninjin'yoeito (人参養栄湯)	Hyde A, May B, Lin Dong L, et al. Herbal medicine for management of the behavioural and psychological symptoms of dementia (BPSD): a systematic review and meta-analysis. *Journal of Psychopharmacology* 2017; 31: 169-83.	2) Meta-analysis included non-Japanese medicines	N
F05.1	Effects in the treatment of cholinesterase inhibitor-resistant visual hallucinations and neuropsychiatric symptoms in patients with dementia and Lewy bodies	yokukansan (抑肝散)	Iwasaki K, Maruyama M, Tomita N, et al. Effects of the traditional Chinese herbal medicine yi-gan san for cholinesterase inhibitor-resistant visual hallucinations and neuropsychiatric symptoms in patients with dementia with lewy bodies. *The Journal of Clinical Psychiatry* 2005; 66: 1612-3.	1)	C
F10.0	Preventive effects on hangover	orengedokuto (黄連解毒湯)	Shichido T, Arichi S. Preventive effects of Kampo medicine (orengedokuto) on hangover - a double-blind randomized pilot study*. *Igaku no Ayumi* (*Journal of Clinical and Experimental Medicine*) 1988; 145: 789-95.	3)	I
F17.2	The efficacy of smoking cessation education with collaboration between pharmacies and healthcare centers	Nicorette	Oguri S, Sakata K. The efficacy study of smoking cessation education with collaboration between pharmacies and healthcare centers*. *Nihon Mibyou Shisutemu Gakkai zasshi* (*The Journal of Japan Mibyou System Association*) 2009; 14: 199-201.	2)	I
F34.9	Effects of Kampo therapy on mood disorder and depression	saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯) etc.	Chijiwa T, Itoh T. Japanese Association of Oriental Psychosomatic Medicine, EBM Team Report: Kampo therapy evidence for psychosomatic disease and stress-related disease 3) Mood disorder. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2009; 24: 80-4 (in Japanese with English abstract).	4)	I
F45.3	Therapeutic effect of Kampo medicine on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯)	Yamagiwa M. Effects of Kampo medicine on abnormal sensation in the throat of neurotic patients *Jibi Inkoka Rinsho* (*Practica Otologica*) 1998; 98 suppl: 52-5.	1) ,3)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
F45.3	Effects on depressive pharyngolaryngeal paresthesia	saibokuto (柴朴湯)	Yamagiwa M. Effects of saibokuto in patients with depressive pharyngolaryngeal paresthesia*. *Kampo Igaku* (*Kampo Medicine*) 1998; 22: 19-22.	1) ,3)	N
F45.3	Therapeutic effect on depressive pharyngolaryngeal paresthesia	saibokuto (柴朴湯)	Furukawa K, Ishii T. Therapeutic effect of saibokuto vs. placebo on depressive pharyngolaryngeal paresthesia*. *Jibiinkoka Tenbo* (*Oto-rhino-laryngology, Tokyo)* 1988; 31: 1111-21.	3)	I
F45.3	Therapeutic effect on pharyngolaryngeal paresthesia	bukuryoingo-hangekobokuto (茯苓飲合半夏厚朴湯)	Kobayashi H, Soma M, Takano S, et al. Therapeutic effects of bukuryoingohangekobokuto on pharyngolaryngeal paresthesia*. *Jibiinkoka Tenbo (Oto-rhino-laryngology, Tokyo)* 1986; 29 suppl: 309-13.	3)	N
F45.3	Effects on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯), saireito (柴苓湯)	Yamagiwa M. Effects of Kampo medicine on abnormal sensation in the throat of neurotic patients. *Kampo to Saishin Chiryo* (*Kampo & The Newest Therapy*) 1998; 7: 153-6.	1) , 3)	N
F45.3	Effects on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯), saireito (柴苓湯)	Yamagiwa M. Effect of saiboku-to on throat discomfort of patients with psychological symptoms. *Kampo to Saishin Chiryo* (*Kampo & The Newest Therapy*) 1999; 7: 353-8.	1)	N
F45.3	Effects on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯), saireito (柴苓湯)	Yamagiwa M. The role of Kampo preparations in treating pharyngolaryngeal paresthesia*. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2001; 16: 36-8 (in Japanese with English abstract).	1) , 3)	N
F45.9	Evaluation of Kampo therapy for unidentified complaints.	keishibukuryogan (桂枝茯苓丸) + orengedokuto (黄連解毒湯) kamishoyosan (加味逍遙散), tokishakuyakusan (当帰芍薬散) + ninjinto (人参湯)	Terasawa K, Kumagai A, Arichi S, et al. Research on Kampo therapy - study overview of clinical controlled trial of Kampo treatments of unidentified complaints*. *Chiryogaku* (*Biomedicine and Therapeutics*) 1986; 16 suppl: 54-5.	3)	N
F45.9	Therapeutic effect on unidentified complaints associated with circulatory insufficiency	rokushingan (六神丸)	Kato H, Yano S, Hanasaki N, et al. Clinical evaluation of rokushin-gan on unidentified clinical complaints with circulatory insufficiencies – double blind comparative study of traditional and modified prescriptions in many hospitals-. *Therapeutic Research* 1988; 9: 785-800.	2)	I
F48.0	Effectiveness of Kampo medicines on fatigue and chronic fatigue syndrome	Various prescriptions	Chijiwa T, Itoh T. Fatigue and chronic fatigue syndrome. *Journal of Japanese Association of Oriental Psychosomatic Medicine* 2010; 25: 90-4.	4) RCT review	I
F48.9	Unidentified complaints with tendency to neurosis (stress disease)	orengedokuto (黄連解毒湯)	Yamada K. 3. Kampo treatment in psychiatry. In: Role of Kampo medicines on the stress-related disorders in a modern society. *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) 1999; 49: 774-80.	5)	N
F60.3	Efficacy in the treatment of borderline personality disorder	yokukansan (抑肝散)	Miyaoka T, Furuya M, YasudaH, et al. Yi-gan san for the treatment of borderline personality disorder: an open-label study. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 2008; 32: 150-4.	1)	C
F95.2	Regulating dopamine, serotonin, and gamma-amino butyric acid in Tourette's Syndrome with ningdong granule	ningdong granule (寧動顆粒)	Wang Shuzhen, Qi Fanghua, Li Jijun, et al. Effects of Chinese herbal medicine Ningdong Granule on regulating dopamine (DA)/serotonin (5-TH) and gamma-amino butyric acid (GABA) in patients with Tourette syndrome. *BioScience Trends* 2012; 6: 212-8.	2)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
F98.0	Effect of traditional Chinese and Western medicine on nocturnal enuresis in children	suoquan (縮泉)	Ma Yanli, Liu Xiaomei, Shen Ying. Effect of traditional Chinese and Western medicine on nocturnal enuresis in children and indicators of treatment success: Randomized controlled trial. *Pediatrics International* 2017; 59(11); 1183-8	2)	I

6. Nervous System Diseases (including Alzheimer's Disease) (14 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
G20	Effectiveness of zengxiao anshen zhichan 1 on sleep disorder in Parkinson's disease	zengxiao anshen zhichan 1 (増効安神止顫1号)	Liu T, Onishi R, Shimokawara A, et al. A quantitative evaluation of the effectiveness of zengxiao anshen zhichan 1 (ZAZ1) on sleep disorder in early-stage Parkinson's disease using wristwatch-type accelerometer recorder. *Journal of Japan Traditional Chinese Medicine Association* 2012; 2: 8-18.	2)	I
G24.0	Efficacy in the treatment of neuroleptic-induced tardive dyskinesia	yokukansan (抑肝散)	Miyaoka T, Furuya M, YasudaH, et al. Yi-gan san for the treatment of neuroleptic-induced tardive dyskinesia: an open-label study. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 2008; 32: 761-4.	1)	C
G30.1	Efficacy of N Chinpi for cognitive impairment	N Chinpi (N陳皮)	Seki T. Clinical effects of the N Chinpi on the cognitive impairment of patients with Alzheimer's disease. *Journal of Pharmacological Sciences* 2015; 145; 234-6.	2)	I
G30.1	A correlation between monoamines changed by yokusankan and pharmacological treatment in BPSD	yokukansan (抑肝散)	Takeyoshi K, Kurita M, Nishino S, et al. Yokukansan improves behavioral and psychological symptoms of dementia by suppressing dopaminergic function. *Neuropsychiatric Disease and Treatment* 2016; 12: 641-9.	1)	C
G30.9	Effects on cognitive function in Alzheimer-type dementia	kamiuntanto (加味温胆湯)	Maruyama M, Tomita N, Iwasaki K, et al. Benefits of combining donepezil plus traditional Japanese herbal medicine on cognition and brain perfusion in Alzheimer's disease: a 12-week observer-blind, donepezil monotherapy controlled trial. *Journal of the American Geriatrics Society* 2006; 54: 869-71.	2)	C
G40.2	Clinical benefits for patients with partial epilepsy	shosaikotogokeishi-kashakuyakuto (小柴胡湯合桂枝加芍薬湯)	Nakane Y, Yamauchi T, Onuma T, et al. Clinical utility of TJ-960 in patients with localization related epilepsy – late phase II study: multicenter, double-blind study in comparison with placebo. *Rinsho Hyoka* (*Clinical Evaluation*) 1999; 26: 419-52.	2)	I
G40.9	Clinical application in arteriosclerosis, neurasthenia, nervous palpitation, epilepsy, and chronic kidney disease	saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯)	Sato J. Clinical application of saikokaryukotsuboreito in arteriosclerosis, neurasthenia, nervous palpitation, epilepsy, and chronic kidney disease*. *Atsugi Byoin ishi* (*Atsugi Medical Journal*) 1991; 11: 52-3.	1)	N
G40.9	Effects on epilepsy	shosaikotogokeishi-kashakuyakuto (小柴胡湯合桂枝加芍薬湯)	Nagakubo S, Niwa S, Kumagai N, et al. Effects of TJ-960 on Sternberg's paradigm results in epileptic patients. *The Japanese Journal of Psychiatry and Neurology* 1993; 47: 609-20.	2)	C
G47.8	Effectiveness and safety of yokukansan on REM sleep behavior disorder (RBD)	yokukansan (抑肝散)	Sasanabe R. Aiming for better sleep – Explanation: The effectiveness of yokukansan on REM sleep behavior disorder (RBD) –A comparison with clonazepam – *Science of Kampo Medicine* 2013; 37: 22-5.	6) Report in article form	N
G47.9	Effect of yokukansanka-chimpihange on sleep in healthy adults	yokukansanka-chimpihange (抑肝散加陳皮半夏)	Kanbayashi T, Aizawa R, Hayashi Y, et al. Aiming for better sleep – Explanation: The effect yokukansanka-chimpihange has on sleep in healthy adults. *Science of Kampo Medicine* 2013; 37: 34-37.	6) Report in article form	N
G47.9	Efficacy of Yokukansankachimpihange on sleep disturbance in Parkinson's disease	yokukansanka-chimpihange (抑肝散加陳皮半夏)	Jang JH, Lee J, Jung I, et al. Efficacy of Yokukansankachimpihange on sleep disturbance in Parkinson's disease: a study protocol of a randomized, double blind, placebo-controlled pilot trial. *Medicine* 2018 ; 97: e11298	2), 5) Reference had only a protocol	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
G62.9	Preventive effect of goshajinkigan on peripheral neurotoxicity of FOLFOX therapy	goshajinkigan (牛車腎気丸)	Kono Toru, Mishima H, Shimada M, et al. Preventive effect of goshajinkigan on peripheral neurotoxicity of FOLFOX therapy: a placebo-controlled double-blind randomized phase II study (the GONE study). *Japanese Journal of Clinical Oncology* 2009; 39: 847-9.	5)	C&I
G90.9	Effects of ninjin, oriental bezoar, and kanzo powder combination capsules on autonomic nerve activity	ninjin (人参), oriental bezoar (牛黄), and kanzo powder combination capsule (甘草末配合カプセル)	Zheng A, Moritani T. Effect of the combination of ginseng, oriental bezoar and glycyrrhiza on autonomic nervous activity as evaluated by power spectral analysis of HRV and cardiac depolarization-repolarization process. *Journal of Nutritional Science and Vitaminology* 2008; 54: 148-53.	2)	I
G90.9	Effects of ninjin, oriental bezoar, and kanzo powder combination capsules on autonomic nerve activity and the immune system	ninjin (人参), oriental bezoar (牛黄), and kanzo powder combination capsule (甘草末配合カプセル)	Zheng A, Moritani T. Effect of the combination of ginseng, oriental bezoar and glycyrrhiza on autonomic nervous activity and immune system under mental arithmetic stress. *Journal of Nutritional Science and Vitaminology* 2008; 54: 244-9.	2)	I

8. Ear Diseases (1 reference)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
H65.9	Efficacy for secretary otitis media in children	saireito (柴苓湯)	Ikeda K, Takasaka T. Treatment of secretory otitis media with kampo medicine. *Archives of Otorhinolaryngology* 1988; 245: 234-6.	1)	C

9. Cardiovascular Diseases (8 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
I10	Anti-hypertensive effect of kampo medicines	rokumigan (六味丸) + daisaikoto (大柴胡湯)	Kajino M, Matumoto Y. Anti-hypertensive effect of therapeutic kanpo extract medicines. *Nihon Toyo Igaku Zasshi (Kampo Medicine)* 1985; 36: 57-60.	3)	I
I25.9	Effects on blood rheology in patients with coronary heart disease	-	Wu X, Harada T, Ishizaki F, et al. Study on the effect of xinnaotongluo liquid on hemorheology in patients with coronary heart disease. *International Medical Journal* 2005; 12: 129-31.	2)	I
I25.9	Effect of Kampo medicines in facilitating functional recovery from brain hemorrhage	keishibukuryogan (桂枝茯苓丸), tokakujokito (桃核承気湯), tsudosan (通導散)	Yokoyama N, Hagiwara N, Yokoyama Y, et al. Use of kampo medicine to facilitate absorption of brain hemorrhage and functional recovery of patients. *Cerebrovascular diseases*. 2012; 34 Suppl 1: 36.	1)	C
I67.9	Therapeutic effect of keishibukuryogan and trapidil on microcirculatory hemodynamics in patients with cerebrovascular accident	keishibukuryogan (桂枝茯苓丸)	Itoh T, Terasawa K, Kohta K, et al. Effect of keishi-bukuryo-gan and trapidil on the microcirculation in patients with cerebro-spinal vascular disease. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1992; 9: 40-6.	2)	I
		keishibukuryogan (桂枝茯苓丸)	Itoh T, Terasawa K, Kohta K, et al. Effects of keishi-bukuryo-gan and Trapidil on the microcirculation in patiens with cerebro- spinal vascular disease. *Toyama Kenritsu Chuo Byoin Igaku Zasshi* (*The Medical Journal of Toyama Prefectural Central Hospital*) 1993; 16: 74-80.		N
I69.8	Effects on sequelae of cerebrovascular accidents	orengedokuto (黄連解毒湯)	Araki G. Effects of TSUMURA Orengedokuto for sequelae of cerebrovascular accident*. *Geriatric Medicine* 1991; 29: 1587-99.	1)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
I67.9	Effectiveness and safety of hachimijiogan in patients with hypertension or cerebrovascular disease and concomitant symptoms	hachimijiogan (八味地黄丸)	Ito K, Yamamoto H, Saibara T, et al. The usefulness of Kanebo Hachimijiogan in patients with hypertension or cerebrovascular disease [excluding acute phase symptoms] and their concomitant symptoms: a multicenter, double-blind, crossover study. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1988; 76: 1096–114 (in Japanese)	3) Included in EKAT 2010 but excluded due to likelihood that pre-1985 Kampo preparations were used.	I
I73.0	Usefulness of TSUMURA Ninjin'yoeito for Raynaud's symptoms	ninjin'yoeito (人参養栄湯)	Tanabe E. Usefulness of TSUMURA Ninjin'yoeito for Raynaud's symptoms*. *Hifuka ni Okeru Kampo Chiryo no Genkyo* 1990; (1): 113-24.	1)	N

10. Respiratory Diseases (including Influenza and Rhinitis) (11 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
J00	Effects on common cold syndrome and acute bronchitis	maobushisaishinto (麻黄附子細辛湯)	Yamamoto T, Ounishi M, Yoshida K. Meta-analysis about effectiveness of mao-bushi-saishin-to in treating common cold syndrome. *Health science* 2001; 17: 94-9.	1)	I
J00	Therapeutic effect on cough in patients with common cold syndrome	maobushisaishinto (麻黄附子細辛湯)	Nishizawa Y, Tomiyo N, Mayumi Y, et al. A randomized comparison of cough-improvement effects between mao-bushi-saishin-to and Western drugs for cold in common patients with allergic cold syndrome. *Kampo to Meneki Arerugi* (*Kampo and Immuno-Allergy*) 2005; 18: 56-67.	5)	N
J10.1	Comparison of the effects of oseltamivir and maoto on pediatric influenza A	maoto (麻黄湯)	Suzuki E, Ichihara K. Impact of Japanese herbal medicine, mao-to, compared to oseltamivir on fever course in children with Influenza type A. *Gairai Shonika* (*The Journal of Ambulatory and General Pediatrics*) 2011; 14: 248-53.	1) Not an RCT The choice of drugs was basically left up to parents/guardians, and only if there was no specific preference were the drugs administered alternately in order of examination. The fact that the drugs were administered in order of examination lends it to being described as a quasi-RCT, however, that fact, and the fact that the drugs were administered according to parents'/guardians' preferences, mean it does not fit the description of an RCT.	I
J12.8	Effects of integrated Chinese and western medicine on QOL in convalescent-phase SARS patients	-	Bian Y, Qi W, Song Q, et al. Effects of integrated Chinese and western medicine on QOL in convalescent-phase SARS patients*. *Toho Igaku* (*Eastern Medicine*) 2003; 19: 51-5.	2)	I
J18.2	Effect on aspiration pneumonia	seihaito (清肺湯)	Mantani N, Kasahara Y, Kamata T, et al. Effect of seihai-to, a Kampo medicine, in relapsing aspiration pneumonia-an open label pilot study. *Phytomedicine* 2002; 9: 195-201.	2)	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
J20.0	Effect and tolerability of EPs 7630 for acute bronchitis	EPs 7630	Kamin W, Ilyenko LI, Malek FA, et al. Treatment of acute bronchitis with EPs 7630: Randomized, controlled trial in children and adolescents. *Pediatrics International* 2012; 54: 219-26	2)	I
J30.1	Outcomes of patients treated with mao-preparations for spring pollinosis	ryokankyomishin-geninto (苓甘姜味辛夏仁湯), eppikajutsuto (越婢加朮湯), daiseiryuto (大青竜湯), keimakakuhanto (桂麻各半湯), gokoto (五虎湯), and maobushisaishinto (麻黄附子細辛湯)	Mori H, Shimasaki M, Kurata F, et al. Outcome after six-year treatment with mao-preparations for spring pollinosis*. *Progress in Medicine* 2003; 23: 1925-9.	4)	I
J44.8	Therapeutic effect on diffuse panbronchiolitis (DPB)	hochuekkito (補中益気湯)	Sugiyama Y. Kampo therapy on diffuse panbronchiolitis. *Kampo to Saishin Chiryo* (*Kampo & The Newest Therapy*) 1997; 6: 263-7.	1)	N
J45.9	Effect on cough thresholds in asthmatic patients compared with emedastine difumarate	bakumondoto (麦門冬湯)	Watanabe N, Gang C, Fukuda T. Comparison of traditional Chinese-Japanese herbal medicine bakumondo-to with emedastine difumarate on asthmatic patients with increase cough sensitivity. *Journal of the World Allergy Organization* 2003; suppl 1: 52 P-2-28.	1)	C
J45.9	Meta-analysis evaluation of the efficacy and safety of adjunctive Chinese therapy for the treatment of pediatric cough variant asthma	Chinese medicines	Song P, Zeng L, Liang Z, et al. Clinical efficacy and safety of Chinese herbal medicine auxiliary therapy for childhood cough variant asthma: a systematic review and meta-analysis of 20 randomized controlled trials. *Internal Medicine* 2017; 55: 2135-43.	2)	I
J84.1	Effectiveness of rikkunshito for gastrointestinal symptoms concurrent with idiopathic pulmonary fibrosis in patients treated with Pirfenidone	rikkunshito (六君子湯)	Shimizu Y, Shimoyama Y, Kawada A, et al. Gastrointestinal symptoms in idiopathic pulmonary fibrosis patients treated with Pirfenidone and herbal medicine. *Journal of Biological Regulators Homeostatic Agents* 2014; 28: 433-42.	1)	N

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases (27 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
K11.7	Recovery effects against psychotropic drug-induced xerostomia	ninjin'yoeito (人参養栄湯), byakkokaninjinto (白虎加人参湯)	Hara R, Yamagishi H, Okubo M, et al. The Effects of Kampo medicine against drug-induced xerostomia. *Journal of Dental Research* 2000; 79: 1239 No.36.	6) This was a basic study.	C
C26.9 K12.1	Clinical impact of Hangeshashinto in the treatment of chemotherapy-induced oral mucositis in gastric cancer and colorectal cancer	hangeshashinto (半夏瀉心湯)	Nishikawa K, Aoyama T, Oba MS, et al.The clinical impact of Hangeshashinto (TJ-14) in the treatment of chemotherapy-induced oral mucositis in gastric cancer and colorectal cancer： Analyses of pooled data from two phase II randomized clinical trials (HANGESHA-G and HANGESHA-C). *Journal of Cancer* 2018; 9: 1725-30.	1)	N
K25.9	Clinical effects of traditional Chinese medicine "wainei" for gastric ulcer	wainei (和胃寧)	Ren Lin-San, Qi Wei-Jin, Mao Ye-Si. The clinical effects of homemade traditional Chinese medicine "wainei" for gastric ulcer. *Progress in Medicine* 1993; 13: 2854-56.	2)	I
K29.5	Therapeutic effect on chronic gastritis	orento (黄連湯)	Nakajima O, Sone M. Treatment with TSUMURA Orento for chronic gastritis*. *Progress in Medicine* 1994; 14: 1713-9.	5)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
K30.0	Evaluation of Kampo preparations for functional dyspepsia	rikkunshito (六君子湯)	Okumi H, Sekiya N, Terasawa K. Japanese Association of Oriental Psychosomatic Medicine, EBM Team Report: Kampo therapy evidence for psychosomatic disease and stress-related disease 1) EBM evaluation of Kampo preparations for functional dyspepsia. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2009; 24: 70-75 (in Japanese with English abstract)	4)	I
K30	Baseline plasma des-acyl ghrelin level and responsiveness to rikkunshito in patients with functional dyspepsia	rikkunshito (六君子湯)	Togawa K, Matsuzaki J, Kobayakawa M, et al. Association of baseline plasma des-acyl ghrelin level with the response to rikkunshito in patients with functional dyspepsia. *Journal of Gastroenterology and Hepatology* 2016; 31(2): 334-341.	1)	C
K51.2	Palliative effect of an herbal preparation on ulcerative proctitis	xilei san suppository (シレイサン)	Fukunaga K, Ohda Y, Hida N, et al. Placebo controlled evaluation of Xilei San, a herbal preparation in patients with intractable ulcerative proctitis. *Journal of gastroenterology and hepatology*. 2012; 27: 1808-15.	2)	C
K58.9	Effects of keishikashakuyakuto on irritable bowel syndrome	keishikashakuyakuto (桂枝加芍薬湯)	Mizuno S, Nagata K, Yoshida K, et al. Effects of keishikashakuyakuto extract on irritable bowel syndrome: comparative study with mepenzolate bromide. *Shindan to Chiryo (Diagnosis and Treatment)* 1985; 73: 1143-52.	3)	I
K59.0	Laxative effects	hyakudoku-kudashi (百毒下し)	Sugimoto K, Ohta H. Comparison of Hyakudoku-kudashi® with Colac® or Withone® in drug –taking satisfactory - Characteristic effect of Hyakudoku-kudashi® as a herbal laxative- . *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2006; 56: 367-76.	2)	I
K59.0	The effect on bowel movement and its safety	young barley leaf powder (大麦若葉粉末)	Matsui N, Yamamoto K, Yamamoto S, et al. Safety and effect of young barley leaf powder on defecation. *Nihon Rinsho Eiyo Gakkai Zasshi* (*Journal of Japanese Society of Clinical Nutrition*) 2008; 29: 406-13.	2)	I
K59.0	Evaluation of the safety and improvement in bowel habits of young barley leaf powder	young barley leaf powder (大麦若葉粉末)	Matsui N, Yamamoto S, Nagao M, et al. Bowel Habit-improving Effect and safety of a young barley leaf powder-containing diet in male and female adult volunteers with low fecal frequency: a dose-finding study and an efficacy confirmation study. *Journal of Japanese Society of Clinical Nutrition* 2011; 32: 243-51.	2)	I
K59.0	Effect of complementary/alternative medicine on constipation in the elderly	–	Cherniack E. P. Use of complementary and alternative medicine to treat constipation in the elderly. *Geriatrics & Gerontology International* 2013; 13: 533-8.	2) Complementary/alternative medicine other than a Kampo preparation	I
K59.8	Effect of daikenchuto on bowel dysfunction after liver transplantation	daikenchuto (大建中湯)	Kaido T, Shimamura T, Sugawara Y, et al. Multicentre, randomised, placebo-controlled trial of extract of Japanese herbal medicine Daikenchuto to prevent bowel dysfunction after adult liver transplantation (DKB 14 Study). *BMJ Open* 2015; 5: 1-5. doi: 10.1136/bmjopen-2015-008356.	5) Publication only includes protocols.	N
K71.9	Preventive effect on danazol-induced hepatic damage	shosaikoto (小柴胡湯)	Yaginuma T, Okamura T, Takeuchi T, et al. Preventive effect of traditional herbal medicine, shosaiko-to, on danazol-induced hepatic damage. *International Journal of Gynaecology & Obstetrics* 1989; 29: 337-41.	1)	C
K72.9	Efficacy and safety for removal of plasma ammonia in hepatectomized patients	daikenchuto (大建中湯)	Kaiho T, Tanaka T, Tsuchiya S, et al. Effect of the herbal medicine dai-kenchu-to for serum ammonia in hepatectomized patients. *Hepato-Gastroenteterology* 2004; 52: 161-5.	1)	C
K73.0	Effect on chronic hepatitis	shosaikoto (小柴胡湯)	Mizuta M, Murata K, Morimoto T, et al. Therapeutical evaluation of shosaikoto on chronic hepatitis – study on double-blind test -. *Kan Tan Sui* 1986; 12: 155-68.	3)	I
K73.9	Therapeutic effect on chronic active hepatitis	shosaikoto (小柴胡湯)	Jia K, Chen N, Peng X, et al. The study of shosaikoto as treatment for chronic active hepatitis*. *Progress in Medicine* 1992; 12: 1180-3.	2)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
K73.9	Effect on the adverse effects of IFN in patients with chronic hepatitis	maoto (麻黄湯), daiseiryuto (大青竜湯)	Kainuma M, Hayashi J, Sakai S, et al. The efficacy of herbal medicine (Kampo) in reducing the adverse effects of IFN-b in chronic hepatitis C. *American Journal of Chinese Medicine* 2002; 30: 355-67.	1) , 2)	C
K73.9	Effect on the adverse effects of IFN in patients with chronic hepatitis	maoto (麻黄湯)	Kainuma M, Sakai S, Sekiya N, et al. The effects of a herbal medicine (mao-to) in patients with chronic hepatitis C after injection of IFN-beta. *Phytomedicine* 2004; 11: 5-10.	1) , 2)	C
K74.6	Usefulness in the treatment of hepatic cirrhosis	saireito (柴苓湯)	Ohkubo H, Shiota A, Amaki S, et al. Oriental medicine in liver cirrhosis: effect of “sairei-tou” in liver cirrhosis with controlled study. *Kampo to Saishin Chiryo* (*Kampo & the Newest Therapy*) 1994; 3: 121-7.	1)	N
K76.9	Effect on immune abnormality in liver disease	shosaikoto (小柴胡湯)	Mizoguchi Y, Sakagami Y, Kodama C, et al. Immune abnormality in liver disease and oriental medicine therapy*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1987; 4: 227-30.	6) This was a basic study.	I
K83.1	Effects in postoperative patients with biliary obstruction	inchinkoto (茵チン蒿湯)	Kobayashi H, Horikoshi K, Yamataka A, et al. Beneficial effect of a traditional herbal medicine (inchin-ko-to) in postoperative biliary atresia patients. *Pediatric Surgery International* 2001; 17: 386-9.	1)	C
K91.3	Effects on bowel movements after colonic and rectal surgery	keishibukuryogan (桂枝茯苓丸) + daikenchuto (大建中湯)	Suehiro T, Matsumata T, Shikada Y,et al. The effect of the herbal medicines dai-kenchu-to and keishi-bukuryo-gan on bowel movement after colorectal surgery. *Hepato-Gastroenterology* 2005; 52: 97-100.	1)	C
K91.3	Effectiveness of daikenchuto for bowel motility and prevention of paralytic ileus after pancreaticoduodenectomy	daikenchuto (大建中湯)	Okada K, Kawai M, Uesaka K, et al. Effect of daikenchuto (TJ-100) on postoperative bowel motility and on prevention of paralytic ileus after pancreaticoduodenectomy: a multicenter, randomized, placebo-controlled phase Ⅱ trial (The JAPAN-PD Study). *Japanese Journal of Clinical Oncology* 2013; 43: 436-8	5)	N
C26.9 K91.3	Meta-analysis evaluation of the efficacy of daikenchuto for prolonged ileus after open surgery	daikenchuto (大建中湯)	Kono T, Shimada M, Nishi M, et al. Daikenchuto administration for intestinal hypomotility after open abdominal surgery: a pooled analysis of three randomized controlled trials. *Annals of Cancer Research and Therapy* 2017; 25: 41-3.	5) Reference had only a protocol	C
K91.3	To assess the efficacy and safety of daikenchuto for reducing prolonged postoperative ileus in persons undergoing elective abdominal surgery	daikenchuto (大建中湯)	Hoshino N, Takada T, Hida K, et al. Daikenchuto for reducing postoperative ileus in patients undergoing elective abdominal surgery. *Cochrane Database of Systematic Review* 2018; 4:1-55.	6) Retracted article	N
C18.9 K91.9	Evaluation of the efficacy of daikenchuto for gastrointestinal symptoms after laparoscopic colon cancer resection	daikenchuto (大建中湯)	Hoshino N, Kawada K, Hida K, et al. Effect of Daikenchuto (TJ-100) on gastrointestinal symptoms following laparoscopic colectomy in patients with colon cancer: study protocol for a randomized controlled trial. *Trials* 18: 1-6.	5) Reference had only a protocol	C

12. Skin Diseases (9 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
L20-L30	Efficacy of shosaikoto for allergic skin disease	shosaikoto (小柴胡湯)	Nakajima H, Tani T. Chinese medicine therapy for inflammatory dermatosis (2nd report): A clinical trial and a double-blind trial of shosaikoto in the dermatological field. *The Japanese Journal of Clinical and Experimental Medicine* 1983; 60:2621-7.	3)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
L20.9	Efficacy of shosaikoto in dermatologic conditions	shosaikoto (小柴胡湯)	Nakajima H, Tani T. Chinese medicine therapy for inflammatory dermatosis (2nd report): A clinical trial and a double-blind trial of shosaikoto in the dermatological field. *The Japanese Journal of Clinical and Experimental Medicine* 1983; 60:2621-7.	3)	I
L20.9	Evaluation of Kampo therapy for atopic dermatitis	shosaikoto, etc. (小柴胡湯ほか)	Toyoda M. Kampo therapy and atopic dermatitis - An EBM evaluation of Kampo therapy for atopic dermatitis. *Hifu no Kagaku* (*Skin Research*) 2010; 9: suppl. 15: 22-7	4)	I
L30.9	Effects on atopic dermatitis and chronic eczema	shosaikoto (小柴胡湯)	Morohashi M, Toyoda M. Evaluation of efficacy of an evidence-based Kampo therapy for atopic dermatitis. *Hifu no Kagaku* (*Skin Research*) 2003; 2: 44-8.	4)	I
L65.9	Clinical evaluation in the treatment of male pattern baldness	Taiho HR-2 preparation (大宝HR-2製剤)	DABAO HR-2Study Group. Topical DABAO HR-2in the treatment of male pattern alopecia – a randomized double-blind trial -. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicines*) 1988; 4: 1955-67.	2)	I
L65.9	Evaluation of kampo treatment for alopecia	hangekobokuto (半夏厚朴湯)	Ohkuma M. Treatment of alopecia by Chinese drug, hange-koboku-to combined with liquid nitrogen application and PUVA – the second report- . *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1998; 15: 422-3.	1)	C
L70.0	Effects on acne vulgaris	jumihaidokuto (十味敗毒湯), seijobofuto (清上防風湯)	Hayashi N, Kawashima M. The usefulness of chemical peeling with 30% glycolic acid (ph 1.5) for acne vulgaris. *Rinsho Hifuka* (*Japanese Journal of Clinical Dermatology*) 2003; 57: 1213-6.	6) Although used in combination, Kampo medicines were not evaluated.	I
L70.9	Clinical efficacy of chemical peels for the treatment of acne	seijobofuto (清上防風湯), jumihaidokuto (十味敗毒湯)	Kishioka A, Yamamoto Y, Miyazaki M, et al. Clinical evaluation of chemical peeling with glycolic acid for acne. *Aesthetic Dermatology* 2004; 14: 195-202.	6) Although used in combination, Kampo medicines were not evaluated.	I
L91.0	Evaluation of moxibustion marks with topical application of shiunko and with no topical application	shiunko (紫雲膏)	Shirouzu Y, Okumura T, Ichiki A, et al. A comparison of the duration of moxibustion scars with topical application of shiunko before moxibustion and with topical application after moxibustion. *The Journal of Japan College Association of Oriental Medicine* 2015; 38: 112-5.	1)	I&N

13. Diseases of the Musculoskeletal System and Connective Tissue (9 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
M06.9	Effects of Kampo medicines on rheumatoid arthritis patients receiving methotrexate	keishinieppi-ryojutsubu (桂枝二越婢苓朮附)	Kogure T, Tatsumi T, Sato H, et al. Traditional herbal medicines (Kampo) for patients with rheumatoid arthritis receiving concomitant methotrexate: a preliminary study. *Alternative Therapies in Health and Medicine* 2009; 16: 46-51.	1) , 2)	C
M06.9	Effects of kampo medecines on chronic rheumatoid arthritis	saireito (柴苓湯), eppikajutsuto (越婢加朮湯), keishikajutsubuto (桂枝加朮附湯)	Oribe M, Oribe K, Oyake K, et al. Effects of kampo medecines on chronic rheumatoid arthritis: using three types of Kampo prescriptions with different patterns(sho). *Kampo Igaku (Kampo Medicine)* 1989; 13: 371-3.	1)	I
M30.3	Efficacy of ohrengedokuto for Kawasaki disease	ohrengedokuto (黄連解毒湯)	Hirota A, Senaga R, Kawashima S. The effects of ohrengedokuto extract on Kawasaki disease by a double-blind study. *Journal of Traditional Medicines* 1985; 2:230-1.	3)	I
M30.3	Efficacy of ohrengedokuto for Kawasaki disease	ohrengedokuto (黄連解毒湯)	Hirota A, Senaga R, Kawashima S. A double blind study of the effects of ohrengedokuto extract on Kawasaki disease. *Pediatric Clinical* 1985; 38:2329-35.	3)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
M35.0	Effects on Sjögren's syndrome	bakumondoto (麦門冬湯)	Doi Y, Suzuki T, Ono S. Effects of bakumondoto on Sjö gren's syndrome*. *Gendai Toyo Igaku* (*The Journal of Traditional Sino-Japanese Medicine*) 1991; 12 suppl 1: 229-31.	1)	N
M35.2	Effects on Behçet's disease	unseiin (温清飲)	Kaneko F. Clinical use of unseiin for Behcet's disease. *Progress in Medicine* 1986; 6: 384-6.	3)	N
M35.9	Effects of Kampo medicines in treating collagen disease	saireito, etc. (柴苓湯ほか)	Ohno S. Roles of Kampo medicine in treating rheumatic diseases. *Journal of Traditional Medicines* 2007; 24: 73-80.	4)	C
M62.81	Effect of the thumb kneading method and thumb compression method on shoulder stiffness	acupressure	Okina Y, Yano T. A comparison study of effect of the thumb kneading method and thumb compression method on shoulder stiffness. *Journal of Japanese of Oriental Physiotherapy*, 2016; 41:57-64	2)	I
M81.9	Preventive effect of fufang for postmenopausal osteoporosis and fragility fractures	Fufang	Deng W-M, Zhang P, Huang H, et al. Five-year follow-up study of a kidney-tonifying herbal Fufang for prevention of postmenopausal osteoporosis and fragility fractures. *Journal of Bone and Mineral Metabolism* 2012; 30: 517-24.	2)	I

14. Genitourinary Tract Disorders (including Climacteric Disorders) (12 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
N02.8	Clinical efficacy for the treatment of IgA nephropathy in children	shosaikoto (小柴胡湯)	Takahashi Y, Uemura M. Clinical efficacy of shosaikoto for the treatment of IgA nephropathy in children*. *Kampo Igaku* (*Kampo Medicine*) 1986; 10: 27-30.	3)	N
N18.9	Improvement of creatinine levels in chronic renal failure with yojinkodakuto	yojinkodakuto (養腎降濁湯)	Nagasaka K, Fukuda H, Hashimoto M, et al. Yozinkodakuto, a traditional Chinese (Japanese Kampo) medicine, improves the creatinine level in chronic renal failure. *Journal of Traditional Medicines* 2007; 24: 87-9.	1), 2)	C
N20.9	Effects on excretion of calculi after extracorporeal shock wave lithotripsy (ESWL)	choreito (猪苓湯)	Takada M, Yano H, Kanbara N, et al. Effect of chorei-to on spontaneous discharge of urinary stones after extracorporeal shock wave lithotripsy (ESWL). *Hinyokika Kiyo* (*Acta Urologica Japonica*) 1997; 43: 311-4.	1)	C
N20.9	Evaluation of the effects on calcium oxalate crystal formation in human urine	choreito (猪苓湯), goreisan (五苓散)	Yoshimura K, Miyake O, Okuyama A, et al. Effect of chorei-to and gorei-san on calcium oxalate crystallization in human urine. *Hinyokika Kiyo* (*Acta Urologica Japonica*) 1998; 44: 13-6.	1)	C
N28.9	Protective effects of anisodamine on renal function in patients with ST-segment elevation myocardial infarction	anisodamine	Wang Y, Fu X, Wang X, et.al. Protective effects of anisodamine on renal function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *The Tohoku Journal of Experimental Medicine* 2011; 224: 91-7.	2)	I
N41.1	Combined effects of hachimijiogan and trimethoprim-sulfamethoxazole on chronic prostatitis	hachimijiogan (八味地黄丸)	Kaneko S, Akiyama T, Kurita T. Combined treatment of chronic prostatitis with sulfamethoxazole-trimethoprim. *Hinyokika Kiyo* (*Acta Urologica Japonica*) 1988; 34: 1091-5.	3)	N
N46	Effects in patients with idiopathic male infertility	ninjin'yoeito (人参養栄湯)	Oeda F, Ichikawa T, Ozawa H, et al. Clinical experience of ninjin-yoei-to on male sterility. *Shinyaku to Rinsho* (*Journal of New Remedies & Clinics*) 1994; 43: 2197-203.	1)	I
N50.8	Clinical efficacy for the treatment of urologic disease	saireito (柴苓湯)	Shida K, Imamura K, Katayama T, et al. Clinical efficacy of sairei-to in various urinary tract diseases centering on fibrosis. *Hinyokika Kiyo* (*Acta Urologica Japonica*) 1994; 40: 1049-57.	1)	C
N74	Effects on infectious vaginal discharge	-	Nazar H, Usmanghani K, Hannan A. Clinical evaluation of unani medicine for infective vaginal discharge. *Journal of Traditional Medicines* 2005; 22: 301-7.	2)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
N94.6	Evaluation of the efficacy of herbal treatments for dysmenorrhea	herbal medicines	Horiba Y, Yoshino T, Watanabe K, et al. Effectiveness of Japanese kampo treatment in dysmenorrhea: single-center observational study. *Traditional and kampo medicine* 2018; 5: 51-5.	1) Observational study	C
N95.1	Effects in climacteric patients with depression	kamishoyosan (加味逍遙散)	Ushiroyama T, Ikeda A, Sakuma K, et al. Changes in serum tumor necrosis factor (TNF-alpha) with kami-shoyo-san administration in depressed climacteric patients. *American Journal of Chinese Medicine* 2004; 32: 621-9.	1)	C
N97.9	Effects on infertility due to ovarian dysfunction	kamishoyosan (加味逍遙散)	Kano T, Ito C, Kasamatsu H, et al. Clinical study of prognosis of 200 deliveries after kampo-treatment for ovarian dysfunctional infertilities and tocolysis. *Nihon Funin Gakkai Zasshi* (*Japanese Journal of Fertility and Sterility*) 1991; 36: 612-20.	1)	N

15. Ante/Post-partum Diseases (2 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
O12.0	Clinical benefits for patients with gestational edema	saireito (柴苓湯)	Iura T, Kuwahara S, Takabayashi H, et al. Clinical benefits of saireito treatment for gestational edema*. *Rinsho Fjinka Sanka* (*Clinical Gynecology and Obstetrics*) 1994; 48: 355-8.	1)	N
O92.3	Clinical efficacy for postpartum galactostasis	kakkonto (葛根湯)	Aisaka K, Kokuho K, Tawada T, et al. Study of the clinical efficacy of kakkonto (EK-1) for treatment of postpartum galactostasis*. *Sanfujinka no Sekai* (*The World of Obstetrics and Gynecology*) 1990; 42: 289-93.	1)	N

18. Symptoms and Signs (23 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
R05	Meta-analysis evaluation of the efficacy and safety of bakumondoto for cough	bakumondoto (麦門冬湯)	Kim KI, Shin S, Lee N, et al. A traditional herbal medication, Maekmoondong-tang, for cough: a systematic review and meta-analysis. *Journal of Ethnopharmacolog* 2016; 3: 144-54.	2) Meta-analysis included non-Japanese medicines	N
R10.4	Effects on lower abdominal pain after surgery	tokishigyakuka-goshuyushokyoto (当帰四逆加呉茱萸生姜湯)	Nishizawa Y, Amakata Y. The clinical effect of tokishigakukagoshuyushokyoto on abdominal pain following to lower abdominal operation. *Toyo Igaku to Pain Clinic* (*Oriental Medicine and the Pain Clinic*) 1988; 18: 138-44.	1)	N
R13	Effects on swallowing reflex	hangekobokuto (半夏厚朴湯)	Iwasaki K, Wang Q, Nakagawa T, et al. The traditional Chinese medicine banxia houpo tang improves swallowing reflex. *Phytomedicine* 1999; 6: 103-6.	1)	C
R19.8	Anomalous abdominal relaxation in Shakuju therapy	-	Takahashi K, Matsuzawa T, Hara O, et al. Research into anomalous abdominal relaxation in Shakuju therapy. *Toyo Ryoho Gakko Kyokai Gakkai Shi* (*The Journal of Japan College Association of Oriental Medicine*) 2012; 35: 81-3.	2)	I
R20.8	Effects on diabetic neuropathy	goshajinkigan (牛車腎気丸)	Sakamoto N, Sato Y, Goto Y, et al. Treatment of diabetic neuropathy with oriental medicines - comparison between goshajinkigan and mecobalamin*. *Tonyobyo* (*Journal of the Japan Diabetes Society*) 1987; 30: 729-36.	3)	I
R20.8	Effect of acupuncture stimulation on depth perception	acupuncture	Tezuka C, Nakamura M. Effect of acupuncture on depth perception. *Journal of the Society for Integrative Medicine Japan* 2017; 10:196-200.	2)	I
R20.8	Effects on diabetic peripheral neuropathy	goshajinkigan (牛車腎気丸)	Toba K, Orimo H. Diabetic peripheral neuropathy*. *Shindan to Chiryo (Diagnosis and Treatment)* 1986; 74: 2330-4.	3)	N
R25.2	Usefulness in the treatment of muscle cramp associated with hepatic cirrhosis	hachimijiogan (八味地黄丸), goreisan (五苓散), shakuyakukanzoto (芍薬甘草湯)	Takamori S, Ando T. A study of the effect of hachimi-jio-gan on painful muscle cramps (komuragaeri). *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1994; 45: 151-7.	1)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
R42.0	Efficacy and safety in the treatment of chronic dizziness	saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯), ryokeijutsukanto (苓桂朮甘湯)	Komatsuzak A, Sakata E, Kamei T, et al. Clinical study of chai-hu-gia-long-gu-nu-li tang and ling-gui-zhu-gan tang on chronic dizziness cares. *Yakuri to Chiryo* (*Japanese Pharmacology & Therapeutics*) 1986; 14: 4479-90.	3)	I
R42.0	Efficacy in the treatment of dizziness	takushato (沢瀉湯)	Yoneta Y, Hashiguchi K, Takiguchi Y, et al. Clinical efficacy of takushato a Kampo (Japanese herbal) medicine, in the treatment of refractory dizziness and vertigo: Comparison between standard and triple dose. *Journal of Traditional Medicines* 2009; 26: 68-73.	2)	I
R42	QOL improvement with combination of hochuekkito and vestibular rehabilitation for patients with dizziness and depression tendency	hochuekkito (補中益気湯)	Arai M, Goto F, Hosaka T. Study of Combination Therapy of Vestibular Rehabilitation and Hochuekkito for Intractable Dizziness. *Shinshin Igaku* (*Japanese Journal of Psychosomatic Medicine*) 2012; 52: 221-8 (in Japanese)	1)	I
R50.9	Effects of on postoperative nonspecific fever	shosaikoto (小柴胡湯)	Ochiai K, Kobayashi S, Shimizu Y, et al. Effect of Chinese medicine for nonspecific fever after operation. *Nippon Sanka Fujinka Gakkai Tokyo Chiho Bukai Kaishi* (*Tokyo Journal of Obstetrics and Gynecology*) 1986; 35: 279-82.	3)	N
R51.0	Usefulness for treating chronic headache	keishininjinto (桂枝人参湯), chotosan (釣藤散)	Matsumoto H, Kashiwagi M, Matsuya M, et al. Study of the usefulness of keishininjinto and chotosan for treating chronic headache*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1995; 72: 1299-303.	1)	N
R51.0	Effects of Kampo therapy on primary headache (other than migraine)	chotosan, etc. (釣藤散ほか)	Chiba N, Oka T, Tsuji S. Japanese Association of Oriental Psychosomatic Medicine, EBM Team Report: Kampo therapy evidence for psychosomatic disease and stress-related disease - Primary headache (non-migraine). *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2009; 24: 85-8 (in Japanese with English abstract).	4)	I
R51	Effectiveness of yangxue qingnao for chronic cerebral circulation insufficiency	yangxue qingnao (養血清脳)	Wu C, Liao L, Yan X, et al. Effects of Yangxue Qingnao Granules on chronic cerebral circulation insufficiency: a randomized, double-blind, double-dummy, controlled multicentre trial. *Psychogeriatrics* 2013; 13: 29-34.	2)	I
R52.9	Effects on postoperative abdominal pain	tokishigyakuka-goshuyushokyoto (当帰四逆加呉茱萸生姜湯)	Nishizawa Y, Amakata Y. The analysis of the effect of tokishigyakukagoshuyushokyoto on the abdominal pain after lower abdominal operation. *Toyo Igaku to Pain Clinic* (*Oriental Medicine and the Pain Clinic*) *1988; 18: 102-8.*	1)	I
R52.9	Effects on postoperative abdominal pain	tokishigyakuka-goshuyushokyoto (当帰四逆加呉茱萸生姜湯)	Nishizawa Y, Amakata Y. The clinical effect of tokishigyakukagoshuyushokyoto on abdominal pain following to abdominal operation. - III Clinical effectiveness in each class of CMI classification-. *Toyo Igaku to Pain Clinic* (*Oriental Medicine and the Pain Clinic*) *1988; 18: 50-7.*	1)	I
R53	Effects on chronic fatigue	various kinds of decoctions (煎剤)	Sekiya N, Shimada Y, Shintani T, et al. Reduction of perception of chronic fatigue in an observational study of patients receiving 12 weeks of Kampo therapy. *The Journal of Alternative and Complementary Medicine* 2005; 11: 895-901.	1) , 2)	C
R53.0	Effect of compound spice extract consumption on subjective symptoms in female with deficiency pattern	uikyo (茴香), sansyo (山椒)	Ide S, Kishi T, Asada K. Effect of compound spice extract consumption on subjective symptoms in female with deficiency pattern. *Kampo to Saishin-chiryo (Kampo & the Newest Therapy)* 2018; 27(2): 175-83.	2)	I
C34.9 R63.0	Effect of rikkunshito on loss of appetite due to cancer chemotherapy	rikkunshito (六君子湯)	Inoue T, Takagi H, Owada Y, et al. The efficacy of the Kampo medicine rikkunshito for chemotherapy-induced anorexia (RICH trial) : study protocol for a randomized controlled trial. *Trials* 2017; 18: 1-8.	5) Reference had only a protocol	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
R68.8	Effects on "*oketsu*" score and erythrocyte deformability in patients with multiple lacunar infarction	keishibukuryogan (桂枝茯苓丸)	Hikiami H, Goto H, Sekiya N, et al. Comparative efficacy of keishi-bukuryo-gan and pentoxifylline on RBC deformability in patients with "oketsu" syndrome. *Phytomedicine* 2003; 10: 459-66.	1) , 2)	C
R68.8	Effects on indefinite complaints including coldness and shoulder stiffness	NT21 fine granules (keishibukuryogan [桂枝茯苓丸] + vitamin E)	Sato N, Takei N, Ikejima K, et al. Effects of a combination preparation of guizhi fuling wan and vitamin E on indefinite complaints such as stiffness of shoulder and cold feeling. *Toho Igaku* (*Eastern Medicine*) 2004; 19: 23-43.	2)	I
R68.8	Improving effect of drinking Yamatotokicha on oversensitivity to cold in young women	toki (当帰)	Kitano N, Nagasawa T, Improving effect of continuous drinking of Yamatotokicha on oversensitivity to cold in young women. *Trace Nutrients Research* 2016; 33:1-8.	2)	I

19. Injury, Poisoning, and Postoperative Pain (5 reference)

ICD-10	Research Question	Kampo Formula	Reference	Reason for Exclusion	Source
S06	Effect of Zhoubo and uncaria tincture in the treatment of concussion sequelae	Zhoubo	Liang J, Wang Y, Liang B. Zhoubo plus uncaria tincture in the treatment of cerebral concussion sequelae. *Journal of Physical Therapy Science* 2017: 28: 2027-30.	2)	I
T14.0	Effect of hochuekkito on skin damage due to UV radiation	hochuekkito (補中益気湯)	Kobayashi H, Yanagihara S, Tamiya Y, et al. Histopathological study of the effects of astragalus bupleurum and gingseng combination formula bupleurum and gingseng combination formula hochuekkito a traditional Japanese herbal medicine on ultraviolet-irradiated skin damage in hairless mice. *American Journal of dermatopathology* 2014; 36: e40-1	6) This was a basic study.	C
T65.8	Effects on yusho (油症)	hochuekkito (補中益気湯), keigairengyoto (荊芥連翹湯), goshajinkigan (牛車腎気丸), bakumondoto (麦門冬湯)	Tokunaga S. Kampo therapy for yusho. Research on the effect of the heating medium on humans, and its therapeutic effects*. *Kosei Rodosho Kagaku Kenkyuhi Hojokin Shokuhin no Anshin Anzen Kakuho Suishin Kenkyu Jigyo Heisei 19 Nendo Sokatsu Buntan Kenkyu Hokokusho* (*Ministry of Health, Labour and Welfare, Science Research Grant, Food Safety and Security Promotion Research Project, Summary and Working-group Research Report Fiscal Year 2006*) 2008; 65-72.	1)	N
T75.2	Combined effects of balneotherapy with other therapies	tokishigyakuka-goshuyushokyoto (当帰四逆加呉茱萸生姜湯), goshajinkigan (牛車腎気丸), bushimatsu (ブシ末)	Wang H, Eboshida A, Kagamimori S. Balneotherapy in combination with other therapies. *The Journal of the Japanese Society of Balneology, Climatology and Physical Medicine* 2010; 73: 143-58.	4)	I
T78.9	Estimated incidence of adverse reactions to kampo medicines in randomized controlled clinical trials	Various prescriptions	Arai I, Hagiwara Y, Motoo Y, et al. Estimated incidence of adverse reactions to Kampo medicines in randomized controlled clinical trials. *Traditional & Kampo Medicine* 2018; 5: 106-12.	1)	C

21. Others (28 reference)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
Z01.8	Effects on plasma levels of gut-regulatory peptides in healthy subjects	keishininjinto (桂枝人参湯)	Sato Y, Katagiri F, Inoue S, et al. Effect of a single treatment with keishininjinto on plasma levels of gut-regulatory peptides in healthy subjects. *Journal of Health Science* 2007; 53: 220-5.	1)	I
Z01.8	Effects on gastrointestinal peptide concentrations in the plasma of healthy subjects	shohangeka-bukuryoto (小半夏加茯苓湯)	Katagiri F, Itoh H, Takeyama M. Effect of sho-hange-ka-bukuryo-to on gastrointestinal peptide concentrations in the plasma of healthy human subjects. *Biological & Pharmaceutical Bulletin* 2004; 27: 1674-8.	1)	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
Z01.8	Effects on human plasma adrenocorticotropic hormone and cortisol levels in patients exposed to continual stress	shohangeka-bukuryoto (小半夏加茯苓湯), nichinto (二陳湯)	Katagiri F, Inoue S, Sato Y, et al. Comparison of the effects of sho-hange-ka-bukuryo-to and nichin-to on human plasma adrenocorticotropic hormone and cortisol levels with continual stress exposure. *Biological & Pharmaceutical Bulletin* 2004; 27: 1679-82.	1)	C
Z01.8	Effects on plasma neuropeptide levels in healthy subjects	daikenchuto (大建中湯)	Sato Y, Inoue S, Katagiri F, et al. Effects of pirenzepine on dai-kenchu-to-induced elevation of the plasma neuropeptide levels in humans. *Biological & Pharmaceutical Bulletin* 2006; 29: 166-71.	1)	I
Z01.8	Effects on plasma levels of calcitonin gene-related peptides and substance P in healthy subjects	ninjinto (人参湯)	Sato Y, Katagiri F, Inoue S, et al. Effects of ninjin-to on levels of calcitonin gene-related peptide and substance P in human plasma. *Biological & Pharmaceutical Bulletin* 2004; 27: 2032-4.	1)	C
Z01.8	Immunological effects in bedridden elderly patients	hochuekkito (補中益気湯), kanzo powder (甘草末), hochuekkito (補中益気湯) + kanzo powder (甘草末)	Oide H, Okuda C. Evaluation of immunological effects of hochuekkito and kanzo powder in bedridden elderly patients*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1988; 5: 555.	5)	N
Z01.8	Changes in serotonin and vasoactive intestinal peptides in human plasma	daikenchuto (大建中湯)	Nagano T, Itoh H, Takeyama M. Effect of dai-kenchu-to on levels of 5-hydroxytryptamine (serotonin) and vasoactive intestinal peptides in human plasma. *Biological & Pharmaceutical Bulletin* 2000; 23: 352-3.	1)	C&I
Z01.8	Effects on plasma levels of brain-gut peptides (motilin, vasoactive intestinal peptide, gastrin, and somatostatin)	ninjinto (人参湯)	Naito T, Itoh H, Nagano T, et al. Effects of ninjin-to on levels of brain-gut peptides (motilin, vasoactive intestinal peptide, gastrin, and somatostatin) in human plasma. *Biological & Pharmaceutical Bulletin* 2001; 24: 194-6.	1)	C&I
Z01.8	Improvement in QOL of patients undergoing bowel preparation for colonoscopy	daikenchuto (大建中湯), shakuyakukanzoto (芍薬甘草湯)	Saida Y. Efficacy of daikenchuto combination in bowel preparation for colonoscopy － 6 prospective study*. *Progress in Medicine* 2005; 25: 3058-9.	5)	N
Z01.8	Effects on corticosteroids	hachimijiogan (八味地黄丸)	Itoh T, Tanaka N, Shibahara N, et al. Effect of hachimi- jio-gan on adrenal corticosteroids. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1998; 15: 155-60.	2)	I
Z01.8	Pharmacokinetics of (-) epicatechin 3-O-gallate, glycyrrhetic acid, and rhein in healthy subjects after unpito administration	unpito (温脾湯)	Takizawa Y, Mizuhara Y, Morita T, et al. Pharmacokinetics of (-) epicatechin 3-o-Gallate, glycyrrhetic acid and rhein in healthy male volunteers after a single dose administration of TJ-8117 (Unpito), a Japanese traditional medicine for renal failure. *Rinsho Yakuri* (*Japanese Journal of Clinical Pharmacology and Therapeutics*) 2006; 37: 33-40.	2)	I
Z01.8	Effects on serum triglyceride levels in healthy young women	azukiyu (azuki bean juice)	Maruyama C, Araki R, Kawamura M, et al. Azuki bean juice lowers serum triglyceride concentrations in healthy young women. *Journal of Clinical Biochemistry and Nutrition* 2008; 43: 19-25.	2)	I
Z01.8	Serum aconitine concentrations after bushi powder administration	shuchibushimatsu (修治ブシ末), bushi powder (ブシ末)	Nakae H, Fujita Y, Igarashi T, et al. Serum aconitine concentrations after taking powdered processed Aconiti tuber. *Biomedical Research* 2008; 29: 225-31.	2) An herbal preparation was used.	C
Z01.8	Effect of bushimatsu on blood plasma serotonin and interleukin 18 levels	bushimatsu (ブシ末)	Nakae H. Plasma serotonin and interleukin 18 levels after taking powdered processed aconiti tuber. *Journal of Complementary and Integrative Medicine* 2010; 7: 1-9.	2) A herbal preparation was used.	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
Z01.8	Effect of bushimatsu on degree of oxidation and antioxidative activity	shuchibushimatsu (修治ブシ末), bushi powder (ブシ末)	Nakae H. Clinical Evaluation of oxidative stress after taking powdered processed Aconiti Tuber. *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) 2010; 61: 15-8 (in Japanese with English abstract).	2) A herbal preparation was used.	N
Z01.8	Physical property of glycyrrhizin contained in kampo extracts and change in the blood levels of glycyrrhetinic acid	shoseiryuto (小青竜湯), shosaikoto (小柴胡湯)	Miyamura M, Ono M, Kyotani S, et al. Properties of glycyrrhizin in Kampo extracts including licorice root and changes in the blood concentration of glycyrrhetic acid after oral administration of Kampo extracts. *Yakugaku Zasshi* (*Journal of the Pharmaceutical Society of Japan*) 1996; 116: 209-16.	1)	C
Z01.8	Comparison of differences in human gene expression induced by tokishakuyakusan containing different grades of crude drug	tokishakuyakusan (当帰芍薬散)	Hayasaki T, Katoh A, Shojo M, et al. Differences in human gene expression induced by tokishakuyakusan containing different grades of Angelica radix. *Journal of Traditional Medicines* 2010; 27: 166-78.	1)	I
Z01.8	Comparison of GLP-1 response and postprandial blood sugar and insulin level to evaluate the effects of the traditional Japanese medicine rikkunshito on postprandial glucose and lipid metabolism	rikkunshito (六君子湯)	Tanaka K, Urita Y, Nara K, et al. Effects of the traditional Japanese medicine rikkunshito on postprandial glucose and lipid metabolism. *Hepato-Gastroenterology* 2011; 58: 1112-8.	6) This is an RCT-cross over paper, however, the RCT-cross over outcomes were not described in the results.	N
Z01.9	Effects on plasma levels of brain-gut peptides (motilin, gastrin, and somatostatin)	hangeshashinto (半夏瀉心湯)	Naito T, Itoh H, Yasunaga F, et al. Hange-shashin-to raises levels of somatostatin, motilin, and gastrin in the plasma of healthy subjects. *Biological & Pharmaceutical Bulletin* 2002; 25: 327-31.	1)	I
Z02.9	Augmentative effect on acupuncture anesthesia	shakuyakukanzoto (芍薬甘草湯)	Kitade T, Jinno H, Hyodo M, et al. Experimental study of the augmentative effect of shakuyakukanzoto on acupuncture anesthesia*. *Kiso to Rinsho* (*The Clinical Report*) 1986; 20: 3309-14.	3)	I
Z04.8	A study of the essential oil components of kamishoyousan extract	components of kamishoyousan extract (加味逍遙散料)	Yomoda S, Kawashima T. A study on essential oil components of kamishoyousan extract, *Phil Kampo* 2017; 63:30-2.	2)	I
Z04.8	Evaluation of the clinical utility of ephedrine alkaloid free ephedra extract (EFE)	ephedrine alkaloid free ephedra extract	Odaguchi H. A clinical study to evaluate the clinical utility of ephedrine alkaloid free ephedra extract (EFE). *Journal of the Pharmaceutical Society of Japan* 2017; 137:195-7.	2)	C
Z04.8	Evaluation of the clinical safety of ephedrine alkaloid free ephedra extract (EFE)	ephedrine alkaloid free ephedra extract	Odaguchi H, Sekine M, Hyuga S, et al. Double-Blind, Randomized, Crossover Comparative Study for Evaluating the Clinical Safety of Ephedrine Alkaloids-Free Ephedra Herb Extract (EFE). *Evidence-based complementary and alternative medicine* 2018: 1-8.	2)	C
Z22.8	Effects of *hozai* (補剤, formulations with tonic effects) on carriers of methicillin-resistant *Staphylococcus aureus* (MRSA) undergoing neurosurgery	juzentaihoto (十全大補湯), hochuekkito (補中益気湯)	Karibe H, Kumabe T, Ishibashi Y, et al. The effect of Japanese herbal medicine on MRSA carrier in neurosurgery. *No Shinkei Geka* (*Neurological Surgery*) 1997; 25: 893-7.	1)	C
-	Pharmacoeconomic analysis	Various prescriptions	Koinuma M, Kamei M, Matsumoto K, et al. Feasibility study for the pharmacoeconomic analysis of Kampo Medicines. *Nihon Toyo Igaku Zasshi* (*Kampo medicine*) 2005; 56: 813-22.	6) This was not a clinical study.	I
-	Effects of abdominal examination practice with simulated patients on acupuncture and moxibustion students	None	Okuno Y, Taniguchi M. Effects of abdominal examination practice with simulated patients on acupuncture and moxibustion students (No. 1) Communication ability among sighted students. *Education of Acupuncture and Manual Therapy* 2010; 6: 10-5.	6) This was a study of acupuncture and moxibustion.	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
-	Results of a survey of Chinese medicine education for training hospitals and residents	Chinese medicine education	Arai M, Nakada Y, Izumi S, et al. The education of traditional Japanese (Kampo) medicine: surveys of training hospitals and residents. *BMC Complementary and Alternative Medicine* 2017: 17:134; 1-11. doi: 10.1186/s12906-017-1634-2.	6) Reference to Chinese medicine education	C
-	Biological effects of toki bath additives	toki bath additives	Mitani A, Tanaka K, Urayama A, et al. Biological effects of herbal foot bath additive produced from Tohki extract in Yamaguchi Prefecture : The viewpoints of relaxation and blood-circulation improving effects. *Academic Archives of Yamaguchi Prefectural University* 2018;11: 19-28.	2)	I

8. Conflict of interests

Based on the “Guidelines for conflict of interests (COI) in medical research” (January 27, 2013) by the Japan Society for Oriental Medicine, COI during the period between January 1, 2019 and December 31, 2019 to be disclosed by current members of the EBM Committee and abstractors is as follows. Belonging of the abstractors to laboratories endowed by companies etc. during the period from the second to fifth phases of the project (June 2005 – December 2019) is separately described.

(1) COI (except for belonging to laboratories endowed by companies) during the period between January 1, 2019 and December 31, 2019 to be disclosed based on the “Guidelines for conflict of interests (COI) in medical research”

Ichiro ARAI, No potential COI; Yasuhito KATO, No potential COI; Masamichi KITAGAWA, No potential COI; Toshiaki KOGURE, No potential COI; Hiroshi KOIKE, No potential COI; Hirozo GOTO, No potential COI; Hiroki TAKUMA, Position as an officer or advisor of a company or for-profit organization and remuneration (Haugen Pharmacy, Co., Ltd.); Hideyuki NAKATA, No potential COI; Etsuo HOSHINO, No potential COI; Miyuki MINARI, Other compensation (TSUMURA & CO.); Yoshiharu MOTOO, Honoraria such as lecture fees, attending conferences received from a company or for-profit organization for the time and labor given by the researcher (TSUMURA & CO.).

(2) Belonging to laboratories endowed by companies etc. (June 2005 – December 2019)

Makoto ARAI	Belongs to endowed lab, TSUMURA & CO. (June 2005 – March 2013)
Takahisa USHIROYAMA	Belongs to endowed labs, FamilyMart Co., Ltd., Paramount Bed Co., Ltd., Fujitsu Ltd., FUJIFILM Medical Co., Ltd., The Zenitaka Corporation, KSK Co. Ltd., Nippon Telegraph and Telephone West Corporation, Mediceo Corporation, Asami Co., Ltd., ROHTO Pharmaceutical Co., Ltd., Godotoho Co., Ltd., Kuraya Sanseido Inc., Paratechno Co. Ltd., Kracie Pharmaceutical, Ltd., Konishi Medical Instruments Co., Ltd., and four personal contributions (from June 2009 – March 2017)
Tetsuro OKABE	Belongs to endowed lab, TSUMURA & CO. (June 2005 – March 2013)
Toshiaki KOGURE	Belongs to endowed lab, TSUMURA & CO. (June 2005 – March 2010)
Hirozo GOTO	Belongs to endowed lab, TSUMURA & CO. (June 2005 – March 2006)
Hiroki TAKUMA	Belongs to endowed lab, Japan Pharmaceutical Manufacturers Association (JMPA) (June 2005 – March 2006)
Kiichiro TSUTANI	Belongs to endowed lab, JMPA (June 2005 – March 2006) Belongs to endowed lab, Towa Pharmaceutical (April 2006 – March 2015)
Hideyuki NAKATA	Belongs to endowed lab, TSUMURA & CO. (July 2005 – March 2008)
Takao NAMIKI	Belongs to endowed lab, TSUMURA & CO. (October 2005 – May 2010)

9. Japan Society for Oriental Medicine EBM Committee members (participants)

First Phase (June 2001 – May 2005)
Special Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Notes: The information below is as of June 2000, and may differ from the current status.

Chairman:

Tetsuo AKIBA	Akiba Hospital

Members (5 persons, order of the Japanese syllabary):

Yoji IIKURA	Department of Pediatrics, School of Medicine, Showa University
Yukio OGIHARA	Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Nagoya City University
Keigo NAKATA	Seikoen Hosono Clinic
Toshihiko HANAWA	Oriental Medicine Research Center, Kitasato University
Kenji FUJIWARA	Department of Internal Medicine, Saitama Medical University

Approach examining members (5 persons, order of the Japanese syllabary):

Makoto ARAI	Institute of Oriental Medicine, Tokyo Women's Medical University
Ko IWASAKI	Department of Integrated Traditional Medicine, University of Tokyo
Hirozo GOTO	Department of Japanese Oriental (KAMPO) Medicine, Toyama Medical and Pharmaceutical University
Hiroyuki SAKAMAKI	Institute for Health Economics and Policy, Association for Health Economics Research and Social Insurance and Welfare
Takao NAMIKI	Department of Internal Medicine, Chiba Prefectural Togane Hospital

Report writing members (2 persons, order of the Japanese syllabary):

Tatsutaka YAMAMOTO	Department of Preventive Medicine, St. Marianna University School of Medicine
Katsumi YOSHIDA	Department of Preventive Medicine, St. Marianna University School of Medicine

Adviser

Akifumi YAFUNE	Oriental Medicine Research Center, Kitasato University

Second Phase (June 2005 – May 2009)
Task Force for Evidence Reports (ER-TF)
Special Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Notes: The information below is as of May 2009, and may differ from the current status.

Chair:

Tetsuro OKABE	Department of Integrated Traditional Medicine, Graduate School of Medicine, University of Tokyo

Members (12 persons, order of the Japanese syllabary):

Makoto ARAI	Department of Oriental Medicine, Tokai University School of Medicine
Takahisa USHIROYAMA	Health Science Clinic, Osaka Medical College
Tetsuo OIKAWA	Department of Clinical Research, Oriental Medicine Research Center, Kitasato University
Masamichi KITAGAWA	Main Library, Academic Information Center, The Jikei University School of Medicine
Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Central General Hospital
Hirozo GOTO	Department of Japanese Oriental (KAMPO) Medicine, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama
Hiroki TAKUMA	Social and Administrative Pharmacy Science Unit, College of Pharmacy, Nihon University
Koki TSURUOKA	Tsurukame Clinic, and Division of Community and Family Medicine, Jichi Medical University
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Takao NAMIKI	Department of Frontier Japanese-Oriental (Kampo) Medicine, Graduate School of Medicine, Chiba University
Michio FUJISAWA	Division for Health Service Promotion, University of Tokyo
Etsuo HOSHINO	Department of Gastroenterology, Cancer Institute Ariake Hospital
Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University

Observers (2 persons, order of the Japanese syllabary):

Ichiro ARAI	Subcommittee to Assess the Efficacy of Kampo Medicines, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association
Sen SHINOHARA	Safety Committee, Japan Kampo Medicines Manufacturers Association

Trustee in charge of Special Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Tetsuo AKIBA	AKIBA Clinic of Traditional Medicine, Department of Kampo Medicine, Keio University School of Medicine
(16 Jun. 2001 – 15 Jun. 2007)	
Mitsugi SUGIYAMA	Advanced Critical Care and Emergency Center, Yokohama City University School of Medicine
(15 Jun. 2007 – 9 Mar. 2009)	

Chairperson, Special Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Kiichiro TSUTANI	Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, University of Tokyo

Third Phase (June 2009 – May 2013)
Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Notes: The information below is as of May 2013, and may differ from the current status.

Chair:

Tetsuro OKABE	Department of Integrated Traditional Medicine, Graduate School of Medicine, University of Tokyo

Members (10 persons, order of the Japanese syllabary):

Masamichi KITAGAWA	Academic Information Center, the Jikei University School of Medicine
Takahisa USHIROYAMA	Health Science Clinic, Osaka Medical College
Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Central and General Hospital
Hirozo GOTO	Department of Kampo Medicine, Hokusei Hospital
Hiroki TAKUMA	Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba
Koki TSURUOKA	Graduate School of Social Service Management, Japan College of Social Work
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Michio FUJISAWA	Division for Health Service Promotion, University of Tokyo
Etsuo HOSHINO	Division of Kampo Support, Cancer Institute Ariake Hospital
Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University

Observers (2 persons, order of the Japanese syllabary):

Ichiro ARAI	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association
Yutaka OHTANI	Medical Media Center, Toho University

Chairperson, Committee for EBM, Japan Society for Oriental Medicine (JSOM) / Trustee in charge of Committee for EBM, JSOM:

Kiichiro TSUTANI	Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, University of Tokyo

Fourth Phase (June 2013 – June 2014)
Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)Organization

Notes: The information below is as of June 2014, and may differ from the current status.

Chair and chairperson of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Kiichiro TSUTANI	Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, University of Tokyo

Members (12 persons, order of the Japanese syllabary):

Ichiro ARAI	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association
Takahisa USHIROYAMA	Health Science Clinic, Osaka Medical College
Tetsuro OKABE	The University of Tokyo Hospital
Masamichi KITAGAWA	Academic Information Center, The Jikei University School of Medicine
Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Central General Hospital
Hirozo GOTO	Department of Kampo Medicine, Hokusei Hospital
Hiroki TAKUMA	Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba
Koki TSURUOKA	Graduate School of Social Service Management, Japan College of Social Work
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Michio FUJISAWA	Division for Health Service Promotion, University of Tokyo
Etsuo HOSHINO	Division of Kampo Support, Cancer Institute Ariake Hospital
Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University

Trustee in charge of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Shin-ichi MURAMATSU	Division of Oriental Medicine, Center for Community Medicine, Jichi Medical University (vice-president of JSOM, and trustee in charge of Committee for EBM, JSOM)
Yukio KANEKO	Kaneko Clinic (vice-trustee in charge of Committee for EBM)

Fourth Phase (June 2014 – September 2015)
Task Force for Evidence Reports (ER - TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Notes: The information below is as of September 2015, and may differ from the current status.

Chair and chairperson of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Kiichiro TSUTANI	Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, University of Tokyo

Members (13 persons, order of the Japanese syllabary):

Ichiro ARAI	Kampo pharmaceutical sciences course, Department of Pharmaceutical Sciences, Nihon Pharmaceutical University
Takahisa USHIROYAMA	Health Science Clinic, Osaka Medical College
Tetsuro OKABE	Department of Integrated Traditional Medicine, Graduate School of Medicine, University of Tokyo
Masamichi KITAGAWA	Academic Information Center, The Jikei University School of Medicine
Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Central General Hospital
Hirozo GOTO	Department of Kampo Medicine, Hokusei Hospital
Hiroki TAKUMA	Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba
Koki TSURUOKA	Graduate School of Social Service Management, Japan College of Social Work
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Michio FUJISAWA	Division for Health Service Promotion, University of Tokyo
Etsuo HOSHINO	Division of Kampo Support, Cancer Institute Ariake Hospital
Miyuki MINARI	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association
Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University

Trustee in charge of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Shin-ichi MURAMATSU	Division of Oriental Medicine, Center for Community Medicine, Jichi Medical University (vice-president of JSOM, and trustee in charge of Committee for EBM, JSOM)
Yukio KANEKO	Kaneko Clinic (vice-trustee in charge of Committee for EBM)

Fifth Phase (September 2015 – June 2018)
Task Force for Evidence Reports (ER - TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Chair and chairperson of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University

Members (10 persons, order of the Japanese syllabary):

Ichiro ARAI	Kampo pharmaceutical sciences course, Department of pharmaceutical sciences, Nihon Pharmaceutical University
Takahisa USHIROYAMA	Health Science Clinic, Osaka Medical College
Masamichi KITAGAWA	Academic Information Center, The Jikei University School of Medicine
Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Chuo Hospital
Hirozo GOTO	Department of Kampo Medicine, Hokusei Hospital
Hiroki TAKUMA	Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba
Koki TSURUOKA	Graduate School of Social Service Management, Japan College of Social Work
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Etsuo HOSHINO	Division of Kampo Support, Cancer Institute Ariake Hospital
Miyuki MINARI	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association

Observer

Kiichiro TSUTANI	Faculty of Health Sciences, Tokyo Ariake University of Medical and Health Sciences

Trustee in charge of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Shin-ichi MURAMATSU	Division of Oriental Medicine, Center for Community Medicine, Jichi Medical University (vice-president of JSOM, and trustee in charge of Committee for EBM, JSOM)
Yukio KANEKO	Kaneko Clinic (vice-trustee in charge of Committee for EBM)

Fifth Phase (June 2018 – June 2019)
Task Force for Evidence Reports (ER - TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Chair and chairperson of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University

Members (10 persons, order of the Japanese syllabary):

Ichiro ARAI	Kampo pharmaceutical sciences course, Department of pharmaceutical sciences, Nihon Pharmaceutical University
Yasuhito KATO	Department of Obstetrics and Gynaecology, Asahikawa Medical University
Masamichi KITAGAWA	Academic Information Center, The Jikei University School of Medicine
Hiroshi KOIKE	Department of Family Medicine, Division of Comprehensive Patient Care, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University
Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Chuo Hospital
Hirozo GOTO	Department of Kampo Medicine, Hokusei Hospital
Hiroki TAKUMA	Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Etsuo HOSHINO	Kukai Memorial Clinic for Integrative Medicine
Miyuki MINARI	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association

Observer

Kiichiro TSUTANI	Faculty of Health Sciences, Tokyo Ariake University of Medical and Health Sciences

Trustee in charge of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Shin-ichi MURAMATSU	Division of Oriental Medicine, Center for Community Medicine, Jichi Medical University (vice-president of JSOM, and trustee in charge of Committee for EBM, JSOM)

Sixth Phase (June 2019 –)
Task Force for Evidence Reports (ER - TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Chair and chairperson of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Chuo Hospital

Members (10 persons, order of the Japanese syllabary):

Ichiro ARAI	Kampo pharmaceutical sciences course, Department of pharmaceutical sciences, Nihon Pharmaceutical University
Yasuhito KATO	Department of Obstetrics and Gynaecology, Asahikawa Medical University
Masamichi KITAGAWA	Academic Information Center, The Jikei University School of Medicine
Hiroshi KOIKE	Department of Family Medicine, Division of Comprehensive Patient Care, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University
Hirozo GOTO	Department of Kampo Medicine, Hokusei Hospital
Nami KONDO	Department of Breast Oncology, Saitama Medical University International Medical Center (April 2020 -)
Hiroki TAKUMA	Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Miyuki MINARI	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association (- August 2020)
Hiroyasu MIWA	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association (August 2020 -)

Observer

Kiichiro TSUTANI	Faculty of Health Sciences, Tokyo Ariake University of Medical and Health Sciences

Trustee in charge of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University (Trustee in charge of Committee for EBM, JSOM)

10. Acknowledgements

Special thanks to the members of Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association, Natsumi TAMAKI, Miyuki MINARI, Fumiko NIINO, Shin-ichi SUZUKI, Masayo TAIRA, Masako MURAYAMA, Ichiro UTAKA, Reiko SAIJO, Miho SHIBAHARA, Sachie HIRATA, Keiji MORI, Madoka KURAHASHI, Masaaki OSHIRO, Tsuneo KAWASHIMA, and Masayuki TAKEZAKI for their cooperation in gathering references and the members of the Japan Medical Abstracts Society for showing how to gather references and select randomized controlled trials.

11. Contact point

We would appreciate it if you would send us your comments on this report to the email address below. Feedback from the authors of the papers abstracted is also welcome. Moreover, please let us know if you find errors or omissions in the papers. The final report will reflect the comments we receive.

ebm-er@jsom.or.jp

12. Structured Abstracts

(502 abstracts describing RCTs)

・Note: Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (*).

・Each bibliographic item is followed by its ID No. from a particular searched database (CENTRAL ID, PubMed ID, or Ichushiweb ID).

・Articles published on the Web are indicated along with the site.

（free of charge）

J-STAGE:

Japan Science and Technology Agency—Electronic Journal Publication/Dissemination Center

http://www.jstage.jst.go.jp/browse/-char/ja

CiNii:

National Institute of Informatics Scholarly and Academic Information Navigator

http://ci.nii.ac.jp/

（payment required）

MOL:

Medical Online

http://www.meteo-intergate.com/

Subscription is needed for viewing.

MOL-Lib:

Medical Online Library

http://www.meteo-intergate.com/library/

Institutions that subscribe to the Medical Online Library have access to articles via the above URL.

1. Infections (including Viral Hepatitis)

References

Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection*. *Nihon Shonika Rinsho* (*Japanese Journal of Pediatrics*). 1992; 45: 1889-91 (in Japanese).

Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection*. *Dai 9-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku Nihon Shoni Toyo Igakkaishi* (*Proceedings of the 9th meeting of the Japan Pediatric Society for Oriental Medicine*) 1993; 9: 20-3 (in Japanese).

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) for rotavirus infection.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

No mention of participating centers (the authors are from the Department of Pediatrics, Kobe Teishin Hospital), Japan.

4. Participants

Forty infants diagnosed with rotavirus infection using Rotalex.

5. Intervention

Patients were allocated alternately to the two treatment groups in the order of consultation.

Arm 1: one intestinal infusion of powdered TSUMURA Saireito Extract Granules (0.3 g/kg body weight) dissolved in 20 mL of warmed saline solution administered by soft catheter immediately after rotavirus diagnosis (n=20).

Arm 2: no treatment (n=20).

6. Main outcome measures

Number of days with diarrhea and total number of vomiting episodes compared before and after administration and between groups; number of transfusion cases and number of hospitalized cases compared between groups.

7. Main results

The mean number of days with diarrhea (1.3–3.4 in arm 1 and 1.1–3.6 in arm 2) was not significantly different between groups. The mean number of vomiting episodes decreased significantly from 3.6 before administration to 0.6 after administration in arm 1 ($P<0.01$), but not in arm 2 (the numbers being 3.3 and 2.8, respectively). There was no significant between-group difference in the number of transfusion cases (8 in arm 1 and 14 in arm 2) and number of hospitalized cases (2 in arm 1 and 6 in arm 2).

8. Conclusions

Saireito administered by intestinal infusion for rotavirus infection effectively decreases the number of vomiting episodes.

9. From Kampo medicine perspective

Saireito was used because it is a combination of shosaikoto (小柴胡湯), which is effective for inflammation, and goreisan (五苓散), which is effective for vomiting.

10. Safety assessment in the article

No adverse effects from saireito intestinal infusion were observed.

11. Abstractor's comments

This clinical study investigated the efficacy of saireito for vomiting and diarrhea due to rotavirus infection. Given the difficulties of following up acute infection after examination, it is a valuable study because it does follow up 40 participants with no dropouts. However, the authors do not mention whether the blood sample taken at initial consultation or the blood sample taken after drug administration was tested, making it unclear whether the presented test results were included to compare severity between groups, or to indicate there is no safety issue with saireito. It is also unclear whether the intestinal infusion itself had any effect on vomiting because the authors did not carry out intestinal infusion using saline solution alone in arm 2, although this is pointed out in the paper. Yet, the authors have devised a possibly groundbreaking therapy, which appears to have relatively few adverse effects, for a disease that has lacked a good therapy, even though it affects many infants each year in winter. A future clinical study with a better defined control group is anticipated.

12. Abstractor and date

Goto H, 31 December 2013.

1. Infections (including Viral Hepatitis)

Reference

Miyazaki R, Tomita H. A study of the efficacy of keihito for diarrhea in children*. *Kampo no Rinsho* (*Journal of Kampo Medicine*) 1996; 43: 217-23 (in Japanese).

1. Objectives

To determine the efficacy of keihito (啓脾湯) for diarrhea in children.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Two clinics, Japan.

4. Participants

Thirty-four children (25 boys and 9 girls; age, 4 months – 12.5 years; weight, 7 – 32 kg) with diarrhea that did not respond to 4-day treatment with intestinal remedies (albumin tannate, multidrug- resistant lactobacillus preparation, and loperamide hydrochloride) followed by fosfomycin (50 mg/kg/day) plus antipyretics as needed.

5. Intervention

Arm 1: treatment with TSUMURA Keihito Extract Granules (啓脾湯) 1.5–2.0 g/10 kg/day (n=18).
Arm 2: treatment with western medicines (control group; n=16).

6. Main outcome measures

Rate of relief of diarrhea, rate of improvement in appetite, and mean number of days to diarrhea resolution.

7. Main results

Mean number of days to diarrhea resolution was significantly lower in arm 1 (6.6±2.0 days) than in arm 2 (8.2±1.7 days) (P<0.05). Rates of relief of diarrhea and improvement in appetite were not significantly different between arms 1 and 2.

8. Conclusions

For children with diarrhea unresponsive to 4-day treatment with the usual western medicines, keihito is an effective prescription inasmuch as it reduces the number of days to diarrhea resolution.

9. From Kampo medicine perspective

After the completion of the study, retrospective evaluation of responders and non-responders in the keihito group revealed that two non-responders had residual cold symptoms including fever and were not considered to have *tai-in-byo* (太陰病, greater yin disease) *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

None.

11. Abstractor's comments

Diarrhea in children can be classified roughly into disease caused by viral or bacterial infection and disease resulting from noninfectious causes such as hypersensitivity to foods and enzyme abnormalities. Most cases are caused by viral infections. For this type of disease, western medicine is not specific and Kampo therapy might be indicated. In the present study, prespecified exclusion of children with bacterial infection, which increases the risk of severe disease, is appreciated. Some problems remain, such as the lack of identification of the cause of diarrhea in participants, the wide variation in age and weight, and the lack of an assessment of safety. In addition, medical economics evaluation would make the study more interesting.

12. Abstractor and date

Arai M, 17 October 2008, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)

Reference

Miura Y, Yamagishi Y, Mikamo H, et al. Investigation into the effects of Kampo therapy for infectious diarrhea*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2011; 28: 102–4 (in Japanese). Ichushi Web ID: 2011211647

1. Objectives

To evaluate the effectiveness of Kampo therapy for infectious diarrhea.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT - envelope).

3. Setting

Izumi Ladies' Clinic, Japan.

4. Participants

Thirty-three patients who presented with watery diarrhea between September 2007 and March 2009 and were diagnosed with infectious gastroenteritis caused by norovirus, identified from stool samples using a rapid testing method.

5. Intervention

Arm 1: goreisan (五苓散) (manufacturer not identified) 2.5 g t.i.d. (n=11).
Arm 2: goreisan (五苓散) (manufacturer not identified) 2.5 g t.i.d. + Shakuyakukanzoto (芍薬甘草湯) (manufacturer not identified) 2.5 g t.i.d. (n=11).
Arm 3: no Kampo therapy (n=11).

6. Main outcome measures

Time to dissipation of vomiting, diarrhea, and abdominal pain.

7. Main results

Time until vomiting dissipated was 79.1 ± 27.5 minutes in Arm 1 (mean ± S.D. and the same below), 83.6 ± 20.1 minutes in Arm 2, and 1701.8 ± 377.2 minutes in Arm 3. Time until diarrhea dissipated was 110.0 ± 30.0 minutes in Arm 1, 129.5 ± 28.6 minutes in Arm 2, and 1728.2 ± 352.0 minutes in Arm 3. Time until abdominal pain dissipated was 122.3 ± 26.5 minutes in Arm 1, 105.0 ± 16.0 minutes in Arm 2, and 1813.6 ± 357.1 minutes in Arm 3.

8. Conclusions

Goreisan and shakuyakukanzoto are effective for vomiting, diarrhea, and abdominal pain due to infectious diarrheal disease caused by norovirus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical trial investigated the therapeutic effects of goreisan and shakuyakukanzoto for infectious diarrheal disease caused by norovirus. It is difficult to assess the therapeutic effects of Kampo medicines on acute-stage diseases, particularly because patients do not return for examination after improvement. In that sense, this is a valuable clinical study as it elucidates the effectiveness of Kampo medicines for an acute-stage disease. Yet, notwithstanding that this written report has the form of an academic article, no mention is made of patient background (age and gender, etc.), the period between onset and examination, and the number (if any) of dropouts. Furthermore, time until dissipation of symptoms are clearly different between the Arms (goreisan, goreisan and shakuyakukanzoto, and no Kampo medicine), but the statistics are not analyzed, meaning there is no mention of significant differences. It is a worthwhile clinical study, so, the authors should have included these details in their article. Yet, the study can rightly be considered excellent because acute-stage disease cannot be easily monitored following therapy, and because it focuses attention on the question of whether Kampo medicines are effective for norovirus infection, a disease without very effective treatment. Hopefully this study will lead to others that examine larger numbers of cases.

12. Abstractor and date

Goto H, , 31 December 2012.

1. Infections (including Viral Hepatitis)

Reference

Morita F, Yokokawa H, Matsuda N, et al. Comparative efficacy of goreisan and probiotics in Japanese adults with acute infectious gastroenteritis: Randomized controlled trial. *Traditional & Kampo Medicine* 2017; 4: 89–93. UMIN ID: UMIN000015875, Ichushi Web ID: 2018243887

1. Objectives

To compare the efficacy and safety of goreisan（五苓散）with that of probiotics in Japanese adults with acute infectious gastroenteritis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Department of General Medicine of Juntendo University Hospital), Japan.

4. Participants

Seventy-six outpatients aged ≥20 years who had diarrhea and/or vomiting caused by acute infectious gastroenteritis as evaluated by internal medicine specialists between December 2014 and December 2015. Exclusion criteria included organic gastrointestinal disease (e.g., colon cancer, inflammatory bowel disease), pregnancy, breastfeeding, and severe liver dysfunction.

5. Intervention

Arm 1: TSUMURA Goreisan（五苓散）Extract Granules 2.5 g t.i.d. orally for 5 days (n=41).
Arm 2: Probiotics (LAC-B Granular Powder; Kowa) 1 g t.i.d. orally for 5 days (n=35).

6. Main outcome measures

Primary endpoints: Duration and frequency of diarrhea and vomiting.
Secondary endpoints: Duration of concomitant symptoms including nausea, abdominal pain, fever, fatigue, and anorexia.

7. Main results

Of the 76 patients, 17 patients in Arm 1 (i.e., 14 patients without a return visit and 3 patients with bacterial gastroenteritis) and 10 patients in Arm 2 (i.e., 8 patients without a return visit, 1 patient with bacterial gastroenteritis, 1 patient who withdrew consent) were discontinued.

No significant intergroup differences were shown for the duration or frequency of diarrhea or vomiting, and also for the duration of nausea, fever, or fatigue. The duration of abdominal pain (median, 2 days [range, 1–5 days] in Arm 1 vs 3 days [range, 1–5 days] in Arm 2; P=0.02) and of anorexia (median, 2 days [range, 1–5 days] vs 2.5 days [range, 1–5 days]; P=0.01) were significantly shorter in Arm 1 than in Arm 2.

8. Conclusions

Goreisan and the probiotics had similar efficacy in the treatment of acute infectious gastroenteritis with diarrhea and/or vomiting. Goreisan may have the potential to improve the general symptoms caused by gastroenteritis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed in either Arm 1 or 2.

11. Abstractor's comments

This RCT evaluated goreisan compared with probiotics in many patients with acute infectious gastroenteritis, and is of significance academically and practically. In terms of the duration and frequency of diarrhea and vomiting, which were the primary endpoints of the study, no significant differences were shown between the goreisan and probiotic groups, but the results suggested similar efficacy between goreisan and the probiotics commonly used in clinical practice. In addition, the duration of concomitant symptoms of abdominal pain and of anorexia were significantly shorter in the goreisan group, which indicates that goreisan may improve the patient's general condition. The authors indicated the need for caution when extrapolating the study results to clinical practice because of selection bias and small sample size. However, the study results appeared to be promising enough for a future multicenter clinical study.

12. Abstractor and date

Kogure T, 12 September 2019.

1. Infections (including Viral Hepatitis)

References

Watanabe A, Hasegawa S. Effect of combined Kampo medicines as adjuvant therapy for pulmonary tuberculosis*. *Nippon Iji Shinpo* (*Japan Medical Journal*) 1992; (3553): 76-7 (in Japanese).

Watanabe A, Takahashi N, Uchida Y, et al. Efficacy of hochuekkito as adjuvant therapy for pulmonary tuberculosis*. *JAMA* (*Japanese version*) 1992; 13 (6) suppl: 20–1 (in Japanese)

1. Objectives

To determine the effect of hochuekkito (補中益気湯) and shosaikoto (小柴胡湯) on improving appetite and host defense in patients undergoing chemotherapy for pulmonary tuberculosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

One hundred and one hospitalized patients with sputum positive for tubercle bacilli and were treated with rifampicin, isoniazid, and streptomycin during a 5-year period from January 1987 to December 1991.

5. Intervention

Arm 1: chemotherapy alone (n=40).

Arm 2: chemotherapy + treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 7.5 g/day (n=31).

Arm 3: chemotherapy + treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 7.5 g/day and TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day (n=30).

6. Main outcome measures

Body weight, degree of sputum smear positivity (on the Gaffky scale), erythrocyte sedimentation rate (ESR), and number of peripheral blood lymphocytes.

7. Main results

After admission, body weight began to increase 2 months after the start of the study treatment in all three arms. The gain was greater in arm 3 than in arm 1 at 3 months and greater in arms 2 and 3 than in arm 1 at 5 months. The weight gain [in kg] at 5 months in arms, 1, 2, and 3 was 3.2, 4.7, and 5.3, respectively. The number of peripheral blood lymphocytes was increased in all 3 arms during the course of treatment and there were no significant between-arm differences. In the subgroup with decreased number of peripheral blood lymphocytes on admission, weight gain was markedly greater in arms 2 and 3 than in arm 1. Furthermore, weight gain was more remarkable in elderly patients aged 60 or older (a total of 45 patients) who received Kampo medicine(s)-combined therapy than in all the patients, including younger patients, who received the combination.

8. Conclusions

Although they affected body weight and the number of peripheral blood lymphocytes but not ESR and sputum smear positivity, Kampo medicines are presumed to be a useful adjunct to antituberculosis therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Hepatic dysfunction occurred and treatment was discontinued in 2 patients of arm 1. In contrast, mild hepatic dysfunction occurred but treatment was continued in arms 2 and 3, indicating the possibility that Kampo medicines help prevent hepatic dysfunction.

11. Abstractor's comments

At the time when this comparative study was conducted, most tuberculosis patients who excreted bacilli had to be hospitalized for treatment. Recently, the number of tuberculosis patients has decreased and, thanks to early detection, most patients present mild disease. Yet some patients with severe disease still require long-term hospitalization. If the lifestyle characteristics of the patients and the severity of their disease had been clearly described, this paper would be helpful today. It is said that shosaikoto or something else was used as treatment for tuberculosis before the war. The both papers were published around the same time as the present paper. It included arms 1 and 2 of the present study and highlights the efficacy of hochuekkito.

12. Abstractor and date

Fujisawa M, 31 March 2009, 1 June 2010, 31 December 2013

1. Infections (including Viral Hepatitis)

References

Shijubo N, Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis – the reducing effect on hepatic dysfunction occurring as an adverse drug reaction–*. *Kampo Igaku* (*Kampo Medicine*) 1993; 17: 241-3 (in Japanese).

Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis*. *Nikkei Medical* 1994; 23 (12): 24-5 (in Japanese).

1. Objectives

To determine the efficacy of hochuekkito (補中益気湯) for reducing hepatic dysfunction and improving digestion and malabsorption in tuberculosis patients undergoing chemotherapy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Eighty hospitalized patients with tuberculosis who had no history of liver disease and no hepatic dysfunction on admission.

5. Intervention

Anti-tubercular agents were RFP+INH+SM (EB) for patients who excreted tubercle bacilli and RFP+INH for patients who tested negative for tubercle bacillus excretion and vomicae.

Arm 1: chemotherapy + treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5 g t.i.d. between meals (n=40).

Arm 2: chemotherapy alone (n=40).

6. Main outcome measures

Hepatic dysfunction and body weight.

7. Main results

Abnormal glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), and GOT and/or GPT levels were observed in 10%, 10%, and 13% of patients in arm 1 and 23%, 28%, and 30% in arm 2. Obviously, the occurrence of hepatic dysfunction was decreased in arm 2. The rate of weight gain began to increase at 1 month in arm 1 and at 2 months in arm 2.

8. Conclusions

Coadministration of hochuekkito reduces hepatic dysfunction resulting from RFP/INH-based chemotherapy and stimulates body weight gain, which is an indicator of improved *hiiqikyo* (impaired digestion and absorption), but does not normalize C-reactive protein level or prevent tuberculosis bacillus excretion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

GOT and GPT levels increased to 200 IU/L or higher and treatment discontinuation was required in 2 patients of arm 1.

11. Abstractor's comments

Nakanishi (1994) adds 16 participants to the paper by Shijubo et al. (1993). Hepatic dysfunction due to anti-tubercular agents increased slightly for the first one to two months of administration, but in most cases it gradually improved even with continued use. However, in some cases, hepatic dysfunction was severely aggravated and required regular monitoring. This RCT provides some interesting outcomes in terms of reducing the occurrence of hepatic dysfunction.

12. Abstractor and date

Fujisawa M, 31 March 2009, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)

Reference

Enomoto Y, Hagiwara E, Komatsu S, et al. Pilot quasi-randomized controlled study of herbal medicine hochuekkito as an adjunct to conventional treatment for progressed pulmonary *mycobacterium avium* complex disease. *PLOS ONE* 2014; 9: 1-8. CENTRAL ID: CN- 00998327, Pubmed ID: 25093868

1. Objectives

To evaluate the effectiveness of hochuekkito (補中益気湯) as an adjunct to conventional treatment for progressed refractory pulmonary *Mycobacterium avium* complex (MAC) disease.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital, Japan.

4. Participants

Eighteen pulmonary MAC disease patients aged 20 years or older who were treated for at least one year but persistently culture-positive, or who were difficult to treat with antibiotics due to drug allergy.

5. Intervention

Prior treatment: Combination of rifampicin, ethambutol, clarithromycin, levofloxacin, kanamycin, and streptomycin or no treatment.
Arm 1: Hochuekkito (補中益気湯) (manufacturer unknown) administered orally 2.5 g b.i.d. or 2.5 g t.i.d. + prior treatment for up to 24 weeks (n=9) (one subject untreated).
Arm 2: Prior treatment (n=9) (one subject untreated).

6. Main outcome measures

Sputum conversion rate at 24 weeks and number of MAC colonies.
Change in shadow size in the lungs at 24 weeks.
Chronic obstructive pulmonary disease assessment test (CAT) scores and serum albumin level, serum C-reactive protein (CRP) level, and erythrocyte segmentation rate (ESR).

7. Main results

The sputum of all subjects remained positive for bacteria throughout the study. The number of colonies from baseline to 24 weeks remained essentially unchanged in Arm 1 or 2. Chest X-ray revealed improvement or no change in 8 subjects in Arm 1, and 3 subjects in Arm 2, showing that the MAC disease had a significantly more favorable course in the hochuekkito arm. CAT scores and ESR and CRP levels were worsened in most subjects in the two arms, but body weight and serum albumin level tended to increase in Arm 1. Interestingly, body weight increased in all subjects with radiographic improvement and decreased in most subjects with radiographic progression.

8. Conclusions

Although patients in the hochuekkito group had higher baseline ESR level and lower baseline blood albumin level, they showed chest radiographic improvement and increased body weight. Thus hochuekkito is useful as a therapeutic drug for pulmonary MAC disease.

9. From Kampo medicine perspective

Hochuekkito is indicated for patients in poor general condition.

10. Safety assessment in the article

No serious adverse events were noted.

11. Abstractor's comments

This RCT selected study subjects from a group of 155 patients with pulmonary MAC disease. These days, the number of pulmonary MAC disease patients is increasing. Since patients are not always responsive to general treatment, this study treatment seems meaningful. Establishing true outcome measures will improve the quality of evidence in a future RCT. Further development of this research is anticipated.

12. Abstractor and date

Fujisawa M,31 March 2017.

1. Infections (including Viral Hepatitis)

Reference

Seki T, Matsumoto T, Deguchi H, et al. Evaluation of the efficacy of hochuekkito in preventing MRSA colonization and infection*. *Kampo Igaku* (*Kampo Medicine*) 1999; 23: 196-7 (in Japanese). Ichushi Web ID: 2000068588

1. Objectives

To evaluate whether hochuekkito has efficacy in preventing colonization and infection with methicillin-resistant *Staphylococcus aureus* (MRSA).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Traumatology and Critical Care Medicine, Dokkyo Medical University Koshigaya Hospital, Japan

4. Participants

Ninety-five patients admitted to the above hospital.

5. Intervention

Arm 1: treatment with hochuekkito (補中益気湯) (2.5 g, t.i.d.) per os (p.o.) or using a nasogastric tube; every day from the third day of hospitalization.
Arm 2: no treatment with hochuekkito.

6. Main outcome measures

From all patients, nasal, throat, and urine specimens were cultured for MRSA on the second hospital day, one week later, and then once a week. Sputum was also cultured from patients who underwent endotracheal intubation or tracheotomy and from those who were able to provide sputum. Similarly wound cultures were performed for patients with wound infection. When at least one culture of any specimen was positive for MRSA, the patient was considered to be MRSA-positive.

7. Main results

A total of 63 patients - 30 of 48 in arm 1 and 33 of 47 in arm 2 - withdrew from the study. Among these withdrawals, 25 patients in arm 1 and 32 in arm 2 were transferred to other wards or died, 3 received no hochuekkito, and 3 underwent no laboratory follow-up (cultures). Thus, 18 patients in arm 1 and 14 in arm 2 were examined and compared. The most common disease was trauma, followed by cerebrovascular disorder. There was no significant difference in MRSA positivity between arm 1 (8 of 18 patients) and arm 2 (9 of 14 patients). Among the trauma patients, however, there was a trend toward lower MRSA positivity in hochuekkito-treated patients (5 of 11 [45.5%] being positive), compared with hochuekkito-untreated patients (5 of 7 [71.4%] being positive). A similar trend toward lower MRSA positivity in hochuekkito-treated patients was found among patients who required mechanical ventilation.

8. Conclusions

It is suggested that administration of hochuekkito can prevent MRSA infection.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The authors deserve praise for conducting this RCT in an emergency care setting. Given the setting, it is not surprising that many patients (66%) withdrew from the study. But the authors' reasons for the withdrawals provide readers with very useful information. They also described gown use and hand washing by medical personnel and visitors, reflecting their consideration of bias and confounding factors. Unfortunately, this study included only a small number of patients. If it had employed a blinded, placebo-controlled design, the report would have been more reliable. The development of future studies is expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)

Reference

Suzuki J, Arata S, Sugiyama M. Improvement of immunity and nutrition by hochuekkito in immuno-compromised hosts – for the control of MRSA –*. *Progress in Medicine* 2002; 22: 1362-3 (in Japanese). Ichushi Web ID: 2002261757 MOL, MOL-Lib

1. Objectives

To evaluate whether hochuekkito (補中益気湯) can improve immune and nutritional status in immuno-compromised hosts.

2. Design

Randomized controlled trial (RCT).

3. Setting

Critical Care and Emergency Center, Yokohama City University Medical Center, Japan.

4. Participants

Twenty-six immuno-compromised patients who were admitted to the above center. Of these, 13 patients received hochuekkito or placebo for three weeks or longer.

5. Intervention

Arm 1: oral or enteral administration of hochuekkito (補中益気湯) (2.5 g t.i.d.) in 7 patients (all males; mean age 53.3±5.6 years).

Arm 2: administration of the same amount of lactose (placebo) in 6 patients (4 males and 2 females; mean age 53.0±7.7 years).

6. Main outcome measures

Serum albumin level and peripheral lymphocyte count (at baseline, 1, 2, 3, and 4 weeks after the start of the treatment).

Change in prognostic nutrition index (PNI=[albumin level]×10+[peripheral lymphocyte count]×0.005).

7. Main results

There was no significant difference between the two arms in serum albumin level and peripheral lymphocyte count. In placebo-treated patients, PNI increased 1 week after the start of treatment, but decreased in the following week, then increased again. PNI was significantly higher in hochuekkito-treated patients than in placebo-treated patients ($P<0.05$).

8. Conclusions

PNI value is significantly increased by hochuekkito treatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The authors deserve praise for attempting the RCT in an emergency care setting. Since PNI is a surrogate outcome measure, future trials focusing on outcomes that involve the presence or absence of infection and quantity of nutrition, as mentioned in the last part of the present results, are anticipated. Although the number of patients in this study is small, future studies are expected to be larger and confirmatory. In the results of this paper, MRSA infection was identified in 4 of 9 previously non-infected patients in the lactose arm and only 1 of 8 in the hochuekkito arm.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 May 2009, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)
10. Respiratory Diseases (including Influenza and Rhinitis)

References

Watanabe N, Makino S, Nakagawa T, et al. Efficacy of bakumondoto on cough in mycoplasma infection. *Science of Kampo Medicine* 2017; 41: 116-8 (in Japanese). Ichushi Web ID: 2017285714

1. Objectives

To evaluate the efficacy of bakumondoto（麦門冬湯）on cough in mycoplasma bronchitis

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

Study sites not stated (authors' institutions: a research center and clinics), Japan.

4. Participants

Twenty-four patients who presented with persistent cough, who underwent chest X-ray that excluded pneumonia findings such as ground-glass opacity, and who had an increased mycoplasma antibody titer (PA method) of 1:80 or above and thus were clinically considered as having mycoplasma bronchitis, and were started on treatment with azithromycin hydrate 500 mg once daily for 3 days.

5. Intervention

Arm 1: oral administration of TSUMURA Bakumondoto（麦門冬湯）Extract Granules 3 g t.i.d. for 2 weeks (n=7)
Arm 2: oral administration of tipepidine hibenzate 20 mg t.i.d. for 2 weeks (n=9)
Arm 3: oral administration of TSUMURA Bakumondoto（麦門冬湯）Extract Granules 3 g plus tipepidine hibenzate 20 mg, t.i.d. for 2 weeks (n=8)

6. Main outcome measures

Change in the cough score

7. Main results

The cough score significantly decreased on day 4 in the bakumondoto group, on day 7 in the tipepidine hibenzate group, and on day 4 in the bakumondoto + tipepidine hibenzate group ($P<0.05$ for all).

8. Conclusion

Add-on use of bakumondoto to a macrolide antimicrobial agent is effective for cough in mycoplasma bronchitis. In particular, combination use of bakumondoto plus a central antitussive agent more promptly alleviates cough in mycoplasma infection.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

This is a meaningful article on evaluation of the effect of bakumondoto on persistent cough as a common complaint in the context of mycoplasma infection. Drawbacks include lack of statement about the specific scale used for the cough scoring, which makes the symptomatic course assessments difficult. In addition, because of lack of intergroup comparison, assessment of the effect of the intervention with bakumondoto is also difficult. A question also remains whether mycoplasma infection can be diagnosed only from a mycoplasma PA antibody titer in single serum of 1:80 or above (rather than 1:320 or above) without a paired serum and without chest X-ray opacity. The authors concluded that combination use of bakumondoto plus a central antitussive agent is useful, but did not specify how the results led to this conclusion. Efficacy of bakumondoto on cough is generally discussed, but has rarely been investigated by RCTs, and such studies are meaningful. Future studies designed to compare symptomatic changes between treatment arms are awaited. Also, while determination of causative bacteria is often difficult in clinical practice, further studies with determination of causative organisms or evolutionary studies without determination of causative organisms would be warranted.

12. Abstractor and date

Koike H, 1 June 2020.

1. Infections (including Viral Hepatitis)

Reference

Higuchi K, Arakawa T, Ando K, et al. Eradication of *Helicobacter pylori* with a Chinese herbal medicine without emergence of resistant colonies. *American Journal of Gastroenterology* 1999; 94: 1419-20. CENTRAL ID: CN-00162864, Pubmed ID: 10235237

1. Objectives

To evaluate the efficacy and safety of triple therapy with proton pump inhibitor, antibiotic, and goshuyuto (呉茱萸湯) for *Helicobacter pylori* (*H. pylori*) infection.

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available; the authors belong to the Third Department of Internal Medicine, Osaka City University Medical School, Japan.

4. Participants

Sixty-three patients infected with *H. pylori.*

5. Intervention

Arm 1: treatment with omeprazole (40 mg/day), amoxicillin (1,500 mg/day), and goshuyuto (呉茱萸湯) (7.5 g/day), n=32.
Arm 2: treatment with omeprazole (40 mg/day) and amoxicillin (1,500 mg/day), n=31.
The duration of treatment was 2 weeks.

6. Main outcome measures

Histologic evaluation of gastric biopsy specimen and rapid urease test were performed.
The outcomes were evaluated at 4 weeks after the treatment.

7. Main results

H. pylori eradication rates were 60% in the double therapy arm and 80% in the triple therapy arm. There was no emergence of goshuyuto- or amoxicillin-resistant bacteria even in cases where treatment failed to eradicate *H. pylori*.

8. Conclusions

The novel triple therapy containing goshuyuto improves the eradication rate without increasing incidences of adverse effects and treatment resistance by *H. pylori*. This therapy is a useful tool for eradicating *H. pylori*.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects were similar in arm 1 (4 patients with diarrhea) and in arm 2 (4 patients with diarrhea and 1 with abdominal pain). No serious adverse effects were observed.

11. Abstractor's comments

In this study, goshuyuto was used differently from its original application of Kampo medicine. This article, as a Letter to the Editor, lacks adequate descriptions, so the submission as an original article is desired.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)

References

Taniguchi S, Terai T, Kono T, et al. The effect of hochuekkito on postherpetic neuralgia*. *Hifu no Rinsho* (*Clinical Practice of Dermatology*) 1999; 41: 601-3 (in Japanese)

Taniguchi S, Kono T, Terai T. Preventive effect of hochuekkito on postherpetic neuralgia*. *Progress in Medicine* 2002; 22: 863-5 (in Japanese). Ichushi Web ID: 2002176936 MOL, MOL-Lib

1. Objectives

To evaluate whether hochuekkito (補中益気湯) has a preventive effect on postherpetic neuralgia (PHN).

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (one department of dermatology), Japan.

4. Participants

Fifty-seven patients with acute-phase herpes zoster.

5. Intervention

Arm 1: oral administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) for 12 weeks (42 patients: 12 males and 30 females; mean age, 69.2 years).

Arm 2: no treatment with hochuekkito (補中益気湯) (15 patients: 5 males and 10 females; mean age, 66.9 years).

6. Main outcome measures

Pain intensity was evaluated by visual analogue scale (VAS) at baseline, and 12 and 24 weeks after the start of treatment. Obtained data are expressed as median (25 percentile, 75 percentile).

7. Main results

VAS score in the hochuekkito arm and control arm was respectively 7.1 (6.5, 7.4) and 6.9 (5.5, 7.9) at baseline, 4.1 (3.0, 5.4) and 3.5 (1.7, 5.1) at 12 weeks, 1.4 (0.5, 2.3) and 2.9 (1.7, 4.2) at 24 weeks. The ratio of VAS score at 24 weeks to that at baseline (rVAS) was significantly different between the hochuekkito arm (0.20 [0.09, 0.30]) and control arm (0.42 [0.33, 0.53]).

8. Conclusions

During the acute phase of herpes zoster, 12-week oral administration of hochuekkito significantly controlled PHN at 24 weeks. Hochuekkito therefore has a preventive effect on PHN.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In one of the 42 hochuekkito-treated patients, transient stomach discomfort developed, which did not interfere with continuation of the treatment.

11. Abstractor's comments

Many patients suffer from PHN for years. This study provides valuable insight. Although the authors found no between-group difference in age, affected area, number of days with symptoms, underlying disease, and concomitant medications, there was a between-group difference in the number of cases. This problem is related to the incidence of PHN, so an examination of the influence of incidence of PHN on the study results is needed. The outcomes of these studies are clinically relevant, and results of further studies are expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 12 October 2011, 31 December 2013.

1. Infections (including Viral Hepatitis)

Reference

Sata M, Amagase H, Koga S, et al. Therapeutic effect of IFN-β (Feron) plus shosaikoto combination therapy on chronic active hepatitis B*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1994; 71: 814-20 (in Japanese). Ichushi Web ID: 1994141311

1. Objectives

To evaluate the therapeutic effect of interferon (IFN)-beta plus shosaikoto (小柴胡湯) on chronic active hepatitis B.

2. Design

Randmized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

Nine university hospitals and 15 general hospitals, Japan.

4. Participants

Sixty-two patients who presented with chronic active hepatitis on liver biopsy histology (obtained within a year of symptom onset) and were positive for both HBsAg and HBeAg.

5. Intervention

Arm 1: treatment with IFN-β (total dose 102×10^6 IU) for 8 weeks + shosaikoto (小柴胡湯) (manufacturer, not specified) 2.0 g or 2.5 g t.i.d. for 8 weeks and 6 months (n=28).
Arm 2: treatment with IFN-β alone (total dose 102×10^6 IU) for 8 weeks (n=34).

6. Main outcome measures

Blood levels of HBsAg, HBeAg, HBeAb, and HBV-DNA-polymerase (DNA-P), blood biochemistry, and urinalysis. These variables were examined 4 weeks before the start of the treatment; on day 1 and weeks 1, 2, and 4 of the treatment, at the end of the treatment, and 1, 2, 3, 4, 5, 6, 9, and 12 months after the completion of the treatment.

7. Main results

Treatment was discontinued in 3 patients in arm 1 and 8 patients in arm 2. After the IFN-β therapy, there were no significant between-arm differences in DNA-P reduction, clearance rate, other changes over time, clearance of HBeAg, rate of HBeAg seroconversion (SC), and time course of serum ALT and AST levels. In 12 patients who cleared HBeAg at 12 months after the completion of IFN-β therapy, AST level tended to be lower in the shosaikoto-combined group. There were no significant between-arm differences in blood biochemistry findings.

8. Conclusions

IFN plus shosaikoto and IFN alone had similar efficacy for chronic hepatitis B.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Treatment was not discontinued due to adverse drug reactions in either arm. Hematemesis developed in one patient in the IFN alone group but resolved with antiulcer drug treatment. The causal relationship between this event and the intervention is not clear. The event may be attributed to NSAIDs (non-steroidal anti-inflammatory drugs) use.

11. Abstractor's comments

The authors of this study deserve praise for conducting an RCT in a multicenter setting. The report would have been more informative if it included evaluation of subjective symptoms and long-term outcomes, in addition to the results of virological examinations.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)

Reference

Sato S, Ishikawa K, Chiba T. Efficacy of sho-saiko-to on chronic type B hepatitis. *Shokakika* (*Gastroenterology*) 1991; 15: 39–49 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) in the treatment of chronic hepatitis B.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Six university hospitals and 15 general hospitals, Japan.

4. Participants

Forty-four patients who met the following criteria: liver biopsy within a year of symptom onset, in principle; Hepatitis (H)Be antigen-positive; abnormal baseline glutamic-pyruvic transaminase (GPT) requiring treatment. However, those who received any immunostimulant agent such as antiviral agents (IFN, Ara-A, etc.) within 12 weeks of recruitment were excluded.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules at a dose of 7.5 g/day for 24 weeks (n=28).
Arm 2: common hepatoprotective agents (Proheparum, etc.) for 24 weeks (n=16).

6. Main outcome measures

HBe antigen/anti-HBe antibody and GPT were continuously monitored and rated on a 6-grade scale: seroconversion (SC), seronegative (SN), decreased antigen titer, unchanged antigen titer, increased antigen titer, and substantially worsened antigen titer.

7. Main results

Decrease in the HBe antigen titer was not significantly different between the two groups at Week 24. The anti-HBe antibody titer was significantly higher in arm 1 than in arm 2 at Weeks 4 ($P<0.05$) and 24 ($P<0.01$). GPT was not significantly different between the two groups at Week 24 or 48. A comparison of the percentage of patients with unchanged or higher HBe antigen titer and the percentage of patients with decreased HBe antigen titer between the two groups revealed a tendency for HBe antigen titer to decrease in arm 1 at Week 24 ($P<0.1$) but revealed no significant between-group difference at Week 48.

8. Conclusions

Compared to the hepatoprotective agents, shosaikoto tends to decrease HBe antigen titer and significantly increase anti-HBe antibody titer.

9. From Kampo medicine perspective

Nothing special.

10. Safety assessment in the article

Not evaluated.

11. Abstractor's comments

It is admirable that a multicenter RCT was conducted. However, the difference in the percentage of patients with SC or SN was not significant. Thus, caution should be used in prescribing this intervention.

12. Abstractor and date

Kogure T, 8 August, 2008, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)

References

Shiraki K, Tanimoto K, Togashi T, et al. A study of the efficacy of shosaikoto in children with HBe antigen-positive chronic hepatitis B*. *Shonika Rinsho* (*Japanese Journal of Pediatrics*) 1991; 44: 2146–51 (in Japanese).

Shiraki K, Tanimoto K. Clinical Evaluation of the efficacy of TSUMURA Shosaikoto in children with chronic hepatitis B*. *Dai 7-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku* (*Proceedings of the 7th meeting of the Japan Pediatric Society for Oriental Medicine*) 1991; 7: 18–22 (in Japanese)

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of HBe antigen-positive children with chronic hepatitis B.

2. Design

Randomized controlled trial (RCT).

3. Setting

Nine university hospitals, Japan.

4. Participants

Forty-three HBe antigen-positive children with chronic hepatitis B.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules was administered before breakfast and dinner according to age (n=23).
Arm 2: no treatment (n= 20).
Follow-up was 6–24 months; mean treatment duration was 18.6± 5.5 months.

6. Main outcome measures

Hepatic function test and effect on the HBe antigen-antibody system (SC: seroconversion, SN: seronegative).

7. Main results

ALT and AST levels tended to progressively decrease from the baseline in arm 1 but not to change in arm 2. The percentage of patients with SC or SN at Month 6, Month 12, and final follow-up was 30.4%, 34.8%, and 43.5% in arm 1, and 5.0%, 10.0%, and 25.0% in arm 2, respectively. The percentage of patients with SC at Month 6, Month 12, and final follow-up was 17.4%, 17.4%, and 30.4% in arm 1, and 0%, 10.0%, and 20.0% in arm 2, respectively.

8. Conclusions

Shosaikoto improves hepatic function and promotes SC from HBe antigen to anti-HBe antibody in children with chronic hepatitis B.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient treated with shosaikoto had epigastric discomfort.

11. Abstractor's comments

It is admirable that a multicenter RCT was conducted and showed the efficacy and safety of shosaikoto in children with chronic hepatitis B. Interestingly, hepatic function was normalized in all patients with SC in the shosaikoto group. The result of a statistical between-group comparison will provide stronger evidence.

12. Abstractor and date

Kogure T, 8 August 2008, 12 October 2011, 31 December 2013.

1. Infections (including Viral Hepatitis)

Reference

Hatakeyama S, Ueki J, Ishizuka M, et al. Comparative study of ursodeoxycholic acid and shosaikoto as treatment for chronic liver diseases type C. *Yakuri to Chiryo* (*Japanese Pharmacology & Therapeutics*) 1994; 22: 3295-305 (in Japanese). Ichushi Web ID: 1995069962

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) for type C chronic liver diseases.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One general hospital, Japan.

4. Participants

A total of 55 patients (27 with chronic hepatitis C [CH] and 28 with type C compensated liver cirrhosis [cLC]).

5. Intervention

Arm 1: treatment with ursodeoxycholic acid (UDCA) 200 mg t.i.d. for 6 months (n=26).
Arm 2: treatment with TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. orally before meals for 6 months (n=29).

6. Main outcome measures

Liver functions and serum bile acid fractions.

7. Main results

Three UDCA-treated and 2 shosaikoto-treated patients withdrew from the study. The percent decrease in GOT and GPT at 6 months was significantly greater in arm 1 than in arm 2 for both CH and cLC patients. γ-GTP and γ-globulin also decreased significantly more in arm 1 than in arm 2. Albumin increased significantly more in arm 1 than in arm 2. The glycine-conjugated UDCA fraction increased significantly while the glycine-conjugated cholic acid (CA) and chenodeoxycholic acid (CDCA) fractions decreased significantly in arm 1. There were no variations in serum bile acid level in arm 2.

8. Conclusions

The efficacy of shosaikoto for type C chronic liver diseases is not clear, and UDCA is more effective than shosaikoto.

9. From Kampo medicine perspective

Not specifically mentioned. The authors commented that UDCA might be a better choice when *sho* (証, pattern) is not a consideration.

10. Safety assessment in the article

One UDCA-treated patient developed pruritus and withdrew from the study. Two shosaikoto-treated patients withdrew due to abnormally high levels of GPT.

11. Abstractor's comments

The authors of this study deserve praise for conducting an RCT using UDCA as a control. Longer-term follow-up and inclusion of virological examination results would enhance the clinical significance of this study.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)

Reference

Nakajima O, Sone M. Interferon plus shosaikoto combination therapy for chronic hepatitis C (the first report) - effectiveness in reducing adverse effects of interferon-*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*). 1993; 70: 2994-3002 (in Japanese). Ichushi Web ID: 1994049432

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for reducing the adverse effects of interferon in patients with chronic hepatitis C.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single institution (National Okura Hospital; current National Center for Child Health and Development), Japan.

4. Participants

Forty-eight patients with chronic hepatitis C.

5. Intervention

Arm 1: treatment with interferon-alpha 6 million units daily for 2 weeks, then three times weekly + Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules 2 g t.i.d. (n=24).
Arm 2: treatment with interferon alone (n=24).
Duration of treatment: at least 12 months.

6. Main outcome measures

Subjective symptoms including fever and laboratory findings including blood cell counts.

7. Main results

Both the severity and frequency of fever were significantly lower in arm 1. Leukopenia at 1 month was significantly reduced in arm 1. There was no significant between-arm difference in the occurrence of other adverse drug reactions.

8. Conclusions

Shosaikoto may reduce adverse effects of interferon.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is the first report on a clinical trial of interferon plus shosaikoto combination therapy for chronic hepatitis C, summarizing only the part related to the occurrence of adverse drug reactions. Interestingly, shosaikoto, which is also used for treating *sho-kan* (傷寒, cold damage), reduces the "*sho-kan* –like" adverse effects of interferon.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)

References

Sone M, Nakajima O. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1995; 72: 3193-7 [in Japanese]). Ichushi Web ID: 1996190408 MOL, MOL-Lib

Nakajima O, Sone M. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy - the second report-*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1998; 75: 1883-8 (in Japanese). Ichushi Web ID: 1999004032 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in chronic hepatitis C after interferon (IFN) therapy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

One hundred and one patients with chronic active hepatitis C who completed IFN therapy.

5. Intervention

Arm 1: IFN therapy (for 6 months) and then administration of liver protector (for 6 months), followed by treatment with Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules 2.0 g t.i.d. 30 minutes before meals for 24 months (n=49).

Arm 2: IFN therapy and then administration of liver protector, followed by continued treatment with liver protector for 24 months (n=52).

6. Main outcome measures

Liver function test, time course of hepatitis C virus (HCV)-RNA level, time course of platelet and white blood cell counts.

7. Main results

Alanine aminotransferase (ALT) level was not significantly different between arms 1 and 2 at 24 months. Aspartate aminotransferase (AST) level and HCV-RNA level were significantly reduced in arm 1 compared with arm 2 at 24 months ($P<0.05$).

8. Conclusions

Shosaikoto is effective as maintenance therapy following IFN treatment for chronic hepatitis C.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Platelet count was significantly different between arms 1 and 2 ($P<0.05$); it was reduced compared with the baseline level in arm 2. White blood cell count was also significantly different between arms 1 and 2; it was reduced, but not significantly different from the baseline level in arm 2. The tendency toward pancreatic dysfunction after the IFN therapy was improved earlier in arm 1 than in arm 2.

11. Abstractor's comments

This is a clinically, highly significant study in that long-term follow-up was conducted in an RCT. Furthermore, between-arm comparisons were sufficient. This study provides high-level evidence.

12. Abstractor and date

Kogure T, 8 August 2008, 31 December 2013.

1. Infections (including Viral Hepatitis)

Reference

Nakajima O, Sone M, Kurokawa K, et al. The Complemental treatment for chronic hepatitis C. *Kagaku Ryoho Kenkyusho Kiyo* (*Bulletin of the Institute of Chemotherapy*) 2003; 34: 40-51 (in Japanese with English abstract). Ichushi Web ID: 2004188041

1. Objectives

To confirm the efficacy of shosaikoto (小柴胡湯) for interferon-resistant chronic hepatitis C.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and general hospitals, Japan.

4. Participants

One hundred patients with chronic active hepatitis C who completed interferon therapy.

5. Intervention

Arm 1: treatment with squalene 1500 mg/day.(n=33)
Arm 2: treatment with cepharanthine (1 mg/kg body weight per day). (n=33)
Arm 3: treatment with shosaikoto (小柴胡湯) 6.0 g/day. **(**n=34**)**
In all arms, study drugs were orally administered in three divided daily doses before meals for 5 years.

6. Main outcome measures

Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), procollagen III peptide (PIIIP), type IV collagen, and hepatitis C virus (HCV)-RNA.

7. Main results

AST and ALT showed overall significant decreases, except for transient elevations after 6 and 30 months of treatment. Type IV collagen, PIIIP, and HCV-RNA also decreased significantly in all arms. No significant differences in these variables were observed among the three arms. AST and ALT were significantly decreased at 50 months in arm 3, but not in arms 1 and 2. Choline esterase (Ch-E) did not change in arm 3, but decreased significantly in arms 1 and 2. Type IV collagen and HCV-RNA decreased significantly in arm 3 and increased significantly in arms 1 and 2. Changes in PIIIP were similar to those of type IV collagen.

8. Conclusions

Shosaikoto is effective for the treatment of chronic hepatitis C and its efficacy is equivalent to that of squalene or cepharanthine.

9. From Kampo medicine perspective

One patient with "*in-sho* (陰証, yin pattern)" and "*kyo-sho* (虚証, deficiency pattern)" was excluded before the allocation, and the study was actually conducted in 99 patients.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study confirmed the efficacy of shosaikoto for the treatment of chronic hepatitis C.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

1. Infections (including Viral Hepatitis)

Reference

Nakajima O, Sone M, Onishi H, et al. Preventive effect of shosaikoto on the progression of chronic hepatitis C to cirrhosis*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1999; 76: 1008-16 (in Japanese). Ichushi Web ID: 1999207089 MOL, MOL-Lib

1. Objectives

To confirm the efficacy of shosaikoto (小柴胡湯) for chronic hepatitis C.

2. Design

Randomized controlled trial (RCT).

3. Setting

Multiple general hospitals, Japan.

4. Participants

Ninety-nine patients with chronic active hepatitis C who completed interferon therapy.

5. Intervention

Arm 1: oral administration of Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules 6 g/day, t.i.d.(n=49)
Arm 2: oral administration of one of the commonly used liver protectors.(n=50)
Patients were followed for 50 months in both arms.

6. Main outcome measures

Level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), choline esterase (Ch-E), procollagen III peptide (PIIIP), type IV collagen, and hepatitis C virus (HCV)-RNA.

7. Main results

AST and ALT were significantly decreased at 50 months in arm 1, but not in arm 2. Ch-E did not change in arm 1, but decreased significantly in arm 2. Type IV collagen and HCV-RNA decreased significantly in arm 1, and increased significantly in arm 2. Changes in PIIIP were similar to those of type IV collagen.

8. Conclusions

Shosaikoto is effective for the treatment of chronic hepatitis C, and its prevention of the progression to cirrhosis is implied.

9. From Kampo medicine perspective

Patients with "*in-sho* (陰証, yin pattern)" and "*kyo-sho* (虚証, deficiency pattern)" were excluded before the allocation.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study confirmed the efficacy of shosaikoto for the treatment of chronic hepatitis C.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

1. Infections (including Viral Hepatitis)

Reference

Tanaka N, Matsuzaki Y, Osuga T, et al. A comparative study of IFN monotherapy versus IFN plus TJ-9 Shosaikoto combination therapy in patients with chronic hepatitis C (interim report)*. *Progress in Medicine* 1993; 13: 2868-72 (in Japanese).

1. Objectives

To evaluate the efficacy of interferon (IFN) plus shosaikoto (小柴胡湯) combination therapy for chronic hepatitis C.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Three hospitals including Tsukuba University Hospital, Japan.

4. Participants

Thirty-six patients aged under 65 years with chronic hepatitis C.

5. Intervention

Arm 1: treatment with interferon-alpha (or -beta) 6 million units daily for 2 weeks, then 3 times weekly for 23 weeks + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. (n=15) for 1.5 year.
Arm 2: treatment with interferon alone for 23 weeks (n=21).

6. Main outcome measures

Alanine aminotransferase (ALT) level.

7. Main results

There was no significant difference in the time course of ALT levels between arms 1 and 2.

8. Conclusions

At the time of this interim report, the shosaikoto and IFN combination did not provide an enhanced therapeutic efficacy for chronic hepatitis C.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This is an interim report on a clinical trial of interferon plus shosaikoto combination therapy for chronic hepatitis C, summarizing data from 36 patients who completed treatment, out of more than 100 patients who enrolled. Efficacy of this therapy was not demonstrated. But this is only an interim report and a final report is anticipated.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

1. Infections (including Viral Hepatitis)

Reference

Isai H. Efficacy of Kampo formulations for reducing adverse effects of interferon therapy in patients with chronic hepatitis C*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1996; 84: 1505-9 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of Kampo formulations for reducing adverse effects of interferon therapy in patients with chronic hepatitis C.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single hospital (Hokkaido Kosei-ren Mukawa Kosei Hospital), Japan.

4. Participants

Twelve patients with chronic hepatitis C.

5. Intervention

Arm 1: treatment with interferon-alpha 6 million units daily on days 1–3 and 10 million units daily on days 4–14, then 10 million units 3 times weekly for 12 weeks + Kampo formulation (TSUMURA Keishito [桂枝湯] Extract Granules 5 g, TSUMURA Maoto [麻黄湯] Extract Granules 5 g, and TSUMURA Kojinmatsu [紅参末] 4 g) daily from the first day of interferon therapy and continuing for 4 weeks (n=6).

Arm 2: treatment with interferon alone (n=6).

6. Main outcome measures

Body temperature, subjective symptoms, blood biochemistry, and usage of diclofenac sodium suppository.

7. Main results

During first 4 weeks, usage of diclofenac sodium suppository was significantly lower in arm 1. Significantly fewer patients complained of anorexia or arthralgia in arm 1.

8. Conclusions

Kampo formulations may have efficacy for reducing the adverse effects of interferon therapy in patients with chronic hepatitis C.

9. From Kampo medicine perspective

Kojinmatsu was added in hope that its immunostimulatory activity would be coupled with the effects of keimakakuhanto (桂麻各半湯).

10. Safety assessment in the article

One patient in arm 1 discontinued treatment because of gastrointestinal symptoms on day 9 of Kampo formulation treatment and was excluded from further evaluation. Another patient complained of nausea/vomiting on day 9 of Kampo formulation treatment. Despite continuation of treatment, the symptoms disappeared after 5 days allowing further continuation of this patient's treatment.

11. Abstractor's comments

This paper describes an attempt to evaluate the efficacy of Kampo formulations against the adverse effects of interferon therapy in patients with chronic hepatitis C. The author's original formula was used and it is suggested that *happyozai* （発表剤, exterior-effusing formula) has certain efficacy for reducing influenza-like adverse effects of interferon. Unfortunately, the number of patients was very small, so future studies including a large number of patients are anticipated.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010, 12 October 2012.

1. Infections (including Viral Hepatitis)

Reference

Fukue H, Hagiwara T, Yoshida S, et al. Efficacy of high-dose shosaikoto for HIV infection*. *HIV Kansensha Hassho Yobo, Chiryo ni kansuru Kenkyuhan Heisei 7 Nendo Kenkyu Hokokusho* (*Research Report by the Study Group on Prevention and Treatment of HIV Infection*) 1996: 203–10 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of human immuno-deficiency virus (HIV) infection.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

No study site was specified (authors belonged to the Department of Diagnostic Pathology, Tokyo Medical University; National Institute of Health; Department of Public Health, Yokohama City University; and Division of Theoretical Epidemiology, Department of Epidemiology, Institute of Public Health), Japan.

4. Participants

Nineteen patients with acquired immunodeficiency syndrome (AIDS) related complex or asymptomatic carriers with 200–500 CD4-positive cells/μL.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules at a dose of 7.5 g t.i.d. for 12 weeks.
Arm 2: placebo.

6. Main outcome measures

Immunology (absolute number of CD4-positive cells, CD4/CD8, and lymphocyte stimulation test), virology (P24 antigen, branched DNA assay), and clinical symptoms.

7. Main results

A total of 15 patients (7 in arm 1 and 8 in arm 2) were included in the analysis. After treatment, no statistically significant between-arm difference was found in the absolute number of CD4-positive cells, CD4/CD8, and results of the lymphocyte stimulation test. Virologically, no analysis could be performed because many patients lacked detectable virus.

8. Conclusions

Shosaikoto may be ineffective for HIV infection.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

In the shosaikoto group, 1 patient was withdrawn from treatment owing to hepatic dysfunction. Two patients in each of the groups had slight gastrointestinal symptoms.

11. Abstractor's comments

This clinical trial suggested that shosaikoto is ineffective for HIV infection. Nonetheless, it is desirable to conduct another trial to overcome the following drawbacks of the present trial as cited by the authors: small sample size and lack of antiviral efficacy evaluation because no virus was detectable.

12. Abstractor and date

Okabe T, 17 September 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Seike J. Efficacy of rikkunshito for anorexia and nausea/vomiting caused by cancer chemotherapy*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 12–3 (in Japanese).

Seike J, Sawada T, Kawakita N, et al. A new candidate supporting drug, rikkunshito, for the QOL in advanced esophageal cancer patients with chemotherapy using docetaxel/ 5-FU/ CDDP. *International Journal of Surgical Oncology* 2011; 2011: 1-7. DOI: 10.1155/2011/715623.

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) for anorexia and nausea/vomiting occurring after cancer chemotherapy for advanced esophageal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Thoracic, Endocrine Surgery and Oncology, Tokushima University Hospital, Japan.

4. Participants

Nineteen patients to receive DFP (docetaxel+5-FU+cisplatin) therapy for advanced esophageal cancer (mainly stage II–III).

5. Intervention

Two-week administration.
Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. (n=9).
Arm 2: no administration (n=10).

6. Main outcome measures

Grade of anorexia and nausea/vomiting (Common Terminology Criteria for Adverse Events [CTC-AE] ver. 3.0), QOL score (the QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs [QOL-ACD]-based original questionnaire).

7. Main results

One of the participants in arm 1 was ineligible because of age violation and excluded from the analysis. Anorexia, nausea, and vomiting occurred as adverse drug reactions by 14 days after the start of chemotherapy in 3 (37.5%), 3 (37.5%), and 1 (12.5%) subject, respectively, in arm 1, and 7 (70%), 8 (80%) and 4 (40%) subjects, respectively, in arm 2, but there was no significant between-group difference. The change in mean vomiting score was 0 in both arms by day 8, but was 0.13 in arm 1 and 0.90 in arm 2 on day 14. Nausea score increased from day 8 and day 5 to 0.50 and 1.80 on day 14 in arm 1 and arm 2, respectively, showing significant difference on day 14 (P<0.05). Likewise, anorexia score reached 0.75 in arm 1 and 1.70 in arm 2 on day 14, showing a tendency toward lower score after rikkunshito administration. Rikkunshito also prevented significant suppression of depressed mood and decreased activities of daily living (both P<0.05).

8. Conclusions

Rikkunshito significantly suppresses anorexia and nausea/vomiting caused by chemotherapy (DFP therapy) for advanced esophageal cancer, and thereby prevents significant decline in QOL.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The paper includes a section on adverse events and mentions that there was no adverse event associated with rikkunshito.

11. Abstractor's comments

This study is highly valued because it demonstrated by RCT that rikkunshito significantly relieves nausea and prevents QOL score from decreasing after chemotherapy. It is possible that the mechanism for improvement of anorexia is mediated by blood ghrelin. The 2010 paper in Japanese mentioned blood ghrelin analysis, but the 2011 paper in English makes no mention of blood ghrelin at all, perhaps because the widely scattered measurement results were an issue. The authors should conduct a large-scale clinical trial to find out whether it significantly alleviates vomiting and anorexia.

12. Abstractor and date

Motoo Y, 30 December 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Nishino T, Yoshida T, Goto M, et al. The effects of the herbal medicine Daikenchuto (TJ-100) after esophageal cancer resection, open-label, randomized controlled trial. *Esophagus* 2018; 15: 75-82. CENTRAL ID: CN-01440554, Pubmed ID: 29892933

1. Objectives

To evaluate the efficacy of daikenchuto（大建中湯）for postoperative recovery of patients with esophageal cancer

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

One university hospital (department of surgery), Japan

4. Participants

Forty patients with esophageal cancer undergoing transthoracoabdominal subtotal esophagectomy with stomach tube reconstruction

5. Intervention

Arm 1: TSUMURA Daikenchuto（大建中湯）Extract Granules 15.0 g/day (5.0 g t.i.d.) via a tube from the day of surgery (postoperatively) to the 21st day (n=20)

Arm 2: no administration of daikenchuto (n=20)

6. Main outcome measures

Primary endpoints: nutritional condition (body weight and serum albumin), postoperative recovery of gastrointestinal function (number of days until the first flatus/defecation, number of days until becoming able to eat meals of 800 kcal/day).

Secondary endpoints: C-reactive protein (CRP), plasma adrenomedullin (ADM), incidence of postoperative complications, length of hospital stay after surgery

7. Main results

One patient in Arm 1 was found to have unresectable cancer, and thus was excluded. Thus, the analysis was conducted on 19 patients in Arm 1 and 20 patients in Arm 2. Change in body weight showed intergroup differences from postoperative day 3, with significantly greater body weight in Arm 1 than in Arm 2 at postoperative day 21 (P=0.014). No significant intergroup differences were shown for serum albumin, serum CRP, plasma ADM, incidence of postoperative complications, parameters of the postoperative recovery of gastrointestinal function, or length of hospital stay after surgery.

8. Conclusion

Postoperative tubal administration of daikenchuto suppresses body weight decrease after subtotal esophagectomy in patients with esophageal cancer.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

The Methods section of the article states that adverse events were evaluated using the CTCAE ver. 3.0. However, the Results section does not include safety data.

11. Abstractor's comments

While daikenchuto has been used for ileus prevention or recovery of gastrointestinal function after surgery for colorectal cancer, gastric cancer, hepatocellular carcinoma, etc., this is the first report to evaluate the efficacy of daikenchuto after highly invasive surgery for esophageal cancer. A groundbreaking finding of this study is that the postoperative body weight change showed an intergroup difference from postoperative day 3, and body weight at postoperative day 21 was significantly greater in the daikenchuto arm than in the control arm. However, other endpoints showed no significant differences. CRP tended to be lower and ADM tended to be higher in the daikenchuto arm compared with the control group, suggesting the anti-inflammatory effect of daikenchuto. Further studies with increased sample sizes may yield significant differences. While daikenchuto can promote movement of the contents of the large intestine or a duodenal pouch, in the setting of post-subtotal esophagectomy, as reported in this article, our concern is the effect of daikenchuto on the residual esophagus and reconstructed stomach tube. Although the authors focused mainly on anti-inflammatory effect, further studies are awaited to characterize involvement of other factors such as gastrointestinal transit or increase in gastrointestinal blood flow.

12. Abstractor and date

Motoo Y, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Moriyama S, Hinode D, Yoshioka M, et al. Impact of the use of Kampo medicine in patients with esophageal cancer during chemotherapy: a clinical trial for oral hygiene and oral condition. *Journal of medical investigation* 2018; 65: 184-90. CENTRAL ID: CN-01702631, Pubmed ID: 30282858, UMIN ID: UMIN000013183 J-STAGE

1. Objectives

To investigate the impact of daiokanzoto（大黄甘草湯）and hangeshashinto（半夏瀉心湯）on oral mucositis, tongue coating bacteria, and gingiva condition in patients with esophageal cancer undergoing chemotherapy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-four esophageal cancer patients aged 52 to 81 years started on chemotherapy between June 2012 and July 2015 and given professional oral healthcare. Patients were excluded if they had severe infection, severe complications, or drug allergy.

5. Intervention

Arm 1: Sherbet containing TSUMURA Daiokanzoto（大黄甘草湯）Extract Granules 2.5 g t.i.d. (between meals) during the chemotherapy (n=7).
Arm 2: Sherbet containing TSUMURA Hangeshashinto（半夏瀉心湯）Extract Granules 2.5 g t.i.d. (between meals) during the chemotherapy (n=7).
Arm 3: Control (no administration of Kampo medicine) (n=10).

6. Main outcome measures

The primary endpoint was oral mucositis evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4. The secondary endpoints were oral cavity condition and tongue coating bacteria. The oral cavity condition was evaluated using the salivary flow rate, plaque index (PlI), gingival index (GI), and tongue coating index (TCI). The tongue coating bacteria were quantified by counting *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *and Campylobacter rectus CFUs*.

7. Main results

One patient in the control group was excluded because of onset of aspiration pneumonia before first evaluation, and the analysis was conducted on 23 patients (7 patients in the daiokanzoto group, 7 patients in the hangeshashinto group, and 9 patients in the control group). Oral mucositis onset and severity did not significantly differ across the Arms. Among other parameters of the oral cavity condition, the salivary flow rate did not significantly differ across the three Arms. The GI for Arm 1 was significantly better than that for Arm 3 (P=0.04). The endpoint results were better in Arm 2 than in Arm 3. The bacterial counts of *F. nucleatum* and *C. rectus* were lower in Arm 1 than in Arm 3 (P=0.02 for both). Between Arm 2 and Arm 3, no significant differences were observed in bacterial counts.

8. Conclusions

Neither daiokanzoto nor hangeshashinto improves oral mucositis in esophageal cancer patients on chemotherapy receiving oral care. Daiokanzoto may attenuate gingival inflammation and reduce the numbers of periodontopathogenic bacteria, and thus may improve oral health of patients on chemotherapy for esophageal cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

This is a meaningful study that evaluated whether oral mucositis, a common adverse effect of chemotherapy, improves with daiokanzoto or hangeshashinto. The sample size of this study may have been too small to detect any effect of the Kampo intervention added to professional oral care. Future reports with more patients are awaited.

12. Abstractor and date

Koike H, 22 October 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Mizuno S, Yamagiwa K, Iwata M, et al. Effect of early treatment with TSUMURA Rikkunshito on gastrointestinal symptoms after resection of gastric cancer – focusing on reflux esophagitis -*. *Progress in Medicine* 2001; 21: 1366-7 (in Japanese). Ichushi Web ID: 2001269379 MOL, MOL-Lib

1. Objectives

To evaluate the preventive effect of rikkunshito (六君子湯) on postoperative reflux esophagitis.

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available; the authors belong to the First Department of Surgery, Mie University School of Medicine, Japan.

4. Participants

Forty-six patients who underwent resection of stage I to II gastric cancer.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules, 7.5 g/day, every day from the start of postoperative oral intake in 25 patients.
Arm 2: no treatment in 21 patients.

6. Main outcome measures

1) Gastrointestinal symptoms including heartburn, dysphagia, nausea/vomiting, dyspepsia, and anorexia; 2) endoscopic findings based on the Los Angeles classification; and 3) mean length of postoperative hospital stay.

7. Main results

At postoperative week 2, gastrointestinal symptoms were observed in 7 untreated patients (33%) and 4 rikkunshito-treated patients (16%). All the symptoms occurred less commonly in the treated patients than in the untreated patients. At postoperative week 4, reflux symptoms and heavy stomach were each seen in only 1 (4%) patient in arm1, whereas reflux symptoms, heartburn, dyspepsia, and anorexia developed in 3 (14%), 1 (5%), 1 (5%), and 2 (10%), respectively, in arm 2. As for endoscopic findings at postoperative week 3, there were grade A in 2 patients (10%) and grade B in 1 (5%) in arm 2, but grade A in only 1 (5%) in arm 1. At postoperative week 6, grade A esophagitis was observed in 1 patient (5%) in arm 2, and none in arm 1. Mean length of postoperative hospital stay was not significantly different between the two arms (47 ± 13 days [arm 2] *vs* 39±13 days [arm 1]), but a reduction of hospital days was noted.

8. Conclusions

Rikkunshito is highly effective not only for the treatment of reflux esophagitis after gastric cancer surgery, but also for the prevention of this disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Studies 1 and 2 are described in the article. Study 1 was conducted to examine the therapeutic effect of rikkunshito on postoperative reflux esophagitis. Rikkunshito at a daily dose of 7.5 g was administered between meals every day from the onset of symptoms in 7 patients with stage I-II gastric cancer. The authors reported that symptoms disappeared in most patients at week 4. But since Study 1 had no control group and provided no details such as evaluation criteria, it was excluded from this structured abstract. Only part of Study 2 was included. In Study 2, 'randomization into two groups' was reported, but the details were not clear. Also, other details, such as statistical procedures and methods of assessing subjective symptoms, were not provided. This study is clinically valuable, but most of the article, which is published in a conference record, lacks adequate descriptions. Thus, submission as an original article is desired.

12. Abstractor and date

Arai M, 1 April 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Ohno T, Yanai M, Ando H, et al. Rikkunshito, a traditional Japanese medicine, suppresses cisplatin-induced anorexia in humans. *Clinical and Experimental Gastroenterology* 2011; 4: 291–6. Pubmed ID: 22235173

1. Objectives

To verify the effects of rikkunshito (六君子湯) on cisplatin-induced anorexia in gastric cancer patients.

2. Design

Crossover randomized controlled trial (RCT-crossover).

3. Setting

Gunma University Hospital, Japan.

4. Participants

Ten unresectable or relapsed gastric cancer patients.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for three weeks (same period as S-1), two-weeks withdrawal, then the next course[1)] without rikkunshito (n=5).

Arm 2: first course without rikkunshito; then after five weeks, the next course with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for three weeks, the same period as S-1 (n=5).

[1)] One course consists of three-weeks of S-1 and two weeks withdrawal, making a total of five weeks, with a cisplatin IV infusion on the eighth day.

6. Main outcome measures

Plasma acyl-ghrelin before and three hours after administration of cisplatin; amount of oral food intake at each meal during hospitalization for five days after cisplatin (scored on a 10-point scale by a nurse); grade of anorexia (using CTC-AE ver. 3.0), nausea, and vomiting; and time to treatment failure (defined as time from administration of cisplatin to vomiting, or time to antiemetic usage).

7. Main results

Plasma acyl-ghrelin level before administration of cisplatin remained unchanged after administration in the rikkunshito-on period, but tended to decrease after administration of cisplatin in the rikkunshito-off period. The mean amount of oral food intake score was significantly higher during the rikkunshito-on period than the -off period (P=0.0496). The grade of anorexia was significantly lower during the rikkunshito-on period than the -off period (P=0.0441). The grade of nausea tended to be lower during the rikkunshito-on period, but the grade of vomiting was unchanged. There was no significant difference in the number of cases considered to be treatment failures between the rikkunshito-on period (n=5) and -off period (n=9).

8. Conclusions

Rikkunshito reduces cisplatin-induced anorexia in gastric cancer patients.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

Particular attention was paid to the possible occurrence of pseudoaldosteronism, however, no adverse event occurred in either arm.

11. Abstractor's comments

This is a valuable study and the first to clinically demonstrate by RCT that rikkunshito reduces cisplatin-induced anorexia in gastric cancer patients. The findings agree with the results of animal experiments (Takeda H, Sadakane C, Hattori T, et al. Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT2 receptor antagonism. *Gastroenterology* 2008: 134; 2004–13.). However, the study found that rikkunshito had no significant effect on plasma acyl-ghrelin level, and on preventing or reducing nausea or vomiting. Hopefully the authors will conduct a large-scale RCT in Japan based on these results, as the authors mention in the discussion.

12. Abstractor and date

Motoo Y, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Uehara R, Isomoto H, Minami H, et al. Characteristics of gastrointestinal symptoms and function following endoscopic submucosal dissection and treatment of the gastrointestinal symptoms using rikkunshito. *Experimental and Therapeutic Medicine* 2013; 6: 1083-8. Pubmed ID: 24223626

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) for gastrointestinal symptoms following endoscopic submucosal dissection (ESD) of early gastric cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Thirteen patients who experienced upper gastrointestinal symptoms 6 to 8 days following stomach ESD. The patients had at least 3 of the following symptoms: epigastric pain, hunger pain, nausea, borborygmus, abdominal distension, eructation, and increased flatus assessed by the Gastrointestinal Symptom Rating Scale (GSRS) Questionnaire.

5. Intervention

Arm 1: Oral administration of proton pump inhibitor (PPI: rabeprazole) 10 mg b.i.d. and TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for 8 weeks (n=8).

Arm 2: Oral administration of PPI for 8 weeks (n=5).

6. Main outcome measures

Gastric emptying (as assessed by the [^{13}C]-labeled acetate breath test) at Weeks 0 and 8.

Scores for the following Gastrointestinal Symptom Rating Scale (GSRS) items: epigastric pain, hunger pain, nausea, borborygmus, abdominal distension, eructation, and increased flatus at Weeks 0, 4, and 8.

7. Main results

Gastric emptying was compared between subjects who underwent ESD and healthy volunteers rather than between Arms 1 and 2 and was significantly decreased in subjects who underwent ESD (P<0.01). Overall GSRS score was significantly decreased at Week 4 (P<0.05) and Week 8 (P<0.01) compared to Week 0 in Arm 1 but not Arm 2, and the GSRS subscale score for abdominal pain at Week 0 was significantly decreased at Week 8 in Arm 1 (P<0.05).

8. Conclusions

The combination of PPI and rikkunshito may alleviate symptoms (especially abdominal pain) in patients with upper gastrointestinal symptoms following ESD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This RCT evaluated the efficacy of PPI + rikkunshito, which is believed to be effective for functional dyspepsia, in patients with upper gastrointestinal symptoms following ESD using change in subjective symptoms (GSRS score) as indicator. This study showed that gastric emptying was decreased following ESD but failed to measure gastric emptying after coadministration of rikkunshito and PPI. The authors suggested that the mechanism of this combined therapy, which improved abdominal pain following ESD, was associated with improved gastric emptying and increased secretion of ghrelin; however, this suggestion is based only on a literature review and was not verified. Future studies to evaluate the effects on frequency of postoperative bleeding (a complication of ESD) or time needed for mucosal defect (ulcer scarring) repair is anticipated. This structured abstract replaces a previous one (which was based on a convention abstract) and utilizes data from the original article.

12. Abstractor and date

Hoshino E, 31 December 2013; Motoo Y, 31 March 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Konno H, Maruo Y, Baba S, et al. Improvement of host-immunity by adding juzen-taiho-to to the postoperative adjuvant chemotherapy for patients with gastric cancer. *Biotherapy* 1997; 11: 193-9 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To evaluate the effect of juzentaihoto (十全大補湯) in host-immunity in gastric cancer patients undergoing postoperative adjuvant uracil+tegafur (UFT, 300 mg/day).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT- envelope).

3. Setting

One university hospital (Second Department of Surgery, Hamamatsu University School of Medicine) and two other hospitals, Japan.

4. Participants

Twenty-three patients who underwent macroscopic curative resection of gastric cancer (stage I-III).

5. Intervention

Arm 1: UFT 300 mg/day + TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. from 2 to 14 weeks after surgery (n=11).

Arm 2: UFT 300 mg/day alone (n=12).

6. Main outcome measures

Hematology (hemoglobin, white blood cell count, lymphocyte count, suppressor T cell %, cytotoxic T cell %): 1, 3, 6, and 12 months after the start of treatment.

Scores of subjective symptoms (performance status [PS], anorexia, general malaise): once a month.

7. Main results

There were no between-arm differences in hemoglobin level, white blood cell count, and lymphocyte count. Suppressor T cells (%) tended to be decreased for 3 months and were significantly lower in arm 1 only at Month 1 ($P<0.05$). Cytotoxic T cells (%) tended to be increased in arm 1 only at Month 1 ($P=0.076$).

Subjective symptoms such as anorexia and general malaise (especially anorexia) improved markedly but not significantly in arm 1. Statistical analysis could not be performed because of a small sample size.

8. Conclusions

Juzentaihoto is useful in gastric cancer patients undergoing postoperative adjuvant UFT.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Decreased white blood cell and granulocyte counts were observed in 1 patient in Arm 1 and 1 patient in Arm 2.

11. Abstractor's comments

The authors concluded that juzentaihoto used in combination with the anticancer agent (UFT) is useful in improving host-immunity and reducing adverse reactions to the anticancer agent. However, the only statistically significant difference was in the suppressor T cell % at Month 1 (significantly lower in the juzentaihoto combination group than in the control group). Otherwise, there was no significant difference between the two groups in suppressor T cell % at any other time points or in cytotoxic T cell % throughout the follow-up period, indicating that their conclusion was unjustified. Throughout the follow-up, white blood cell count and lymphocyte % tended to be higher in the combination group, indicating that the absolute lymphocyte count may have been significantly higher in the combination group. In addition, anorexia improved more in the combination group suggesting greater improvement in its nutritional status (but no significance could be demonstrated because of a small sample size). Difference in body weight gain % may have been significant although changes in body weight were not assessed. The data in this article needs re-analysis and re-interpretation.

12. Abstractor and date

Hoshino E, February 15 2009, 6 January 2010, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Sugimachi K. A study of the usefulness of ninjin'yoeito in the postoperative adjuvant chemotherapy for gastric cancer*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1995; 72: 454–8 (in Japanese). Ichushi Web ID: 1995168756 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人参養栄湯) for reducing adverse effects and improving performance status (PS) in patients undergoing postoperative adjuvant chemotherapy (fluoropyrimidine anticancer drug) for gastric cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Three university hospitals (2nd Department of Surgery, Kyushu University, 2nd Department of Surgery, Fukuoka University, 2nd Department of Surgery, University of Occupational and Environmental Health) and 19 other hospitals, Japan.

4. Participants

Forty-six postoperative patients with stage I‐IV gastric cancer undergoing gross curative resection.

5. Intervention

Arm 1: fluoropyrimidine anticancer drug + KANEBO Ninjin'yoeito (人参養栄湯) Extract Granules 2.5 g t.i.d. from 2 to 14 weeks postoperatively (n=27).
Arm 2: fluoropyrimidine anticancer drug alone (n=19).

6. Main outcome measures

Hematological measures (white blodod cell [WBC], red blood cell [RBC], and platelet counts), body weight, PS, subjective symptoms (appetite, nausea/vomiting, and diarrhea) at 14 weeks after the start of administration.

7. Main results

Change in body weight, PS: no significant difference between arms.
Decrease in RBC count, platelet count: a smaller decrease in arm 1, although not significantly smaller.
Decrease in WBC count: no significant between-arm difference.
Degree of improvement in subjective symptoms: no significant between-arm difference.

8. Conclusions

Ninjin'yoeito (人参養栄湯) tends to suppress the decreases in RBC count and platelet count but not the decrease in WBC count and does not improve PS in patients undergoing postoperative adjuvant fluoropyrimidine-based chemotherapy for gastric cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions in arm 1 did not occur, and adverse events in arm 2 were not mentioned.

11. Abstractor's comments

The authors concluded that ninjin'yoeito combined with the anticancer drug (fluoropyrimidine) has therapeutic usefulness. However, given that the physicians were not blinded to the patient's clinical information and medical status, the finding that the intervention was effective may have been biased. It is problematic that the extent of intraoperative progression and invasion varied between patients and that patients were included who had early-stage and advanced gastric cancer; differentiated and undifferentiated gastric cancer; partial, subtotal, and total gastrectomy; and stage I to IV disease. The fluoropyrimidine drugs also varied. Comparison should have been made between groups of patients with homogeneous baseline characteristics. Such heterogeneity may have contributed to the failure to show a significant improvement in subjective symptoms. Use of a protocol designed to optimally rather than uniformly administer ninjin'yoeito or to select the optimal Kampo medicine [*hozai* (補剤, formulations with tonic effects)] (i.e., hochuekkito, juzentaihoto, or ninjin'yoeito) would have resulted in a significant difference.

12. Abstractor and date

Hoshino E, 15 February 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yamada T. Randomized controlled trial of the efficacy of Juzentaihoto (TJ-48) combined with oral 5-FU for gastric cancer*. *Progress in Medicine*. 2004; 24: 2746-7 (in Japanese)

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯; TJ-48) combined with oral 5-FU as postoperative adjuvant chemotherapy in patients with surgically treated gastric cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifteen hospitals associated with Gifu University, Japan.

4. Participants

Ninety-four patients with surgically treated gastric cancer satisfying the following 8 criteria were included: (1) curability A or B; (2) no serious complications; (3) no preoperative treatment; (4) no double or multiple cancer; (5) WBC ≥3,000/mm^3, Plt ≥70,000/mm^3, total protein ≥ 6.0g/dL, AST/ALT ≤60 IU/L, and urinary protein (-), before the start of chemotherapy; (6) no possibility of pregnancy; (7) performance status of grade 0 or 1; (8) receipt of consent to participate in the study from patient or family member.

5. Intervention

Arm 1: combination therapy group; continuous treatment with 5-FU tablets (200 mg/day) combined with TSUMURA Juzentaihoto (十全大補湯) Extract Granules (TJ-48; 7.5 g/day) for 2 years starting 2 weeks after surgery; 43 patients.

Arm 2: monotherapy group; continuous treatment with 5-FU tablets (200 mg/day) for 2 years starting 2 weeks after surgery; 51 patients.

6. Main outcome measures

Five-year survival rate, 5-year survival rate by clinical stage.

7. Main results

Five-year survival rate was 74.3% in arm 1 and 73.5% in arm 2, indicating no significant difference between arms. By clinical stage, patients with stage I or II had 2-year and 5-year survival rates of 92% and 90%, respectively, in arm 1 (n=42), and 91% and 83%, respectively, in arm 2 (n=35), indicating no significant difference between arms. In contrast, patients with stage III or IV had 2-year and 5-year survival rates of 22% and 0%, respectively, in arm 1 (n=9), and 87% and 25%, respectively, in arm 2 (n=8), with median survival of 35.1 months in arm 2 and 14.2 months in arm 1, demonstrating significantly extended survival of patients treated with juzentaihoto.

8. Conclusions

Combination of juzentaihoto with oral 5-FU is effective for patients with surgically treated stage III or IV gastric cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The finding that the combination with juzentaihoto extends the postoperative survival of patients with surgically treated gastric cancer is clinically very impressive. The adverse drug reactions (ADRs) associated with this anticancer treatment are also of interest. Also, some information on study design (such as blinding) is lacking, making further evaluation difficult. Publication of the original paper is awaited.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Aoyama T, Nishikawa K, Takiguchi N, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis. *Cancer Chemotherapy and Pharmacology* 2014; 73: 1047-54. CENTRAL ID: CN-00993423, Pubmed ID: 24652604

1. Objectives

To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for gastric cancer chemotherapy-induced oral mucositis.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Ten facilities (four university hospitals and 6 hospitals).

4. Participants

Ninety-one patients with oral mucositis induced by gastric cancer chemotherapy rated at grade 1 or more on CTC-AE v4.0.

5. Intervention

Arm 1: TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules (2.5 g t.i.d.) taken until the start of the next round of chemotherapy (n=45).

Arm 2: Placebo administration group (n=46).

6. Main outcome measures

Severity of oral mucositis, its frequency and duration.

7. Main results

The frequency of oral mucositis of grade 2 or more was 40% in the hangeshashinto group (arm 1) and 41.3% in the control group (arm 2), so no significant between-group difference was found. Nor was any significant between-group difference found for oral mucositis duration (14 days in arm 1 and 16 days in arm 2). However, median oral mucositis duration among all grades was 9.0 days in arm 1 and 17.0 days in arm 2: although this was not a significant difference, oral mucositis duration tended to be shorter in the hangeshashinto group compared to the placebo group (P=0.290).

8. Conclusions

Hangeshashinto tends to shorten the duration of oral mucositis induced by gastric cancer chemotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Being an adverse effect induced by an anticancer drug, no adverse event attributable to hangeshashinto was observed.

11. Abstractor's comments

Being a double-blind RCT using placebo, this is a high-quality study that tested the effects of hangeshashinto for oral mucositis induced by gastric cancer chemotherapy. Unfortunately there was no significant difference in frequency or duration of oral mucositis of grade 2 or more, although hangeshashinto did tend to shorten oral mucositis duration among all grades. The authors point to a decrease in the anticancer dose as a possible reason why no significant difference was found. Yet the authors mention the need for a larger scale phase III trial in which the anticancer drug dose is not decreased, which is a valid observation. This follows the principle of "Kampo for the successful accomplishment of standard treatment": alleviating the oral mucositis with hangeshashinto allows for the anticancer drug to demonstrate its inherent effect to the full, without the need to decrease the dose. Further progress in this research is anticipated.

12. Abstractor and date

Motoo Y, 31 March 2017

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Omori K. Prospective randomized controlled study of daikenchuto for postoperative dysmotility after total gastrectomy*. *Progress in Medicine* 2012; 32: 614-5 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the effectiveness and safety of daikenchuto (大建中湯) for postoperative bowel dysmotility after gastric cancer and total gastrectomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital surgery department, Japan.

4. Participants

One-hundred patients (age range: 44–80 years) with curability A/B who underwent total gastrectomy (Roux-en Y) for gastric cancer.

5. Intervention

Arm 1: daikenchuto (manufacturer not specified) (7.5 g/day) for three months (n=51).
Arm 2: lukewarm water (20 mL) for three months (n=49).

6. Main outcome measures

Frequency of post-surgical complications (post-surgical ileus), gastrointestinal symptom quality of life (QOL, measured on the gastrointestinal symptom rating scale [GSRS]), bowel regularity, intestinal gas.

7. Main results

After 15 participants dropped out, the data for 85 participants were evaluated. There was no significant difference in the incidence of ileus, with one case in arm 1 and three in arm 2. Improvement in constipation was greater in arm 1 than arm 2 at one month and three months. Apart from that, there was no significant between-group difference in gastrointestinal symptom QOL (GSRS). Bowel regularity during hospitalization was significantly higher in arm 1 (1.1 ± 0.6) than arm 2 (0.7 ± 0.4) (P<0.05). Stools were significantly softer in arm 1 than arm 2. Intestinal gas had decreased significantly in arm 1 compared to arm 2 at one week, one month, and three months after surgery.

8. Conclusions

Daikenchuto contributes to early improvement in intestinal dysmotility in patients following total gastrectomy and is effective in reducing post-operative complaints.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events were reported.

11. Abstractor's comments

This study was a randomized clinical trial that evaluated the effectiveness and safety of daikenchuto for postoperative bowel dysmotility after gastric cancer and total gastrectomy. The authors suggest that daikenchuto is effective for early improvement of intestinal dysmotility following surgery. The study confirms a reduction in the area of intestinal gas (an objective indicator) in the daikenchuto group at one week after surgery, as well as subjective symptoms including an increase in bowel-movement frequency.

12. Abstractor and date

Okabe T, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Endo S, Nishida T, Nishikawa K, et al. Dai-kenchu-to, a Chinese herbal medicine, improves stasis of patients with total gastrectomy and jejunal pouch interposition. *American Journal of Surgery* 2006; 192: 9-13. CENTRAL ID: CN-00556925, Pubmed ID: 16769267

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction.

2. Design

Randomized crossover controlled trial (RCT-cross over).

3. Setting

Osaka University Hospital, Japan.

4. Participants

Seventeen patients who underwent total gastrectomy with jejunal pouch interposition reconstruction for gastric cancer (mean age, 62 years).

5. Intervention

Arm 1: treatment with TSUMURA daikenchuto (大建中湯) Extract Granules 5 g t.i.d. before meals for 2 weeks followed by no treatment for 2 weeks (n=10).

Arm 2: no treatment for 2 weeks followed by treatment with TSUMURA daikenchuto (大建中湯) Extract Granules 5 g t.i.d. before meals for 2 weeks (n=7).

6. Main outcome measures

Gastrointestinal symptoms, emptying, motility, and quality of life (QOL) (using Visick grading scale with modification).

7. Main results

Daikenchuto significantly relieved postprandial stasis-related symptoms including upper abdominal fullness, discomfort, and abdominal pain. Scintigraphy with ^{111}In- and ^{99m}Tc-labeled meals showed that daikenchuto significantly accelerated clearance of both the liquid (P<0.01) and solid (P=0.015) components of food from the jejunal pouch. Manometric assessment of pouch motility (contraction time in 6 patients found a significant increase from the pretreatment levels after daikenchuto treatment (P=0.028).

8. Conclusions

Daikenchuto accelerates gastrointestinal emptying and motility and improves QOL after total gastrectomy followed by jejunal pouch interposition reconstruction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper reports the effects of daikenchuto on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction. The authors evaluated a small number of patients in a RCT crossover and obtained highly accurate results. They deserve high praise, especially for exploring not only subjective symptoms but also gastrointestinal emptying and motility measured by relatively invasive procedures.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Akamaru Y, Takahashi T, Nishida T, et al. Effects of daikenchuto, a Japanese herb, on intestinal motility after total gastrectomy: a prospective randomized trial. *Journal of Gastrointestinal Surgery* 2015; 19: 467-72.

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) for promoting peristalsis in patients with reduced intestinal peristalsis after total gastrectomy

2. Design

Randomized controlled trial (RCT)

3. Setting

Department of Gastroenterological Surgery, University Hospital and surgical departments of 7 affiliated hospitals

4. Participants

Patients with gastric cancer scheduled for a total gastrectomy. Subjects were 20 to 80 years old, and had histologically confirmed stage I, II, or III gastric cancer without previous cancer treatment or past history of other cancers. One hundred patients underwent D2 lymphadenectomy (with spleen preservation), Roux-en-Y reconstruction, and R0 surgery (no remaining cancer).

5. Intervention

Arm 1: The intervention group had 51 patients who received oral administration of TSUMURA Daikenchuto Extract Granules 2.5 g with 20 mL of tepid water three times per day. The administration was started after the operation when oral intake was allowed, and continued for 3 months.

Arm 2: The control group had 49 patients who only received 20 mL of tepid water three times per day.

6. Main outcome measures

Gut motor function (time to first bowel movement, the frequency of stools, and the properties of stools according to the Bristol stool form scale [BSFS]), the gas volume score (GVS) based on abdominal roentgenograms, the quality of life (QOL) (Gastrointestinal Symptom Rating Scale [GSRS]), and the occurrence of postoperative ileus.

7. Main results

Because of the non-curative intent of the operation, changes in operative procedures, complications, withdrawal of informed consent, etc., 10 patients in Arm 1 and 9 patients in Arm 2 dropped out, reducing the number of subjects for analysis to 41 in Arm 1 and 40 in Arm 2. There were statistically significant differences between Arm 1 and Arm 2 in the number of stools (1.1±0.6 vs 0.8±0.4, P=0.037) and the properties of stools (BSFS 3.7±0.8 vs 3.1±0.8, P=0.041) during hospitalization. The GVS were lower in Arm 1 than Arm 2 at day 7 (78±25 vs 108±35%, P<0.05), 1 month (70±26 vs 95±49%, P<0.05), and 3 months (62±33 vs 90±38%, P<0.05) after the operation. There were no statistically significant differences in the GSRS, which indicates the QOL, or the occurrence of postoperative ileus (one case in Arm 1, or 2.4%, and two cases in Arm 2, or 5.0%) between the groups.

8. Conclusions

Daikenchuto promotes intestinal peristalsis to improve stool properties and intestinal gas.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

There were no adverse events associated with daikenchuto.

11. Abstractor's comments

In order to promote intestinal peristalsis after surgery, daikenchuto is routinely administered in clinical practice. Therefore, this study, which proved its efficacy, is very important. Although daikenchuto is called "a Japanese herb" in the title of the paper, it is not a single herb and should be called "a Japanese herbal medicine". If the study had been done blindly, which is hard to do, the results could have been more reliable. The difference in the occurrence of postoperative ileus might have become significant if the sample size had been larger. Moreover, the authors should have known that the usual dose of daikenchuto is 15 g per day when they designed the RCT. Different doses might have produced different results.

12. Abstractor and date

Tsuruoka K, 20 April 2017

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yoshikawa K, Shimada M, Wakabayashi G, et al. Effect of daikenchuto, a traditional Japanese herbal medicine, after total gastrectomy for gastric cancer: a multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Journal of American College of Surgeons* 2015; 221: 571-8.

1. Objectives

To verify the effects of daikenchuto (大建中湯) for intestinal tract motility after total gastrectomy for gastric cancer patients.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Multiple centers (40 centers), Japan.

4. Participants

Two hundred and seven gastric cancer patients with total gastrectomy (aged 20-85).

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 15.0g/day (5g t.i.d. before meals) taken orally (or by tube) from day 1 to 12 after surgery (n=102).

Arm 2: Placebo (TSUMURA & Co.) taken orally (or by tube) for the same period as above (n=105).

6. Main outcome measures

Primary endpoints: time until first flatus and bowel movement after completion of surgery (intratracheal tube removal), and frequency of bowel movements per day after surgery.

Secondary endpoints: QOL evaluated from Gastrointestinal Symptom Rating Scale (GSRS) and Functional Assessment of Cancer Therapy-Gastric (FACT-Ga), serum CRP level, presence or absence of severe disorder in intestinal tract motility after surgery, presence or absence of postoperative ileus.

7. Main results

There were 6 dropouts in arm 1 and 6 in arm 2: 96 patients were analyzed in arm 1 and 99 in arm 2. There was no significant difference in the primary endpoints with the median time until first flatus after tube removal being 68.9 hours in the daikenchuto (DKT) group and 68.3 hours in the placebo group (P=0.95). Similarly, median time until first bowel movement was 94.7 hours in the DKT group and 113.9 hours in the placebo group, showing a shorter tendency in the DKT group (P=0.051). There was no difference between groups for the secondary endpoints QOL and CRP. However, the frequency of intestinal motility disorder was significantly lower in the DKT group on day 12 after surgery (P=0.02). Postoperative ileus was observed in 3 participants in the DKT group and 2 in the placebo group, but there was no difference. Subgroup analysis showed that time until first bowel movement was significantly shorter in the group with lymph node dissection below D2, and the group who took 125g or more of DKT in total (P=0.02 and P=0.01, respectively).

8. Conclusion

Administration of daikenchuto immediately after total gastrectomy promotes early recovery of intestinal motility.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events of at least grade 3 were observed in six participants in the DKT group (2 cases of diarrhea, etc.) and 3 in the placebo group (1 case of diarrhea, etc.), but there was no significant difference between groups.

11. Abstractor's comments

Daikenchuto (DKT) is commonly used in clinical practice, and is known for its preventive effect for postoperative ileus, this is the first such large scale multicenter trial and has attracted attention for being a double-blind trial using a placebo. The results show that administering DKT from day 1 significantly reduced the frequency of intestinal tract motility disorder on day 12. However, there was no significant difference in the primary endpoints, only a trend toward shorter times until first bowel movement in the DKT group. Yet, the P value of 0.051 was close to a significant difference. Although subgroup analysis showed that time until first bowel movement was significantly shorter in the group that took larger doses of DKT and the group with less surgical invasion among the DKT group. However, it should be clearly noted in the abstract that these significant differences were seen only in subgroup analysis. Nevertheless, this is a valuable paper that verified the efficacy and safety of DKT in a high-quality RCT.

12. Abstractor and date

Motoo Y, 4 January 2017

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Toda T, Matsuzaki K, Kawano T, et al. Preoperative and postoperative combination therapy with slow-release tegafur capsules and juzen-taiho-to in patients with colorectal cancer - Tissue concentrations and thymidine phosphorylase activity -. *Gan no Rinsho* (*Japanese Journal of Cancer Clinics*) 1998; 44: 317-23 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To elucidate the mechanism by which juzentaihoto (十全大補湯) reduces the adverse reaction to treatment with 5-fluorouracil (5-FU) (hepatopathy) by determining the distribution of 5-FU in tissues of patients with colorectal cancer receiving slow-release tegafur preoperatively.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital, Japan.

4. Participants

Forty-four patients with colorectal cancer who received the anti-cancer drug tegafur (slow-release capsules, 800 mg/day) preoperatively and postoperatively.

5. Intervention

Arm 1: combination of juzentaihoto (十全大補湯) (manufacturer unknown) 7.5 g/day with slow-release tegafur capsules for 7–20 days preoperatively (n=24).
Arm 2: administration of slow-release tegafur capsules alone for 7–20 days preoperatively (n=20).
As postoperative adjuvant chemotherapy, the treatment was continued as long as possible in both arms.

6. Main outcome measures

Tegafur and 5-FU concentrations in peripheral blood, tegafur and 5-FU concentrations and thymidine phosphorylase (TP) activity in surgical specimen tissues (tumor and normal tissues), amount of tegafur converted to 5-FU per TP activity unit in tumor and normal tissues, tumor/normal tissue ratio of the amount of tegafur converted to 5-FU per TP activity unit, hematology/liver function test/total protein at start and completion of administration.

7. Main results

The 5-FU concentration in non-tumor tissues was higher in arm 2 than in arm 1 ($P<0.05$). There were no significant between-arm differences in tegafur and 5-FU concentrations in peripheral blood and tumor tissue, or in tegafur concentration in normal tissues. The common adverse drug reactions to slow-release tegafur (anorexia, nausea/vomiting, and diarrhea) occurred later in arm 2 (9/23) than in arm 1 (6/28). The change in glutamic pyruvic transaminase (GPT) between the start and completion of administration was not significant in arm 1 but it was significant in arm 2 ($P<0.01$), suggesting that juzentaihoto may suppress development of liver dysfunction. Thymidine phosphorylase (TP) activity was higher in tumor tissues than in normal tissues both in arm 1 ($P<0.01$) and arm 2 ($P<0.05$). Conversion of tegafur to 5-FU per TP activity unit was higher in tumor tissues than in normal tissues in arm 1. The ratio of the conversion to 5-FU per TP activity unit in tumor tissue to that in normal tissue was higher in arm 1 than in arm 2 ($P<0.05$).

8. Conclusions

Administration of juzentaihoto in patients receiving slow-release tegafur capsules increases 5-FU concentration in tumor tissues but decreases 5-FU concentration in normal tissues, enhancing the tumor selectivity of tegafur. This effect may be partly due to the modulation by juzentaihoto of TP activity in tissues and of cytochrome P-450 (CYP).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

It is attractive to suppose that a Kampo medicine modulates the effect of a drug-metabolizing enzyme to increase the tumor selectivity of an anti-cancer drug. Identification of the active component(s) of the Kampo medicine may pave the way for development of novel anti-cancer drugs. However, given the large standard error of the mean (SEM), it is unreasonable to conclude from higher GPT values at the completion of treatment that juzentaihoto suppresses hepatopathy associated with slow-release tegafur capsules. It would be more reasonable to attribute the higher GPT values to discontinuation of treatment in a few patients who developed hepatopathy.

12. Abstractor and date

Hoshino E, 26 April 2009, 6 January 2010, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Sasaki K, Takashima K, Kitagawa K, et al. Immunostimulation and suppression of liver metastasis by Kampo medicines in postoperative patients with colorectal cancer*. *Progress in Medicine* 1992; 12: 1652–5 (in Japanese).

1. Objectives

To evaluate the suppression of liver metastasis and stimulation of the immune response by shosaikoto (小柴胡湯) in postoperative patients with colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (1st Department of Surgery, Sapporo Medical College), Japan.

4. Participants

Twenty postoperative patients with colorectal cancer on chemotherapy.

5. Intervention

Arm 1: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day started 3–4 weeks postoperatively (n=10).

Arm 2: administration of Krestin (polysaccharide Kureha: PSK) 3 g/day started 3–4 weeks postoperatively (n=10).

6. Main outcome measures

Peripheral blood white blood cell (WBC) count, lymphocyte count, CD3-, CD4-, CD8-, CD57-, CD16-positive cells (%), and phytohemagglutinin (PHA)-stimulated lymphocyte proliferation, measured at baseline, 2, 4, and 12 weeks after administration as immunological indices. Patient prognosis (observation for 3 years and 6 months to 4 years and 4 months) in both arms.

7. Main results

CD4/CD8 ratio: There was no difference between arms.

CD57: At week 2, the percent increase was significantly larger in arm 1 than in arm 2. At week 4, a significant increase from baseline was noted in both arms.

CD16: At weeks 4 and 12, a significant increase from baseline was noted in both arms.

PHA-stimulated lymphocyte proliferation: A significant increase from baseline was noted at weeks 2, 4, and 12 in arm 1 and at week 12 in arm 2.

Prognosis: In arm 1, there was 1 patient with tumor recurrence in the abdominal wall who survived after re-operation and 1 death. In arm 2, there was 1 patient with liver metastasis who died and 1 patient with local recurrence who survived after re-operation.

8. Conclusions

Saiko agents increased PHA-stimulated lymphocyte proliferation and NK cell activity, evaluated by CD57 and CD16, suggesting its immunostimulating effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The above immunological findings were in patients on chemotherapy started 3–4 weeks postoperatively. Generally, the immune system is compromised postoperatively because of trauma and malnutrition. Cellular immunity is thought to be reduced for 2–4 weeks postoperatively and restored to preoperative level in 6 weeks. Therefore, it is impossible to conclusively attribute the increase in PHA lymphocyte proliferation and NK activity at 2–12 weeks postoperatively to the effect of shosaikoto or PSK without a no treatment control. Also, there is a wide distribution of disease stages, making it impossible to discuss prognosis. It is necessary to compare two groups of patients with stage III–IV on specified chemotherapy after confirmation of sufficient recovery from surgery: one group treated with Kampo medication and one group without such treatment.

12. Abstractor and date

Hoshino E, 26 April 2009.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Araki Y, Tanaka T, Ogata Y, et al. Immunological evaluation of the efficacy of Kampo prescription for postoperative patients with colorectal cancer*. *Shinyaku to Rinsho* (*Journal of New Remedies and Clinic*) 1992; 41: 1670–6 (in Japanese).

1. Objectives

To evaluate the immunostimulation and improvement of nutritional status by ninjin'yoeito (人参養栄湯) in postoperative patients with colorectal cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (1st Department of Surgery, Kurume University), Japan.

4. Participants

Twenty-three postoperative patients with colorectal cancer on chemotherapy.

5. Intervention

Arm 1: TSUMURA Ninjin'yoeito (人参養栄湯) Extract Granules 9.0 g/day from the start of postoperative oral feeding (n=12).

Arm 2: no treatment (n=11).

6. Main outcome measures

Peripheral blood white blood cell (WBC) count, lymphocyte count, percentage of T cells (%), phytohemagglutinin (PHA) lymphocyte transformation, lymphocyte surface markers (CD4, CD8, and CD25), NK cell activity (%), and interleukin (IL)-2 responsiveness, measured preoperatively, and at postoperative week 2 and months 3 and 6 as indices of immunological status. Patient prognosis (observation for 3 years and 6 months to 4 years and 4 months) in both arms. Prognostic nutritional index (PNI).

7. Main results

Percent change in lymphocyte count: greater in arm 1 than arm 2 at postoperative week 2 and month 3 ($P<0.05$).

Change in the T cell number (in %): greater in arm 2 than arm 1 ($P<0.05$) at postoperative week 2, but greater in arm 1 than arm 2 ($P<0.05$) at postoperative months 3 and 6.

Percent change in PHA-stimulated lymphocyte proliferation: greater in arm 1 than arm 2 at postoperative month 6 ($P<0.05$).

Change in NK cell activity (in %) and prognostic nutritional index (PNI): no significant difference between arms.

Change in the number of CD4- and CD8-positive cells (in %) and IL-2 responsiveness ratio: all tended to be greater in arm 1 than arm 2 at postoperative week 2 and month 3.

IL-2 receptor-positive cell ratio: tended to be greater in arm 1 than arm 2 at postoperative week 2 and month 6. At postoperative month 6, there was a significant reduction from preoperative value in arm 1 ($P<0.05$).

8. Conclusions

Ninjin'yoeito significantly promotes improvement of lymphocyte count and PHA-stimulated lymphocyte proliferation in postoperative patients with colorectal cancer, suggesting its role as a possible biological response modifier.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study demonstrated that administration of ninjin'yoeito increased lymphocyte count, the percentage of T lymphocytes, and PHA-stimulated lymphocyte proliferation but had no effect on NK cell activity, IL-2 responsiveness ratio, or IL-2 receptor-positive cell ratio (indices of unknown immunological significance), or nutritional state (PNI). (Although the authors concluded that NK cell activity was enhanced, a similar increase was noted in the control group; thus, it is impossible to conclude that NK cell activity was enhanced by the Kampo medicine.) However, certain cellular immune functions may have been stimulated one of the mechanisms underlying Kampo medicine activity.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Sasaki K, Ezoe E, Araya J, et al. Effects of Kampo medicine on the immune functions in gastrointestinal gastroenteric cancer patients– utility from the perspective of immunity. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2006; 15: 9-14 (in Japanese).

Sasaki K, Takasaka H, Furuhata T, et al. Effect of Kampo medicine on the cancer chemotherapy of cancer. *Geka Chiryo* (*Surgical Therapy*) 2007; 97: 504-10 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the clinical efficacy of juzentaihoto (十全大補湯) for the prevention of postoperative recurrence of colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

The First Department of Surgery of Sapporo Medical University and other institutions (their names, unspecified), Japan.

4. Participants

One hundred and sixty-eight patients (mean age, 65 years) with stage II or III colorectal cancer who received curative resection and adjuvant chemotherapy between July 2001 and March 2005.

5. Intervention

Arm 1: treatment with oral 5-FU and juzentaihoto (十全大補湯) (manufacturer, not specified) 7.5 g/day, n=86.
Arm 2: treatment with oral 5-FU, n=82.

6. Main outcome measures

Recurrence rate, time to recurrence, and survival time.

7. Main results

Mean postoperative follow-up was 38.6 months. Recurrence rate for patients with stage II disease was slightly, though not significantly, more favorable in arm 1 (6.9%) than in arm 2 (14.0%). Mean times to recurrence were 18.2 months in arm 1 and 16.9 months in arm 2. The 3-year recurrence-free survival rate was slightly, though not significantly, better in arm 1: 92.2% in arm 1 and 85.9% in arm 2 for patients with stage II disease, and 67.5% and 62.9%, respectively, for patients with stage III disease.

8. Conclusions

Juzentaihoto may have a metastasis-suppressive effect, but since these are interim reports, the follow-up is still ongoing.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

These two papers are interim reports on a multicenter clinical study that evaluated the clinical efficacy of juzentaihoto for the prevention of postoperative recurrence of colorectal cancer. The data from slightly less than 100 patients in each arm were analyzed. At this point, no clear difference is observed between the juentaihoto-treated arm and the control arm, although the outcomes tend to be slightly more favorable in the former. A final report is anticipated. This abstract summarized mainly data from the second, recently published, paper mentioned above.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Nishimura G. Evaluation of clinical efficacy of hochuekkito in improving nutritional/immune status in patients with surgery for large intestine carcinoma*. *Progress in Medicine.* 2009; 29: 84-85. MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of 1-week preoperative treatment with hochuekkito (補中益気湯) for improving pre- and postoperative nutritional status and immune function in patients scheduled to undergo laparotomy for large intestine carcinoma.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital (Kanazawa Red Cross Hospital), Japan.

4. Participants

Twenty patients scheduled to undergo laparotomy for large intestine carcinoma.

5. Intervention

Arm 1: TSUMURA Hochuekkito (補中益気湯) Extract Granules at a dose of 2.5 g t.i.d. from 7 days to 1 day before the operation (n=10).
Arm 2: not treated (n=10).

6. Main outcome measures

Height, body weight (body mass index [BMI]), white blood cell count, and levels of C-reactive protein (CRP), total protein, albumin, prealbumin, and immunological parameters (IL-6, CD4, CD8) were determined before and after administration preoperatively and 1, 3, and 7 days postoperatively.

7. Main results

One patient in arm 1 dropped out. The remaining 19 patients (9 in arm 1 and 10 in arm 2) were included in the analysis. There was no between-arm difference in the age, sex, affected site, duration of the operation, blood loss, or percentage of patients who received blood transfusion and no significant between-arm difference in body weight (BMI), white blood cell count, CRP, total protein, or albumin. Mean prealbumin level tended to be higher in arm 1 than in arm 2 from the day before surgery to 7 days after surgery, with a significant difference observed only 3 days after surgery (P=0.02). IL-6 tended to be lower in arm 1 than in arm 2 on postoperative day 1.

8. Conclusions

Preoperative treatment with hochuekkito may be useful for early recovery from surgery for large intestine carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events: one patient in arm 1 dropped out because he/she refused the treatment due to “no Kampo medicine was accepted constitutionally.”

11. Abstractor’s comments

Administering hochuekkito for 1 week prior to surgery for large intestine carcinoma to improve perioperative nutritional/immune status and reduce complications and thereby to reduce hospital stay and medical costs is an interesting issue. In revitalization therapy, hochuekkito is an *hozai* (補剤; formulations with tonic effects) that is focused on “*qi* (気虚, *qi* deficiency)” and on improving anorexia, general malaise, sleep disorder, etc. Prealbumin is a short-lived protein that reflects recent protein intake. Hochuekkito may have acted by reducing the patient’s anxiety and thus preventing loss of appetite before surgery. Appetite, sleep, bowel movement, etc., which were not followed in this study, should also be monitored. It would be desirable to confirm the usefulness of hochuekkito in randomized controlled trials using other *hozai* (juzentaihoto and ninjin’yoeito) or anxiolytics as controls.

12. Abstractor and date

Hoshino E, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Nishioka M, Shimada M, Kurita N, et al. The Kampo medicine, goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen. *International Journal of Clinical Oncology* 2011; 16: 322–7. CENTRAL ID: CN-00812737, Pubmed ID: 21258836

Nishioka M, Shimada M, Kurita N, et al. The significance of Kampo as needed for cancer therapy – How to put it to use in clinical settings – Goshajinkigan alleviates FOLFOX-related peripheral neuropathy*. *Sanfujinka Kanpo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2012; (29): 22–7 (in Japanese). Ichushi Web ID: 2013030031

1. Objectives

To clarify the efficacy and adverse effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by oxaliplatin therapy for advanced or recurrent colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Tokushima Hospital, Japan.

4. Participants

Forty-five outpatients who received mFOLFOX6 (oxaliplatin＋l-LV＋5FU) therapy for advanced colorectal cancer from Jan. 2007 to Dec. 2009. Each patient had performance status (PS) 0–2, and no patient had bone marrow, hepatic, renal, or cardiac function abnormalities, clinical neuropathy, diabetes, alcohol-related diseases, or brain lesions.

5. Intervention

Arm 1: TSUMURA Goshajinkigan Extract Granules (7.5 g/day, in 2 or 3 divided doses) in combination with mFOLFOX6 therapy (n=22).

Arm 2: mFOLFOX6 therapy alone (n=23).

6. Main outcome measures

Incidence of grade 3 peripheral neuropathy, percentage of patients who developed grade 2 or 3 peripheral neuropathy after each treatment period, grade 3 adverse effects other than peripheral neuropathy, and modification of the effects of mFOLFOX6 therapy. (Peripheral neuropathy was assessed according to DEB-NTC [Neurotoxicity Criteria of Debiopharm]).

7. Main results

There were no significant differences in background factors between groups (age, gender, PS, proportion of rectal/colon cancer, site of metastasis, proportion of previously treated patients, proportion of patients taking bevacizumab in combination, number of completed courses, and cumulative oxaliplatin dose). Grade 3 peripheral neuropathy incidence was significantly lower in arm 1 than arm 2 ($P<0.01$) and percentage of patients with grade 2 and 3 peripheral neuropathy at the beginning of each course was lower in arm 1. However, goshajinkigan did not modify the incidence of other adverse effects (grade 3) or therapeutic effects of mFOLFOX6 therapy.

8. Conclusions

Goshajinkigan decreased the incidence of severe peripheral neuropathy induced by mFOLFOX6 therapy (oxaliplatin＋l-LV＋5FU) in patients treated for non-resectable or recurrent colon cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects mentioned.

11. Abstractor's comments

The recent advent of oxaliplatin has been a major advance in the chemotherapy of colorectal cancer. Because peripheral neuropathy is the main dose-limiting toxicity of the therapy, its prevention is vital to improve the effectiveness of chemotherapy. Varieties of options have so far been tested in vain. The present trial suggested that goshajinkigan effectively decreased the incidence of severe peripheral neuropathy induced by mFOLFOX6. But it did not improve the prognosis of the patients, because it did not extend the treatment period of mFOLFOX6. We look forward to the investigations of the mechanisms of action of goshajinkigan for peripheral neuropathy as well as the establishment of the measures to increase the courses of mFOLFOX6 for colorectal cancer.

12. Abstractor and date

Hoshino E, 1 December 2012, 6 June 2015.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Kono T, Hata T, Morita S, et al. Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE): a phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. *Cancer Chemotherapy and Pharmacology* 2013; 72: 1283-90. CENTRAL ID: CN-00961704, Pubmed ID: 24121454

1. Objectives

To investigate the inhibitory effect of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules(TJ-107) on oxaliplatin-induced peripheral neuropathy (OPN).

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Twenty centers including university hospitals, Japan.

4. Participants

Patients with pathologically confirmed colorectal cancer receiving a chemotherapy regimen including oxaliplatin (85 mg/m^2 oxaliplatin every two weeks in FOLFOX4 or mFOLFOX6) (n=93).

5. Intervention

Arm 1: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (2.5 g t.i.d.) administered before meals, continued for 26 weeks after start of chemotherapy (n=47).

Arm 2: placebo administered under the same schedule as above (control group, n=46).

6. Main outcome measures

An investigating physician graded peripheral neuropathy and other adverse effects between 0 and 4 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver. 3 before the start of chemotherapy, then every 2 weeks (8 times), then every 4 weeks until the 26th week. The patients also graded themselves for degree of numbness before therapy and then before each chemotherapy treatment between grade 0 and 4 according to the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12 items questionnaire (FACT/GOG-Ntx-12).

7. Main results

Three patients in arm 1 and one patient in arm 2 dropped out of the study. OPN appearing by the 8th anticancer drug administration and graded at least grade 2 occurred in 39% of arm 1 and in 51% of the placebo group, and of those, 7% in arm 1 and 13% in arm 2 had grade 3: arm 1 had the lower scores in both cases. TJ-107 inhibited the advance of OPN severity, with the median length of time to reach at least Gr. 2 being 5.5 months in arm 1 and 3.9 months in arm 2. The percentage of patients displaying OPN by the 26th week was 54.1% in arm 1 and 62.5% in arm 2. The degree of OPN as measured by the patients showed no significant difference between groups in the 8th and 26th weeks. There was no difference between the effects of TJ-107 for FOLFOX4 and mFOLFOX6. There was no difference between groups for other adverse effects, although there were fewer cases of vomiting in arm 1. There was no difference between groups for antitumor effects (percentages of complete response [CR] + partial response [PR] and CR+PR+ stable disease [SD]): TJ-107 had no adverse effect.

8. Conclusions

Goshajinkigan delays onset of peripheral neuropathy of Grade 2 or more induced by oxaliplatin.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no difference in adverse drug reaction incidence for arms 1 and 2. There was no issue with the safety of goshajinkigan.

11. Abstractor's comments

The results of chemotherapy for colorectal cancer have dramatically improved with the advent of oxaliplatin in recent years. However, overcoming OPN has been an issue as it is a dose-limiting toxicity. The authors used goshajinkigan for this study as it has previously been useful for diabetes-induced peripheral neuropathy. Starting with a retrospective trial, they conducted a multi-center RCT before this multi-center DB-RCT, which suggested the preventative effect of goshajinkigan for OPN. The authors consider that goshajinkigan's main mechanism of action lies in the analgesic action of bushi, as well as the neuroprotection, neurotransmitter modification, bloodstream improvement mediated by the production of nitric oxide, and various actions of the other crude drugs. However, as the quantity of bushi in goshajinkigan is no more than 1 g per day, increasing the quantity of bushi may increase its anti-OPN effect. Further investigation into the therapeutic effects of Kampo for OPN under a protocol including an increased quantity of powdered processed Aconite Root for ethical dispensing in the goshajinkigan is anticipated.

12. Abstractor and date

Hoshino E. 6 June 2015.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Oki E, Emi Y, Kojima H, et al. Preventive effect of Goshajinkigan on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial): a placebo-controlled, double-blind, randomized phase III study. *International Journal of Clinical Oncology* 2015; 20: 767-75.

1. Objectives

To evaluate the preventive effect of goshajinkigan (牛車腎気丸) for FOLFOX-induced peripheral neurotoxicity.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Multiple centers, Japan.

4. Participants

One hundred and eighty-six colon cancer patients receiving mFOLFOX6 as adjuvant chemotherapy after surgery.

5. Intervention

Arm 1: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 7.5 g/day (2.5g t.i.d. before meals or between meals) taken orally from mFOLFOX start date until the end of the 12-cycle regimen (n=93).

Arm 2: Placebo (Yamato Logistics Co., Ltd.) taken orally for the same period as above (n=93).

6. Main outcome measures

Primary endpoints: Time until onset of peripheral neuropathy (NCI CTCAE ver.3.0 grade 2 or higher) (time to neuropathy: TTN); Secondary endpoints: Rate of discontinuation of treatment due to peripheral neuropathy, oxaliplatin (L-OHP) relative dose intensity.

7. Main results

In arm 1, 89 participants were analyzed after 4 dropped out. The peripheral neuropathy (grade 2 or higher) incidence rate was 50.6% in the goshajinkigan group (arm 1) which was higher than the placebo group (arm 2) rate of 31.2%. The TTN curve also showed significantly shorter times for the goshajinkigan group (P=0.007, HR=1.908 [1.181-3.083]). Goshajinkigan did not demonstrate preventive effect against grade 1 peripheral neuropathy. No between-group difference was observed for adverse events other than neurotoxicity. The secondary endpoint, L-OHP relative dose intensity, was 78.99% in the placebo group and 83.41% in the goshajinkigan group, which was significantly higher (P=0.033). The rate of discontinuation of treatment was not mentioned.

8. Conclusion

Goshajinkigan indicated a preventive effect against FOLFOX-induced peripheral neuropathy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No significant between-group difference was observed for hematotoxicity or non-hematotoxicity.

11. Abstractor's comments

This is an important study that sought to verify for the first time in a phase III double-blind, placebo-controlled trial of the preventive effect of goshajinkigan for FOLFOX-induced peripheral neuropathy in colon cancer patients. But as a result of interim analysis at 142 participants out of the target 310, there were more cases of peripheral neuropathy in the goshajinkigan group, and the independent monitoring committee recommended discontinuation. The trial was discontinued at 186 registered participants. The authors surmise that chronic/accumulative peripheral neuropathy cases increased due to larger doses of L-OHP in the goshajinkigan group. However, it seems that it was the only possible cause of the results in this study. The paper mentions that overall survival time and recurrence-free survival time would be investigated after 5 years. If there would be survival benefit in the goshajinkigan group, conducting this RCT would have significance. Furthermore, the ingredients with a neuroprotective action reach their highest blood concentration about at 60 minutes after administration of goshajinkigan. It is difficult to understand what the authors mean by their consideration that the timing of goshajinkigan administration might be related to prevention of chronic peripheral neuropathy and L-OHP relative dose intensity.

12. Abstractor and date

Motoo Y, 27 December 2016.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Miyauchi H. A comparative study of the preventive effects of hangeshashinto and oral alkalizer for delayed diarrhea in chemotherapy for colorectal cancer (FOLFILI)*. *Progress in Medicine* 2012; 32: 628-9 (in Japanese). MOL, MOL-Lib

1. Objectives

To compare the preventive effects of hangeshashinto (半夏瀉心湯) for delayed diarrhea following administration of CPT-11 for colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

No mention of participating centers (the authors are from the Department of Frontier Surgery, Graduate School of Medicine, Chiba University), Japan.

4. Participants

Thirty patients (age range: 20–80 years) with advanced recurrent colorectal cancer.

5. Intervention

Arm 1: oral administration of hangeshashinto (半夏瀉心湯) (manufacturer not specified) 7.5 g/day during FOLFILI-3 treatment (n=14).

Arm 2: administration of oral alkalizers (sodium bicarbonate 1.8 g and ursodeoxycholic acid 300 g) from the first day of FOLFILI-3 treatment (n=15).

6. Main outcome measures

Grade of diarrhea, grade of adverse events other than diarrhea, drug compliance, response rate, treatment duration.

7. Main results

No significant difference between arms 1 and 2 was noted in diarrhea grade (3/14 [21.4%] participants in arm 1 and 4/15 participants [26.7%] in arm 2 scored grade III or higher),
neutropenia grade (4/14 [28.5%] participants in arm 1 and 6/15 participants [40%] in arm 2 scored grade III or higher), drug compliance (81.2% in arm 1, with 87.5% for sodium bicarbonate and 96.8% for ursodeoxycholic acid in arm 2), antitumor effect (complete response [CR] in no participants and partial response [PR] in six participants in arm 1; CR in two participants and PR in eight participants in arm 2), response rate/disease control rate (response rate of 46.2% and disease control rate of 92.3% in arm 1; response rate of 71.4% and disease control rate of 100% in arm 2), and number of FOLFILI cycles (16.1 in arm 1 and 14.5 in arm 2).

8. Conclusions

Oral alkalizer and hangeshashinto have the same preventative effect on delayed diarrhea in FOLFILI.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The authors originally held the notion that oral alkalizer prevented delayed diarrhea, which is a dose-limiting toxicity (DLT) and an adverse effect in patients receiving CPT-11 for advanced recurrent colorectal cancer. This study evaluated the previously reported inhibitory effect of hangeshashinto compared with oral alkalizer (the control group) and found no difference in their inhibitory effects. However, there is no indication that intestinal alkalizers taken orally do in fact prevent delayed diarrhea from CPT-11. A trial that uses a therapy without established efficacy as a control has little significance. It is of fundamental importance to clarify the clinical effectiveness by including a hangeshashinto group and a non-hangeshashinto group in the trial.

12. Abstractor and date

Hoshino E, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Matsuda C, Munemoto Y, Mishima H, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. *Cancer Chemotherapy and Pharmacology* 2015; 76: 97-103.

1. Objectives

To verify the clinical effects of hangeshashinto (半夏瀉心湯) for chemotherapy-induced oral mucositis.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Ten centers including a medical care center, Japan.

4. Participants

Ninety-three participants administered a fluorinated-pyrimidine-based anti-cancer agent for colorectal cancer, who developed moderate-to severe chemotherapy-induced oral mucositis (WHO grade ≥1).

5. Intervention

Arm 1: TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules 7.5g/day (2.5g t.i.d.) (n=46) starting administration together with the start of chemotherapy cycle 2 for 2 weeks.

Arm 2: Placebo formulation (n=47).

In each arm, administration continued for 2 weeks from commencement of chemotherapy.

6. Main outcome measures

Oral mucositis symptoms and objective findings at screening and on days 3, 5, 7, 9 and 14 of chemotherapy cycle 2.

7. Main results

In arm 1, 3 participants were excluded: 43 were administered hangeshashinto. There was no significant difference between the hangeshashinto group (48.8%) and the placebo group (57.4%) for occurrence of oral mucositis of grade 2 or higher. However, the mean period to improvement of oral mucositis of grade 2 or higher was significantly shorter in the hangeshashinto group (5.5 days) compared to the placebo group (10.5 days) (P＝0.018).

8. Conclusion

Hangeshashinto has a therapeutic effect as it accelerates improvement of oral mucositis of grade 2 or higher induced by an anti-cancer agent.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no significant difference in occurrence of adverse effects between the placebo group and the hangeshashinto group.

11. Abstractor's comments

This study compared the therapeutic effect of hangeshashinto extract granules with placebo on oral mucositis induced by an anti-cancer agent. It found that administering hangeshashinto shortened the period until recovery from oral mucositis of grade 2 or higher, suggesting it fulfills a certain role as a therapeutic drug, so it is a clinically significant study. The authors investigate its preventive effect against oral mucositis by starting administration of hangeshashinto together with the start of the anti-cancer agent therapy, however, the occurrence of oral mucositis was the same as the placebo, which showed that preventive administration was not effective. A characteristic of Kampo medicine is that it takes a presymptomatic approach with the existence of *sho* (証, patterns) underlying it, so it would be advisable to allocate participants to groups based on their pattern if possible, when examining its preventive effects.

12. Abstractor and date

Ushiroyama T, 16 January 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yoshikawa K, Shimada M, Nishioka M, et al. The effects of the Kampo medicine (Japanese herbal medicine) "Daikenchuto" on the surgical inflammatory response following laparoscopic colorectal resection. *Surgery Today* 2012; 42: 646-51. Ichushi Web ID: 2013248005, Pubmed ID: 22202972

1. Objectives

To evaluate the anti-inflammatory effects of daikenchuto (大建中湯) on patients with colorectal cancer following laparoscopic resection.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Tokushima University Hospital, Japan.

4. Participants

Thirty patients with colorectal cancer following laparoscopic resection.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (7.5 g/day) for seven days from the day after surgery (n=15).

Arm 2: no administration of daikenchuto (大建中湯) (n=15).

6. Main outcome measures

Number of days to first flatus and number of days to discharge after surgery were recorded and measurements were taken before surgery and on days 1, 3, 5, and 7 after surgery for body temperature, heart rate, white blood cell count, lymphocyte count, C-reactive protein (CRP), β-D-glucan, and Candida antigen.

7. Main results

Mean age was significantly lower in arm 1 than arm 2. The number of days to first flatus was significantly lower in arm 1 (1.8 ± 0.5) than arm 2 (2.7 ± 0.5). Only on the third day of hospitalization, CRP was significantly lower in arm 1 (4.6 ± 0.6) than arm 2 (8.3 ± 1.1). Body temperature was significantly lower in arm 1 (36.2 ± 0.4) than arm 2 (36.9 ± 0.6). There was no significant difference between arms for number of days to discharge after surgery, heart rate, white blood cell count, β-D-glucan, and Candida antigen.

8. Conclusions

Administering daikenchuto for seven days from the day after laparoscopic colorectal cancer surgery is useful for inhibiting inflammation and promoting flatus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

If it were possible to inhibit the inflammatory response (CRP) and shorten the period of intestinal paralysis through some form of intervention after colorectal surgery, there would be a decrease in hospitalization periods and in the need for treatment for complications, which would be useful from the point of view of controlling medical costs; however, hospitalization periods did not decrease in this study. The authors of this study chose patients who underwent laparoscopic surgery for their study with an aim to demonstrate that daikenchuto has an anti-inflammatory effect after surgery with low invasiveness. The inflammation inhibitory action mechanisms of daikenchuto soon after surgery that the authors listed include 1) promotion of intestinal motility through increased release of acetylcholine from cholinergic nerves mediated by Japanese Pepper (sansho), 2) the subsequent inhibition of enteric bacterial growth, 3) increase in dose-dependent intestinal tract blood flow mediated by Processed Ginger (kankyo), and 4) the inhibition of bacterial translocation and homeostasis maintenance in the intestinal epithelium mediated by inhibition of the production of inflammatory cytokines such as IFN-γ, IL-6, and TNF-α attributable to daikenchuto, observed in rats. While inhibiting inflammation after abdominal surgery might be useful for recovery from surgical invasion, it is liable to be disadvantageous from the point of view of defense. And the multifaceted effects of Kampo medications are a merit as well as a demerit. There needs to be careful verification of whether surgeons' current habit of indiscriminately prescribing daikenchuto for long periods after abdominal surgery is valid or not. Furthermore, while the authors have published a study undertaken at the same time under the same protocols in conference proceedings (*Proceedings of the 5th Annual Meeting of the Japanese Gastroenterological Association* 2009: 9-10), the results of that paper differ from the results of this one. This appears to be due to differences in some of the cases enrolled in the study (for that reason, the structured abstract, which had been included in the previous version of Evidence Reports of Kampo Treatment [EKAT], was excluded from EKAT Appendix 2014 [added to the list of excluded abstracts]).

12. Abstractor and date

Hoshino E. 6 June 2015

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Nagashima Y, Tanaka N, Furukawa K, et al. Effects of Daikenchuto (TJ-100) on intestinal paralysis after surgery for colorectal cancer*. *Progress in Medicine* 1998; 18: 903-5 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on intestinal paralysis after surgery for colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Nippon Medical School Hospital), Japan.

4. Participants

Eighteen patients who underwent low anterior resection for rectal cancer. Exclusion criteria were: age 75 or older; history of laparotomy; American Society of Anesthesiologists (ASA) class II disease with complications.

5. Intervention

Arm 1: treatment with infusion of TSUMURA Daikenchuto (大建中湯) Extract Granules (7.5 g/day) dissolved in lukewarm water (20 mL) through a gastric tube (oral administration after the removal of gastric tube) (n=8).

Arm 2: no treatment (n=10).

6. Main outcome measures

Times to passage of flatus and first bowel movement, and transit times (upper gastrointestinal, colorectal, and whole-bowel) as assessed by radiopaque markers.

7. Main results

Among the outcome measures, time to passage of flatus and upper gastrointestinal and whole-bowel transit times were shorter in arm 1 than arm 2 and the difference in upper gastrointestinal transit time was significant.

8. Conclusions

Daikenchuto is useful for relieving intestinal paralysis by reducing the intestinal transit time after colorectal cancer surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes an evaluation of the effects of daikenchuto on intestinal paralysis after surgery for colorectal cancer. Few transit time studies using radiopaque markers in daikenchuto (Kampo medicine)-treated patients have been reported and the present study is appreciated in that regard. Future studies including a larger number of patients are anticipated.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Ota M. A Randomized controlled trial of perioperative daikenchuto for colorectal cancer surgery*. *Progress in Medicine* 2012; 32: 618–9 (in Japanese). MOL, MOL-Lib

1. Objectives

To verify inhibition of inflammatory cytokine production and post-operative enhanced reactivation of intestinal function by daikenchuto (大建中湯) in colorectal cancer patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Yokohama City University Hospital, Japan.

4. Participants

Eighteen colorectal cancer patients scheduled for surgery.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 15.0 g/day for nine days[1)] (n=8).
Arm 2: no administration of daikenchuto (大建中湯) (n=10).

[1)] Daikenchuto was started two days before surgery, then restarted on the second day after surgery and continued until the eighth day.

6. Main outcome measures

Period between initial flatus and defecation, postoperative hospital stay (days), incidence of postoperative ileus, and postoperative white blood cell (WBC) count, C-reactive protein (CRP) level, interleukin (IL)-6 level, tumor necrosis factor (TNF)-α level, and natural killer (NK) cell activity (days 1, 3, and 7)

7. Main results

The period to initial flatus lasted one to two days in most cases and there was no between-arm difference. The period to initial defecation was significantly shorter in arm 1. There was no significant difference in the occurrence of ileus (two patients in arm 1, no patients in arm 2). CRP level tended to be decreased in patients with body mass index (BMI) under 23 in arm 1 but not in patients with a BMI over 23 in both groups. Between-group difference in IL-6 level, TNF-α level, or NK activity was not significant.

8. Conclusions

Daikenchuto enhances postoperative intestinal reactivation.

9. From Kampo medicine perspective

The tendency for reduced CRP among patients with lower BMI suggests that daikenchuto may be effective for patients with *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study was an attempt to clinically prove through evidence provided by RCT that perioperative daikenchuto enhances postoperative intestinal reactivation in colorectal cancer patients. However, the trial design (which tries to avoid bias related to the surgical procedure [laparoscopic vs. open] and disease location [colon vs. rectum]) introduces potential randomization problems. In addition, the actual sample size was 18 patients rather than the target sample size of 30; the significant difference in period until initial defecation was very small; two patients in the daikenchuto group but no patient in the no administration group suffered ileus; the tendency for decreased CRP level in patients with a BMI under 23 was very slight; and generally differences in laboratory test results were not significant. This leaves the undeniable impression that the evidence for the conclusion is fairly weak. Hopefully the author will recruit a larger sample population and include types of surgery and pathological findings (colorectal cancer invasion depth, etc.) in the analysis.

12. Abstractor and date

Motoo Y, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yaegashi M, Otsuka K, Itabashi T, et al. Applying a Kampo medication to lower gastrointestinal tract surgery*. *Shokaki Geka* (*Gastroenterological Surgery*) 2013; 36: 1315-24.

Yaegashi M, Otsuka K, Itabashi T, et al. Daikenchuto stimulates colonic motility after laparoscopic -associated colectomy. *Hepato-Gastroenterology* 2014; 61: 85-9. CENTRAL ID: CN-00991603, Pubmed ID: 24895799

1. Objectives

To evaluate the effectiveness of daikenchuto (大建中湯) for perioperative intestinal paralysis following laparoscopic colon cancer surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Department of Surgery, Iwate Medical University, Japan.

4. Participants

Fifty-four cases of laparoscopic colon cancer surgery (aged between 43 and 89 years).

5. Intervention

Arm 1: Daikenchuto (大建中湯) (manufacturer unknown) 7.5 g/day two days before surgery then from the first day after surgery until discharge from hospital (n=27, aged 51 to 83 years).

Arm 2: Intestinal disorder medication two days before surgery then from the first day after surgery until discharge from hospital (n=27, aged 43 to 89 years).

6. Main outcome measures

Time until first flatus and until bowel movement. Time to the first toleration of solid food (50% rice gruel diet). Colonic transit time with radiopaque markers.

7. Main results

Since 1 patient in arm 1 and 2 patients in arm 2 dropped out of the study, the efficacy analysis set included 26 and 25 patients in arm 1 and arm 2, respectively. Greater acceleration of first flatus and bowel movement from post-operative extubation was observed in arm 1 compared to arm 2 ($P<0.05$). Time to toleration of the first solid food was similar between the arms. Colonic transit time was significantly shorter in arm 1 (no description of P-value). White blood cell count and CRP showed no significant difference between arms.

8. Conclusions

Daikenchuto is effective for accelerating improvement of intestinal paralysis following laparoscopic surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were observed.

11. Abstractor's comments

This paper is a randomized controlled trial (RCT) investigating the effectiveness of daikenchuto in improving intestinal paralysis after laparoscopic surgery. Previous papers have reported early administration of daikenchuto to be effective in improving gastrointestinal dysfunction, however, this paper suggests even greater efficacy by commencing administration before surgery. Although 7.5 g/day was selected in this RCT as the standard dose of daikenchuto, the authors should have recognized that the usual dose is 15.0 g/day. In the DISCUSSION, the authors state that doses depending on body weight should have been considered if daikenchuto had dose-dependent effects. However, since body weight-dependent dosing is impossible in actual clinical settings, an RCT selecting the dose of 15.0 g/day should be conducted at first. A larger clinical trial evaluating the effectiveness of daikenchuto and its administration timing in the perioperative period is anticipated in the future.

12. Abstractor and date

Okabe T, 6 June 2015; Motoo Y, 31 March 2017

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Watanabe K. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 346–7 (in Japanese). MOL, MOL-Lib

Fujii S. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* *Progress in Medicine* 2011; 31: 468–9 (in Japanese).

1. Objectives

To evaluate the effectiveness and safety of daikenchuto (大建中湯) soon after colorectal cancer surgery.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Center for Gastroenterological Disease, Yokohama City University, Japan.

4. Participants

Participants received surgery (cur A resection) for colon cancer or sigmoid colon cancer between September 2009 and August 2010 (n=151). They were all over 20 years old, with performance status 0 or 1, and ability to eat and drink 2 days after surgery. No participants were asked for their laparotomy history or type of abdominal surgery (laparotomy or laparoscopic surgery). Participants with a history of emergency surgery, double cancer, or colostomy were excluded.

5. Intervention

Arm 1: daikenchuto (大建中湯) group (manufacturer not identified): 5 g t.i.d. (n=57).
Arm 2: mosapride (Gasmotin®) group: 5 g t.i.d. (n=54).
Arm 3: control group: no treatment (n=40).

6. Main outcome measures

Recovery of intestinal movement after surgery (period until both gas and stool passed), number of days in hospital after surgery, anti-inflammatory action (leucocytes, C-reactive protein [CRP] level), intestinal obstruction incidence, adverse events.

7. Main results

The period until gas was passed was significantly shorter in arm 1 and arm 2 than in arm 3 (2.6 days in arm 1 [P= 0.001], 2.8 days in arm 2 [P= 0.036], and 3.4 days in arm 3). No significant difference in the period until stool was passed was evident among the groups (arm 1, 3.4 days; arm 2, 3.8 days; arm 3, 3.8 days). The incidence of intestinal obstruction was lower but not significantly lower in arm 1 (arm 1, 1.8%; arm 2, 5.8%; arm 3, 10%). No among-group difference was observed in the leucocyte count, but the decrease in CRP in arm 1 was significant from the third day (P<0.05), suggesting that daikenchuto had anti-inflammatory effect. The number of days spent in the hospital after surgery was 8.7 in arm 1, 10.8 in arm 2, and 10.1 in arm 3, so hospital stay was the shortest for arm 1, and significantly shorter than that of arm 2 (P= 0.045). Comparison with arm 3 yielded a P-value of 0.061.

8. Conclusions

Patients treated with daikenchuto soon after colorectal cancer surgery recover intestinal movement more rapidly. The results suggest that daikenchuto may shorten post-surgery hospital stay and decrease the incidence of intestinal obstruction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Rash was observed in one participant in the daikenchuto group, and liver dysfunction in one participant in the mosapride group, however, the causal relation to the medications remains unclear.

11. Abstractor's comments

This abstract summarizes the article by Fujii (2011). The trial is clinically significant for suggesting the effectiveness of Daikenchuto. The two references listed above reported on the same study. Watanabe's article (2010) appears to be an interim paper. This trial is not an RCT in the strict sense of the word because treatment was assigned on an alternate month basis. The study seems to offer the possibility of subanalysis, so further work is anticipated.

12. Abstractor and date

Tsuruoka K, 31 December 2012.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Katsuno H, Maeda K, Kaiho T, et al. Clinical efficacy of Daikenchuto for gastrointestinal dysfunction following colon surgery: a randomized, double-blind, multicenter, placebo-controlled study (JFMC39-0902). *Japanese Journal of Clinical Oncology* 2015; 45: 650-6.

1. Objectives

To evaluate the efficacy of daikenchuto (大建中湯) for gastrointestinal dysfunction following colon surgery.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Fifty-one centers, including university hospitals.

4. Participants

Three hundred and eighty-six patients, colon cancer stage I-IIIb, T=1-3, N=0-2, M=0, who had colon resection by laparotomy.

5. Intervention

Among 386 patients, 354 were allocated.

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (n=181) 15g/day (5g t.i.d.) administerd orally from day 2 to day 8 after surgery.

Arm 2: Placebo granules (n=173) 15g/day (5g t.i.d.) administerd orally for the same period as above.

Administration from day 2 to day 8 after surgery.

6. Main outcome measures

Time until first flatus after surgery, flatus frequency per day from day 2 to day 8 after surgery, stool shape, blood CRP level, patient QOL score using GSRS.

7. Main results

In arm 1, there were 7 dropouts (174 were analyzed), while in arm 2 there were 11 dropouts with 162 being analyzed. No significant difference was observed for time until first flatus after surgery, blood CRP level, or GSRS score. Flatus frequency per day from day 2 to day 8 after surgery was enhanced in the daikenchuto group from day 2 to 6, but decreased on days 7 and 8. Frequency of bowel movement was significantly lower compared to the placebo group on day 8 after surgery (P=0.024).

8. Conclusion

Drug efficacy is observed in daikenchuto for 1 week after surgery, but it is slow, and no clinical significance is observed for patients following laparotomy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

7 adverse events of grade 3 or higher occurred among the trial subjects, but no significant difference between the groups was observed.

11. Abstractor's comments

No significant difference was found in time until flatus, stool shape, or QOL score by taking daikenchuto after laparotomy. Nevertheless, there was a strong flatus trend in the daikenchuto group up to day 6 after surgery, but the flatus trend was then found to reverse, decreasing on days 7 and 8. These results correspond to a sense of clinical usability, and it may be possible to elicit significant differences by increasing the number of participants and reexamining them. And in regard to the problem of when to end daikenchuto use started after surgery, this paper also suggests the possibility that it might be appropriate to divide the time after surgery into weeks.

12. Abstractor and date

Nakata H, 2 February 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Katsuno H, Maeda K, Ohya M, et al. Clinical pharmacology of daikenchuto assessed by transit analysis using radiopaque markers in patients with colon cancer undergoing open surgery: a multicenter double-blind randomized placebo-controlled study (JFMC39-0902 additional study). *Journal of Gastroenterology* 2016; 51: 222-9.

1. Objectives

To verify the effects of daikenchuto (大建中湯) for gastrointestinal function recovery after laparotomy in patients with sigmoid colon cancer or rectosigmoid cancer.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Multiple centers (11 centers), Japan.

4. Participants

Eighty-four patients with sigmoid colon cancer or rectosigmoid cancer who underwent laparotomy (colon resection).

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 15.0g/day (5.0g t.i.d. before meals) taken orally from day 2 to day 8 after surgery (n=44)

Arm 2: Placebo (TSUMURA & Co.) taken orally for the same period as above (n=40).

6. Main outcome measures

Primary endpoints: Time to first flatus and intestinal transit time using radiopaque markers.

7. Main results

There were 13 dropouts: 71 patients (38 in arm 1, 33 in arm 2) were analyzed. For the primary endpoints, the numbers of the radiopaque markers on the anal side of the small intestine at 6 hours (in other words, transit time from stomach to small intestine) were significantly higher in the daikenchuto group than the placebo group (i.e. shorter) (15.19 vs. 10.06, P=0.008), but total intestinal tract transit times and mean times to first flatus showed no significant difference between the groups.

8. Conclusion

Daikenchuto shortens transit time from stomach to small intestine in sigmoid colon cancer or rectosigmoid cancer who have undergone laparotomy (colon resection), but its improvement of postsurgical paralytic ileus is limited.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

All cases were evaluated for adverse events using NCI-CTC-AE (ver. 3.0), grade 3 diarrhea was observed in 2 participants in the placebo group, but no significant difference between groups was found.

11. Abstractor's comments

This is a valuable placebo controlled, double-blind RCT that analyzed the effects of daikenchuto in promoting recovery of intestinal tract function after surgery and in promoting gastrointestinal motility using radiopaque markers. The paper is praiseworthy for having made use of the characteristics of radiopaque markers to analyze gastrointestinal transit time from stomach to rectum by part. However, there was an unexpected significant difference in clearance from stomach to small intestine, while no significant difference was found in subsequent transit times from the small to large intestine. Until now daikenchuto has been reported to have an effect mainly on the small and large intestines. The authors also mention in their subgroup analyses that daikenchuto shortened transit time to sigmoid colon to 72 hours in the 65-years and younger group. This would mean that the younger the patient, the faster the recovery of intestinal function. There are a number of papers reporting that daikenchuto significantly shortened time to first flatus after open hepatectomy, laparoscopic large intestine surgery, and open colon resection, however, they did not use radiopaque markers as in this study. Given the results of this study that there was no significant difference in time until first flatus or in overall intestinal tract transit time, and that clearance from stomach to small intestine was promoted, without finding that postsurgical paralytic ileus was prevented, the authors' conclusion that commencement of food intake by mouth would be hastened is valid.

12. Abstractor and date

Motoo Y, 11 January 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Takagi K, Nagata H, Horie T, et al. Effect of the preventive herbal therapy using dai-kenchu-to on intestinal obstruction following curative resection for colorectal cancer: prospective, randomized study. *Kampo Kenkyu* (*Kampo Research*) 2007; (429): 270-1 (in Japanese). Ichushi Web ID: 2008028028

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on intestinal obstruction following colorectal cancer surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

Second Department of Surgery, Dokkyo University School of Medicine, Japan.

4. Participants

One hundred and seventy-five patients who underwent surgery for colorectal cancer (cecal colon [n=119] or rectal [n=56] cancer).

5. Intervention

Arm 1: treatment with daikenchuto (大建中湯) (manufacturer, not specified) 27 g/day (n=86).
Arm 2: no treatment (n=87).

6. Main outcome measures

The percentage of patients who postsurgically developed each of the following: ileus, abdominal pain, abdominal distention, and irregular bowel movements.

7. Main results

The between-arm difference in the percentage of patients who developed ileus in arms 1 (1.16%) and 2 (5.75%) or who experienced abdominal distension in arms 1 (2.33%) and 2 (6.90%) was not significant.
A significantly smaller percentage of patients in arm 1 developed abdominal pain (1.16% *vs* 9.20% [for arm 2]; *P*=0.042) or experienced irregular bowel movements (3.49% *vs* 13.79% [for arm 2]; *P*=0.033).

8. Conclusions

Daikenchuto extract fine granules do not prevent ileus following colorectal cancer surgery, but do result in the reduction of postoperative abdominal pain and irregular bowel movements.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The description of the study method in the present paper is extremely inadequate, and the protocol itself is problematic. Details, such as duration of treatment with daikenchuto extract fine granules, outpatient or inpatient setting, length of follow-up, and definitions of abdominal pain, abdominal distention, or irregular bowel movement are not given. Significant results would have been obtained if the authors had defined these specifics. Therefore, I recommend a rewrite of this paper after these details are clarified and the results are reviewed.

12. Abstractor and date

Hoshino E, 17 March 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Nagatomo H, Shigehira M. Efficacy of TSUMURA Juzentaihoto for reducing the adverse effects of the anticancer drug cisplatin*. *Kampo Igaku* (*Kampo Medicine*) 1992; 16: 116–9 (in Japanese).

1. Objectives

To evaluate the effect of juzentaihoto (十全大補湯) for reducing adverse effects of Spongel + Lipiodol + phosphatidyl choline + cisplatin treatment in transarterial embolization (TAE) for hepatocellular carcinoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Twenty patients undergoing transarterial embolization with Spongel + Lipiodol + cisplatin 100 mg + phosphatidyl choline 300 mg for hepatocellular carcinoma. On the day of TAE, Primperan 1 mg/kg and Solu-Cortef 200 mg were administered for anti-emesis.

5. Intervention

Grouping by block randomization.
Arm 1: TSUMURA Juzendaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. (from 3 days before through 5 days after TAE) (n=10).
Arm 2: no administration of juzendaihoto (十全大補湯) (n=10).

6. Main outcome measures

Gastrointestinal symptoms: number of nausea/vomiting episodes until 24 hr after TAE, number of days until recovery of food intake.
Renal disorder: blood urea nitrogen, creatinine (comparison between 7 days before and 7 days after TAE)
Nutritional state: albumin, total cholesterol, choline esterase (comparison between 7 days before and 7 days after TAE), number of weeks until recovery of body weight to pre-TAE level.

7. Main results

The number of nausea/vomiting episodes was significantly decreased in Arm 1 compared with Arm 2, but changes in the renal function and nutrition status indices were similar in both arms.

8. Conclusions

Juzentaihoto significantly suppresses nausea/vomiting after transarterial embolization (TAE) with Spongel + Lipiodol + phosphatidyl choline + cisplatin for hepatocellular carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The authors concluded that juzentaihoto administered before and after TAE for hepatocellular carcinoma relieved nausea/vomiting for 24 hr after TAE. However, whether juzentaihoto should have been administered within the timeframe 3 days before through 5 days after TAE has no basis and should have been investigated before beginning the controlled trial. Traditionally, juzentaihoto is not used to suppress nausea/vomiting. Therefore, a clinical study of the antiemetic use of this Kampo medicine should not have been performed in patients with advanced hepatocellular carcinoma who are not indicated for surgery and who are "relatively *kyosho* (虚証, deficiency pattern)." The traditional Kampo antiemetic medicines (shohangekabukuryoto [小半夏加茯苓湯], bukuryoin [茯苓飲], shinbuto [真武湯], and kankyoninjinhangegan [乾姜人参半夏丸]) should have been investigated first.

12. Abstractor and date

Hoshino E, 15 February 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Ayukawa K, Sato T, Nagase S, et al. Preventive effect of shosaikoto on liver carcinogenesis*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1994; 71: 1874–6 (in Japanese). Ichushi Web ID: 1995019997

1. Objectives

To evaluate the preventive effect of shosaikoto (小柴胡湯) on the progression of cirrhosis to liver cancer.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One university hospital (3rd Department of Internal Medicine, Kyushu University) and 8 other hospitals, Japan.

4. Participants

Ninety-five patients with cirrhosis diagnosed by laparoscopy, liver biopsy, and laboratory examination.

5. Intervention

Randomization based on whether the birth month is odd or even.
Arm 1: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 5.0–7.5 g/day (n=52).
Arm 2: no administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules (n=43).

6. Main outcome measures

Incidence of liver cancer during the 3-year period, alpha-fetoprotein (AFP) level, and blood biochemistry.

7. Main results

There was no significant difference in 3-year incidence of liver cancer between arms. AFP tended to be lower in arm 1, although not significantly lower. GOT was significantly lower in arm 1 only at weeks 12 and 15.

8. Conclusions

While not significant, the Shosaikoto treatment tends to lower the incidence of liver cancer and AFP.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events in arm 1 did not occur and adverse events in arm 2 were not mentioned.

11. Abstractor's comments

This study is a sequel of the study by Oka et al. (Oka H, Yamamoto S. Controlled prospective study of prevention of hepatocellular carcinoma of the liver. *Shokakika* (*Gastroenterology*) 1991; 15: 71-8.) and may have failed to demonstrate significant differences because the follow-up period of 3 years was too short and the doses of TSUMURA Shosaikoto Extract Granules (5.0–7.5 g) were too low. Thereafter, shosaikoto was contraindicated for cirrhosis in principle, further compromising the usefulness of this study.

12. Abstractor and date

Hoshino E, 22 February 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Tarao K, Shibuya A, Ohkawa S, et al. Prevention of hepatocarcinogenesis by anti-inflammatory therapy: is combination anti-inflammatory therapy targeting an ALT level of under 80 units effective for hepatitis C virus-related cirrhosis (Child A)?: comparison with monotherapy*. *Kanagawa Cancer Center – Nenpo* (*Annual Report*) 2003; 19: 92 (in Japanese).

Tarao K. Persistent inflammation and hepatocarcinogenesis in chronic hepatitis C and hepatitis C virus-related cirrhosis*. *Kanagawa Igakkai Zasshi* (*The Journal of the Kanagawa Medical Association*) 2006; 33: 115-8 (in Japanese).

Tarao K. Prevention of HCC by anti-inflammatory agents in patients with chronic hepatitis C. *Rinsho Shokaki Naika* (*Clinical Gastroenterology*) 2007; 22: 961-9 (in Japanese).

1. Objectives

To evaluate the efficacy of liver protectors for preventing carcinogenesis in patients with chronic hepatitis C.

2. Design

Randomized controlled trial (RCT).

3. Setting

None (the author belongs to a specialized hospital), Japan.

4. Participants

One hundred and fifty-six patients with hepatitis C virus-related cirrhosis (stage Child A).

5. Intervention

Arm 1: target alanine aminotransferase (ALT) level ≤80; monotherapy with Stronger Neo-Minophagen C (SNMC; 40–100 mL, two or three times per week), ursodeoxycholic acid (UDCA), shosaikoto (小柴胡湯), or juzentaihoto (十全大補湯) (manufacturers, not specified) was administered. When the target level was not achieved in 2–3 months, dual therapy with SNMC + UDCA, UDCA + juzentaihoto (十全大補湯), or UDCA + shosaikoto (小柴胡湯) was administered. If the target level was still not achieved, triple therapy with SNMC + UDCA + shosaikoto (小柴胡湯) or SNMC + UDCA + juzentaihoto (十全大補湯) was administered. The choice of the therapy in each patient was not described, n=78.

Arm 2: monotherapy with UDCA, SNMC, shosaikoto (小柴胡湯), or juzentaihoto (十全大補湯) was administered; the choice of the drug was based on the ALT-lowering effect. Details, including the drug used, dose, and the number of patients who received each drug, were not available, n=50.

6. Main outcome measures

Incidence of liver cancer.

7. Main results

The incidence of liver cancer was lower in arm 1 than in arm 2.

8. Conclusions

Therapy consisting of combined Kampo medicines for liver protection is effective for suppressing carcinogenesis in patients with chronic hepatitis C.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study reports an effective treatment for suppressing carcinogenesis in patients with chronic hepatitis C. But since the specific design was not described and details (such as the choice of the therapy or the number of patients who received each drug in arm 2) were unclear, we cannot decide which of the treatments resulted in response. Studies employing easy-to-understand designs are desired.

The two studies by Tarao et al (2003) and Tarao (2008) are the interim reports

12. Abstractor and date

Kogure T, 26 January 2009, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Higuchi K, Watanabe A. Study on liver cancer-preventive effect of juzentaihoto in patients with liver cirrhosis*. *Methods in Kampo Pharmacology* 2000; 5: 29-33 (in Japanese).

1. Objectives

To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

A university hospital (Department of Internal Medicine, Toyama Medical and Pharmaceutical University [now Toyama University Hospital]), Japan.

4. Participants

Seventy-two patients with liver cirrhosis due to hepatitis B or C virus (B, n=14; C, n=58). However, one patient who had liver cancer within half a year after entry into the study was excluded.

5. Intervention

Arm 1: juzentaihoto (十全大補湯)-treated group (B, n=8; C, n=18).
Arm 2: juzentaihoto (十全大補湯)-untreated group (B, n=6; C, n=39).

6. Main outcome measures

Cumulative survival curve by Kaplan-Meier method (log-rank test [Mantel-Cox]).
Cumulative hazard curve for hepatocellular carcinoma development by Kaplan-Meier method (log-rank test [Mantel-Cox]).
The threshold of liver cancer development was set at the time when liver cancer was first detected on imaging-based clinical diagnosis.

7. Main results

For overall liver cirrhosis, there was no significant difference in the cumulative survival curve between arms (chi-square=3.167, *P*=0.0751), but juzentaihoto-treated patients tended to have a more favorable prognosis. For overall liver cirrhosis, the cumulative hazard curve for hepatocellular carcinoma development showed the risk was significantly lower in the juzentaihoto-treated group than in juzentaihoto-untreated group (chi-square=5.832, *P*=0.0157). Analysis limited to liver cirrhosis type C also revealed significantly lower risk in the juzentaihoto-treated group (chi-square=4.197, *P*=0.0405).

8. Conclusions

It is suggested that administration of juzentaihoto prevents hepatocellular carcinoma from developing in patients with liver cirrhosis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is valuable, since hepatocellular carcinoma frequently develops as a result of underlying hepatitis virus infection. Using sealed envelopes for allocation, this study is regarded as a randomized controlled trial. Information on the method of juzentaihoto administration and blinding may have made this report clinically more meaningful.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Higuchi K, Shimizu Y, Yasumura S, et al. Preventive effect of liver carcinogenesis by juzen-taiho-to in the patients with liver cirrhosis. *Kan-Tan-Sui* 2002; 44: 341-6 (in Japanese) Ichushi Web ID: 2002240679 MOL, MOL-Lib

1. Objectives

To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

A university hospital (Department of Internal Medicine, Toyama Medical and Pharmaceutical University [now Toyama University Hospital]), Japan.

4. Participants

Fifty-two patients with liver cirrhosis due to hepatitis B or C virus. However, patients who had liver cancer within a year after entry into the study and those who received shosaikoto or interferon were excluded.

5. Intervention

Arm 1: juzentaihoto (十全大補湯)-treated (type B, n=8; type C, n=15; type B + type C, n=1).
Arm 2: juzentaihoto (十全大補湯)-untreated (type B, n=5; type C, n=22; type B + type C, n=1).

6. Main outcome measures

Cumulative survival curves were drawn by the Kaplan-Meier method (with difference between curves analyzed by the log-rank test [Mantel-Cox test], Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test). Cumulative hazard curves for hepatocellular carcinoma development were drawn by the Kaplan-Meier method (with difference between curves analyzed by the log-rank test [Mantel-Cox test], Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test). The threshold of liver cancer development was set when liver cancer was first detected on imaging-based clinical diagnosis.

7. Main results

For all liver cirrhosis, the cumulative survival curve showed that vital prognosis was significantly more favorable in arm 1 than arm 2, with chi-square values of 4.066, 6.467, and 5.217 (P=0.0438, 0.0190, and 0.0224) by the log-rank test (Mantel-Cox test), Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test, respectively. Analysis of the cumulative survival curve limited to patients with liver cirrhosis type C showed a tendency toward more favorable vital prognosis in arm 1, but no significant between-group difference. For all liver cirrhosis, the cumulative hazard curve for hepatocellular carcinoma development showed significantly lower incidence of hepatocellular carcinoma in arm 1 than in arm 2, with chi-square values of 5.265, 5.578, and 5.921 (P=0.0218, 0.0182, and 0.0150) by these tests, respectively. Analysis limited to liver cirrhosis type C revealed significantly lower incidence of hepatocellular carcinoma in arm 1 by the Bleslow Gehan-Wilcoxon test and Peto-Peto-Wilcoxon test (chi-square=4.659, 4.483, respectively; P=0.0309, 0.0342, respectively).

8. Conclusions

It is suggested that in liver cirrhosis, administration of juzentaihoto prevents hepatocellular carcinoma development.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is valuable since hepatocellular carcinoma frequently develops from underlying hepatitis virus infections. This study seems to be similar to the study published in *Methods in Kampo Pharmacology* (2000; 5: 29-33). There were fewer participants in the present study because stricter exclusion criteria were followed: liver cancer development within a year *vs* half a year in the previous study, and shosaikoto or interferon not permitted. Furthermore, use of diverse statistical tests made the results more meaningful, particularly clinically. Use of a placebo and blinding may have made the results more reliable.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto*. *Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai* (*5th Annual Meeting of the Japanese Gastroenterological Association*) (*Workshop 5*) 2009: 9-10.

1. Objectives

To evaluate the anti-inflammatory efficacy of daikenchuto (大建中湯) in postoperative patients with liver carcinoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Tokushima University Hospital), Japan.

4. Participants

Twenty patients who underwent hepatectomy.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (dose and duration of treatment, unknown; n=11).
Arm 2: not treated with daikenchuto (大建中湯) (n=9).

6. Main outcome measures

In addition to the number of days to postoperative flatulence, white blood cell count, lymphocyte count, C-reactive protein (CRP) level, β-D glucan level, and *Candida* antigen level were determined before and 1, 3, 5, and 7 days after the operation.

7. Main results

There were between-arm differences in age, sex, stage, duration of the operation, blood loss, etc., but no mention of their significance. The number of days to postoperative flatulence, white blood cell count, lymphocyte count, or *Candida* antigen level was not described. The CRP and β-D glucan levels were significantly lower in arm 1 than in arm 2 on postoperative day 3 ($P<0.05$).

8. Conclusions

Daikenchuto may be useful in inhibiting early postoperative inflammation after surgery for liver carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Inhibition of postoperative inflammation after surgery for liver carcinoma to reduce medical costs and hospital stay is an interesting issue. β-D glucan, a fungal cell wall component, is measured to determine fungal infection. In this study, no mechanism has been offered to explain the transient increase in β-D glucan after surgery for liver carcinoma in arm 2 (the control group). Transient bacterial translocation is unlikely after only a few days of postoperative fasting. To explain the early postoperative anti-inflammatory effect of daikenchuto, the author referred to daikenchuto-mediated inhibition of inflammatory cytokine production, intestinal mucosal villous damage, and bacterial translocation demonstrated in a fasted rat model. Further analysis of the effects of daikenchuto after abdominal surgery on the general condition (appetite, sleep, bowel movement, hot flushes, etc.) of postoperative patients will be needed before its use in treatment is deemed appropriate.

12. Abstractor and date

Hoshino E, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Nishi M, Shimada M, Uchiyama H, et al. The beneficial effects of Kampo medicine dai-ken-chu-to after hepatic resection: a prospective randomized control study. *Hepato-Gastroenterology* 2012; 59: 2290-4. CENTRAL ID: CN-00912891, Pubmed ID: 23435143

1. Objectives

To evaluate the usefulness of daikenchuto (大建中湯) in postoperative patients who underwent hepatectomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Tokushima University Hospital, Japan).

4. Participants

Thirty-two patients who underwent partial hepatectomy for primary/metastatic liver cancer or other liver diseases, except patients undergoing laparoscopic surgery, gastrointestinal resection, or splenectomy, etc.

5. Intervention

Arm 1: group receiving TSUMURA Daikenchuto (大建中湯) Extract Granules 2.5 g t.i.d. before meals via a nasogastric tube or orally, starting from the day after operation (n=16).

Arm 2: control group receiving no TSUMURA Daikenchuto (大建中湯) Extract Granules 2.5 g (n=16).

6. Main outcome measures

Hematology of the following parameters on the day of and 1, 3, 5, and 7 days after operation: WBC, total bilirubin, ALT, total protein, prothrombin time (INR), ammonia, CRP, and β-D-glucan. The numbers of days until the postoperative initial passage of flatus, initial defecation, initial intake of ordinary diet, and discharge, and complications.

7. Main results

There were no significant differences between groups in WBC, total bilirubin, ALT, total protein, prothrombin time (INR), or ammonia. On the third hospital day, CRP was significantly lower in arm 1 than in arm 2 ($P<0.05$). On the third hospital day, mean β-D-glucan level was significantly lower in arm 1 than in arm 2 ($P<0.05$). There were no differences in postoperative complications between groups. The numbers of days until the postoperative initial passage of flatus, defecation, and intake of ordinary diet were smaller in arm 1 than in arm 2. In contrast, there was no significant difference in the number of days until discharge.

8. Conclusions

Daikenchuto can be safely used as a useful medication to suppress inflammation, promotes bowel motility, and stimulates appetite after hepatectomy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Daikenchuto is associated with no adverse reactions.

11. Abstractor's comments

The study demonstrated that daikenchuto administered at a low dose (half the usual dose) early after partial hepatectomy significantly decreased blood CRP and β-D glucan levels on postoperative day 3 and promoted postoperative improvement in bowel peristalsis. Daikenchuto has traditionally been used for relief of abdominal symptoms including abdominal pain, abdominal distension, Crohn's disease, and irritable bowel syndrome. Mentioning recent studies that have shown the effects of daikenchuto to improve bowel motility and defecation and shorten the duration of hospitalization after colon cancer surgery, to exert efficacy for intestinal obstruction after abdominal surgery, and to reduce postoperative complications after total gastrectomy by improving bowel motility, etc. The authors explained that they conducted this study since there was only one previous study on daikenchuto administration after hepatectomy. The authors assumed the following possible mechanisms of action of daikenchuto: enhancement of gastrointestinal motility through stimulation of $5HT_3$ receptors and promotion of VIP and motilin secretions; increase in blood flow in gastrointestinal tract and portal vein mediated by calcitonin gene-related peptides; anti-inflammatory effect via inhibition of COX-2 activity; and suppression of bacterial translocation via suppression of proinflammatory cytokines. The authors did not explain the reason for reducing the dose of daikenchuto by half. Use of the usual dose may produce different results (effects and adverse reactions), necessitating investigation of the optimal dose.

12. Abstractor and date

Hoshino E, 6 June 2015.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Hanazaki K, Ichikawa K, Munekage M, et al. Effect of Daikenchuto (TJ-100) on abdominal bloating in hepatectomized patients. *World Journal of Gastrointestinal Surgery* 2013; 5: 115-22. Pubmed ID: 23671738

1. Objectives

To evaluate the effect of daikenchuto (大建中湯) on abdominal bloating in patients who underwent hepatectomy for liver malignancies

2. Design

Randomized controlled trial (RCT).

3. Setting

Surgery Department, Kochi Medical School Hospital, Japan.

4. Participants

Eighteen patients who underwent hepatectomy for liver malignancies.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 15.0 g/day (5.0 g t.i.d.) for 3 days before surgery and for 10 days after surgery (n=9).

Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules 15.0 g/day (5.0 g t.i.d.) + lactulose at least 48 g/day for the same period as above (n=9).

6. Main outcome measures

Visual analog scale (VAS) scores for abdominal bloating (at baseline and on postoperative days 2, 4, 6, 8, and 10), Gastrointestinal Symptom Rating Scale (GSRS) scores (on the day before surgery, before daikenchuto treatment, and on postoperative day 10), and GSRS scores for abdominal bloating in sub-analyses.

7. Main results

A total of 18 patients were included in the analysis. The VAS score for abdominal bloating peaked on postoperative day 2, and then decreased gradually to the preoperative level with no statistically significant difference by postoperative day 10. Although no significant difference was noted in overall GSRS score, GSRS score for abdominal bloating was significantly higher on postoperative day 10 than prior to surgery (P<0.05). The VAS score for abdominal bloating had recovered to preoperative levels by postoperative day 6 in arm 1 but not to preoperative levels even on postoperative day 10 in arm 2. On postoperative days 2 and 10, the VAS scores for abdominal bloating were significantly lower in arm 1 than in arm 2 (P<0.05). On postoperative day 10, the overall GSRS score was significantly lower in arm 1 than in arm 2 (P<0.05). GSRS scores for abdominal bloating were similar preoperatively and on postoperative day 10 in arm 1, but significantly higher on postoperative day 10 than preoperatively in arm 2 (P<0.05). Patients in arm 1 showed a tendency for fewer postoperative complications (biliary tract infection, bile leaks, etc.) and shorter postoperative hospital stays compared with arm 2.

8. Conclusions

Daikenchuto monotherapy relieves and ameliorates abdominal bloating early in hepatectomized patients compared to combination therapy with lactulose.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Notably, no adverse event was associated with administration of daikenchuto.

11. Abstractor's comments

This is a report of the first RCT to demonstrate the effectiveness of daikenchuto in relieving abdominal bloating in hepatectomized patients. Lactulose, which has been used to reduce ammonia production, has been found not to alleviate abdominal bloating when combined with daikenchuto. Although the Discussion section describes the mechanism by which daikenchuto suppresses inflammatory cytokine production, the mechanism by which daikenchuto alleviates abdominal bloating remains to be elucidated because both groups were treated with daikenchuto in this study. Therefore, it may be necessary to add a daikenchuto-untreated group. As stated by the authors, additional RCTs of daikenchuto in a large number of patients are needed to further evaluate its efficacy and safety in postoperative recovery. Although the present study does not use Kampo diagnosis, most patients become *kyo-sho* (虚証, deficiency pattern) after surgery, and most patients with liver malignancies have underlying chronic liver diseases (especially liver cirrhosis). In addition, the *sho* (証, pattern) for daikenchuto includes cold abdomen, abdominal pain, and abdominal bloating. Therefore, it is hoped that the authors will clearly state that the outcome measures in this study were the *sho* for daikenchuto.

12. Abstractor and date

Motoo Y, June 2015

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Shimada M, Morine Y, Nagano H, et al. Effect of TU-100, a traditional Japanese medicine, administered after hepatic resection in patients with liver cancer: a multi-center, phase III trial (JFMC40-1001). *International Journal of Clinical Oncology* 2015; 20: 95-104.

1. Objectives

To evaluate the safety and effectiveness of daikenchuto (大建中湯) for gastrointestinal motility after surgery for liver cancer.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Twenty-six centers, including University Hospitals, Japan.

4. Participants

Patients (231) with primary or metastatic liver cancer who met the following conditions: 1) resection by laparotomy or laparoscopy, 2) ECOG Performance Status of 0-2, 3) drugs can be taken orally, 4) age of 20 years or more, 5) no chemotherapy or radiotherapy in the 4 weeks before surgery, 6) function in heart, lungs, liver and kidneys retained, 7) can tolerate hepatic resection, 8) serum CRP <2.0 mg/dL.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 15.0g/day (5g t.i.d.) (n=119).
Arm 2: Placebo 15.0g/day (5g t.i.d.) (n=112).
Administration in each group was from 3 days before surgery to the 10th day after surgery, excluding the day of surgery.

6. Main outcome measures

FBM-T (period from decannulation to first bowel movement). Serum CRP and serum ammonia levels. Presence/absence of post-operative ileus or complications. Period of hospital stay after surgery.

7. Main results

In arm 1, 4 participants were excluded due to worsening condition, and 7 were excluded as they could not take the Daikenchuto: 108 patients were evaluated. In arm 2, 11 were excluded due to worsening condition: 101 patients were evaluated. There were no significant differences in clinical features between arms 1 and 2. With FBM-T of 88.2h (95% CI 74.0-94.1) in arm 1, and 93.1h (95% CI 83.3-99.4) in arm 2, it was significantly shorter in arm 1 (P=0.0467). There was no significant difference in CRP ($AUC_{-3\text{-}10\ day}$) or ammonia ($AUC_{-3\text{-}10day}$). 4 patients in arm 1 (3.7%) and 2 in arm 2 (2.0%) had post-operative ileus, and 13 patients in arm 1 (12.0%) and 19 in arm 2 (18.8%) had postoperative complications, but there was no significant difference. There was no significant difference in period of hospital stay after surgery. Analysis of the subgroup of patients with liver damage B found CRP ($AUC_{-3\text{-}10day}$) was 29.9±18.5 in arm 1 and 62.0±56.7 in arm 2, showing a trend toward lower levels in arm 1 (P=0.0587).

8. Conclusion

Taking daikenchuto accelerated improvement of gastrointestinal motility impairment after liver resection and tended to decrease inflammation responses in patients with liver damage B.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Arm 1: Hyperbilirubinemia (1 patient), paralytic ileus (1), diarrhea (1), upper gastrointestinal bleeding (1).
Arm 2: Abdominal pain (3 patients), nausea (1), vomiting (1), intra-abdominal hemorrhage (1). There was no significant difference between the 2 groups.

11. Abstractor's comments

This research paper studied the effects of daikenchuto for gastrointestinal motility impairment after liver resection through a multicenter randomized placebo controlled trial and has a high evidence level. It is praiseworthy for having elucidated once more the effectiveness of this preparation for gastrointestinal motility impairment, which has been suggested in the classic texts, with the period to first bowel movement in the 10 days of observation after surgery having been significantly shortened. It also suggested that by having decreased CRP levels in patients with liver damage B, it improves blood flow and also has an anti-inflammatory effect. Yet, there were no significant differences in secondary endpoints such as postoperative complications or postoperative ileus, etc., so further study (with extension of observation period, etc.) of its clinical significance is required.

12. Abstractor and date

Kogure T, 31 December 2016.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Mizutani T, Yokoyama Y, Kokuryo T, et al. Does inchinkoto, a herbal medicine, have hepatoprotective effects in major hepatectomy? A prospective randomized study. *HPB : The Official Journal of The International Hepato Pancreato Biliary Association* 2015; 17: 461-9. Pubmed ID: 25581163

1. Objectives

To evaluate the hepatoprotective effects of inchinkoto (茵蔯蒿湯) in patients after major hepatectomy.

2. Design

Randomized controlled trial (RCT)

3. Setting

Not mentioned. (The authors belong to university and graduate school surgery departments.)

4. Participants

73 patients undergoing major hepatectomy (resection of 3 or more Couinaud segments) between June 2010 and January 2012. Patients who required choleretic administration for severe icterus; patients who had chemotherapy before surgery; and patients whose remnant liver volume was predicted to fall below 20% before portal vein embolization (PVE) were excluded. The number of participants was determined on the basis of animal experiment results.

5. Intervention

Arm 1: TSUMURA Inchinkoto (茵蔯蒿湯) 7.5g t.i.d from day of participation to day before surgery. Minimum administration period 7 days (n=30).

Arm 2: No TSUMURA Inchinkoto (茵蔯蒿湯) to day before surgery (n=31).

There were no significant differences between arms in age, gender, underlying disease, ICG-F value, or remnant liver volume (based on CT). The operative procedures, surgery time, hemorrhage volume, etc. were the same for the 2 arms. PVE was carried out in at least 50% of participants in the two arms.

6. Main outcome measures

Primary endpoint: Severity of hepatopathy after surgery (serum AST and ALT, postoperative complication, hepatic failure, etc.)

Secondary endpoint: Antioxidant expression in liver

7. Main results

Twelve out of 73 participants were excluded due to peritoneal metastasis, hepatic metastasis, or distant lymph node metastasis. There was no difference between arms 1 and 2 for maximum T-Bil, AST, ALT, or PT-INR after surgery; postoperative complication; or hepatic failure (Clavien-Dindo classification). Induction of antioxidant enzyme gene expression (HO-1 and SOD) was significantly higher in arm 1. Expression of HO-1 RNA was 12 times higher. Expression of Nrf protein was also significantly higher in arm 1, and immunohistochemistry found intranuclear expression was prominent in arm 1. Sub-analysis of patients with ICG-F less than 0.08 (postoperative hepatic failure high-risk group) showed significant reductions in serum AST (days 1 and 3), ALT (days 1, 3, and 5), and LDH in arm 1. Coincidence of grade B or C postoperative hepatic failure was 50% in arm 1 and 75% in arm 2.

8. Conclusions

Preoperative administration of inchinkoto did not have any effect on clinical results after hepatectomy. However, it may induce intrahepatic antioxidant enzyme expression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

An RCT with a large number of participants, this is excellent research of clinical significance, having analyzed the effects of inchinkoto administration on hepatic function after major hepatectomy. Although no significant difference was found in complications or postoperative hepatic function, monitoring of postoperative antioxidant enzyme expression in the liver using RNA (RT-PCR), protein (Western blot), and immunohistochemistry tests suggested that the expression of antioxidant enzymes was higher in the preoperative inchinkoto administration group. The results show promise for future clinical application, and in fact, sub-analysis of the postoperative hepatic failure high-risk group showed marked improvement in hepatic function tests in the preoperative inchinkoto administration group. The selection of administration method and participating patients may be important in reducing the antioxidant action of inchinkoto into clinical results.

12. Abstractor and date

Kogure T, 18 May 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Watanabe S, Yokoyama Y, Oda K, et al. Choleretic effect of inchinkoto, an herbal medicine, on livers of patients with biliary obstruction due to bile duct carcinoma. *Hepatology Research* 2009; 39: 247–55. Ichushi Web ID: 2009201648

1. Objectives

To evaluate the drug efficacy of inchinkoto (茵チン蒿湯) as a choleretic drug on livers of patients with biliary obstruction due to bile duct carcinoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Surgery, Nagoya University Graduate School of Medicine, Department of Gastroenterology and Hepatology, University of Tsukuba, and Department of Strategic Surveillance for Functional Food and Comprehensive Traditional Medicine, Wakayama Medical University, Japan.

4. Participants

From December 2006 to June 2006, a total of 31 patients with perihilar cholangiocarcinoma or gallbladder carcinoma with hilar invasion were enrolled. Of these patients, 4 were excluded because they underwent probe laparotomy due to peritoneal dissemination.

5. Intervention

Arm 1: Inchinkoto (Tsumura Inchinkoto (茵チン蒿湯) Extract Granules (TJ-135) 7.5 g/day for at least one week before surgery (average 21 days) (n=13).
Arm 2: no treatment with inchinkoto (n=14).

6. Main outcome measures

Levels of MRP2, MRP3, and MRP4 mRNAs and proteins in the liver were determined.

7. Main results

There were no significant between-arm differences in MRP2, 3, and 4 mRNA levels. MRP2 and 3 protein levels were significantly increased in the inchinkoto arm. Postoperatively, there were no between-arm differences in serum total bilirubin, direct bilirubin, and alanine aminotransferase (ALT). Bile samples were collected from some of the patients in arm 1 by percutaneous transhepatic biliary drainage (PTBD) before and after administration of inchinkoto, and increase in the concentration of bilirubin was observed after administration.

8. Conclusions

Inchinkoto may be useful for treating obstructive cholestasis due to bile duct carcinoma, and its beneficial effect may be mediated through induction of MRP2 expression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No significant adverse drug reactions were observed for inchinkoto treatment.

11. Abstractor's comments

MRP2 protein is a transporter involved in bile acid secretion. It is interesting that the authors found and increase in MRP2 protein levels but no change in MRP2 mRNA levels. They demonstrated increased bilirubin concentration in the bile samples collected by PTBD only in the subjects in the inchinkoto arm, however, they should have studied the subjects in the both arms to make the data more reliable. Some of the documentation in this article is insufficient; even though the MRPs gene expression data for the control group is shown, the background data of the control group is not. Although there are issues regarding the methodology used in this study, it is very meaningful that administration of inchinkoto is shown clinically to increase MRP2 protein levels.

12. Abstractor and date

Nakata H, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yutani S, Komatsu N, Matsuda S, et al. Juzentaihoto failed to augment antigen-specific immunity, but prevented deterioration of patients' conditions in advanced pancreatic cancer under personalized peptide vaccine. *Evidence-Based Complementary and Alternative Medicine* 2013: 1-10. doi: 10.1155/2013/981717. CENTRAL ID: CN-00919989, Pubmed ID: 23840274

1. Objectives

To evaluate the effect of juzentaihoto (十全大補湯) for antigen-specific immunity and performance status of advanced pancreatic cancer patients receiving peptide vaccine therapy.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Immunology and Immunotherapy, Kurume University School of Medicine, Japan; Research Center for Innovative Cancer Therapy, Kurume University, Japan; Department of Surgery, Kurume University Hospital, Japan.

4. Participants

Fifty-seven patients with standard therapy-resistant advanced pancreatic cancer.

5. Intervention

Arm 1: cycles of 6 weeks of weekly subcutaneous injection of up to 4 kinds of peptide vaccines. administration of TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. (7.5 g/day) for 35 days from the first day of the first cycle (n=28).

Arm 2: the above peptide vaccine therapy alone (n=29).

6. Main outcome measures

Cytokines such as interferon-γ as a measure of cellular immunity and peptide-specific IgG as a measure of humoral immunity. Performance status (PS) and laboratory values.

7. Main results

Five patients in the juzentaihoto group and 2 patients of the vaccine therapy group failed to complete the first cycle of the vaccine therapy and provided no post-vaccination data. After exclusion of these dropouts, remaining 50 were included in the analysis population. There were no significant differences between groups in the changes from baseline in antigen-specific T cell response (cellular immunity), antigen-specific IgG (humoral immunity), or overall survival after initiation of the vaccine therapy. However, after initiation of the vaccine therapy, PS was not significantly changed from baseline in the juzentaihoto combination group but was significantly decreased from baseline in the vaccine alone group (P=0.0156). After initiation of the vaccine therapy, significant decreases in hemoglobin concentration (P=0.0203), lymphocyte count (P=0.0351), and serum albumin level (P=0.0214) were noted in the vaccine alone therapy, but not in the juzentaihoto combination group.

8. Conclusions

Juzentaihoto does not potentiate antigen-specific immunity but prevents aggravation of general conditions and declines in hemoglobin concentration, lymphocyte count, and serum albumin level in pancreatic cancer patients receiving peptide vaccine therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The article describes that there were no significant differences in the incidence or severity of adverse events between groups and that the independent Safety Monitoring Committee judged all adverse events observed to be due to progression of pancreatic cancer or concomitant anticancer drugs, but not due to the peptide vaccine or juzentaihoto.

11. Abstractor's comments

This is the first study to verify the clinical effect of juzentaihoto combined with the peptide vaccine therapy in advanced pancreatic cancer patients. Since the study population consisted of patients with chemotherapy-resistant, rapidly-progressive pancreatic cancer, the study period may have been too short for the authors to confirm the immunity-potentiating effect. Nevertheless, it should be appreciated that they demonstrated the benefits of juzentaihoto, including improvement in performance status and suppression of aggravation in hematological values, in an RCT. The authors are expected to conduct similar clinical research with postoperative adjuvant chemotherapy for cancer or in patients with slowly-progressive cancer in future. Readers can take the study results that peptide vaccine plus juzentaihoto combination has virtually no safety problem but inconclusive efficacy.

12. Abstractor and date

Motoo Y, 6 June 2015.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Okada K, Kawai M, Hirono S, et al. Evaluation of the efficacy of daikenchuto (TJ-100) for the prevention of paralytic ileus after pancreaticoduodenectomy: a multicenter, double-blind, randomized, placebo-controlled trial. *Surgery* 2016; 159: 1333-41. CENTRAL ID: CN-01153778, Pubmed ID: 26747224, UMIN ID: UMIN000007975

Maeda H, Okada KI, Fujii T, et al. Transition of serum cytokines following pancreaticoduodenectomy: A subsidiary study of JAPAN-PD. Oncol Lett 2018; 16: 6847-53. CENTRAL ID: CN-01651625, Pubmed ID: 30333892, UMIN ID: UMIN000007975

1. Objectives

To evaluate the preventive effects of daikenchuto (大建中湯) for paralytic ileus after pancreaticoduodenectomy.

2. Design

Double-blind randomized controlled trial (DB-RCT)

3. Setting

Nine hospitals.

4. Participants

224 patients who underwent pancreaticoduodenectomy due to duodenal papillary tumor or pancreatic head tumor.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (15g t.i.d for 17 days) (n=112)
Arm 2: Placebo extract granules (15 g t.i.d. for 17 days)
Of the 17 days mentioned above, the daikenchuto or placebo were fed via tube retained in the duodenum on the day of surgery and on day 1 after surgery.

6. Main outcome measures

Primary outcome measures: Occurrence of paralytic ileus persisting for at least 72 hours after surgery; time from surgery to onset of paralytic ileus.
Secondary outcome measures: QOL evaluation using GSRS; evaluation of abdominal pain and bloating using VAS, assessment of 27 serum cytokine levels on day 1 after surgery (POD1) and day 3 after surgery (POD3), etc.

7. Main results

No significant differences were observed between the 2 groups in any of the primary or secondary outcome measures. Among the POD3/POD1 ratios evaluated for 27 serum cytokines, the POD3/POD1 ratios for IL-4, IL-9, IL-10, PFGF-BB, and TNF-α were significantly higher (P<0.05).

8. Conclusions

Daikenchuto does not reduce the occurrence of paralytic ileus after surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events of at least grade 3 occurred in the daikenchuto group (11.5%) and the placebo group (7.8%), however, most of them were diarrhea and abnormal laboratory values (no significant difference detected).

11. Abstractor's comments

This is a valuable study using a double-blind RCT to analyze the effectiveness of daikenchuto for the prevention of paralytic ileus in a limited patient group, namely pancreaticoduodenectomy (PD) patients. It is recognized as a rigorous RCT that took risk of bias into very careful consideration. Although the study included a limited number of patients who underwent pylorus-preserving PD (PPPD) (n=23), the results of sub-group analyses showed that time to first flatus was significantly shorter for those in the daikenchuto group than those in the placebo group (P=0.034). In the additional article, the ratio of POD3/POD1 for some of the cytokines was significantly higher in the daikenchuto group than in the placebo group but its significance is unclear. As to why the efficacy of daikenchuto, which has been reported in basic and clinical studies, was not demonstrated in the present study, the authors consider that complex factors are involved in the postoperative course of PD. While daikenchuto is known in Japan as a Kampo preparation useful for the treatment and prevention of paralytic ileus, the approach of the authors in rigorously evaluating a restricted patient group, namely PD patients, has major implications for the future direction of clinical research into Kampo treatment in Japan.

12. Abstractor and date

Motoo Y, 18 May 2020, 14 Feb 2021.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yamagata T, Ajimura K, Yukawa S. Effect of juzentaihoto on myelosuppression during lung cancer chemotherapy*. *Therapeutic Research* 1998; 19: 705-8 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the preventive effect of juzentaihoto (十全大補湯) on myelosuppression in patients undergoing chemotherapy (carboplatin + etoposide) for primary lung cancer (squamous cell carcinoma, adenocarcinoma, or small cell carcinoma).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (third Department of Internal Medicine, Wakayama Medical University), Japan.

4. Participants

Thirty-six patients with stage III-IV primary lung cancer (25 with small-cell carcinoma, 6 with squamous cell carcinoma, and 5 with adenocarcinoma) receiving carboplatin on day 1 + etoposide 40 mg/m^2 on days 1–5.

5. Intervention

Arm 1: administration of the above-mentioned anti-cancer drugs + juzentaihoto (十全大補湯) (manufacturer unknown) 7.5 g/day (7 days before through 21 days after the start of administration of the anti-cancer drugs) (n=20).

Arm 2: the above-mentioned anti-cancer drugs alone (n=16).

6. Main outcome measures

Changes in platelet, white blood cell (WBC), and red blood cell (RBC) counts, and hemoglobin value during treatment, and change in each item between pre- and post-treatment.

7. Main results

Because baseline platelet and WBC counts were significantly lower in arm 1, there were no significant between-arm differences in their minimum values. However, decrements in these values from pre- to post-treatment were significantly smaller in arm 1 (platelet count, $P<0.01$; WBC count, $P<0.05$). The decrement in RBC count was significantly smaller in arm 1 ($P<0.05$), although there was no significant between-arm difference in hemoglobin value.

8. Conclusions

Juzentaihoto extract helps reduce the severity of myelosuppression in patients on chemotherapy (carboplatin + etoposide) for primary lung cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse drug reactions in arm 1 (adverse events in arm 2, not indicated).

11. Abstractor's comments

The authors concluded that combination of juzentaihoto with anti-cancer drugs (carboplatin + etoposide) is effective for reducing myelosuppression associated with anti-cancer drug treatment, and thus useful in administering potent chemotherapy and improving quality of life. However, the significant differences in pre-treatment platelet and WBC counts between arm 1 and arm 2 as well as the conclusion drawn from comparison of the degree of decrements were problematic.

12. Abstractor and date

Hoshino E, 22 February 2009, 6 January 2010, 22 October 2011, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Inui H, Yamagata T, Minakata Y, et al. Prevention of side effects during lung cancer chemotherapy by Hochuekki-to. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 1993; 2: 56–60 (in Japanese).

1. Objectives

To evaluate the preventive and relieving effect of hochuekkito (補中益気湯) on general malaise in patients undergoing chemotherapy (including cisplatin for 5 days) for advanced primary lung cancer.

2. Design

Cross over randomized controlled trial (RCT-cross over).

3. Setting

One hospital, Japan.

4. Participants

Nine patients with advanced (stage III–IV) lung cancer (small cell [n=4] and non-small cell [n=5]) who underwent gross curative resection and postoperative cisplatin + etoposide and postoperative cisplatin + mitomycin + vindesine, respectively.

5. Intervention

Arm 1: hochuekkito (補中益気湯) (manufacturer unknown) 2.5 g t.i.d. in combination in the first course and anticancer drugs alone in the second course.

Arm 2: anticancer drugs alone in the first course and hochuekkito (補中益気湯) (manufacturer unknown) 2.5 g/day in combination in the second course.

Comparison between anticancer drugs alone and hochuekkito (補中益気湯) (manufacturer unknown) 2.5 g t.i.d. in combination.

6. Main outcome measures

Subjective symptoms (appetite, mood, sleep, general malaise, daily life, and face scale) with and without hochuekkito rated on a 5-point scale and recorded in a quality of life diary for 3 weeks. CD4/8 and NK activity before and after administration of hochuekkito.

7. Main results

General malaise, mood, and appetite showed a tendency for improvement during administration of hochuekkito. There were no significant between-arm differences in CD4/8 or NK activity.

8. Conclusions

Hochuekkito administered during chemotherapy for lung cancer relieves and improves mood and general malaise.

9. From Kampo medicine perspective

The *sho* (証, pattern) concept was not used as a rationale for inclusion or exclusion and was not discussed, although “calculation based on the Kampo score questionnaire revealed 7 patients with *kyosho* (虚証, deficiency pattern) and 2 patients with *chukansho* (中間証, intermediate pattern).”

10. Safety assessment in the article

None.

11. Abstractor’s comments

Despite the lack of statistically significant differences, the authors concluded that hochuekkito may be used to relieve and improve adverse reactions to anticancer drugs (cisplatin +α). The bar chart showing the severity of each symptom is meaningless. Although “the data were compared by sign test,” the analysis seems to be incorrect.

12. Abstractor and date

Hoshino E, 24 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Kato S, Kishiro I, Machida S, et al. Combined effects of hochu-ekki-to (*bu-zhong-yi-qi-tang*) and clarithromycin on Lung Carcinoma. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 1999; 13: 83-8 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of hochuekkito (補中益気湯) combined with clarithromycin (CAM) for improvement in the prognosis of lung cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

A university hospital (Department of Internal Medicine, Dokkyo Medical University Hospital), Japan.

4. Participants

Thirty-five patients with primary lung cancer lesions that responded to chemotherapy or radiotherapy either partially or completely (21 males, 14 females; mean age, 63.2±6.7 years; performance status [P.S.] 0-2; baseline clinical stage Ia [n=5], Ib [n=21], and II [n=9]; squamous cell carcinoma [n=14], adenocarcinoma [n=21]).

5. Intervention

Arm 1: combination therapy group; 400 mg/day of CAM + 7.5 g/day of hochuekkito (補中益気湯) extract granules administered to 17 patients (10 males, 7 females; mean size reduction of the primary lesion, 62.8 ± 11.2%).

Arm 2: monotherapy group; 400 mg/day of CAM administered to 18 patients (11 males, 7 females; mean size reduction of the primary lesion, 66.7±8.6%).

6. Main outcome measures

Tumor markers, NK cell activity (at baseline, and 2 and 12 months after the start of treatment), and 1-year survival.

7. Main results

Serum levels of tumor markers were significantly elevated in both treatment groups compared with the control group**.** In patients surviving 1 year after the start of treatment, NK cell activity, representing immunoreactivity, was elevated in both treatment groups, and was significantly higher in the combination therapy group than the control group.

8. Conclusions

The combination (hochuekkito plus CAM) seems to be effective for maintaining the efficacy of chemotherapy and radiotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study deserves praise for attempting to conduct RCT targeting a difficult-to-treat pathology of lung cancer prognosis. Regrettably, however, it is unclear whether "the control group" mentioned here refers to the CAM monotherapy group or yet another group, or to a before-after comparison in the same group. Clarification of the study is expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Mori K, Saito Y, Tominaga K. Utility of hochu-ekki-to in general malaise accompanying lung cancer chemotherapy. *Biotherapy* 1992; 6: 624–7 (in Japanese with English abstract). Ichushi Web ID: 1993020654

1. Objectives

To evaluate the efficacy of hochuekkito (補中益気湯) for the prevention and relief of general malaise related to chemotherapy for primary lung cancer (squamous cell carcinoma, adenocarcinoma, and small cell carcinoma).

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Forty-one patients with stage III–IV lung cancer receiving (cisplatin 25 mg/m^2 for 5 days) + (vindesine 3 mg/m^2 at days 1 and 8 or etoposide 100 mg/m^2 at days 1, 3, and 5) every 3 or 4 weeks.

5. Intervention

A table of random numbers was used for group assignment.

Arm 1: TSUMURA Hochuekkito (補中益気湯) Extract Granules 7.5 g/day (beginning from 7 or more days before the start of anticancer drug treatment) (n=21).

Arm 2: no administration of hochuekkito (補中益気湯) (n=20).

6. Main outcome measures

Subjective symptoms (general malaise, mood, appetite, and nausea/vomiting) after 1–4 cycles of chemotherapy in arm 1 or 2–4 cycles in arm 2, recorded in a health diary for comparison.

7. Main results

General malaise, mood, and appetite were significantly improved in arm 1 (P<0.01), but there was no significant between-arm difference in the severity of nausea/vomiting.

8. Conclusions

Hochuekkito is useful for prevention of general malaise and improvement of mood and appetite in patients on chemotherapy (including cisplatin) for primary lung cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse drug reactions in arm 1, and none was mentioned in arm 2.

11. Abstractor's comments

The authors concluded that hochuekkito combined with anticancer drugs (cisplatin +α) is useful for prevention of general malaise and improvement of mood and appetite. Symptoms were graded ensuring objectivity to some degree, although the study was not blinded. However, improvement was not rated at the same time point in arm 1 (after 1–4 cycles) and arm 2 (after 2–4 cycles). Improvement should have been evaluated over time in both arms after a fixed number of chemotherapy cycles.

12. Abstractor and date

Hoshino E, 6 May 2009, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Mori K, Machida S, Yoshida T, et al. Usefulness of Kampo medicine (hangeshashin-to) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Proceedings of the American Society of Clinical Oncology* 1999; 18: 518a, Abstract 1996 CENTRAL ID: CN-00716751

Mori K, Hirose T, Machida S, et al. Kampo medicines for the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Gan to Kagaku Ryoho* (*Japanese Journal of Cancer and Chemotherapy*) 1998; 25: 1159-63 (in Japanese with English abstract) CENTRAL ID; CN-00153138, Pubmed ID: 9679578 MOL, MOL-Lib

Mori K. Hangeshashin-to (Kampo medicined) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Progress in Medicine* 1999; 19: 886-90 (in Japanese with English abstract) MOL, MOL-Lib

Mori K, Kondo T, Kamiyama Y, et al. Preventive effect of Kampo medicine (hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. *Cancer Chemotherapy and Pharmacology* 2003; 51: 403-6. CENTRAL ID: CN-00437238, Pubmed ID: 12687289

1. Objectives

To evaluate the safety and efficacy of hangeshashinto (半夏瀉心湯) (TJ-14) for CPT-11-induced diarrhea during combination chemotherapy with cisplatin (CDDP) plus irinotecan hydrochloride (CPT-11) for advanced non-small-cell lung cancer (NSCLC).

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

One hospital; the authors belong to the Department of Respiratory Disease, Tochigi Cancer Center, Japan.

4. Participants

From among inpatients with NSCLC who received dual therapy with CDDP plus CPT-11 from November 1993 through December 1996, forty one patients who met the following selection criteria were enrolled: 1) treatment-naïve with unresectable NSCLC (stage III, IV); 2) performance status 0 to 2; 3) preserved major organ function; 4) 75 years or younger; and 5) informed consent. Patients with serious complications, diarrhea, severe pleural effusion, or symptomatic cerebral metastasis were excluded from the study.

5. Intervention

Arm 1: treatment with TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules (TJ-14) 2.5 g t.i.d. before meals in 18 patients.

Arm 2: no treatment in 23 patients.

In the arm 1, hangeshashinto was administered every day from at least 3 days before through 21 days or more after the start of chemotherapy.

6. Main outcome measures

Stool properties and frequency of defecation, presence and severity of abdominal pain associated with defecation, presence or absence of bowel movements at night and bloody diarrhea.

7. Main results

The onset and the highest daily frequency of diarrhea were respectively recorded at 6.3 and 9.2 days after the start of chemotherapy in arm 1, and at 5.9 and 9.0 days in arm 2. During the first cycle of chemotherapy, the severity of diarrhea was significantly improved and the incidence of grade 3 or higher diarrhea was lower in arm 1 than in arm 2. The number of diarrhea episodes and the duration (in days) of diarrhea were not significantly different between the two arms.

8. Conclusions

Hangeshashinto is effective for preventing and relieving CPT-11-induced diarrhea in advanced NSCLC.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Mild constipation was reported in 2 hangeshashinto-treated patients. Other significant adverse effects were not observed.

11. Abstractor's comments

This clinical study indicated that the concomitant use of hangeshashinto is effective for diarrhea, which can occur during chemotherapy containing CPT-11. This study lacked a placebo control group and was not double-blinded. In a study using Kampo medicines as a control, it is difficult to prepare the placebo because Kampo medicines have specific textures and smells. Nonetheless, double-blind design should be considered in order to improve the quality of study. "

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery. *Kampo to Meneki Arerugi* (*Kampo and Immuno-Allergy*) 2008; 22: 43-55 (in Japanese with English abstract).
Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery — QOL analysis with 36-Item Short Form (SF-36) v2*.. *Progress in medicine* 2010; 30: 100-1 (in Japanese). MOL, MOL-Lib

1. Objectives
To evaluate the efficacy of bakumondoto (麦門冬湯) on improvement in cough after lung cancer surgery.

2. Design
Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting
One hospital, Japan.

4. Participants
Thirty-two outpatients with prolonged cough for more than three weeks after lung cancer surgery, who were recruited between November 2005 and December 2007. Patients with apparent respiratory disease or antitussive drug use were excluded.

5. Intervention
The duration of administration was 4 weeks.
Arm 1: Tsumura Bakumondoto (麦門冬湯) Extract Granules (TJ-29) 9.0 g/day, n=17.
Arm 2: Medicon (dextromethorphan) 90 mg/day, or Astomine (dimemorfan) 60 mg/day, n=15.

6. Main outcome measures
Cough points, QOL score (36-Item Short Form [SF-36] v2 Health Survey).

7. Main results
Cough points showed significant decrease after 5 days of administration in arm 2, and after 3 days in arm 1 (P<0.05). Also, cough frequency was significantly less in arm 1 compared to arm 2 after 6 days of treatment until the end of the 4-week observation period (P<0.05). As for effect of improvement in cough, cough points decreased from 7 to 3.76 in arm 1, and from 7.2 to 4.58 in average after 4 weeks of administration. Cough disappeared in 3 patients in arm 1. Of 5 non-responders in arm 1, 3 showed improvement with proton pump inhibitor (PPI). QOL scores of the patients at the baseline were much lower than that of national standard. After the treatment, arm 2 showed improvement only in physical components, whereas arm 1 showed statistical improvements in general health, in both physical and mental components; mental health was significantly better in Arm 1 compared to arm 2.

8. Conclusions
Bakumondoto is effective in improving not only prolonged cough after lung cancer surgery, but also mental health components in QOL, when compared with Medicon or Astomine.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Not mentioned.

11. Abstractor's comments
Tsunezuka (2008) demonstrated that bakumondoto not only has efficacy in reducing cough frequency in cases of prolonged cough after lung cancer surgery but also has efficacy in reducing psychological stress. Bakumondoto treatment eliminated the symptoms of cough in 3 patients and use of PPI improved cough in 3 patients; the high rates were interesting. Another report by Tsunezuka (2010) based on this study, which added three months to the registration period and two patients to arm 2, also shows the same efficacy.

12. Abstractor and date
Fujisawa M, 1 June 2010, 14 January 2011, 31 December 2013

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Oteki T, Ishikawa A, Sasaki Y, et al. Effect of rikkunshi-to treatment on chemotherapy-induced appetite loss in patients with lung cancer: a prospective study. *Experimental and Therapeutic Medicine* 2016; 11: 243-6.

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) for chemotherapy-induced appetite loss.

2. Design

Randomized controlled trial (RCT).

3. Setting

1 university hospital.

4. Participants

Forty-eight lung cancer patients without surgical indication who underwent CDDP, CBDCA, or non-platimum based chemotherapy (analyzing treatment over 140 courses in all. There were an extended total of 140 participants in the study).

5. Intervention

CBDCA

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5g/day (2.5g t.i.d) before meals for 7 days (64 courses).

Arm 2: No administration (27 courses).

CDDP

Arm1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5g/day (2.5g t.i.d) before meals for 7 days (10 courses).

Arm2: No administration (11 courses).

Non-platimum based chemotherapy

Arm1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5g/day (2.5g t.i.d) before meals for 7 days (16 courses).

Arm2: No administration (12 courses).

6. Main outcome measures

Food intake amount.

7. Main results

Although no significant difference in food intake amount was found in days 1-6 after commencement of chemotherapy in the CBDCA group, food intake amount increased significantly (P=0.0078) in the rikkunshito extract granule group on day 7 (increased food intake trend observed on day 6, P=0.0626). No significant difference in food intake amount was found between with and without rikkunshito in the CDDP and the non-platinum groups.

8. Conclusion

Using rikkunshito during chemotherapy could be useful for decreased appetite.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Rikkunshito has been frequently prescribed in recent years for functional gastrointestinal symptoms. In the broader sense, chemotherapy-induced appetite loss is a functional gastrointestinal symptom, so there is great meaning in studying the usefulness of rikkunshito in this manner. Allocation in this study was arbitrary (for CBDCA, administration group: non administration group allocation was 2:1), which one can understand was a way of dealing with a small number of cases, however, it is rather unfortunate in the sense that the authors were conducting a randomized controlled trial. Furthermore, hangeshashinto, frequently used for diarrhea during chemotherapy, is recognized for its stomachic action, so from an oriental medicine perspective it could be effective, and as the abstractor, I would advise that it be an additional arm.

12. Abstractor and date

Nakata H, 2 February 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yoshida T, Sawa T, Ishiguro T, et al. The efficacy of prophylactic Shakuyaku-Kanzo-to for myalgia and arthralgia following carboplatin and paclitaxel combination chemotherapy for non-small cell lung cancer. *Support Care Cancer* 2009; 17: 315-20.

1. Objectives

To evaluate the preventive effect of shakuyakukanzoto (芍薬甘草湯) for arthralgia and myalgia following carboplatin and paclitaxel combination chemotherapy for non-small cell lung cancer

2. Design

Randomized controlled trial (RCT).

3. Setting

1 hospital, Japan.

4. Participants

50 unresectable, advanced, non-small cell lung cancer patients.

5. Intervention

Arm 1: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 7.5g/day (2.5g t.i.d. before meals) taken orally from the day of chemotherapy (day 1) to day 21 (n=25).

Arm 2: No administration (n=25).

6. Main outcome measures

Primary endpoints: Myalgia and arthralgia grade (JCOG-CTC).

Secondary endpoints: Myalgia and arthralgia duration, number of patients requiring additional non-steroidal anti-inflammatory drugs (NSAIDs) administration.

7. Main results

Primary endpoints: Myalgia and arthralgia grades were significantly lower in the shakuyakukanzoto group (P=0.018). Secondary endpoints: Pain durations were significantly shorter (P=0.002), and the numbers of patients requiring additional NSAID administration were significantly lower (P=0.036) in the shakuyakukanzoto group.

8. Conclusion

Shakuyakukanzoto alleviates arthralgia and myalgia following carboplatin and paclitaxel combination chemotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Duodenal ulcer, possibly attributable to NSAIDs, occurred in one participant in the control group.

11. Abstractor's comments

Paclitaxel sometimes causes arthralgia and myalgia. The promotion of prostaglandin production is thought to be one of the causative factors, and NSAIDs are commonly used for it. However, NSAIDs have adverse effects, such as peptic ulcer. There is great significance in this study having verified the effectiveness of preventive administration of shakuyakukanzoto through an RCT. The authors also mention that continued administration of shakuyakukanzoto from cycle 2 resulted in a significantly higher number of chemotherapy cycles (P=0.001) and that the anti-tumor effects (response rate) tended to be higher in the administration group compared to the control group (P=0.113). This outcome is real corroboration of the concept of using Kampo to allow for the successful completion of standard therapies. Although 7.5g of shakuyakukanzoto was continually administered daily, there was no case of pseudoaldosteronism. The authors raise some problematic points such as the high number of patients with good PS in the shakuyakukanzoto group, the differences in initial paclitaxel doses, the lack of a placebo in the control group, and the small number of participants. Hopefully they will conduct another RCT that resolves those problems.

12. Abstractor and date

Motoo Y, 25 January 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Abe H, Kawai Y, Mori T, et al. The Kampo medicine goshajinkigan prevents neuropathy in breast cancer patients treated with docetaxel. *Asian Pacific Journal of Cancer Prevention* 2014; 14: 6351-6. Pubmed ID: 24377531

1. Objectives

To verify the effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy during chemotherapy for breast cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (hospital).

4. Participants

Sixty women aged 20-70 who were receiving chemotherapy with docetaxel for invasive breast cancer.

5. Intervention

Arm 1: GJG group: TSUMURA Goshajinkigan Extract Granules (7.5 g divided in two to three doses per day) taken either before or between meals (n=33).

Arm 2: B12 group: Mecobalamin (1500μg/day) taken after meals (n=27).

6. Main outcome measures

Assessment of the frequency of peripheral neuropathy (Neurotoxicity Criteria of Debiopharm [DEB-NTC], Common Terminology Criteria for Adverse Events [CTC-AE], and Visual analogue scale [VAS]).

7. Main results

The incidence of chemotherapy-induced peripheral neuropathy in the GJG group was 39.3% compared to 88.9% in the B12 group, which was significantly (P<0.01) lower. Twelve patients in the B12 group were assessed as DEB-NTC grade 3, a severe assessment, while 5 patients in the GJG group received that assessment, which was a significant difference (P<0.01). Similarly, 12 patients were assessed as CTC-AE grade 2 and 1 as grade 3 in the B12 group, while 6 patients in the GJG group were assessed as grade 2 and none as grade 3, which was a significant difference (P<0.01). The VAS scores for subjective symptom assessment were also significantly lower (P<0.01) in the GJG group (2.7±2.2) compared to the B12 group (4.9±2.4). Taking goshajinkigan during chemotherapy with docetaxel significantly reduced not only the occurrence of peripheral neuropathy but also the severity of subjective symptoms.

8. Conclusions

Preventive oral administration of goshajinkigan suppresses the occurrence of peripheral neuropathy and even when such neuropathy does occur, it reduces symptom severity, during chemotherapy with docetaxel for invasive breast cancer in female patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no clinically problematic adverse effect.

11. Abstractor's comments

This study confirmed the preventive effects of goshajinkigan for peripheral neuropathy, an inevitable adverse effect of chemotherapy for invasive breast cancer. It has great significance in clinical medicine and is a valuable study. Confirmation of this significant effect through a randomized trial, not based on the *zuisho* (随証, patterns) of Kampo medicine, means the results are worthy of being included in the guidelines for Western medical treatment. Hopefully the authors will conduct a robust study of its clinical effects under protocols including goshajinkigan's *zuisho* (随証, pattern), or at least whether *jinkyo* (腎虚, kidney deficiency) is present or not. Further research is anticipated.

12. Abstractor and date

Ushiroyama T, 31 March 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Kawabata K, Nakano T, Tsutsumi J, et al. Evaluation of alleviation for lower-extremity peripheral neuropathy due to cancer chemotherapy. Effectiveness of the carbonate spring foot bath and goshajinkigan*. *Journal of the Japanese Society of Footcare.* 2014; 12: 145-50 (in Japanese). Ichushi Web ID: 2015126257

1. Objectives

To evaluate the efficacy of the carbonate spring foot bath and goshajinkigan (牛車腎気丸) for lower-extremity peripheral neuropathy due to cancer chemotherapy.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

One university hospital, Japan.

4. Participants

Eighteen females with breast cancer aged <75 years who were to receive preoperative chemotherapy with paclitaxel (80 mg/m^2 once weekly, infused for 12 consecutive weeks).

5. Intervention

Arm 1: Spring foot bath with Kao carbonated tablets (炭酸足浴剤) diluted in 6 L of warm water maintained at 38°C to 40°C and administered for 15 minutes daily at a convenient time for 12 weeks (n=8).

Arm 2: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules orally administered at 2.5 g t.i.d. for 12 weeks (n=4).

Arm 3: No treatment (n=6).

6. Main outcome measures

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), peripheral neuropathy (i.e., numbness measured on the CTC-AE version 4.0 grading scale), and foot skin temperature (measured by thermography) at Weeks 4, 8, and 12.

7. Main results

Peripheral neuropathy in the lower extremity (all grade 2 or less) occurred in 11 of the 18 subjects (61%). In the carbonate spring foot bath arm (n=8), the 4 subjects with no numbness compared to the remaining 4 subjects with numbness had higher median skin temperature (34.8°C vs. 31.1°C) and higher percent change in foot skin temperature over time. At Week 12 of paclitaxel chemotherapy, 4 subjects in the carbonate spring foot bath arm, 0 subjects in the goshajinkigan arm, and 3 subjects in the control arm had no numbness, and 2 subjects in the carbonate spring foot bath arm had no numbness for 12 consecutive weeks.

8. Conclusions

Lower-extremity numbness caused by preoperative once-weekly paclitaxel chemotherapy may be alleviated by bathing in carbonate spring foot bath; however, the number of subjects in this study was too small to draw clear conclusions.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This was a unique study evaluating the effects of carbonate spring foot bath on vasodilation, such as increased muscle blood flow, increased skin temperature, and alleviation of numbness. Presented only at the convention of the Japanese Society of Footcare, the study suggested that carbonate spring foot bath was effective for numbness in patients with non-small-cell lung cancer (NSCLC). Although there were 2 control arms (a goshajinkigan arm and no treatment arm), the number of subjects in each arm was small and no statistical analysis was mentioned in the article. Skin temperature should have been measured at baseline. Although the authors valued that the severity of peripheral neuropathy at the completion of the scheduled 12-week treatment was Grade 2 or lower in all subjects, it was not mentioned whether the treatment could be effective without dose reduction of paclitaxel. In addition, the description of the carbonate spring foot bath arm was mistakenly replaced by the description of the goshajinkigan arm in the third line of the Results section, and the number of subjects in the carbonate spring foot bath arm should be 8 instead of 6 in Table 4. It is anticipated that statistical evaluation of the efficacy of the carbonate spring foot bath will be possible once the number of subjects is increased.

12. Abstractor and date

Motoo Y, 31 March 2017.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Nagao K, Nishimura R, Matsuda M, et al. Clinical evaluation of the combined effect of tegafur and *hozai* (補剤; formulations with tonic effects)*. *Toho Igaku* (*Eastern Medicine*) 1998; 14: 63-71 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of hochuekkito (補中益気湯) or ninjin'yoeito (人参養栄湯) for reducing adverse drug reactions and improving quality of life (QOL) in breast cancer patients undergoing postoperative (after curative resection or initial treatment) Sunfral S (800 mg/day).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital, Japan.

4. Participants

Patients with breast cancer receiving the anti-cancer drug Sunfral S (800 mg/day) postoperatively (21 of 26 were evaluated).

5. Intervention

Arm 1: Sunfral S 400 mg/day b.i.d.+ Kanebo Hochuekkito (補中益気湯) Extract Fine Granules 2.5 g t.i.d. for at least 5 months (n=13).
Sunfral S 400 mg/day b.i.d. + Kanebo Ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d. for at least 5 months (n=1).

Arm 2: Sunfral S 400 mg/day b.i.d. alone (n=12).

6. Main outcome measures

Adverse drug reactions; white blood cell (WBC), lymphocyte, and red blood cell (RBC) counts; carcinoembryonic antigen (CEA) evaluated before treatment and at 2, 4, and 6 months after treatment; immunological indices including CD2 CD4, CD8, CD16, and NK cell counts, and lymphocyte stimulation index; and duration of administration.

7. Main results

The Kampo medicines did not significantly reduce adverse drug reactions associated with tegafur/uracil (UFT). There were no between-arm differences in WBC, lymphocyte, or RBC counts (statistical analysis not performed). CEA was increased in 0/5 patients in arm 1 and 4/7 patients in arm 2 (not determined in all patients, statistical analysis not performed). Among patients with adverse drugs reactions to Sunfral S, those in arm 1 received Sunfral S for a longer duration.

8. Conclusions

In patients with adverse drug reactions to postoperative Sunfral S (800 mg/day) for breast cancer, hochuekkito was immunostimulatory (according to percent change noted in the lymphocyte stimulation index) and Sunfral S could be administered for a longer period than the control group.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no differences in the incidence or severity of adverse events between arm 1 and arm 2 (statistical analysis not performed).

11. Abstractor's comments

The authors concluded that combination of hochuekkito with the anti-cancer drug (Sunfral S) was immunostimulatory, as indicated by the increase in lymphocyte stimulation index, and thereby facilitated long-term treatment with anti-cancer drugs. This conclusion is however not supported by evidence that the lymphocyte stimulation data reflect the degree of immunostimulation, considering that there were no significant differences in the percent changes in tumor immunity-related markers including lymphocyte surface markers (helper T/suppressor T/NK cell activities). Furthermore, changes in CEA were not evaluated in the total population, and the evaluation depended on an unsound criterion (i.e., change by 1 μg/mL or more). Moreover, arm 1 in this study included more than one Kampo medicine; 13 patients receiving hochuekkito and 1 patient receiving ninjin'yoeito, and thus the amount of data available for statistical analysis was insufficient and a meaningful conclusion cannot be drawn from these findings.

12. Abstractor and date

Hoshino E, 23 April 2009, 6 January 2010, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Takanami I, Ohnishi H. Clinical effects of ninzin-yoei-to as the immunopotentiator. *Kiso to Rinsho* (*The Clinical Report)* 1988;22: 1835-46 (in Japanese). Ichushi Web ID: 1989107413 MOL, MOL-Lib

1. Objectives

To evaluate effects of ninjin′yoeito（人参養栄湯）prophylaxis dosing on the postoperative immune status in breast cancer patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Thirteen patients with stage I or II breast cancer, aged ≤60 years.

5. Intervention

Arm 1: KANEBO Ninjin′yoeito（人参養栄湯）Extract Fine Granules 6.0 g/day (dosing frequency not stated), started 7 days before surgery and continued at the same dose up to approximately 4 weeks after surgery, excluding the day of surgery (n=7).
Arm 2: Control (no administration of ninjin′yoeito) (n=6).

6. Main outcome measures

Immunological parameters of peripheral white blood cell count, lymphocyte count, levels of OKT_3, OKT_4, OKT_8, $OKla_1$, Leu 7, and Leu 11 antibodies, NK cell activity, and phytohaemagglutinin (PHA)-induced lymphocyte blastogenesis at 1 week before surgery as well as 1 day and 1, 2, 3, and 4 weeks after surgery.

7. Main results

At 4 weeks after surgery, the OKT3 (pan T cell antibody) level was significantly higher in the ninjin′yoeito group (Arm 1) than in the control group (Arm 2) (P<0.05). Other endpoints showed no significant differences between the two groups.

8. Conclusions

Ninjin′yoeito has no apparent immunopotentiating effect in patients with stage I or II breast cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

Indications for ninjin′yoeito include "decreased physical strength after illness." This RCT evaluated ninjin'yoeito based on postoperative immune recovery in patients with stage I or II breast cancer. Among the immunological parameters examined, only OKT_3 showed significantly higher levels in the ninjin′yoeito group than in the control group. No other parameters showed significant differences between the groups. The authors reasonably concluded that ninjin′yoeito had no apparent immunopotentiating effect. However, the authors also stated that, in the ninjin′yoeito group compared with the control group, the OKT_4 (Th1) levels over time showed smaller decrease after surgery and also other immunological parameters appeared to have better recovery after surgery, which could be misleading. Since the sample size was very small and the extent of surgical invasion is not specified, the data appear to be insufficient to draw a conclusion. Nevertheless, immunopotentiation is one of the important mechanisms of action of ninjin′yoeito, which is one of three major tonifying Kampo formulae. Further RCTs with adequate sample sizes and due consideration given to the extent of surgical invasion are desired.

12. Abstractor and date

Motoo Y, 18 August 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Adachi I. Supporting therapy with shi quan da bu tang in advanced breast cancer patients. *Biomedical Research* 1990; 11 suppl: 25–31.

Adachi I, Watanabe T, Chen JY, et al. Supportive therapy of oriental medicine for patients with advanced breast cancer. *Gan to Kagaku Ryoho* (*Japanese Journal of Cancer and Chemotherapy*) 1989; 16: 1538–43 (in Japanese with English abstract). CENTRAL ID: CN-00060398, Pubmed ID: 2730051, Ichushi Web ID: 1990185338

Adachi I. Juzen-taiho-to as a supporting therapy in advanced breast cancer. Biotherapy 1989; 3: 782–8. Ichushi Web ID: 1991039494

1. Objectives

To evaluate the efficacy of supportive therapy with juzentaihoto (十全大補湯) for advanced breast cancer patients.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Not mentioned (Dr. Adachi belongs to the faculty of the National Cancer Center), Japan.

4. Participants

A total of 119 patients were included in the study. Inclusion criteria: 1) advanced breast cancer with metastasis; 2) 6-month or longer survival expected; 3) no history of gastrointestinal surgery; 5) ability to take drugs orally; 6) no cancer other than breast cancer; and 7) use of anticancer drugs for breast cancer but no use of other Kampo medicines.

5. Intervention

Arm 1: chemotherapy + hormone therapy + juzentaihoto (十全大補湯) (manufacturer unknown) 5–7.5 g (n=58).
Arm 2: chemotherapy + hormone therapy (n=61).

6. Main outcome measures

Significance test using Kaplan-Meier survival curve.

7. Main results

There were no significant differences in survival and biochemistry between the control group and juzentaihoto group; however, when the juzentaihoto group was stratified by Kampo diagnosis (diagnostic criteria not mentioned), a significant difference was noted in survival ($P<0.05$).

8. Conclusions

If used appropriately, supportive therapy with juzentaihoto is effective for patients with breast cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Within 2 weeks of treatment initiation, edema and skin pruritus appeared in 2 patients, one of whom withdrew from treatment.

11. Abstractor's comments

This study evaluated the efficacy of juzentaihoto as supportive therapy for breast cancer. The conclusion that use of juzentaihoto as supportive therapy should be based on Kampo diagnosis is very suggestive. Considering the significance of this point, the rationale for diagnostic criteria for juzentaihoto-indicated patients should be specified.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Aoe H, Matsuo T, Ebisutani M, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation in cancer patients*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2000; 17: 67-71 (in Japanese)

Aoe H, Ota M, Kawahara N, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation*. *Rinsho Kensa* (*Journal of Medical Technology*) 2003; 47: 395-9 (in Japanese). Ichushi Web ID: 2003251978

Aoe H. Effect of Juzen-taiho-to on haematological recovery from predeposit autologous blood donation. *Pharma Medica* 2007; 25: 11-4. Ichushi Web ID: 2008070612 **MOL, MOL-Lib**

1. Objectives

To evaluate the efficacy of using juzentaihoto (十全大補湯) to augment preoperative autologous blood donation in cancer patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not identified (but the abstractor infers a Department of Obstetrics and Gynecology in each of the following three facilities: Japanese Red Cross Society Himeji Hospital, Fukuyama City Hospital, and Chugoku Central Hospital), Japan.

4. Participants

One-hundred and twenty patients who visited the above institutions within the past 5 years and 2 months and donated 800 mL or more autologous blood before undergoing surgery for gynecologic malignant tumors. Patients receiving preoperative chemotherapy and patients with collagen disease were excluded.

5. Intervention

Arm 1: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly, from the day of the first donation through the day before the operation in patients with pre-donation Hb value of < 14 g/dL, n=52.

Arm 2: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly + oral administration of a sachet (2.5 g) of TSUMURA Juzentaihoto (十全大補湯) Extract Granules t.i.d (before meals), from the day of the first donation through the day before the operation in patients with pre-donation Hb value of < 14 g/dL, n=51.

Arm 3: intravenous administration of an iron preparation (240 mg weekly), n=17.

6. Main outcome measures

Hematological profile: RBC count, hemoglobin, hematocrit, reticulocyte count, etc., measured before donation (before administration) and preoperatively (immediately after completion of administration).

Serum biochemical profile: total protein, albumin, and iron concentrations, determined before donation (before administration) and preoperatively (immediately after completion of administration).

Hemoglobin increment: pre-donation hemoglobin concentration × volume of donation blood/volume of circulating blood – (pre-donation hemoglobin concentration – preoperative hemoglobin concentration).

7. Main results

Decrements in RBC count and hematocrit after donation were significantly smaller in the EPO combination groups than in the iron monotherapy group, and significantly smaller in the juzentaihoto and EPO combination group than in the EPO combination group (P<0.05). There was also a significant difference in hemoglobin increment between arms (P<0.05).

8. Conclusions

An iron preparation combined with EPO and additionally with juzentaihoto enhances the clinical efficacy of preoperatively donated autologous blood.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study demonstrated that adding juzentaihoto to the preoperative donation management protocol successfully suppresses reductions in RBC count and hematocrit after donation and enhances the increase in blood hemoglobin concentration. This suggests that the hematological profile of donated autologous blood is better after use of this combination than after use of only an iron preparation plus EPO. Thus, this finding is clinically significant. With the accumulation of more cases, a safety study, including an examination of the possibility that complementary medicines promote cancer cell growth, is expected.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 19 December 2008, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Mori T, Tauchi K, Yokoyama S, et al. Effects of sho-saiko-to (xiao-chai-hu-tang) on thrombocytopenia bei therapy with anti-cancer drugs. *Sanfujinka Chiryo* (*Obstetrical and Gynecological Therapy*) 1992; 65: 102–5 (in Japanese).

1. Objectives

To evaluate the effects of preoperative administration of shosaikoto (小柴胡湯) on thrombocytopenia in gynecologic cancer patients receiving anti-cancer drugs.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (Department of Gynecology and Obstetrics, Kyoto University Hospital) and 12 other hospitals, Japan.

4. Participants

Eighty-nine gynecologic cancer patients receiving anti-cancer drugs (ovarian cancer, 68; endometrial cancer, 16; cervical cancer, 5; choriocarcinoma, 1; uterine sarcoma, 1).

5. Intervention

Arm 1: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day for 14 days after white blood cell (WBC) count fell below 3000 (n=49).
Arm 2: no administration of Kampo medicines after WBC count fell below 3000 (n=40).

6. Main outcome measures

Peripheral blood leukocytes, platelet count, IgG, IgA, IgM, OKT 4, OKT 8, and NK cell activity before administration of anti-cancer drugs, on the day the WBC fell below 3000 and 14 days after the WBC count fell below 3000, as well as days to recovery of the WBC count to ≥3000.

7. Main results

Days to recovery of the WBC count to ≥3000: no significant difference between groups.
Increase in platelet count for 14 days: greater in arm 1 than arm 2 (P<0.05).
IgG, IgA, IgM, OKT 4, OKT 8, and NK cell activity: no significant difference between groups.

8. Conclusions

Administration of shosaikoto in patients with leukopenia associated with anti-cancer therapy leads to the recovery of platelet count.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned in the article.

11. Abstractor's comments

The authors reported that shosaikoto was effective in raising the platelet count in patients with thrombocytopenia associated with anti-cancer drugs. However, the platelet counts had decreased to within the normal range and these decreases might not be due to myelosuppression. The platelet count reduction was therefore not by definition indicative of "thrombocytopenia associated with anti-cancer drugs." Shosaikoto was started at the time the WBC count had fallen below 3000. Inasmuch as lymphocyte count may be decreased by undernutrition, granulocyte count should be used as a measure of myelosuppression. There is a lack of consistency in terms of endpoints, that is, for the WBC count, it was the time to recovery to ≥3000, while for the platelet count, it was the difference in values at the time and 14 days after the WBC count fell below <3000. It is also not clear why the duration of treatment with shosaikoto is two weeks. An appropriate strategy for analysis would be to perform serial WBC and platelet counts beginning just after the start of shosaikoto, and analyze these measurements.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Inoue S, Kuwahara H, Kato Y, et al. Thrombopoietic and leukopoietic effects of a traditional Chinese herbal medicine, formula reverti lienalis compositae (Japanese name: *Kami-kihi-to TJ-137*) in cancer patients. *Biotherapy* 1998; 12: 1071-6 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To evaluate the effect of kamikihito (加味帰脾湯) on thrombocytopenia and leukopenia in patients receiving anti-cancer drugs.

2. Design

A randomized cross-over controlled trial (RCT-cross over).

3. Setting

Two hospitals, Japan.

4. Participants

Six patients with gynecological cancer (four with ovarian cancer, one with endometrial cancer, and one with cervical cancer) receiving cisplatin-based anti-cancer therapy.

5. Intervention

Since allocation of patients to treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen. Cycles of anti-cancer therapy up to the fourth cycle in each patient were randomly assigned to either treatment or no treatment with TSUMURA Kamikihito (加味帰脾湯) Extract Granules (7.5 g/day) (Granisetron was administered to all patients for antiemetic purposes, and granulocyte colony-stimulating factor (G-CSF) was prophylactically administered in all cycles in all 6 patients except 1.

Arm 1: administration of TSUMURA Kamikihito (加味帰脾湯) Extract Granules 7.5 g/day during the treatment period (n=6, 11 cycles).

Arm 2: no administration of kamikihito (加味帰脾湯) (n=6, 12 cycles).

6. Main outcome measures

Peripheral blood platelet and white blood cell (WBC) counts, minimum value of hemoglobin, severity of adverse drug reactions (WHO grade), decrease in area under the platelet-time curve (area of the platelet-time curve below the lower limit of the normal range [130,000/μ]), dose of G-CSF.

7. Main results

The minimum platelet count was higher in treated cycles (arm 1) than in untreated cycles (arm 2) in 5 of 6 patients (P=0.0127). The area of the decrease in platelet count was smaller in arm 1 than in arm 2 (P=0.0126). The minimum value of WBC count was higher in arm 1 than in arm 2 (P=0.0025).

The dose of G-CSF was lower in arm 1 than in arm 2 (significance of difference not tested).

There was no significant difference in the minimum value of hemoglobin between arms.

8. Conclusions

Kamikihito is expected to prevent thrombocytopenia and leukopenia associated with anti-cancer drugs.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Although this report is attractive in that a Kampo medicine can suppress or reverse thrombocytopenia, leukopenia (granulocytopenia), and anemia associated with anti-cancer drugs, establishment of the criteria for patient entry requires careful consideration. The present study failed to consider platelet count at the baseline of each cycle. Baseline platelet count was higher in kamikihito-treated cycles in all 6 patients except 1, and quite different between arms. Naturally, decrements due to anti-cancer treatment are smaller when baseline platelet count (and probably WBC count as well) is higher. Even though cycles were randomly assigned to Kampo treatment or no treatment, the evidence in this report is not sufficiently convincing, given that the differences in background values between arms were not considered in the analysis of the results.

12. Abstractor and date

Hoshino E, 26 April 2009, 6 January 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Fujiwara M, Koumoto Y. Effect of juzentaihoto on myelosuppression due to chemotherapy for gynecologic malignant tumor*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 1998; 15: 86-9 (in Japanese).

1. Objectives

To evaluate the effect of combined juzentaihoto (十全大補湯) on myelosuppression during chemotherapy in patients with gynecologic cancers.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Department of Obstetrics and Gynecology, Kawasaki Medical School Hospital.

4. Participants

Ten patients who underwent chemotherapy following surgery for gynecological malignancies at the Department of Obstetrics and Gynecology, Kawasaki Medical School Hospital, Japan.

5. Intervention

Arm 1: Juzentaihoto (十全大補湯) 7.5 g/day administered for 21 days beginning the day before administration of the anticancer drug in the odd-day cycle and no administration in the even-day cycle (n=5 patients with odd numbers).

Arm 2: Juzentaihoto (十全大補湯) 7.5 g/day administered for 21 days beginning the day before administration of the anticancer drug in the even-day cycle and no administration in the odd-day cycle (n=5 patients with even numbers).

In both arms, chemotherapy consisted of intraabdominal administration of carboplatin (CBDCA) at 500 mg/m^2 and parenteral administration of cyclophosphamide (CPA) at 450 mg/m^2.

6. Main outcome measures

White blood cell (WBC) count, neutrophil count, red blood cell (RBC) count, hemoglobin value, platelet count, and use of granulocyte colony-stimulating factor (G-CSF).

7. Main results

The juzentaihoto and non-juzentaihoto groups completed 20 courses of treatment.

Decrements in WBC, neutrophil, and RBC counts were significantly smaller in arm 1 (P<0.01, P<0.05, and P<0.01, respectively), as was the number of G-CSF units used (P<0.05). Hemoglobin value was significantly increased in arm 1 (P<0.05). There was no significant between-arm difference in platelet count.

8. Conclusions

Juzentaihoto is highly effective in reducing subjective/objective adverse drug reactions during cancer chemotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes the preventive effect of juzentaihoto on myelosuppression during chemotherapy. It is meaningful that the use of G-CSF was almost halved by juzentaihoto treatment.

12. Abstractor and date

Nakata H, 1 January 2009, 6 January 2010, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Miyabe Y, Taniguchi C, Kawashima M, et al. Effect of Kampo medicines (sokeikakketsuto, shakuyakukanzoto) for taxol-caused peripheral nerve disorder – evaluation by current perception threshold measured by Neurometer®*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2006; 23: 65-8 (in Japanese).

1. Objectives

To evaluate the potential use of sokeikakketsuto (疎経活血湯) and shakuyakukanzoto (芍薬甘草湯) in preventing peripheral nerve disorder in patients receiving taxol.

2. Design

A randomized crossover controlled trial (RCT-crossover).

3. Setting

Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, University Hospital, Japan.

4. Participants

Seven patients who received monthly paclitaxel–carboplatin (TJ) as the initial anticancer therapy (18 cycles) for gynecological malignant tumors (ovarian cancer, uterine cervical cancer, and endometrial cancer) at the above facility between April 2002 and March 2005.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: monthly TJ + oral administration of Kampo medicines (sokeikakketsuto (疎経活血湯), shakuyakukanzoto (芍薬甘草湯)) (manufacturer unknown) before meals for 14 days before and after TJ therapy.

Arm 2: monthly TJ.

6. Main outcome measures

Current perception threshold (CPT) measured by Neurometer® (2000 Hz, 250 Hz, and 5 Hz) 7 days before and 7 days after the start of TJ therapy: CPT value.

7. Main results

The value (predose CPT – postdose CPT)/predose CPT × 100 (%) decreased after TJ therapy, indicating deteriorating perception without Kampo treatment but remained unchanged with Kampo treatment.

8. Conclusions

TJ therapy when combined with Kampo medicines (sokeikakketsuto, shakuyakukanzoto), but not TJ therapy alone, reduces the severity of peripheral nerve disorder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Administration of medicines caused no adverse drug reactions.

11. Abstractor's comments

This is a valuable study verifying the efficacy of sokeikakketsuto and shakuyakukanzoto for peripheral nerve disorder, an occasional adverse reaction to anticancer drug treatment that is evaluated by current perception threshold measurement. However, considering the small sample size (7 subjects), individual characteristics may greatly affect and bias the results; thus, increased number of cases may change the results. It is also important to ensure symptoms are consistent and relief of actual symptoms is documented by measured values, warranting continued research efforts. Furthermore, logically, the effect of a Kampo medicine is not constant but depends on the physical status of the host in each cycle of anticancer therapy. Therefore, identification of the "*sho*" (証, pattern) of each individual in each cycle is recommended to investigate the correlation between pathological analysis in Kampo medicine and the objective evaluation by current perception threshold used in this study. This may lead to proper usage of Kampo medicines and establishment of highly effective regimens in cancer treatment.

12. Abstractor and date

Ushiroyama T, 19 December 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Kaku H, Kumagai S, Onoue H, et al. Objective evaluation of the alleviating effects of goshajinkigan on peripheral neuropathy induced by paclitaxel/carboplatin therapy: A multicenter collaborative study. *Experimental and Therapeutic Medicine* 2012; 3: 60-5. Pubmed ID: 22969845

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by chemotherapy (paclitaxel and carboplatin) for uterine and ovarian cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Obstetrics and gynecology departments at four university hospitals (Iwate Medical University, Tottori University, Kitasato University, and Keio University), Japan.

4. Participants

Twenty-nine patients (20–70 years old) with peripheral neuropathy rated grade 1 or higher under the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and treated with paclitaxel/carboplatin after uterine or ovarian cancer had been histologically diagnosed.

5. Intervention

Arm 1: oral administration of vitamin B12 (1.5 g/day) and TSUMURA Goshajinkigan (牛車腎気丸) (7.5 g/day) (n=14).

Arm 2: oral administration of vitamin B12 (1.5 g/day) (n=15).

6. Main outcome measures

Visual analogue scale (VAS) evaluation of subjective numbness symptoms at 0, 3, and 6 weeks.

Rating of peripheral neuropathy (movement and sensation) under the NCI-CTCAE at 0, 3, and 6 weeks.

Evaluation of subjective peripheral neuropathy symptoms using the Functional Assessment of Cancer Treatment (FACT)-Taxane questionnaire at 0, 3, and 6 weeks.

Measurement of the current perception threshold (CPT) range in both index fingers at 0, 3, and 6 weeks.

7. Main results

There was no significant difference between groups at 0, 3, or 6 weeks in the VAS score for numbness and FACT-Taxane score for peripheral neuropathy (movement and sensation), or peripheral neuropathy symptoms. Peripheral neuropathy (sensation) was rated grade 3 under the NCI-CTCAE at 6 weeks in 2 patients of arm 2; however, no patient in arm 1 scored grade 3 or higher at 6 weeks. There was no significant difference between groups for the CPT range.

The frequency of abnormal CPT range was significantly lower in arm 1 than arm 2.

8. Conclusions

Goshajinkigan is effective for controlling the advance of peripheral neuropathy induced by paclitaxel/carboplatin.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This multicenter RCT tested whether goshajinkigan in combination with vitamin B12 can improve peripheral neuropathy induced by paclitaxel/carboplatin for gynecologic cancer patients. The study did not find effectiveness of goshajinkigan based on subjective numbness symptoms (VAS) score, NCI-CTCAE grade, or FACT-Taxane score. However, 6 weeks after administration commenced, CTCAE grade deteriorated to 3 in two participants in the vitamin B12-only group and no participant in the vitamin B12 plus goshajinkigan group (arm 1). Additionally, the frequency of abnormal CPT range was significantly lower in arm 1. On those grounds, the authors assert that goshajinkigan is useful for controlling subjective symptoms. Nevertheless, the authors did not observe any positive effect of goshajinkigan, thereby raising the issue of whether goshijinkigan is a suitable drug for controlling subjective symptoms, and whether the 6-week period of administration is appropriate. When conducting a trial such as this, researchers should first elucidate what kinds of Kampo medications are effective and for what periods by carrying out an exploratory study whereby a physician expert in Kampo medical treatment provides appropriate Kampo treatment based on Kampo patterns, and then create study protocols.

12. Abstractor and date

Hoshino E, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Hasegawa K, Mizutani Y, Kuramoto H, et al. The Effect of L-glutamine and shakuyaku-kanzo-to for paclitaxel-induced myalgia/arthralgia. *Gan to Kagaku Ryoho* (*Japanese Journal of Cancer and Chemotherapy*) 2002; 29: 569-74 (in Japanese with English abstract). Ichushi Web ID: 2002217069 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) and L-glutamine for paclitaxel-induced myalgia and arthralgia.

2. Design

Crossover randomized controlled trial (RCT-crossover).

3. Setting

Department of Obstetrics and Gynecology, Okayama University Medical School, Japan.

4. Participants

Fifteen patients with ovarian (n=13), cervical (n=1), or vulva (n=1) cancer who: 1) had received chemotherapy including paclitaxel (TXL) in December 1999 through July 2000; 2) had developed myalgia and arthralgia; and 3) were scheduled for 2 or more cycles of chemotherapy. The data from twelve of these patients were analyzed.

5. Intervention

Arm 1: TXL treatment combined with shakuyakukanzoto (芍薬甘草湯) 7.5 g/day (three divided doses) in the second cycle and with L-glutamine 2.0 g/day (three divided doses) in the third cycle, in 7 patients.

Arm 2: TXL treatment combined with L-glutamine 2.0 g/day (three divided doses) in the second cycle and with shakuyakukanzoto (芍薬甘草湯) 7.5 g/day (three divided doses) in the third cycle, in 8 patients.

The first cycle (TXL monotherapy), in which pain occurred, was considered to be a control.

Shakuyakukanzoto (芍薬甘草湯) and L-glutamine were orally administered from 1 week before the TXL treatment until the pain resolved.

A single dose of an NSAID (Voltaren: 25 mg) was given if the effects of test drugs were poor. The washout period was at least one week

6. Main outcome measures

The efficacy was evaluated based on: 1) sum of pain scores; 2) duration of myalgia and arthralgia; 3) duration of grade 2 or greater myalgia and arthralgia; 4) number of analgesics used; and 5) final subjective impressions.

7. Main results

Twelve patients were evaluated in the final analysis. Reductions of the duration of myalgia and arthralgia were significantly different between the control and the L-glutamine-treated patients. Reductions of the duration of grade 2 or greater myalgia and arthralgia in the shakuyakukanzoto- and the L-glutamine-treated patients differed significantly from that of the control patients. No significant differences occurred in any variable between the shakuyakukanzoto- and the L-glutamine-treated patients.

8. Conclusions

Shakuyakukanzoto and L-glutamine have no dramatic effects on paclitaxel-induced myalgia and arthralgia, except for the reduction of the duration of grade 2 or greater pain.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One L-glutamine-treated patient reported nausea and one shakuyakukanzoto-treated patient could not take the drug for an unspecified reason.

11. Abstractor's comments

Shakuyakukanzoto is effective for pains associated with smooth and skeletal muscle spasm. In contrast, arthralgia (a paclitaxel-induced adverse reaction) is not included as an indication for treatment with shakuyakukanzoto. However, excellent responses were reported in the present study. The efficacy of this drug for this indication might be confirmed in the future by increasing the number of patients, as well as by identifying candidate patients for this treatment from an analysis of responders and non-responders.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
18. Symptoms and Signs

References

Ohnishi S, Watari H, Sakuragi N, et al. Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: results of a randomized phase II study (JORTC KMP-02). *Journal of Gynecologic Oncology* 2017; 28: 1-10. doi: 10.3802/jgo.2017.28. e44 CENTRAL ID: CN-01403248, Pubmed ID: 28657216

1. Objectives

To evaluate the efficacy and safety of add-on rikkunshito（六君子湯）to antiemetics for nausea, vomiting, and anorexia in patients receiving cisplatin plus paclitaxel for uterine cervical or corpus cancer

2. Design

Randomized controlled trial (RCT)

3. Setting

Four institutions, Japan

4. Participants

Forty patients aged 20 years or older, with histologically diagnosed uterine cervical or corpus cancer, and with an ECOG Performance Status score of 0 to 2.

Patients were excluded if they had brain metastasis, seizure, unconsciousness, gastrointestinal obstruction, vomiting, or nausea of CTCAE (version 4.0) grade ≥3, or had received treatment within one month with steroids, androgens, progesterones, other herbal medicines, other medicines with the potential to increase appetite, or opioids.

Efficacy was analyzed in 19 patients in the rikkunshito group and 17 patients in the control group. Safety was analyzed in 20 patients in the rikkunshito group and 19 patients in the control group.

5. Intervention

Arm 1: oral administration of rikkunshito（六君子湯）(manufacturer unknown) 7.5 g (on days 0-13) plus antiemetics (n=20)

Arm 2: administration of antiemetics alone (n=20)

6. Main outcome measures

Nausea using a 100-mm visual analog scale (VAS) with 0–5 mm indicating “no nausea” and 5–25 mm indicating “no significant nausea”, the rate of complete control (CC) (i.e., no emesis, no rescue medication, and no significant nausea), and the rate of complete response (CR) (i.e., no emesis and no rescue medication) were assessed.

7. Main results

Two-tailed $P<0.20$ was considered significant. For the overall phase (0–120 hours), both the CC rate and the CR rate were significantly higher in the rikkunshito group ($P=0.175$ and $P=0.042$, respectively). When the overall phase was divided into acute (0–24 hours) and delayed (24–120 hours) phases, the CC and CR rates were similar between the two groups during the acute phase and significantly higher in the rikkunshito group during the delayed phase ($P=0.095$ for the CC rate, $P= 0.042$ for the CR rate). In terms of anorexia and nausea VAS scores, rikkunshito appeared to be effective from day 2 through day 6 (without significant difference), but no differences were shown between the groups from day 7 through day 13.

8. Conclusion

Rikkunshito provides an additive effect to antiemetic therapy for vomiting and anorexia.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

In the rikkunshito group, there was increased ALT in 2 patients (10.0%), increased AST in 1 patient (5.0%), and increased GGT in 1 patient (5.0%).

11. Abstractor’s comments

Severe gastrointestinal symptoms during chemotherapy may make chemotherapy completion difficult. In cancer therapy, whether chemotherapy is completed or not is important because it changes the prognosis. This study showed significant reductions of nausea and vomiting by add-on rikkunshito to antiemetics. Add-on use of rikkunshito is considered to be particularly effective in highly emetogenic anticancer drug therapy.

12. Abstractor and date

Nakata H, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Yoshimura A, Sawada K, Sasano T, et al. Effect of Japanese Kampo medicine therapy for menopausal symptoms after treatment of gynecological malignancy. *Obstetrics and Gynecology International* 2018: 1-6. Pubmed ID: 29805451

1. Objectives

To evaluate the effect of Kampo medicines kamikihito（加味帰脾湯）and kamishoyosan（加味逍遙散）on menopausal symptoms in gynecological cancer patients.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (Osaka University Hospital), Japan.

4. Participants

Patients who had menopausal symptoms after receiving treatment of gynecological malignancy between November 2012 and December 2015, and had a Kupperman Menopausal Index (KI) total score of 21 (Moderate) or more. Exclusion criteria were receiving Kampo preparations, herbal preparations, or hormone replacement therapy; a history of or being suspected of having aldosteronism; myopathy, or hypokalemia.

5. Intervention

Arm 1: KRACIE Kamikihito（加味帰脾湯）Extract Fine Granules 3.75 g b.i.d. (before or with a meal) for 8 weeks (n=18).

Arm 2: KRACIE Kamishoyosan（加味逍遙散）Extract Fine Granules 3.0 g b.i.d. (before or with a meal) for 8 weeks (n=15).

6. Main outcome measures

The treatment was given for 8 weeks. A KI questionnaire was used to assess subjective symptoms, and the KI total score and each domain score were examined. For the safety evaluation, any adverse events during the study period were evaluated.

7. Main results

Three patients in Arm 1 and 1 patient in Arm 2 were withdrawn from the study, and missing data were noted in 1 patient in Arm 1. Thus, the analysis of therapeutic efficacy was performed on 14 patients in Arm 1 and 14 patients in Arm 2. In both groups, the KI total scores before Kampo therapy (baseline) were significantly increased from the scores before anticancer therapy . After the start of Kampo therapy, the KI total scores decreased in both groups, and significantly improved from baseline at Weeks 4 and 8. Among the KI subscores, significant improvements were shown for 3 domains in Arm 1 and 6 domains in Arm 2.

8. Conclusions

Kampo therapy may contribute to the tailored medical management of patients with symptoms after receiving treatment for gynecologic malignancy, thus improving the patient's QOL.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two patients in Arm 1 had adverse events of unknown causality (i.e., diarrhea in 1 patient and joint pain in another patient).

11. Abstractor's comments

This clinical study is of interest in that it was designed to determine the effect of Kampo medicines on menopausal symptoms after treatment of cancer. Some menopausal symptoms after treatment of cancer are speculated to improve with the administration of Kampo medicines. This study compared two Kampo medicines of kamikihito and kamishoyosan, and showed that both were effective, with no significant difference between the two groups. As an RCT, however, adequate selection of the control group should be an issue. Further studies in more patients and the determination of similar effects of other Kampo medicines are awaited.

12. Abstractor and date

Kato Y, 1 September 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Mizuno M, Yoshikawa H, Taketani Y, et al. Clinical effects of ninjin'yoeito on performance status (PS) and recovery of physical strength in patients following gynecologic cancer treatment – comparison with no-treatment controls–*. *Sanka to Fujinka* (*Obstetrics and Gynecology*) 1993; 60: 1533–45 (in Japanese). Ichushi Web ID: 1994139265 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人参養栄湯) for relieving subjective symptoms and improving activities of daily living in patients following gynecologic cancer surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Tokyo Hospital, National Hospital Organization Medical Center, and 21 other facilities, Japan.

4. Participants

Inclusion criteria: gynecologic cancer (uterine cervical, uterine corpus, ovarian, etc.); more than 1 month since the completion of the initial treatment or treatment for recurrence; outpatient with at least one of the following subjective symptoms: anorexia, fatigue/malaise, decreased physical strength, cold limbs, night sweats, and lightheadedness; age, 15–75 years; Eastern Cooperative Oncology Group (ECOG) performance status (P.S.).≤2; and no recurrence of cancer.

5. Intervention

Arm 1: oral administration of Kanebo (currently Kracie) Ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d. for 12 weeks (n=46).
Arm 2: no administration for 12 weeks (n=44).

6. Main outcome measures

Improvement in subjective symptom scores was used to measure efficacy.

7. Main results

Ten patients were excluded. Global improvement rating was significantly higher in arm 1. Stratified analysis revealed no significant between-arm difference for patients only receiving surgery, and significantly higher efficacy in arm 1 for patients also receiving chemotherapy and radiotherapy.

8. Conclusions

Ninjin'yoeito is expected to be useful for relieving subjective symptoms such as fatigue/malaise and regaining ability to perform activities of daily living following gynecologic cancer surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study evaluated the efficacy of ninjin'yoeito for relieving subjective symptoms and improving activities of daily living after surgery to remove a gynecologic cancer. Considering that patients can be expected to value a therapy that relieves subjective symptoms such as fatigue/malaise and restores their ability to perform activities of daily living following gynecologic cancer surgery, a study report like this one is very meaningful. It would be interesting to investigate prognosis.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Hasegawa K, Fukunishi H, Kiyoshige K, et al. Clinical usefulness of Kampo medicines (ninjin-yoei-to, juzen-taiho-to) for side effects in gynecologic cancer chemotherapy – Effects on reducing side effects by CDDP in CAP therapy–. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 181–7 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of combination of ninjin'yoeito (人参養栄湯) and juzentaihoto (十全大補湯) for reducing adverse effects of cyclophosphamide, adriamycin, cisplatin (CAP) chemotherapy including myelosuppression, renal impairment, and gastrointestinal symptoms.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Hyogo Medical Center for Adults, Department of Obstetrics and Gynecology, Kobe National Hospital (currently National Hospital Organization Kobe Medical Center), Department of Obstetrics and Gynecology, Kobe City Medical Center West Hospital, and another 4 facilities, Japan.

4. Participants

Thirty-two patients with ovarian, uterine cervical, or uterine corpus cancer undergoing CAP therapy.

5. Intervention

Arm 1: oral administration of Kanebo (currently Kracie) Ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d and Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. for 5 weeks from 1 week before to 4 weeks after administration of anticancer drugs (n=19).

Arm 2: no administration (n=13).

6. Main outcome measures

Pre- and post-treatment myelosuppression and nephrotoxicity evaluated by hematology (blood counts, urea nitrogen, serum creatinine), and subjective symptoms (general malaise, anorexia, and vomiting) evaluated on a 4-point scale using a standard questionnaire.

7. Main results

Kampo medicine treatment did not significantly affect decreases in white blood cell (WBC), red blood cell (RBC), and platelet counts but tended to promote their reversal. Kampo medicine also reduced nephrotoxicity (i.e., normalized blood urea nitrogen [BUN] level and reduced creatinine fluctuation). Subjective gastrointestinal symptoms were not improved.

8. Conclusions

The combination of ninjin'yoeito and juzentaihoto is effective for reducing myelosuppression and nephrotoxicity associated with anticancer drug administration.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse drug reactions worth special mention.

11. Abstractor's comments

This study investigated the possible efficacy of combination of ninjin'yoeito and juzentaihoto for relieving myelosuppression and nephrotoxicity, which are important factors affecting completion of anticancer drug treatment. Further investigation is expected. While reduction in subjective symptoms by ninjin'yoeito has been reported, the present study did not demonstrate such an effect. This may be attributable to the increased amount of jio and toki resulting from the combination of ninjin'yoeito with juzentaihoto, given that one-third of patients failed to take the full dose of 7.5 g. It would be interesting to investigate this point in the future.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yamamoto T, Fujita H, Okada H, et al. Clinical evaluation of the effects of ninjin'yoeito on subjective and objective symptoms and bone-marrow function during chemotherapy or radiotherapy in female patients with genital cancer*. *Oncology & Chemotherapy* 1994; 10: 126–34.

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人参養栄湯) against subjective and objective symptoms and myelosuppression due to postoperative chemotherapy or radiotherapy in female patients with genital cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, and 8 related facilities, Japan.

4. Participants

Forty patients undergoing cancer chemotherapy or radiotherapy (excluding those with serious complications or Eastern Co-operative Oncology Group (ECOG) performance status (PS) 4 at entry, or those judged by the investigator to be ineligible).

5. Intervention

Arm 1: chemotherapy + Kanebo (currently Kracie) Ninjin’yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d (n=11).
Arm 2: chemotherapy + cepharanthine 2 tablets t.i.d. (n=12).
Arm 3: radiotherapy + Kanebo (currently Kracie) Ninjin’yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d (n=10).
Arm 4: radiotherapy + cepharanthine 2 tablets t.i.d. (n=7).
Duration of administration: at least 2 weeks (more than 4 weeks if possible)

6. Main outcome measures

Four performance status items evaluated on a 5-point scale, nausea/vomiting evaluated on a 4-point scale, hematology (blood counts, biochemistry), and urinalysis (protein, glucose, and urobilinogen).

7. Main results

Kampo medicine treatment significantly improved myelosuppressive symptoms but not subjective and objective symptoms associated with anticancer drug administration. It also improved anorexia and fatigue/malaise during radiotherapy.

8. Conclusions

Ninjin’yoeito is effective for reducing myelosuppression associated with anticancer drug administration and radiotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient had acute hepatitis with unknown causal relationship to ninjin’y oeito.

11. Abstractor’s comments

This study investigated the possible efficacy of ninjin’yoeito for relieving myelosuppression caused by anticancer drugs. Ninjin’yoeito improved anticancer drug-caused myelosuppression but not severe anorexia, consistent with other papers. A future report on its efficacy in patients treated with three or more cycles of chemotherapy is also awaited.

12. Abstractor and date

Nakata H, 1 January 2009 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Oda T. My prescription – clinical application of ninjin'yoeito during chemotherapy for gynecologic cancer: the preventive effect on bone marrow suppression*. *WE* 2004; 9: 5-6 (in Japanese). Ichushi Web ID: 2006050757

Oda T, Ohnuki T, Kihara K, et al. A clinical study of a traditional Chinese herbal medicine, ninjin-youei-to in bone marrow suppression due to chemotherapy in gynecologic cancer. *Yamagata Kenritsu Byoin Igaku Zasshi (The Yamagata Journal of Medicine)* 2004; 38; 6-9 (in Japanese). Ichushi Web ID: 2004222295

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人参養栄湯) for reducing myelosuppression due to chemotherapy for gynecologic cancer.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital, Japan.

4. Participants

Eight patients who underwent surgery for gynecologic cancer (ovarian [n=6], uterine [n=1], or fallopian tube [n=1] cancer) and received granulocyte colony-stimulating factor (G-CSF) for neutropenia during the first cycle of chemotherapy (CAP: cyclophosphamide, Farmorubicin [epirubicin], cisplatin).

5. Intervention

Arm 1: treatment with Kanebo Ninjin'yoeito (人参養栄湯) Extract Fine Granules (7.5 g/day in two divided doses) continuously from 1 to 2 weeks prior to the start of the second cycle of chemotherapy (n=4).

Arm 2: no treatment with ninjin'yoeito (n=4).

6. Main outcome measures

The following measures during the second and third cycles of chemotherapy: nadir leukocyte and neutrophil counts, the length of time for neutrophil count to fall below 1,000/μL, total dose of G-CSF, duration of neutrophil counts under 1,000/μL, and nadir hemoglobin level and platelet count.

7. Main results

There were no significant between-arm differences in nadir leukocyte, neutrophil, and platelet counts or in the length of time for the neutrophil count to fall below 1,000/μL. Duration of neutrophil count under 1,000/μL tended to be shorter in arm 1 than in arm 2 during the second cycle, and became significantly shorter during the third cycle. Total dose of G-CSF tended to be lower in arm 1 than in arm 2 during the second cycle, and became significantly lower during the third cycle. Nadir hemoglobin level during the second cycle, compared with that during the first cycle, was significantly lower in arm 1, but not in arm 2.

8. Conclusions

It is strongly suggested that Kanebo Ninjin'yoeito Extract Fine Granules may exert neutropenia-preventing effects by inducing pluripotent stem cells to multiply and differentiate and by increasing the activity of G-CSF.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Because of the small sample size (only four in each arm), it seems difficult to address the statistical significance of differences observed in this study. Furthermore, although G-CSF administration affects "total dose of G-CSF" and "duration of neutrophil counts under 1,000/μL," administration criteria for G-CSF are not described. Thus the data are not objective. The significant decrease in hemoglobin level in arm 1 may indicate that Kanebo Ninjin'yoeito Extract Fine Granules is effective against neutrophil suppression, but not against suppression of erythropoietic cells. It is necessary to include more patients and to investigate not only the efficacy, but also the adverse events induced by G-CSF.

12. Abstractor and date

Hoshino E, 15 March 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Aoe H, Sumida Y, Kawahara N, et al. Efficacy of an erythropoietin preparation and Kampo medicines in preoperative autologous blood donation in cancer patients*. *Jikoketsu Yuketsu* (*Journal of Japanese Society of Autologous Blood Transfusion*) 1999; 12: 100-4 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯) and ninjin'yoeito (人参養栄湯) combined with an erythropoietin (EPO) preparation in preoperative autologous blood donation in cancer patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single hospital (Department of Obstetrics and Gynecology, Japanese Red Cross Society Himeji Hospital), Japan.

4. Participants

Ninety patients with gynecologic malignant tumors who visited the above institution between January 1992 and the end of November 1997 and preoperatively donated 800 mL or more of autologous blood.

5. Intervention

Intravenous administration of an iron preparation to patients with hemoglobin concentration of ≥14 g/dL. Randomization of patients with hemoglobin concentration of <14 g/dL to receive intravenous iron preparation + Kampo formulation + EPO or intravenous iron preparation + EPO.

Arm 1: intravenous administration of an iron preparation (240 mg weekly) from the day of the first donation through the day before the operation.

Arm 2: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly, from the day of the first donation through the day before the operation.

Arm 3: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly + oral administration of TSUMURA Juzentaihoto (十全大補湯) Extract Granules or Ninjin'yoeito (人参養栄湯) Extract Granules 2.5 g t.i.d (before meals), from the day of the first donation through the day before the operation.

6. Main outcome measures

Hematological profile: RBC count, hemoglobin, hematocrit, reticulocyte count, etc., measured before donation (before administration) and preoperatively (immediately after completion of administration).

Serum biochemical profile: total protein, albumin, and iron concentrations, determined before donation (before administration) and preoperatively (immediately after completion of administration).

Hemoglobin increment: pre-donation hemoglobin concentration × volume of donated blood/volume of circulating blood – (pre-donation hemoglobin concentration – preoperative hemoglobin volume).

7. Main results

The increase in reticulocyte count from the time of donation to the time of operation was larger in the Kampo group (n=36) and EPO group than in the iron group (n=15). The increase in hemoglobin level was larger in the EPO group (1.73±1.30 g/dL) than the iron group (0.92±0.70 g/dL), and significantly (P<0.05) larger in the Kampo group (2.33±1.11 g/dL) than the EPO group.

8. Conclusions

Combining a Kampo formulation with an iron preparation plus EPO enhances the clinical effectiveness of preoperatively donated autologous blood.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The finding that adding juzentaihoto or ninjin'yoeito to the preoperative donation management protocol enhances the increase in blood hemoglobin concentration suggests that the hematological profile of donated autologous blood is better after use of the combination than after use of only the iron preparation plus EPO. Thus, this finding is clinically significant. With the accumulation of more cases, a safety study is expected including an examination of the possibility that complementary medicines promote cancer cell growth.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Sato Y, Yamamoto S, Tagami K, et al. Efficacy of Kampo Medicine on Side Effects (muscular pain, arthralgia and paralysis) in TC therapy – Cross-Over study of goshajinkigan and keishikajutsubuto. *Recent Progress of Kampo Medicine in Obstetrics and Gynecology* 2015; 32: 68-71 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) and keishikajutsubuto (桂枝加朮附湯) for chemotherapy-related muscular pain, arthralgia, and paralysis in patients with ovarian cancer

2. Design

Randomized controlled trial (cross over) (RCT-cross over)

3. Setting

Study sites not stated (Authors' institution: Gifu Prefectural General Medical Center)

4. Participants

Twelve patients on a monthly TC therapy (paclitaxel and carboplatin) postoperatively for ovarian cancer or uterine body cancer

5. Intervention

Arm 1: Administration of goshajinkigan in the chemotherapy cycle after the onset of muscular pain/arthralgia, followed by administration of keishikajutsubuto in the next cycle (GK group)

Arm 2: Administration of keishikajutsubuto in the chemotherapy cycle after the onset of muscular pain/arthralgia, followed by administration of goshajinkigan in the next cycle (KG group)

6. Main outcome measures

Intensity of paralysis, muscular pain (VAS), and arthralgia (VAS) associated with the TC therapy

7. Main results

Paralysis was lessened in slightly more patients in the GK group than in the KG group.

There were greater muscular pain and arthralgia reductions on the visual analog scale (VAS) in the GK group than in the KG group.

8. Conclusions

Keishikajutsubuto is more effective than goshajinkigan for muscular pain and arthralgia as side effects of the TC therapy.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

None

11. Abstractor's comments

This article reports that keishikajutsubuto is more effective for muscular pain and arthralgia after TC therapy than goshajinkigan commonly used currently. This study with a limited sample size provided insufficient results to establish consensus. Further studies, including evaluation of prophylactic use, with larger samples sizes are warranted. Evaluation of long-term use would also be helpful. It is expected that consideration will be given to the clinical use of keishikajutsubuto for muscular pain and arthralgia after the TC therapy.

12. Abstractor and date

Kato Y, 18 May 2020

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Koga N, Moriya F, Waki K, et al. Immunological efficacy of herbal medicines in prostate cancer patients treated by personalized peptide vaccine. *Cancer Science* 2017; 108: 2326-32. Pubmed ID: 28898532

1. Objectives

To evaluate the immune-enhancing efficacy and safety of Kampo medicines using hochuekkito （補中益気湯） and keishibukuryogan（桂枝茯苓丸)in combination with personalized cancer peptide vaccination (PPV) in patients with castration-resistant prostate cancer (CRPC)

2. Design

Randomized controlled trial (RCT)

3. Setting

One university hospital, Japan

4. Participants

Seventy patients with CRPC aged 20 years or older with a Performance Status score of 0 or 1 (ECOG).
Inclusion criteria: life expectancy of 12 weeks or more, HLA haplotype of A2, A24, A26, A3, A11, A31, or A33, and normal hepatorenal functions.
Exclusion criteria: acute infection, history of severe allergic reactions, cardiac or pulmonary insufficiency

5. Intervention

Arm 1: PPV (weekly 8 times) plus TSUMURA Hochuekkito（補中益気湯）Extract Granules 7.5 g/day and TSUMURA Keishibukuryogan（桂枝茯苓丸）Extract Granules 7.5 g/day (2.5 g t.i.d. administered orally before meals for 50 days) (n=31)
Arm 2: PPV alone (weekly 8 times) (n=35)

6. Main outcome measures

Primary endpoint: immune response to PPV.
Secondary endpoints: overall survival (OS), progression-free survival (PFS), and safety.

7. Main results

Four patients withdrew consent prior to treatment in Arm 1. Treatment was discontinued because of disease progression or death in 3 patients in Arm 1 and 4 patients in Arm 2. At the end of follow-up, 19 patients in Arm 1 (63%; median duration of follow-up 14.9 months) and 26 patients in Arm 2 (74%; 13.6 months) had disease progression or died. The OS and PFS did not differ significantly between the arms. The baseline and Week 8 cancer peptide-specific IgG, CTL, and regulatory T cells (Treg) did not significantly differ between the arms. Comparing before to after the treatment, the frequency of monocytic myeloid-derived suppressor cells (Mo-MDSC) (before-after: 1.91%–1.92%) and the IL-6 level (19.2 pg/mL–16.1 pg/mL) were stable in Arm 1 but significantly increased in Arm 2 (0.91%–1.49% for Mo-MDSC [*P*=0.012] and 9.2 pg/mL–19.4 pg/mL for IL-6[*P*=0.043]).

8. Conclusion

In CRPC patients, the use of herbal medicines of hochuekkito and keishibukuryogan during PPV treatment had no impact on clinical outcome but has the potential to modify the immune response to PPV.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

No treatment-related deaths occurred in either arm. Adverse events such as injection site reactions did not differ between the two treatment arms. Appetite loss was less frequent in the PPV + herbal medicines arm than in the PPV alone arm.

11. Abstractor's comments

While cancer immunotherapies are entering a new phase, this pioneering study applied a novel immunotherapy with personalized cancer peptide vaccination (PPV) to patients with CRPC, and analyzed whether herbal medicines could modify the immune response to PPV. Since the RCT design was employed, the study yielded objective results, and was meaningful both basically and clinically. In Arm 1, the frequency of Mo-MDSC (%) and the IL-6 level were stable, suggesting the possibility that these herbal medications may prevent a decrease in the immune response to PPV, although clinical endpoints unfortunately failed to show significant differences. The results of this study are clinically interesting, considering that the authors previously reported significantly lower IL-6 levels in long-term survivors of prostate cancer. As the authors state that more research is needed, new results are awaited in the future.

12. Abstractor and date

Kogure T, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Oh-oka H. The clinical usefulness of gargling with hangeshashinto for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer. *Kampo Medicine* 2018;69: 1-6 (in Japanese with English abstract). Ichushi Web ID: 2018142526 J-STAGE

1. Objectives

To evaluate the clinical usefulness of gargling with hangeshashinto（半夏瀉心湯）for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (department of urology) (the author belongs to National Hospital Organization, Kobe Medical Center), Japan.

4. Participants

Twenty-two patients (11 men and 11 women) with metastatic renal cancer whose global response to sunitinib was assessed as "stable disease (SD) or better" as of January 2016, and who had sunitinib-induced oral mucositis. These participants had onset of oral mucositis despite oral hygiene instructions (e.g., tooth brushing, gargling, caries treatment) given to all patients before the start of oral sunitinib therapy.

5. Intervention

Arm 1: Gargling with TSUMURA Hangeshashinto（半夏瀉心湯）Extract Granules 2.5 g three times daily, for 30 seconds after each meal, followed by refraining from eating and drinking for 30 minutes (n=12).
Arm 2: Non-gargling group (n=10).

6. Main outcome measures

Changes from baseline in the Karnofsky Performance Status (KPS), oral mucositis grade, body weight, albumin level, hemoglobin level, global self-assessment (GSA) of eating status, etc. in the treatment cycle with highest severity of oral mucositis were analyzed.

7. Main results

Patient baseline characteristics did not statistically differ between the two groups. In Arm 1, the KPS (P=0.046), oral mucositis grade (P=0.002), and GSA (P=0.002) significantly improved after the start of treatment, but body weight, albumin level, and hemoglobin level showed no significant changes. In Arm 2, the oral mucositis grade was not significantly improved, while GSA (P=0.005) significantly improved, but the KPS (P=0.007), body weight (P=0.005), albumin level (P=0.005), and hemoglobin level (P=0.005) significantly decreased.

8. Conclusions

Gargling with hangeshashinto is very effective for treating oral mucositis associated with sunitinib for metastatic renal cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No clinically relevant adverse effects were observed.

11. Abstractor's comments

This clinical study is of interest in that it was designed to determine the effect of gargling with hangeshashinto on oral mucositis associated with sunitinib for metastatic renal cancer. This article failed to specify whether or not the gargled hangeshashinto was ingested after gargling. This study makes us wonder whether similar results can be obtained with irinotecan or the fluorinated pyrimidine class of anticancer drugs, as with the multi-kinase inhibitor sunitinib. Further study results from more patients are awaited.

12. Abstractor and date

Kato Y, 1 September 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Fukui I, Gotoh S, Kihara K, et al. Adjuvant chemotherapy for invasive bladder cancer. Multicenter study. *Nippon Hinyokika Gakkai Zasshi* (*Japanese Journal of Urology*) 1992; 83: 1633-9 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of postoperative adjuvant chemotherapy for bladder cancer on survival (the efficacy of the combination with juzentaihoto (十全大補湯) was assessed in patients stratified into 3 groups).

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (Tokyo Medical and Dental University) and 9 other institutions, Japan.

4. Participants

Forty-eight patients undergoing total cystectomy for bladder cancer.

5. Intervention

Arm 1: chemotherapy + TSUMURA Juzentaihoto Extract Granules (十全大補湯) 7.5 g/day (n=16).
Arm 2: chemotherapy + Picibanil (OK432) (n=15).
Arm 3: chemotherapy only (n=17).
Patients received chemotherapy with one of three cis-platinum-based combinations (5-fluorouracil + adriamycin + cis-platinum [FAP], cyclophosphamide + vincristine + methotrexate [COM] alternating with FAP, or ifosfamide + 5-fluorouracil + cis-platinum [IFP]) for at least 3 cycles, and 6 to 8 cycles if possible.

6. Main outcome measures

Survival.

7. Main results

There was no significant difference between groups.

8. Conclusions

The combination with juzentaihoto for patients with bladder cancer had no effect on their survival.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Since the main objective of this multicenter study was to examine the effect of adjuvant chemotherapy for invasive bladder cancer, main analysis was not conducted on the combination with or without juzentaihoto, and the sample size was too small (17 patients) to draw firm conclusions on the efficacy of juzentaihoto. Investigation with a larger sample size is expected.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Ohkawa T, Ebisuno S, Watanabe T, et al. Clinical evaluations of saireito, a herbal drug, for the urological side-effects of cancer chemotherapy. *Biotherapy* 1990;4:1445–60 (in Japanese with English abstract). Ichushi Web ID: 1991149339

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) for relieving the adverse urological effects of anticancer drugs.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The departments of urology of 12 university hospitals including those of Wakayama Medical University, Nara Medical University, and Osaka University School of Medicine; and the departments of urology of 16 non-university affiliated hospitals, Japan.

4. Participants

Two-hundred and seventeen patients with urological cancer treated or to be treated with anticancer drugs.

5. Intervention

Arm 1: anticancer drug maintenance therapy + TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d for at least 12 weeks (n=42).
Arm 2: anticancer drug maintenance therapy without administration of Kampo medicine (n=44).
Arm 3: intermittent anticancer therapy + TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d for at least 2 courses (n=38).
Arm 4: intermittent anticancer therapy without administration of Kampo medicine (n=33).

6. Main outcome measures

Subjective symptom score (with subscales including general condition, anorexia, general malaise, nausea, vomiting, diarrhea, stomach discomfort, and stomatitis), hematological parameters, and blood biochemistry.

7. Main results

Of 217 patients, 60 were excluded from the analyses. There were no significant differences in subjective symptoms between those receiving saireito (arm 1 and arm 3) and those not receiving saireito (arm 2 and arm 4). The decrease in serum creatinine level after 4 weeks was greater in arm 1 than in arm 2, and was significantly greater after 3 courses in arm 3 than in arm 4.

8. Conclusions

Saireito is not effective for relieving the adverse effects of anticancer drugs, except for decreasing serum creatinine level.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions occurred in 7 patients (6%): 5 in arm 1 and 2 in arm 3. Treatment was discontinued in 4 of the 5 patients in arm 1 and 1 of the 2 patients in arm 2. Adverse drug reactions included vomiting, diarrhea, anorexia, and stomach pain.

11. Abstractor's comments

Although reduction in the adverse effects of anticancer drugs by Kampo formulations has frequently been observed in clinical settings, few full-fledged controlled clinical trials have been conducted. The present study is a valuable multicenter RCT investigating whether saireito relieves the adverse urological effects of anticancer drugs. Although allocation by the envelope method is likely to lead to incomplete randomization, the study found that saireito did not relieve the adverse effects of anticancer drugs. However, saireito did suppress elevation in serum creatinine level suggesting it improves renal function, raising expectations for future studies.

12. Abstractor and date

Okabe T, 15 August 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Kosaka A, Hojyo M, Osaku M, et al. The value of TSUMURA Juzentaihoto (TJ-48) in reducing adverse effects of anticancer drugs from the perspective of QOL improvement*. *Progress in Medicine* 1993; 13: 1072-9 (in Japanese).

Kosaka A, Kamiya T, Sumiyama M, et al. Usefulness of TSUMURA Juzentaihoto (TJ-48) for reducing adverse effects of anticancer drugs and improving QOL*. *Progress in Medicine* 1994; 14: 2259–64 (in Japanese).

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯) for reducing adverse effects and improving quality of life (QOL) in postoperative patients undergoing chemotherapy (tegafur-uracil [UFT] 4 capsules/day) for gastric, colorectal, or breast cancer (curative resection/non-curative resection).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Twelve hospitals, Japan.

4. Participants

Two-hundred and eighty-four postoperative patients undergoing chemotherapy for at least 3 months for gastric, colorectal, or breast cancer.

5. Intervention

Arm 1: UFT 4 capsules/day + TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day (n=124).
Arm 2: UFT 4 capsules/day alone (no administration of juzentaihoto (十全大補湯)) (n=127).
Arm 3: surgical excision alone (n=33)

6. Main outcome measures

Presence or absence of adverse drug reactions to the anticancer drug. QOL, evaluated using an interview sheet preoperatively, and 2 weeks, 1, 3, and 6 months postoperatively.

7. Main results

Adverse drug reactions to UFT: arm 1 < arm 2 for colorectal cancer; arm 1 = arm 2 for gastric cancer; arm 1 > arm 2 for breast cancer (data not analyzed statistically, no definite differences).

QOL: significantly improved in breast cancer patients only for disease symptoms 2 weeks postoperatively and only for adverse drug symptoms and social life 6 weeks postoperatively and not significantly improved in patients with any other cancer for any symptoms, mood, and social life at any time point.

8. Conclusions

Juzentaihoto reduces the number of adverse drug reactions and improves QOL in postoperative patients on chemotherapy (UFT 4 capsules/day) for gastric, colorectal, or breast cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events were vomiting and difficulty taking medications in 1 and 3 patients with colorectal cancer, respectively, in Arm 1.

11. Abstractor's comments

The authors wrongly conclude that combination of juzentaihoto with the anticancer drug (UFT) reduces adverse drug reactions and improves QOL, since there was almost no statistically significant difference. The conclusion should be guided by the correct interpretation of the results. Since the study failed to demonstrate the hypothesized usefulness of juzentaihoto, the authors should have discussed in the paper why postoperative patients with cancer receiving UFT did not respond to juzentaihoto. The possible reasons include: patients with cancer on postoperative chemotherapy may not be indicated for a *hozai* (補剤, formulations with tonic effects); may have a *sho* (証, pattern) indicated for a *hozai* other than juzentaihoto; or may respond to different *hozai* depending on cancer type. Even before that, this study should have begun with confirmation that the participants suffered from adverse drug reactions to UFT, had reduced QOL, did not respond to western medicine, and required treatment with Kampo medicine.

There is another report by the same first author of a study limited to one center (Kosaka et al [1993]). This study was then expanded to a multicenter trial with a larger sample size and produced similar results.

12. Abstractor and date

Hoshino E, 28 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Tanaka Y, Hashimoto S. Effects of TSUMURA Juzentaihoto on various complaints occurring as adverse reactions during radiotherapy*. *JAMA* (Japanese version) 1988; (6) suppl: 70-1 (in Japanese).

Hashimoto S, Tanaka Y. Adverse reactions to cancer radiotherapy*. *Sanfujinka no Sekai* (*World of Obstetrics and Gynecology*) 1990; 42 suppl: 176-84 (in Japanese).

1. Objectives

Efficacy and safety of juzentaihoto (十全大補湯) for reducing adverse reactions during cancer radiotherapy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Multi-center study involving 9 institutions: 6 university hospitals and 3 community hospitals, Japan.

4. Participants

Eighty-three patients who underwent radiotherapy of the chest or abdomen (the irradiated area was about 100 cm^2 and exposure dose was 50–60 Gy).

5. Intervention

Arm 1: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. (n=43).
Arm 2: no treatment (n=40).

6. Main outcome measures

Subjective symptoms: anorexia, general malaise, nausea and vomiting, and diarrhea.
White blood cell, red blood cell, and platelet counts, and blood biochemical values.

7. Main results

Before radiotherapy, there was no significant between-group difference. For anorexia, a trend towards improvement in the treatment group was observed after 4–6 weeks and the difference was significant after 5 weeks ($P<0.05$). There were also between-group differences in general malaise after 4 weeks, in nausea and vomiting after 5 weeks, and in diarrhea after 3–5 weeks. There were no differences in white blood cell, red blood cell, and platelet counts, and in blood biochemical values.

8. Conclusions

Juzentaihoto for adverse reactions during cancer radiotherapy reduced the symptoms of anorexia, general malaise, nausea and vomiting, and diarrhea.

9. From Kampo medicine perspective

This study did not take into account *sho* (証, pattern), according to the related article indicated below.

10. Safety assessment in the article

Juzentaihoto has few adverse effects, according to the related article.

11. Abstractor's comments

The present study was a multicenter RCT based on a previous single-center open trial and controlled trial examining the effect of juzentaihoto for GI side-effects during cancer radiotherapy. The study is valuable in that it was carefully planned for many years.

Although almost the same number of patients assigned to each group, the study included more women (male:female ratio = 1:3). Therefore, further investigation is required to determine whether the observed improvements in symptoms are related to the treatment of only female-related cancer or all cancers. Investigation taking into consideration *sho* to amplify the effect is also expected in the future.

The paper by Tanaka et al (1988) described the allocation method using sealed envelopes, which is not stated in the main article by Hashimoto et al (1990), and also described that mainly patients with breast or uterine cancer were included.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yamada T. Clinical study of juzen-taiho-to administration for postoperative esophageal carcinoma, gastric carcinoma, and colorectal carcinoma – Influence of surgical intervention and postoperative chemotherapy on cell mediated immunity–. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1992; 9: 157-64 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of juzentaihoto (十全大補湯) on the cell-mediated immunity of postoperative patients with esophageal, gastric, or colorectal cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

A university hospital (Kyorin University Hospital), Japan.

4. Participants

One hundred seventy-four postoperative patients with esophageal, gastric, or colorectal cancer.

5. Intervention

Arm 1: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day beginning 2 weeks after surgery (n=75).
Arm 2: no treatment (n=99).
Patients in arms 1 and 2 who received anticancer agents within 1 month after surgery were considered to be separate groups, i.e., combination therapy groups (cf., arm 3 and arm 4), and their data were analyzed separately.
Arm 3: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day + anticancer agents beginning 2 weeks after surgery (n=49).
Arm 4: no treatment with juzentaihoto (十全大補湯) + anticancer agents (n=55).
The duration of treatment was 6 months.

6. Main outcome measures

Hemoglobin, white blood cell count, lymphocyte count, and levels of serum albumin, CD3, CD4, CD8, phytohemagglutinin (PHA) lymphocyte proliferation, and NK-cell activity.

7. Main results

In patients undergoing total gastrectomy in arm 3, hemoglobin and red blood cell count increased significantly and the white blood cell count decreased significantly. Immune function as indicated by PHA-induced lymphocyte proliferation and NK-cell activity was enhanced in patients with esophageal cancer or total gastrectomy in arm 3.

8. Conclusions

Juzentaihoto postoperatively administered for treatment of esophageal, gastric, or colorectal cancer may act as a biological response modifier (BRM).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study evaluates the change in cell-mediated immunity in response to postoperative administration of juzentaihoto in patients with esophageal, gastric, or colorectal cancer. The data suggest that juzentaihoto may act as a BRM. This study included a variety of cancers, operative procedures, and medical conditions. Investigation (including survival analysis) with a larger sample size in limited populations is expected.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Suzuki S, Abe R, Nomizu T, et al. Effect of Juzentaihoto (TJ-48) on leukopenia in patients receiving cancer chemotherapy*. *Progress in Medicine* 1995; 15: 1968-71 (in Japanese). Ichushi Web ID: 1996098925

1. Objectives

To evaluate the effects of juzentaihoto (十全大補湯) on leukopenia in patients receiving cancer chemotherapy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Four university and community hospitals, Japan.

4. Participants

Ninety patients who received chemotherapy for cancer.

5. Intervention

Arm 1: treatment with TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day (n=47 patients, including 17 with gastric, 20 with colorectal, and 10 with breast cancer).
Arm 2: no treatment (n=43 patients, including 16 with gastric, 19 with colorectal, and 8 with breast cancer).
Duration of treatment: 12 months.

6. Main outcome measures

Leukocyte count was measured before and after 1, 2, 3, and 4 weeks of treatment, then monthly for 12 months. The frequency and time course of leukopenia (defined as a leukocyte count less than 4,000 cells/m^3) were also evaluated during the follow-up.

7. Main results

Leukocyte counts were not significantly different between the two arms. Significantly fewer patients developed leukopenia （<4,000mm^3） in arm 1 (30 patients) than in arm 2 (38 patients). The onset of leukopenia was significantly delayed and the time from onset to nadir was significantly increased in arm 1. There was no between-arm difference in the time from nadir to recovery. Juzentaihoto had a beneficial effect on leukopenia in gastric or colorectal cancer patients, but not in breast cancer patients.

8. Conclusions

Juzentaihoto delays the onset of leukopenia and also increases the time from onset to nadir in patients receiving chemotherapy for gastric or colorectal cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper demonstrates the usefulness of prophylactic administration of juzentaihoto for leukopenia, which is one of the serious adverse reactions to cancer chemotherapy in patients with gastric or colorectal cancer. The authors explored the factors influencing the effects in detail and demonstrated that juzentaihoto delayed the onset of leukopenia, increased the time from onset to nadir, but had no influence on the time to recovery, thereby reducing the number of patients who developed leukopenia. Recently, even more severe cases of leukopenia have become treatable with granulocyte colony-stimulating factor (G-CSF). Nevertheless, oral administration of juzentaihoto as a prophylaxis is valuable. Although the evaluation based on cancer type failed to find an effect in breast cancer patients, it was a secondary objective of this study and therefore reexamination in those patients is needed. Also, studies taking into account the Kampo concept of *sho* (証, pattern) are anticipated.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Ohara T, Onda M, Futagawa S, et al. Clinical evaluation of the combined effect of bu-zhong-yi-qi-tang (Japanese name, hochu-ekki-to) or ren-shen-yang-rong-tang (Japanese name, ninjin-youei-to) and the anticancer drug tegafur. *Yakuri to Chiryo* (*Japanese Phamacology & Therapeutics*) 1993; 21: 4423–34 (in Japanese). CENTRAL ID: CN-00546092, Ichushi Web ID: 1994154383 MOL, MOL-Lib

1. Objectives

To evaluate the clinical effects of hochuekkito (補中益気湯) and ninjin'yoeito (人参養栄湯) in patients undergoing chemotherapy (tegafur).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fourteen university hospitals (3rd Department of Surgery, University of Tokyo, 1st Department of Surgery, Nippon Medical School, 2nd Department of Surgery, Juntendo University, etc.) and 11 other hospitals, Japan.

4. Participants

One-hundred and seventy-eight patients with cancer receiving an anticancer drug (tegafur 400 mg/day or 600 mg/day). The cancer types were gastric cancer (n=91), colorectal cancer (n=63), breast cancer (n=18), and other cancers (n=6). The efficacy analysis population consisted of 162 patients who could receive the above treatment for at least 1 month.

5. Intervention

Arm 1: Kanebo Hochuekkito (補中益気湯) Extract Fine Granules 2.5 g t.i.d. for 6 months (n=57).
Arm 2: Kanebo Ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d. for 6 months (n=56).
Arm 3: Tegafur alone for 6 months (n=49).

6. Main outcome measures

Subjective symptoms (appetite, nausea/vomiting, etc.), objective symptoms (performance status [PS], body weight, blood pressure, etc.), hematology (blood counts, carcinoembryonic antigen, and immunosuppressive acidic protein), and biochemistry at baseline and after 2, 4, and 6 months of treatment.

7. Main results

Subjective symptom improvement (comparison between pre- and post-dose): Appetite was significantly improved in arm 1, while nausea/vomiting, bowel movement abnormality, motivation, and fatigue/malaise were significantly improved in arm 2. In arm 3, no symptoms were improved. Overall, improvement was noted in 21/57 patients (36.8%) in arm 1, 19/56 patients (33.9%) in arm 2, and 7/49 patients (14.3%) in arm 3, with significant differences in the percentage of patients showing improvement between arm 1 and arm 3 and between arm 2 and arm 3.
Objective symptom improvement: Overall, improvement was noted in 21/57 patients (36.8%) in arm 1, 22/56 patients (39.3%) in arm 2 and 10/49 patients (20.4%) in arm 3, with significant differences in the percentage of patients showing improvement between arm 1 and arm 3 and between arm 2 and arm 3.
Hematology: There were no significant differences between any 2 of the 3 arms.
Cancer type: Only in patients with gastric cancer, the percentage showing improvement in both subjective and objective symptoms was significantly greater in arm 1 than arm 3 and greater in arm 2 than arm 3. For colorectal cancer, there were no significant differences between any 2 of the 3 arms.

8. Conclusions

Combination of either hochuekkito or ninjin'yoeito is useful in patients on chemotherapy with tegafur.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no significant difference in the incidence of adverse events between arm 1 (2/57 patients) and arm 2 (7/56 patients).

11. Abstractor's comments

Kampo medicine combined with anticancer drug treatment is intended to maintain quality of life (QOL), suppress adverse events during treatment, and potentiate the action of the anticancer drug. In this study, Kampo medicine treatment and anticancer drug treatment were both started at the same time. In this case, the endpoint should be either 1) time-course of QOL score including PS during the treatment period rather than significance of the difference in the percentage of patients showing improvement or 2) differences in QOL score and adverse events between groups treated with the anticancer drug alone and treated with the anticancer drug/Kampo drug combination. The results of this study are based on a comprehensive evaluation of various symptoms. However, the patient's physician may partially bias the findings because of lack of blinding. Regarding the safety evaluation, adverse events can be caused by either the anticancer drug itself or the Kampo medicine (when combined with the anticancer drug). Therefore, some thought is required to distinguish between the causes for these adverse events.

12. Abstractor and date

Hoshino E, 23 April 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Saito S, Iwagaki H, Kobayashi N, et al. Effects of a Japanese herbal medicine (TJ-41) on surgical stress of patients with gastric and colorectal cancer*. *Nihon Rinsho Geka Gakkai Zasshi* (*Journal of Japan Surgical Association*) 2006; 67: 568-74 (in Japanese). Ichushi Web ID: 2006114494, J-STAGE

1. Objectives

To evaluate whether preoperative administration of hochuekkito (補中益気湯) relieves surgical stress in patients with gastric or colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Gastroenterological Surgery, Transplant and Surgical Oncology, Okayama University, and six other institutions, Japan.

4. Participants

Forty-eight patients who underwent surgery for gastric (n=10) or colorectal (n=38) cancer.

5. Intervention

Arm 1: treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5 g, t.i.d. for 1 week prior to surgery (n=22).

Arm 2: no preoperative treatment (n=26).

6. Main outcome measures

The levels of cortisol, soluble tumor necrosis factor receptor (sTNF-R), and soluble interleukin-2 receptor (sIL-2R) measured right before surgery and on postoperative day 1; total and differential white blood cell counts measured preoperatively and postoperatively at days 1 and 7; C-reactive protein level measured preoperatively and postoperatively at days 1, 3, and 7; postoperative course of body temperature and pulse rate; length of postoperative stay; the number of patients who received therapeutic antibiotics after surgery.

7. Main results

There were no significant between-arm differences in total and differential white blood cell counts, CRP level, and rates of increase in sTNF-R and sIL-2R from before to after surgery. The rate of increase in cortisol from before to after surgery was significantly lower in arm 1. The body temperature from postoperative day 6 was significantly lower in arm 1. The pulse rate on postoperative days 6 and 7 was significantly lower in arm 1. The number of patients who received therapeutic antibiotics after surgery was significantly smaller in arm 1 (3/22) than in arm 2 (11/22).

8. Conclusions

Preoperative administration of TSUMURA Hochuekkito Extract Granules reduces the response to surgical stress and may be helpful for accelerating postoperative recovery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events: no adverse drug reactions occurred in arm 1.

11. Abstractor's comments

The authors postulate that preoperative administration of hochuekkito improves quality of life, helps control body temperature and heart rate, and reduces therapeutic administration of antibiotics in patients during postoperative recovery, and thus may lead to reduction of medical costs. They also suggest that the mechanism underlying these effects may involve Kampo medicine-induced attenuation of the increase in cortisol blood level. The principle of this treatment is similar to that of "immunonutrition," which involves omega-3 fatty acids, arginine, and nucleic acids. These approaches attempt to reduce postoperative surgical complications by means of preoperative nutritional supplementation. Cancer patients before surgery are in a state of *qikyo* (気虚, qi deficiency) with various anxieties, and at the same time in a relatively mild state of *kekkyo* (血虚, blood deficiency) if they are operable. Hochuekkito and other comparable *hozai* (補剤; formulations with tonic effects) seem to be suitable for these patients. The investigation of hochuekkito combined with the immunonutritional approach and further elucidation of the mechanism are anticipated in the future.

12. Abstractor and date

Hoshino E, 15 March 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: A pilot randomized clinical trial. *Integrative Cancer Therapies* 2010; 9: 331–8. CENTRAL ID: CN-00770648, Pubmed ID: 21059621

1. Objectives

To evaluate the effectiveness of hochuekkito (補中益気湯) for cancer-related fatigue.

2. Design

Randomized controlled trial (RCT).

3. Setting

East-West Neo Medical Center, Kyung Hee University, Republic of Korea.

4. Participants

Forty patients with cancer-related fatigue (May to October 2009).

5. Intervention

Arm 1: TSUMURA Hochuekkito (補中益気湯) Extract Granules 7.5 g/day for 2 weeks (n=20).
Arm 2: no treatment, course monitored for 2 weeks (n=20).

6. Main outcome measures

Primary outcome measure: Visual Analogue Scale of Global Fatigue (VAS-F)
Secondary outcome measures: Functional Assessment of Cancer Therapy-General (FACT-G), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Trial Outcome Index-Fatigue (TOI-F).

7. Main results

Eighteen patients were included in each group for evaluation. Significant improvements were observed in arm 1 compared to arm 2 for before/after changes in all measures, VAS-F (P=0.040), FACT-G (P=0.047), FACT-F (P=0.025), and TOI-F (P=0.049).

8. Conclusions

Hochuekkito improves cancer-related fatigue.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Blood tests (aspartate amino transferase [AST], alanine aminotransferase [ALT], creatinine, blood urea nitrogen [BUN]) were performed before and after administration, and participants were asked about subjective symptoms using a questionnaire based on version 2.0 of the NCI-CTC-AE questionnaire. Although these results showed no significant change in liver or kidney function, two participants complained of grade 1 stomach discomfort.

11. Abstractor's comments

While fatigue is the most commonly known indication for hochuekkito, this study is valuable for having verified its effectiveness and safety for cancer patients through an RCT. Yet, the inclusion criteria included a two-month gap since chemo- or radiotherapy, which raises questions about whether their influence could really be ruled out. Furthermore, a placebo effect cannot be completely ruled out because no treatment was administered in arm 2, and the administration period was only two weeks. In future, such a study would hopefully give the control group a placebo, or increase the number of subjects, for treatment over a longer period.

12. Abstractor and date

Motoo Y, 31 December 2012.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Iwagaki H, Saito S. Regulation of post-operative systemic inflammatory response syndrome (SIRS) by preoperative administration of hochuekkito (a Japanese herbal medicine). *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) 2010; 61: 78–83 (in Japanese with English abstract). Ichushi Web ID: 2010110656 J-STAGE

1. Objectives

To evaluate the efficacy of preoperative administration of hochuekkito (補中益気湯) for postoperative systemic inflammatory response syndrome (SIRS) in gastric/colon cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Okayama University Hospital and 8 related facilities, Japan.

4. Participants

Fifty-one patients undergoing laparotomy for advanced gastric/colon cancer in the period between February and December 2004.

5. Intervention

Medication taken for 7 consecutive days preoperatively to the day before surgery.
Arm 1: hochuekkito (補中益気湯) extract granules (manufacturer not indicated) 2.5 g t.i.d. (n=24).
Arm 2: no administration (n=27).

6. Main outcome measures

Serum cortisol level and soluble interleukin (IL)-2 receptor (sIL-2R) level immediately before and at 1 day after the operation; white blood cell (WBC) count and differential WBC count before and 1 and 7 days after the operation; C-reactive protein (CRP) level before and 1, 3, and 7 days after the operation; body temperature/pulse rate from the day before to 14 days after the operation; use of antibiotics until 14 days after the operation.

7. Main results

The analysis population consisted of 48 patients (after 2 and 1 patient dropped out in arm 1 and arm 2, respectively). There was no significant between-arm difference in preoperative serum cortisol level, but a tendency toward lower preoperative sIL-2R level in the hochuekkito group (P=0.08). The percent decline in cortisol level from preoperative baseline to postoperative day 1 value was significantly greater in arm 1 than in arm 2 (P=0.04), while there was no significant between-arm difference in the decline in sIL-2R level, WBC count, differential WBC count, or CRP level before and 1 and 7 days after the operation. The pre- to postoperative declines in mean body temperature and mean pulse rate were significantly greater in arm 1 (P=0.0002 and P=0.03, respectively). Fewer patients used second-line antibiotics postoperatively in the hochuekkito group than in the control group (P=0.05).

8. Conclusions

Preoperative administration of hochuekkito significantly suppresses the postoperative inflammatory response to surgical wounding.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is significant because it demonstrates by RCT that preoperative 1-week administration of hochuekkito significantly suppresses postoperative SIRS, while focusing on the characteristics of Kampo medicine for treating *mibyou* (未病, subclinical state). The use of antibiotics, mentioned in the last section of the results, was said to be "significantly different between arms" even though P=0.05. The criterion for significance, indicated in the text, was P <0.05. Preoperative administration of hochuekkito reduced postoperative complications and duration of hospitalization, which is medically and economically beneficial. Furthermore, administration of hochuekkito may raise the awareness of patients and prepare them for surgery.

12. Abstractor and date

MotooY, 30 December 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Okawa T, Hashimoto S, Sakamoto S, et al. Ninjin-yoei-to in the treatment of leukopenia and symptoms associated with radiotherapy of malignant tumors. *Gan no Rinsho* (*Japanese Journal of Cancer Clinics*) 1995; 41: 41–51 (in Japanese with English abstract). Ichushi Web ID: 1995174288 MOL, MOL-Lib

1. Objectives

To evaluate the improvement in subjective symptoms and leukopenia after ninjin'yoeito (人参養栄湯) administration in patients undergoing radiotherapy for thoracoabdominal tumors.

2. Design

Randomized controlled trial (RCT).

3. Setting

Thirteen university hospitals (Tokyo Women's Medical University [Department of Radiology], Keio University School of Medicine [Department of Radiology], Tohoku University School of Medicine [Department of Radiology], and 10 other universities) and 9 other hospitals, Japan.

4. Participants

One hundred sixteen patients with thoracoabdominal tumors undergoing radiotherapy (lung cancer: 42, esophageal cancer: 19, breast cancer: 9, rectal cancer: 7, cervical cancer: 33, and other cancers: 16).

5. Intervention

Arm 1: administration of Kanebo ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d. during radiotherapy (n=63).

Arm 2: radiotherapy only (without ninjin'yoeito [人参養栄湯]) (n=63).

6. Main outcome measures

Subjective symptoms (anorexia, general malaise, diarrhea, coldness, nausea, and vomiting) were evaluated weekly on a 4-point scale. Hematological parameters (white blood cell [WBC], differential WBC, platelet, red blood cell, and reticulocyte counts, hemoglobin, and hematocrit), body weight, and blood pressure were measured weekly. Biochemical values (glutamic-oxaloacetic transaminase [GOT], glutamic-pyruvic transaminase [GPT], albumin, total protein, cholinesterase [Ch-E], blood urea nitrogen [BUN], Cr, Na, K, and Cl) were measured biweekly. Primary physicians evaluated the response of patients based on the above measures on a 4-point scale (marked, moderate, mild, or none).

7. Main results

There were no between-group differences in the mean WBC counts at baseline and at weeks 1–4. The proportion of patients with WBC count >3000 at the end of the treatment (weeks 4–8) was higher in arm 1 (51/56) than in arm 2 (42/60) (P=0.005).

Improvement in subjective symptoms (at least mild response) was observed more frequently in arm 1 (44/56) than in arm 2 (6/60) (P=0.0001).

Improvement in laboratory test results (at least mild response) was observed more frequently in arm 1 (43/56) than in arm 2 (23/60) (P=0.0003).

8. Conclusions

Ninjin'yoeito may prevent subjective symptoms and leukopenia associated with radiotherapy.

9. From Kampo medicine perspective

After the study, a retrospective analysis based on *sho* (証, pattern) was conducted, and *sho* was determined from an assessment of subjective symptoms (anorexia, general malaise, cold hands and feet, and night sweats). However, no correlation between *sho* and effectiveness was found.

10. Safety assessment in the article

Adverse events: 4 patients in arm 1 had, respectively, drug eruption, abdominal discomfort, abdominal pain + diarrhea, and diarrhea.

11. Abstractor's comments

It would be interesting to know whether Kampo medicines can prevent leukopenia associated with radiotherapy. In this study, although the mean WBC counts were similar in both arms, the proportion of patients with WBC counts >3000 was significantly higher in arm 1 than in arm 2 at the end of the treatment (weeks 4–8). The reason should be considered. The WBC count is the only laboratory test result shown. The granulocyte and platelet counts, hemoglobin level, and the biochemical test results are not reported. It was also unclear which subjective symptom was improved. The reliability of this study remains questionable because each result was a composite evaluation by physicians using a 4-point scale and this was an open trial. In the discussion of results, "overall improvement" based on physician's judgment was considered the gold standard. In addition, they just compare "overall improvement" with patient characteristics and test data in the stratified analysis. In this kind of open trial, objectivity is not assured unless the presence and degree of each subjective symptom as well as the test data are recorded sequentially and are compared between groups.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Saito Y, Mitsuhashi N, Takahashi I, et al. Effect of TSUMURA Saiboku-to as an agent for healing damage in treatment of radiomucositis due to irradiation of the head and neck area and mediastinum. *Biotherapy* 1992; 6: 1899–906 (in Japanese with English abstract).

1. Objectives

To evaluate the healing effect of TSUMURA Saibokuto (柴朴湯) on mucositis induced by head-and-neck and mediastinal irradiation.

2. Design

Randomized controlled trial (RCT).

3. Setting

Gunma University Hospital and 9 other hospitals (a total of 10 institutions), Japan.

4. Participants

Fifty-four cancer patients were included without regard to their age, sex, primary disease, disease stage, prior treatment, and inpatient or outpatient status. These patients developed symptoms of mucosal irritation in response to head-and-neck or mediastinal irradiation. Exclusion criteria were: serious concomitant diseases of the heart, lung, bone marrow, liver, or kidney; Eastern Cooperative Oncology Group performance status 4; and a determination of ineligibility by the treating physician.

5. Intervention

A telephone system was used for treatment allocation.

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 mg t.i.d. was administered orally (before or between meals) for 4 weeks from the onset of some mucosal irritation symptoms after the start of irradiation (12 males and 11 females). The primary diseases included malignant lymphoma, cervical lymph node metastasis, lung cancer, breast cancer, oropharyngeal cancer, and esophageal cancer (in descending order of frequency).

Arm 2: current therapy was continued but TSUMURA Saibokuto (柴朴湯) Extract Granules was not administered. The primary diseases included malignant lymphoma, lung cancer, breast cancer, and cervical lymph node metastasis (in descending order of frequency).

6. Main outcome measures

Severity of subjective symptoms (pharyngolaryngeal pain, foreign-body sensation in the pharyngolarynx, pain on swallowing, difficulty in swallowing, burning sensation, smarting pain) rated on a 4-point scale; objective findings of mucosa (redness, erosion, edema); and global utility (rated on a 3-point scale [marked, moderate, or no response] based on subjective and objective symptoms, laboratory values, and adverse drug reactions).

7. Main results

Three out of 54 enrolled patients in arm 1 were excluded and 20 in arm 1 and 31 in arm 2 were included in the analysis. The comparison of subjective symptom improvements failed to show any efficacy of TSUMURA Saibokuto. Marked and moderate increases in global utility scores were observed in 6 and 6 patients, respectively, in arm 1 and in 0 and 10 patients, respectively, in arm 2; the between-arm difference was significant ($P<0.01$).

8. Conclusions

TSUMURA Saibokuto may heal mucositis induced by head-and-neck or mediastinal irradiation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

A mild increase in glutamic-oxaloacetic transaminase (GOT) and glutamic pyruvic trans- aminase (GPT) levels developed in 2 patients in arm 1 who required no specific treatment.

11. Abstractor's comments

Randomization is assumed because treatment allocation used a telephone system (though the details are not clear); so the study was classified as an RCT. There is concern that concurrent use of Predonine (prednisolone) might have influenced outcome in some patients. In this paper, rating criteria for global utility are not clear. More description of these criteria would have aided interpretation of the results. Further studies on this treatment are anticipated.

12. Abstractor and date

Tsuruoka K, 3 April 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Hibi S, Ina K, Furuta R, et al. Clinical effects of hange-shashin-to on combination therapy of S-1/irinotecan for patients with metastatic gastric and colorectal cancer*. Gan to Kagaku Ryoho (*Japanese Journal of Cancer Chemotherapy*) 2009; 36: 1485–8 (in Japanese with English abstract). CENTRAL ID: CN-00728899, Pubmed ID: 19755817, Ichushi Web ID: 2009352672, MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for delayed diarrhea induced by irinotecan (CPT-11) in patients with metastatic gastric and colorectal cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single facility, Japan.

4. Participants

Twenty patients with inoperable advanced recurrent gastric cancer or colorectal cancer (12 males and 8 females).

5. Intervention

Patients received a course of chemotherapy consisting of 2 weeks on and 2 weeks off oral S-1 (tegafur/gimeracil/oteracil potassium) at 80–120 mg according to body surface area and intravenous irinotecan (CPT-11) at 100–125 mg once every 2 weeks.

Arm 1: Hangeshashinto (半夏瀉心湯) extract 7.5 g/day for 3 days starting on the day of administration of irinotecan (CPT-11) (n=10).

Arm 2: no administration of hangeshashinto (半夏瀉心湯) extract (n=10).

6. Main outcome measures

Anti-tumor effect (RECIST criteria), adverse events (Common Terminology Criteria for Adverse Events v3.0), and quality of life (QOL score developed by Kurihara et al.) evaluated on days 1, 15, and 29.

7. Main results

There was no significant difference in anti-tumor effect between arms. Chemotherapy-associated adverse events were more common in arm 2 than in arm 1 (significance of difference not tested). A decrease in QOL score from day 1 to day 15 was larger in more patients in arm 2 than in arm 1. Overall QOL score was decreased by 15 points or more in 1 patient in arm 1, compared with 4 patients in arm 2, with the mean±standard deviation significantly changed from 79±19 and 87±13 on day 1 to 77±21and 75±23 on day 15 in arm 1 and arm 2, respectively (P<0.05). In particular, QOL in the “social” domain decreased 2 points or more in 7 of 10 patients in arm 2 and 0 of 10 patients in arm 1.

8. Conclusions

Hangeshashinto (半夏瀉心湯) is a useful supportive therapy from the viewpoint of QOL in patients treated for advanced gastric and colorectal cancer with S-1/irinotecan (CPT-11) combination therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

Post-marketing surveillance identified gastrointestinal symptoms such as nausea/vomiting (52.5%), anorexia (48.1%), and abdominal pain (12.2%) as frequent adverse drug reactions of CPT-11, besides diarrhea (43%, serious in 10.2% of cases). Hangeshashinto has well known efficacy not only for diarrhea, as reported by Kamataki et al. (1994), but also for nausea/vomiting, anorexia, and epigastric pain. This study demonstrated that hangeshashinto improves QOL. But the study had the following problems: (1) the rationale for the 3-day hangeshashinto administration period after administration of CPT-11 is not indicated. Although the authors seem to assume that the hangeshashinto-*sho* (証, pattern) induced by CPT-11 disappears in 3 days, delayed diarrhea attributable to intestinal mucosal injury by an active metabolite (SN-38) 24 hr after administration, for example, does not disappear in 3 days, warranting consideration of duration of administration in the future; (2) hangeshashinto is effective in only some cases. As QOL score was decreased by 15 points or more in 4 of 10 patients in arm 2 in this study, only these 4 patients are likely to have exhibited hangeshashinto-*sho* (証, pattern). It is recommended that patients be enrolled in the study from the second cycle onward after determining the presence or absence of hangeshashinto-*sho* (証, pattern) and the duration of the *sho* (証, pattern), based on the response to the first cycle of CPT-11.

12. Abstractor and date

Hoshino E, 15 January 2011.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
5. Psychiatric/Behavioral Disorders

References

Sugano N, Aoyama T, Sato T, et al. Randomized phase II study of TJ-54 (Yokukansan) for postoperative delirium in gastrointestinal and lung malignancy patients. *Molecular and Clinical Oncology*. 2017; 7: 569-73. CENTRAL ID: CN-01421749, Pubmed ID: 28855990

1. Objectives

To evaluate the efficacy and safety of yokukansan（抑肝散）for postoperative delirium in patients with gastrointestinal or lung cancer

2. Design

Randomized controlled trial (RCT)

3. Setting

Nine hospitals, including one university hospital, Japan

4. Participants

A total of 186 patients aged 70 years or older who underwent surgery for gastrointestinal or lung cancer with an Eastern Cooperative Oncology Group Performance Status score of 2 or less, who underwent a mini-mental state examination (MMSE), and who had normal hepatic, renal, and bone marrow functions. Patients were excluded if they had a history of severe hypersensitivity to drugs, had serious constipation, were pregnant, or were lactating.

5. Intervention

Arm 1: TSUMURA Yokukansan（抑肝散）Extract Granules 7.5 g/day (2.5 g t.i.d.) administered orally for 7 days preoperatively and 4 days postoperatively, excluding the operation day (n=93)
Arm 2: Control group (n=93)

6. Main outcome measures

Primary endpoints were the incidence of postoperative delirium and safety. Secondary endpoint was the length of hospital stay. Delirium was assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, independently by two physicians.

7. Main results

The incidence of delirium was 6.5% in Arm 1 (n=6) and 9.7% in Arm 2 (n=9), showing no significant difference between the two arms. A subgroup analysis showed that, among patients with MMSE scores of ≤26, the incidence of postoperative delirium was 9.1% in Arm 1 and 26.9% in Arm 2 (risk ratio, 0.338; 95% CI, 0.078–1.462, *P*=0.115). Among patients with MMSE scores of ≥27, the incidence of postoperative delirium was 6.8% in Arm 1 and 3.6% in Arm 2 (risk ratio, 1.864; 95% CI, 0.356–9.778, *P*=0.453). The length of hospital stay was 16 days in Arm 1 and 15 days in Arm 2, showing no difference between the arms.

8. Conclusion

In patients with MMSE scores of ≤26, yokukansan reduces the risk of delirium after surgery for gastrointestinal or lung cancer.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Occurrence of adverse reactions did not differ between the two arms. No adverse reactions appeared to be related to yokukansan.

11. Abstractor's comments

Postoperative delirium is an important postoperative management issue. With a focus on this, and using yokukansan, which has been widely used recently for delirium in patients with other behavioral and psychological symptoms of dementia (BPSD), the authors conducted this interesting clinical study evaluating the effects of yokukansan on postoperative delirium in patients with gastrointestinal or lung cancer. Analysis of the primary endpoint failed to show an intergroup difference, partly because the incidence of delirium in the control group was lower than expected, as stated by the authors in the Discussion section, for which further studies in larger samples would be needed. The subgroup analysis showed reduction in the risk of delirium after yokukansan administration in those with MMSE scores of ≤26. This indicates that yokukansan may be effective in suppressing delirium in patients with lower cognitive function. However, regarding those with MMSE scores ≥26, the article does not provide details such as the number of the patients. Furthermore, the article does not provide any basis for the MMSE cutoff score of 26, and therefore the efficacy may not be convincing. Given that this was a phase 2 study, a phase 3 clinical study based on these data is awaited to further clarify the disease conditions for which yokukansan is indicated.

12. Abstractor and date

Goto H, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Yamamoto K, Hirano F, Ikoma N, et al. Efficacy of keishibukuryogan for hysteromyoma/uterine adenomyosis*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 135-7 (in Japanese). Ichushi Web ID: 2004068783

1. Objectives

To evaluate the anti-tumor effect of keishibukuryogan (桂枝茯苓丸) in patients with hysteromyoma/uterine adenomyosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single hospital (Department of Obstetrics and Gynecology, Sakai Hospital, Kinki University School of Medicine), Japan.

4. Participants

The 24 patients seen at the above institution and diagnosed with hysteromyoma or uterine adenomyosis were randomized into two arms: 1) the gonadotropin-releasing hormone (GnRH) analogue + keishibukuryogan arm (mean age, 45.9 years; mean tumor diameter, 35.7 mm) and 2) the GnRH analogue arm (mean age, 46.3 years; mean tumor diameter, 34.1 mm).

5. Intervention

Arm 1: subcutaneous injection of a GnRH analogue (1.88 mg) once monthly for 4 consecutive months + oral administration of a sachet of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (2.5 g) t.i.d (before meals) for 12 months (n=14) .

Arm 2: subcutaneous injection of a GnRH analogue (1.88 mg) once monthly for 4 consecutive months (n=10).

6. Main outcome measures

Tumor response was evaluated on a 3-point scale: tumor diameter reduction: remarkably effective, ≥50%; effective, >0 - 50%; not effective, 0%. Evaluation was performed at baseline, 4, 8, and 12 months after intervention.

7. Main results

Four months after treatment, complete response was achieved in 42.9% (6/14) of arm 1 and 10% (1/10) of arm 2, showing that GnRH + keishibukuryogan tended to have a higher anti-tumor effect although there were no between-group differences in tumor size reduction 8 or 12 months after treatment. Analysis limited to hysteromyoma revealed that 4-month treatment produced complete response in a significantly higher percentage of arm 1 (50%) than arm 2 (0%) (P=0.012). When the analysis was limited to the GnRH analogue leuprorelin, 4-month treatment produced a significantly higher complete response rate in arm 1 (62.5%) than in arm 2 (0%) (P=0.016). GnRH + keishibukuryogan exerted clinical efficacy in the short-term but not in the long-term (8 or 12 months after treatment).

8. Conclusion

Keishibukuryogan increases the efficacy of standard GnRH therapy for tumor size reduction in 4-month, short-term treatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

As the contents of this paper have also been described in several previous case reports and clinical studies, the present study provided additional supportive evidence. Nevertheless, the present results are not sufficient to conclude that the effect can be generalized beyond the study sample because of the small sample size, but it will serve as a helpful reference in determining the future direction of research. Although the measure of tumor response (use of a 3-point scale) was rather crude, further accumulation of cases may enable more reliable determination — for clinical practice — of mean tumor reduction and differences in tumor reduction with time after administration.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia

Reference

Akase T, Akase T, Onodera S, et al. A comparative study of the usefulness of tokishakuyakusan and an oral iron preparation in the treatment of hypochromic anemia in cases of uterine myoma. *Yakugaku Zasshi* (*Journal of the Pharmaceutical Society of Japan*) 2003; 123: 817-24. CENTRAL ID: CN-00457950, Pubmed ID: 14513774, Ichushi Web ID: 2004068366 J-STAGE

1. Objectives

To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for hypochromic anemia in patients with uterine myoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

A university hospital (Outpatient Department of Obstetrics and Gynecology, Kitasato University Hospital), Japan.

4. Participants

Twenty-three patients having hypochromic anemia associated with uterine myoma visiting the above institution between August 1999 and the end of January 2000. Mean age: 45.4±1.99 years in the tokishakuyakusan group; 42.9 ± 1.68 years in the oral iron preparation group. Range of blood hemoglobin concentration: 8 – 12 g/dL.

5. Intervention

Arm 1: oral administration of a sachet of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules (2.5 g) t.i.d. (before meals) for 3 months.

Arm 2: oral administration of a tablet containing sodium ferrous citrate (50 mg) q.d or b.i.d. (after meals) for 3 months.

6. Main outcome measures

Laboratory: hematology (RBC, hemoglobin, hematocrit, etc.), blood chemistry (serum iron, ferritin concentration, etc.), blood coagulation function (PT, APTT), evaluated at baseline, and 4 and 8 weeks.after dosing. Improvement in subjective symptoms, including pallor, dizziness on standing up, and dizziness/vertigo, evaluated on a 5-point scale at baseline, and 4 and 8 weeks after dosing. Adverse drug reactions (ADRs): incidences of heartburn, nausea/vomiting, diarrhea, etc. during 8-week administration.

7. Main results

Although there was no between-group difference in blood profile, subjective symptoms such as cold, pallor, spoon nail, and dizziness/vertigo were significantly improved with tokishakuyakusan (P<0.05). In particular, cold was improved significantly efficiently in the tokishakuyakusan group (score at 8 weeks: 0.3±0.2 for tokishakuyakusan, 2.0±0.6 for oral iron; P<0.05). ADRs occurred in 80% of patients receiving the oral iron preparation (heartburn and nausea noted with the highest incidences of 46.7% each) but in no patients receiving tokishakuyakusan.

8. Conclusions

Three-month treatment with tokishakuyakusan is more effective in improving subjective symptoms and is safer than an oral iron preparation for mild to moderate anemia in women with uterine myoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

ADRs occurred in none of 10 patients receiving tokishakuyakusan, while in 12 (80%) of 15 patients receiving the oral iron preparation.

11. Abstractor's comments

If clinicians designed a noninvasive antianemic treatment plan for the present study population, i.e., patients with anemia (defined as blood hemoglobin concentration, 8–12 g/dL) and uterine myoma, the oral iron preparation would be the treatment of choice. However, in the present study, tokishakuyakusan had higher efficacy for subjective symptom improvement. In addition, tokishakuyakusan was clinically more efficacious and safer (i.e., had no ADRs). However, since tokishakuyakusan (unlike the oral iron preparation) did not improve the blood profile, a combination of these drugs might be more efficacious. A new research protocol to investigate the efficacy of Kampo formulations combined with oral iron to reduce the severity of anemia is expected in the future.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia

Reference

Yanagihori A, Miyagi M, Hori M, et al. Efficacy of ninjin'yoeito for iron deficiency anemia*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1995; 72: 2605-8 (in Japanese). Ichushi Web ID: 1996162428, MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人参栄養湯) for iron deficiency anemia due to menorrhagia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Obstetrics and Gynecology, Toho University Sakura Medical Center, Japan.

4. Participants

Thirty-nine patients diagnosed with iron deficiency anemia (hemoglobin, 9.0 mg/dL or less) due to menorrhagia and metrorrhagia associated with uterine myoma, uterine adenomyoma, endometrial polyp, etc.

5. Intervention

Arm 1: Kanebo (currently Kracie) Ninjin'yoeito (人参栄養湯) Extract Granules 5 g/day ＋ ferrous citrate (Ferromia) 100 mg/day for 4 weeks (n=21).
Arm 2: ferrous citrate (Ferromia) 100 mg/day for 4 weeks (n=18).

6. Main outcome measures

Changes in hematological values, including serum iron and ferritin and subjective symptoms (general malaise, shortness of breath, and palpitation) from pre- to post-dose.

7. Main results

Elevation in hemoglobin value from pre- to post-dose was significantly higher in arm 1 (P<0.01). Palpitation and shortness of breath and symptoms for which ninjin'yoeito should be effective (anorexia, night sweats, and cold limbs) were similarly improved in both arms.

8. Conclusions

Ninjin'yoeito combined with an iron preparation is effective for iron deficiency anemia due to menorrhagia.

9. From Kampo medicine perspective

The effects of the components of ninjin'yoeito (*ninjin* [人参], *byakujutu* [白朮], and *onji* [遠志]) on bone marrow are suggested.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study investigated the hematopoietic effect of ninjin'yoeito on anemia due to menorrhagia. Given accumulated clinical reports supporting the efficacy of ninjin'yoeito for myelosuppression associated with anticancer drug treatment, its effect on iron deficiency anemia was expected. Lack of improvement in the symptoms for which ninjin'yoeito should be effective other than anemia, such as night sweats and cold limbs, may warrant review of the Kampo criteria for application of ninjin'yoeito, as pointed out by the authors in the text. Future reports are awaited.

12. Abstractor and date

Nakata H, 1 January 2009, 6 January 2010, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia

Reference

Aoe H, Takada K, Kawahara N, et al. Effectiveness of erythropoietin and ninjin'yoeito in preoperative autologous blood donation*. *Jikoketsu Yuketsu* (*Journal of Japanese Society of Autologous Blood Transfusion*) 1997; 10: 145–51 (in Japanese).

1. Objectives

Combined effect of erythropoietin and ninjin'yoeito (人参養栄湯) on anemia after autologous blood donation.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Himeji Red Cross Hospital, Japan.

4. Participants

Patients who donated 800 mL or more of blood for autologous transfusion between January 1994 and December 1996. The control group (iron preparation only) consisted of patients who donated blood for autologous transfusion between June 1992 and December 1993; treatment assignment was not randomized.

5. Intervention

Arm 1: iron preparation monotherapy (intravenous administration of 80 mg three times a week) (n=10).
Arm 2: iron preparation (intravenous administration of 80 mg three times a week) + Epogin (6000 units three times a week) (n=37).
Arm 3: iron preparation (intravenous administration of 80 mg three times a week) + Epogin (6000 units three times a week) ＋TSUMURA Ninjin’yoeito (人参養栄湯) Extract Granules (9 g/day) (n=26).

6. Main outcome measures

Blood tests (red blood cell count, hemoglobin, hematocrit, reticulocyte count, white blood cell count, and serum iron) before blood donation and before surgery.

7. Main results

Compared to patients in arm 1, patients in arm 3 but not arm 2 had significantly increased red blood cell count, hemoglobin, and hematocrit at the time of preoperative blood collection.

8. Conclusions

The addition of ninjin'yoeito to iron and erythropoietin preparations is considered to be effective in raising red blood count, hemoglobin, and hematocrit of blood donated for autologous transfusion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor’s comments

This paper describes the hematopoietic effect of ninjin’yoeito, which appears to be useful for improving the quality of blood units donated for autologous transfusion. Although significant differences were observed between arms 1 and 3 but not between arms 2 and 3, it may not simply be concluded that the addition of ninjin’yoeito is effective. However, considering the increasing numbers of patients who are undergoing autologous blood transfusion, this attempt should be appreciated. Including postoperative results in the evaluation of ninjin’yoeito would enhance another efficacy of this formulation. Further results are awaited.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010.

3. Blood Diseases including Anaemia

Reference

Motoo Y, Mouri H, Ohtsubo K, et al. Herbal medicine ninjinyoeito ameliorates ribavirin-induced anemia in chronic hepatitis C: a randomized controlled trial. *World Journal of Gastroenterology* 2005; 11: 4013-7. CENTRAL ID: CN-00522971, Pubmed ID: 15996025

1. Objectives

To evaluate the efficacy and safety of ninjin'yoeito (人参養栄湯) for ribavirin-induced anemia.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-three chronic hepatitis C patients treated with interferon alpha-2b and ribavirin. Five of them withdrew from the study.

5. Intervention

Arm 1: designated "the NY group" and treated with IFNα-2b and ribavirin plus TSUMURA Ninjin'yoeito (人参養栄湯) Extract Granules (9 g, orally), n=10.
Arm 2: designated "the control group" and treated with interferon alpha-2b (IFNα-2b) and ribavirin,n=13

IFNα-2b was administered for a total of 24 weeks at a dose of 10 MU intramuscularly, 6 days per week for the first 2 weeks and 3 days per week for the following 22 weeks. Ribavirin was orally administered for 24 weeks at a dose of 800 mg/day (if the patient's body weight was ≥ 60 kg) or 600 mg/day (body weight < 60 kg).

6. Main outcome measures

Maximum increase in red blood cell count (maxΔRBC), maximum increase in hemoglobin level (maxΔHb) minimum hemoglobin level (min Hb), white blood cell count (WBC), platelet count (Plt), T-helper 1 cell (Th1) count, T-helper 2 cell (Th2) count, Th1/Th2, and glutathione peroxidase level in peripheral blood.

7. Main results

Peripheral maxΔHb and min Hb were significantly improved in the NY group (P=0.026 and P=0.079, respectively). No between-group differences were observed in maxΔRBC, WBC count, Plt count, Th1 count, Th2 count, Th1/Th2, and glutathione peroxidase level. Antiviral effects were not different, either.

8. Conclusions

Ninjin'yoeito is an effective and safe treatment for ribavirin-induced anemia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions specific to ninjin'yoeito were not observed.

11. Abstractor's comments

This study showed the efficacy of ninjin'yoeito for ribavirin-induced anemia. The authors speculated that the mechanism of action of this drug is the activation of undifferentiated erythroid cells and antioxidation.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

3. Blood Diseases including Anaemia

Reference

Nakamaoto H, Mimura T, Honda N. Orally administrated Juzen-taiho-to/TJ-48 ameliorates erythropoietin (rHuEPO)-resistant anemia in patients on hemodialysis. *Hemodialysis International* 2008; 12: S9-14. CENTRAL ID: CN-00667345, Pubmed ID: 18837771

1. Objectives

To evaluate the efficacy and safety of juzentaihoto (十全大補湯) for erythropoietin-resistant anemia in patients on hemodialysis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital and 1 general hospital, Japan.

4. Participants

Forty-two patients on hemodialysis with erythropoietin-resistant anemia.

5. Intervention

Arm 1: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. for 12 weeks (n=22).
Arm 2: not treated with TSUMURA Juzentaihoto (十全大補湯) Extract Granules (n=20).
Patients in the two groups were on the same dietary regimen and dialysis program.

6. Main outcome measures

Hemoglobin level.

7. Main results

While Hb level increased nonsignificantly from 8.3±0.7 to 8.5±0.5 g/dL in arm 2, it increased significantly from 8.4±1.1 to 9.5±1.3 g/dL in arm 1 (P＝0.0272).

8. Conclusions

Treatment with TSUMURA Juzentaihoto Extract Granules is effective for erythropoietin-resistant anemia in patients on hemodialysis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse event (complication, abnormality in blood chemistry) was reported in the juzentaihoto group.

11. Abstractor's comments

This RCT was conducted in many patients with erythropoietin-resistant anemia and using a double-blind design. However, it is questionable that this trial was not placebo-controlled and no statistical analysis was mentioned. Given the decrease in serum C-reactive protein (CRP) level and negative correlation between serum CRP and Hb levels in the juzentaihoto group (and the absence of a decrease in serum CRP level and negative correlation in the non-treatment group), the authors assume that juzentaihoto may act, at least in part, as an anti-inflammatory agent. This is an interesting assumption that may suggest a basic research question.

12. Abstractor and date

Kogure T, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia

Reference

Seki M. Efficacy of goreisan for preventing thrombocytopenia and activating vascular endothelial cells after cholecystectomy*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1990; 7: 510–1 (in Japanese).

1. Objectives

To evaluate the efficacy of goreisan (五苓散) and shosaikoto (小柴胡湯) for thrombocytopenia after cholecystectomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Forty-seven female patients who underwent cholecystectomy for gallbladder stones or polyps.

5. Intervention

Arm 1: administration of TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. until the day before surgery for a mean of 8.4±6.0 days (n=14).
Arm 2: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. until the day before surgery for a mean of 6.5±3.4 days (n=12).
Arm 3: bed rest in the hospital for a mean of 8.5±3.7 days (n=21).

6. Main outcome measures

Blood counts and urinary excretion of prostaglandin E1 (PGE1) and F1 alpha (6-keto-PGF1α).

7. Main results

Platelet counts were significantly higher on postoperative day 1 in arms 1 and 2 than in arm 3. Excretion of urinary PGE1 was significantly higher in arm 1 on postoperative days 1, 5, 6, and 7 and in arm 2 only on postoperative day 1 than in arm 3. Excretion of urinary 6-keto-PGF1α was significantly higher on postoperative days 1, 5–7, and 8–14 in arm 1, and on postoperative day 1 in arm 2, than in arm 3.

8. Conclusions

Goreisan is effective for consumptive thrombocytopenia after cholecystectomy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study showed that administration of goreisan before cholecystectomy reduced postoperative thrombocytopenia.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

3. Blood Diseases including Anaemia

Reference

Hatano T. Mitigation of postoperative lymphopenia and protection of T cells by preoperative administration of xial-chai-hu-tang. *Saitama Ika Daigaku Zasshi* (*Journal of Saitama Medical School*) 1990; 17: 357–63 (in Japanese with English abstract).

1. Objectives

To evaluate the preventive effect of preoperative administration of shosaikoto (小柴胡湯) on postoperative lymphopenia in female patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (Second Department of Surgery, Saitama Medical Center, Saitama Medical School), Japan.

4. Participants

Hundred and twenty-two postoperative female patients (breast cancer, 37; cholecystolithiasis, 65; gastric cancer, 20).

5. Intervention

Arm 1: preoperative administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for a mean of 7.3 days in breast cancer patients, 5.4 days in cholecystolithiasis patients, and 9.0 days in gastric cancer patients (n=27: breast cancer, 9; cholecystolithiasis, 14; gastric cancer, 4).

Arm 2: no administration of Kampo medicines (n=95).

6. Main outcome measures

(1) Lymphocyte counts and subsets (OKT3, OKT4, OKT8, OKIA, and Leu 7).
These were measured before and after preoperative administration of shosaikoto and on 14 consecutive postoperative days.
(2) Assessment of the impact of surgery (blood loss, duration of surgery, anesthesia, postoperative stay, and complications).

7. Main results

(1) Lymphocyte counts: only the mean value was plotted on a line chart, standard deviation (error) was not shown. No significance test between arms was performed.
(2) Comparison of lymphocyte counts and subsets before and after preoperative administration of shosaikoto: in cholecystolithiasis patients, no significant differences between arms were observed.
(3) Lymphocyte subsets at 1 day after surgery (in cholecystolithiasis patients): OKT3 and OKT4 decreased significantly in arm 2, while no significant decrease was observed in arm 1. No significance test between arms was performed.
(4) Impact of surgery: blood loss, duration of surgery, anesthesia, and postoperative stay, and complications did not differ significantly between arms.

8. Conclusions

Preoperative administration of shosaikoto attenuates postoperative lymphopenia. This effect is supposed to be due to protection of the biomembranes of mature cells, especially helper/inducer T-cells.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In the Method section, the authors noted that the number of peripheral blood lymphocytes and the number of lymphocyte subsets were sequentially measured beginning before surgery and ending on postoperative day 14. However, the available results do not include lymphocyte counts for postoperative days 8–13 and show only mean lymphocyte count at each measurement day without standard deviation (error). The tests might not have been performed for all patients included. Moreover, lymphocyte subsets in breast or gastric cancer patients are not provided. Since statistical tests between arms for disease-specific lymphocyte counts were not performed, it cannot be concluded that "preoperative administration of shosaikoto attenuated postoperative lymphopenia." Besides, a clinical trial (like an animal study) should not collect blood postoperatively for 14 consecutive days to sequentially measure lymphocyte counts and subsets.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010.

3. Blood Diseases including Anaemia

References

Inagaki M, Nakazawa T, Michimata H, et al. Treatment experience with TSUMURA Keishikajutsubuto for pulmonary sarcoidosis*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1990; 7: 316–7 (in Japanese).

Inagaki M. Effectiveness of Kampo medicine in relieving complaints associated with chronic intractable diseases*. *Kampo Shinryo* 1993; 12: 1–3 (in Japanese)

1. Objectives

To evaluate the effects of Keishikajutsubuto (桂枝加朮附湯) on the levels of angiotensin-converting enzyme and lysozyme in sarcoidosis patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Nine patients with ophthalmic manifestations whose sarcoidosis was confirmed by bronchoscopic lung biopsy. Corticosteroid was used in five of these patients. Chest X-ray showed lymphadenopathy only in six patients, lymphadenopathy and lung field lesions in one, and lung field lesions only in two.

5. Intervention

Keishikajutsubuto (桂枝加朮附湯) was administered for at least 1 year.
Arm 1: TSUMURA Keishikajutsubuto (桂枝加朮附湯) extract granules 2.5 g t.i.d. (n=4).
Arm 2: no treatment (n=5).

6. Main outcome measures

The levels of angiotensin converting enzyme (ACE) and lysozyme.

7. Main results

At the end of the follow-up period, the levels of ACE and lysozyme were decreased in all patients in both arms 1 and 2, including participants using steroids. At the end of the follow-up period, the levels of ACE and lysozyme were decreased in both arms. The decrease in ACE was greater in arm 1. In nonusers of steroids, the decreases in ACE and lysozyme were also greater in arm 1.

8. Conclusions

TSUMURA Keishikajutsubuto, with or without steroids, reduces the levels of ACE and lysozyme in sarcoidosis patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor's comments

ACE and lysozyme are referred to as markers for sarcoidosis activity and diagnosis. This paper does not mention improvement on chest X-rays, which suggests there were no changes. Sarcoidosis follow-up takes a long time, so a long-term study with accumulated cases would be more interesting. Furthermore, the sample size in this study was small (four participants in arm 1 and five in arm 2), which makes interpretation of the statistical analysis difficult. Hopefully the authors will conduct an RCT with greater statistical power and an adequate sample size. Inagaki's study (1993) included a large number of cases. Keishikajutsubuto was chosen because sarcoidosis patients often complain of symptoms such as fatigability, cold hands and feet, or joint pain; however, knowing the frequency of such complaints would improve the paper.

12. Abstractor and date

Fujisawa M, 31 March 2009, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Azuma M, Motomiya M, Toyota T. Effects of Seishin-renshi-in (TJ-111) on blood sugar levels of patients with non-insulin-dependent diabetes mellitus. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1994; 45: 339-44 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the efficacy and safety of seishinrenshiin (清心蓮子飲) in the treatment of glucose tolerance.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and three community hospitals, Japan.

4. Participants

Eighteen patients with non-insulin-dependent diabetes mellitus.

5. Intervention

Arm 1: TSUMURA Seishinrenshiin (清心蓮子飲) Extract Granules 2.5 g t.i.d. for 2 weeks (n=12; male:female = 8:4).
Arm 2: no treatment (n=6; all males).
Patients were allowed to continue only an antidiabetic agent that had been taken at baseline.

6. Main outcome measures

Blood tests: HbA1, HbA1c, diurnal variation in blood glucose (once a week), fasting blood glucose (every other day), and other common blood tests.
Severity was classified into 3 grades based on HbA1 level. Efficacy was assessed in 5 grades based on blood glucose level.
Subjective symptoms: thirst, pollakiuria, pain in arms/legs, numbness in arms/legs, blurred vision, dizziness/orthostatic dizziness, heaviness of the head, and general malaise.

7. Main results

There was a significant difference between groups in glucose tolerance. In arm 1, four patients had improvement, four had mild improvement, and four had no improvement, while, in arm 2, no patient had improvement.

8. Conclusions

Seishinrenshiin is an effective and safe treatment for glucose tolerance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No patient in the seishinrenshiin arm had adverse reactions. Although one in seishinrenshiin arm had increased dizziness, orthostatic dizziness, and heaviness of head (symptoms that had been observed before treatment), their direct association with seishinrenshiin was not clear. In addition, one had mild increase in total cholesterol and triglyceride, and another had mild increase in BUN and creatinine, but the association of these events with seishinrenshiin was uncertain.

11. Abstractor's comments

This meaningful article describes the efficacy and safety of seishinrenshiin in treating glucose tolerance. However, the problems of this study are the short duration of treatment as well as allocation bias, that is, all members of the no treatment group were male and there were between-group differences in diabetic history and treatment at baseline. So the reliability of the assessment should be considered. Recently, treatment of metabolic abnormalities such as metabolic syndrome has received attention. Further evaluation of the effectiveness of seishinrenshiin in improving glucose tolerance is expected.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010.

4. Metabolism and Endocrine Diseases

Reference

Watanabe K, Shimada A, Miyaki K, et al. Long-term effects of goshajinkigan in prevention of diabetic complications: A randomized open-labeled clinical trial. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-8. doi: 10.1155/2014/128726 CENTRAL ID: CN-00993596, Pubmed ID: 24812564

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for treatment of diabetic complications.

2. Design

Randomized controlled trial (RCT).

3. Setting

Nine hospitals, Japan.

4. Participants

A total of 149 type 2 diabetic patients with HbA1c of ≥6.5%, aged 40 to 75 years. Exclusion criteria were macroangiopathies including cerebral infarction, myocardial infarction, angina pectoris, leg gangrene, and arteriosclerosis obliterans; nephropathy associated with microalbuminuria or serum creatinine of 1.0 mg/dL; and proliferative or pre-proliferative retinopathy. Other exclusion criteria were related to *sho* (証, pattern) for goshajinkigan and included BMI of 30 kg/m^2 or more; two or more digestive system symptoms including gastrointestinal weakness, anorexia, nausea, and diarrhea; and three or more symptoms or activities indicative of sensitivity to heat such as a preference for dressing lightly, sweating upwards from the neck, a tendency to drink cold water, flushed face, congestion of the eyeballs, and a high body temperature of 36.7°C or higher.

5. Intervention

Arm 1: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules administered orally at 2.5 g t.i.d. (n=100).

Arm 2: No treatment (n=49).

6. Main outcome measures

The primary outcome measures were occurrence of nonfatal myocardial infarction or cerebral infarction and frequency of diabetic nephropathy or retinopathy; the progression of diabetic nephropathy as indicated by a new onset of renal failure or an increase in urinary protein; and the progression of diabetic retinopathy as evaluated by fundus photography performed annually by ophthalmologists. Secondary outcome measures were body weight, blood pressure, fasting blood glucose, glycosylated hemoglobin, blood insulin, diabetic neuropathy, etc. Diabetic neuropathy was evaluated on the basis of characteristic symptoms: ankle reflex, lightheadedness, abnormal sweating, occurrence of constipation or diarrhea, etc.

7. Main results

A total of 116 subjects, i.e., 149 subjects minus 33 subjects who stopped visiting the hospital, were included in the analysis (74 subjects in the goshajinkigan arm; 42 subjects in the no treatment arm). The mean observation period was 28 months in Arm 1, and 15 months in Arm 2. No macroangiopathies such as myocardial infarction and cerebral infarction occurred in the two arms. The occurrence of diabetic nephropathy and retinopathy was not significantly different between arms. The deterioration of ankle reflex was significantly more frequent in Arm 2 than in Arm 1 (P=0.04). Glycosylated hemoglobin level was significantly lower in Arm 1 than in Arm 2 at 60 months (P<0.05). The fasting blood glucose level was significantly decreased from baseline in Arm 1 at 36 months (P<0.05).

8. Conclusions

Goshajinkigan inhibits worsening of ankle reflex and improves glycosylated hemoglobin and fasting blood glucose levels.

9. From Kampo medicine perspective

To evaluate patients with *sho* (証, pattern) for goshajinkigan, patients with obesity, gastrointestinal weakness, and sensitivity to heat were excluded from the study.

10. Safety assessment in the article

No dropouts due to adverse reactions to goshajinkigan were noted.

11. Abstractor's comments

This is an interesting clinical study planned to elucidate the long-term effects of goshajinkigan, which is frequently used for treatment of diabetes mellitus. As stated by the authors, however, the desired number of subjects could not be included in the study and the available macroangiopathies occurrence data were inadequate. On the other hand, there were data suggesting that goshajinkigan was effective. Future studies with more subjects are anticipated.

12. Abstractor and date

Goto H, 31 March 2017.

4. Metabolism and Endocrine Diseases

Reference

Ushiroyama T, Ikeda A, Sakai M, et al. Effects of unkei-to, a herbal medicine, on endocrine function and ovulation in women with high basal level of luteinizing hormone secretion. *The Journal of Reproductive Medicine* 2001; 46: 451-6. CENTRAL ID: CN-00355871, Pubmed ID: 11396371

1. Objectives

To evaluate the efficacy of unkeito (温経湯) for reducing high luteinizing hormone (LH) levels and improving ovulation disorder.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital (Osaka Medical College Hospital), although not mentioned, Japan.

4. Participants

One-hundred patients with ovulation disorder and an LH level of ≥10 mIU/mL, aged 21 to 32 years. Of these 100 patients, 38 were diagnosed with polycystic ovarian syndrome (PCOS).

5. Intervention

Arm 1: oral administration of a sachet (2.5 g) of TSUMURA Unkeito (温経湯) Extract Granules (TJ-106) t.i.d, 30 min before meals, for 8 weeks, n=52.
Arm 2: clinical observation (without administration of placebo granules) for 8 weeks, n=48.

6. Main outcome measures

Comparison of plasma LH level.
Comparison of ovarian follicle size evaluated by ultrasonography.

7. Main results

Of 52 patients receiving unkeito, 34 showed decreased LH level, and 28 showed improved menstrual cycle regularity. In addition, ovulation was confirmed in 11 patients. Decreased LH level was significant in patients without PCOS.

8. Conclusions

Unkeito improves ovulation disorder by normalizing the high level of LH in patients with ovulation disorder. It also increases E2 hormone level in non-PCOS patients. Control patients remained unchanged. Thus, unkeito is an effective treatment for ovulation disorder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study is highly significant in that it demonstrated the ovulation disorder-improving effect of unkeito at the hormonal level. However, the underlying mechanism of this improvement is not explained. Further investigation to determine, for example, why some patients do not respond to unkeito, is awaited. Nevertheless, it can be concluded that unkeito contributes to normalization of the menstrual cycle and stimulation of ovulation.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010.

4. Metabolism and Endocrine Diseases

Reference

Ushiroyama T, Hosotani T, Mori K, et al. Effects of switching to wen-jing-tang (unkei-to) from preceding herbal preparations selected by eight-principle pattern identification on endocrinological status and ovulatory induction in women with polycystic ovary syndrome. *The American Journal of Chinese Medicine* 2006; 34: 177-87. CENTRAL ID: CN-00563518, Pubmed ID: 16552830

1. Objectives

To evaluate the efficacy of switching to unkeito (温経湯) from treatment based on the traditional diagnostic criterion "eight-principle pattern identification" in women with polycystic ovary syndrome (PCOS).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Obstetrics and Gynecology, Osaka University Faculty of Medicine, Japan.

4. Participants

Sixty-four patients who visited the outpatient department and were diagnosed with PCOS between 1993 and 2004.

5. Intervention

Sixty-four patients were randomly assigned to one of 2 groups using the diagnostic criterion "*in-yo* (陰陽, yin and yang), *kyo-jitsu* (虚実, excess or deficiency), *hyo-ri* (表裏, interior and exterior), *kan-netsu* (寒熱, cold and heat)" to receive 8-week preliminary administration of either "keishibukuryogan (桂枝茯苓丸)" or "tokishakuyakusan (当帰芍薬散)." Then, 54 non-ovulating patients were further assigned via the RCT-envelope method to receive either a continuation of the same treatment (the continuous treatment group; n = 27) or unkeito (温経湯) (the unkeito group; n = 27) for 8 weeks.

Arm 1: TSUMURA Unkeito (温経湯) Extract Granules 7.5 g/day group, n = 27.

Arm 2: continuous administration group (TSUMURA Keishibukuryogan Extract Granules 7.5 g or TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 7.5 g), n = 27.

6. Main outcome measures

Blood follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels and ovulation status.

7. Main results

Switching to unkeito decreased blood LH level and significantly stimulated ovulation.

8. Conclusions

Unkeito has an ovulatory inductive effect, regardless of conventional "*sho*"(証, pattern) identification.

9. From Kampo medicine perspective

Although eight-principle pattern identification is an important criterion for treatment selection, it was not used for the selection unkeito, which was found to stimulate ovulation. Traditional diagnosis based on clinical findings, pathology, and hematology can be an important guide to the selection of Kampo formulae.

10. Safety assessment in the article

No special problems noted.

11. Abstractor's comments

This paper indicates that switching to unkeito after treatment based on traditional "*sho*" identification improves outcome. The requirement for more objective criteria to make a Kampo diagnosis is extremely important. Other Kampo formulae beside keishibukuryogan and tokishakuyakusan should be considered to treat PCOS. It is of interest to determine whether monotherapy with unkeito would be more effective than monotherapy with other formulae. Future research is expected.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Ushiroyama T, Ikeda A, Higashino S, et al. Unkei-to for correcting luteal phase defects. *The Journal of Reproductive Medicine* 2003; 48: 729-34. CENTRAL ID: CN-00458287, Pubmed ID: 14562640

1. Objectives

To evaluate the efficacy of unkeito (温経湯) for luteal phase deficiency.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Not mentioned (the authors belong to a clinic of the Department of Obstetrics and Gynecology, Osaka Medical College), Japan.

4. Participants

One-hundred and ninety-seven patients with a luteal phase of <10 days or a luteal-phase blood progesterone concentration of <10 ng/mL, who had not received hormone therapy for the past 12 months.

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Unkeito (温経湯) Extract Granules (TJ-106) t.i.d (daily dose 7.5 g), n=103.

Arm 2: untreated control group, n=94. (88 included for analysis)

(Note) During 2 to 8 days after ovulation, 5,000 IU of human chorionic gonadotropin (hCG) was injected three times in 71 of 103 patients in arm 1 and all 94 patients in arm 2.

6. Main outcome measures

Ovarian follicle size, endometrial thickness, and luteal function improvement rating (prolongation of luteal phase or elevation in progesterone value).

7. Main results

During days 14 to 18 of the menstrual cycle, most of the unkeito group showed significant improvement in both ovarian follicle size and endometrial thickness (83/103 patients in arm 1 vs. 13/88 patients in arm 2). Luteal functions were also significantly improved by unkeito treatment

8. Conclusions

Unkeito improves luteal phase defect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned

11. Abstractor's comments

This paper is a follow-up of "Effects of unkeito, an herbal medicine, on endocrine function and ovulation in women with high basal level of luteinizing hormone secretion (*The Journal of Reproductive Medicine* 2001; 46: 451-6.) by Ushiroyama T, Ikeda A, Sakai M, et al." In addition to the previously reported efficacy of unkeito for ovulation disorder, the present paper reports its luteal phase-stabilizing effects including thickening of the endometrium and elevating progesterone value. Although the mechanism of action of unkeito remains unclear, this report provides further details of the effects of unkeito.

12. Abstractor and date

Nakata H, 1 April 2008.

4. Metabolism and Endocrine Diseases

Reference

Namiki T. Basic and clinical investigation of the effect of Kampo medicines on arteriosclerosis*. *Uehara Kinen Seimei Kagaku Zaidan Kenkyu Hokokushu* (*Research Reports of Uehara Memorial Foundation*) 2007; 21: 60-3 (in Japanese). Ichushi Web ID: 2008156867

1. Objectives

To evaluate the anti-obesity effect of bofutsushosan (防風通聖散) extract granules in obese patients and the course of high-sensitivity C-reactive protein (HS-CRP) as an arteriosclerosis-promoting factor.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The outpatient department of internal medicine at a general hospital, Japan.

4. Participants

Patients who were obese (body mass index [BMI] of 25 or greater), hypertensive (diastolic blood pressure of 90 mmHg or higher and/or a systolic blood pressure of 140 mmHg or higher), treatment-naïve or taking oral antihypertensives, and aged ≥20 to <80 years were included after giving written informed consent. Exclusion criteria were: 1) serious complications (cardiac disease, renal disease, malignancy, etc.); 2) use of medications that might affect the outcome of this trial; 3) pregnant, lactating, or likely to become pregnant; and 4) considered ineligible by the investigator.

5. Intervention

Arm 1: bofu group: conventional therapy plus oral administration of bofutsushosan (防風通聖散) extract granules (manufacturer, not specified) 7.5 mg/day before or between meals for 12 weeks in 25 patients (16 males and 9 females; mean age, 63.3±12.3 years).

Arm 2: control group: continuation of conventional therapy in 30 patients (19 males and 11 females; mean age, 64.2±10.3 years).

6. Main outcome measures

1) Body weight, BMI, blood pressure, pulse; 2) levels of fasting blood glucose, hemoglobin a1c (Hba1c), and insulin; 3) levels of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride; 4) visceral fat (measured by computed tomography [CT]); and 5) blood biochemistry including HS-CRP level, hepatic and renal functions, and electrolyte levels. 1) to 3) were measured at weeks 0, 4, 12, and 24; 4) at weeks 0 and 24; and 5) at weeks 0, 4, 8, 12, and 24.

7. Main results

Body weight was reduced by 1.16 kg (–1.5%) (from 77.82±17.53 kg at week 0 to 76.63±17.66 kg at week 24) in the bofu group, in contrast to the reduction of 1.49 kg (–2.8%) (from 71.79±10.16 kg at week 0 to 70.30±10.36 kg at week 24) in the control group. But the between-group difference was not significant. BMI was decreased by 1.6% (from 30.62±5.81 at week 0 to 30.14±5.78 at week 24) in the bofu group and 2.1% (from 27.80±2.56 at week 0 to 27.22±2.79 at week 24) in the control group.

HS-CRP was 1199.00±1040.46 μg/dL at week 0, then gradually increased by 914.54 μg/dL to 2113.54±4524.08 μg/dL at week 24 in the control group, while it was 2918.17±4239.03 μg/dL at week 0, transiently increased to 5229.26±11066.85 μg/dL at week 4, then decreased to 2694.92±3606.66 μg/dL at week 24 (decrease of 223.25 μg/dL from the week 0 level) in the bofu group.

8. Conclusions

Although body weight and BMI were higher in the bofu group than in the control group, HS-CRP at week 24 was decreased in the bofu group and increased in the control group.

9. From Kampo medicine perspective

As a basic evaluation, the anti-arteriosclerosis effect of keishibukuryogan is also described in this paper.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study is an RCT that used HS-CRP as an outcome measure to evaluate arteriosclerosis. The study is very interesting in that it used a novel approach to assess a Kampo medicine. Although results on body weight and BMI were negative, further studies are expected to reveal some positive effects.

12. Abstractor and date

Tsuruoka K, 26 January 2009, 1 June 2010.

4. Metabolism and Endocrine Diseases

References

Takashima T, Ohmori K, Higuchi N, et al. Combination therapy with probucol and daisaikoto (a Kampo medicine) - Effects of daisaikoto on HDL metabolism -. *Domyaku Koka* (*The Journal of Japan Atherosclerosis Society*) 1993; 21: 47-52 (in Japanese with English abstract).

Yamamoto K. A study of the hepatic triglyceride (TG)-lowering effects and antioxidant capacity of various Kampo preparations*. *Proceedings of the 4th Kampo Treatment Seminar at Kyoto University* 1995: 48-56 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of daisaikoto (大柴胡湯) combined with probucol in patients with hyperlipidemia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Ten institutions (1 university hospital, 7 hospitals, and 2 clinics), Japan.

4. Participants

Ninety-six patients with untreated hyperlipidemia (28 to 81 years of age) (33 with type IIa, 26 with type IIb, and 37 with type IV, according to WHO classification).

Patients with total cholesterol ≥220 mg/dL and triglyceride ≥500 mg/dL were excluded.

5. Intervention

Arm 1: probucol 500 mg/day for 16 weeks (n=35).
Arm 2: TSUMURA Daisaikoto (大柴胡湯) Extract Granules 7.5 g/day for 16 weeks (n=36).
Arm 3: combination of probucol 500 mg/day and TSUMURA Daisaikoto (大柴胡湯) Extract Granules 7.5 g/day for 16 weeks (n=25).

6. Main outcome measures

Blood level of fasting total cholesterol (T-CHO), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C), apoprotein A-I, A-II in the early morning, and B before treatment and at week 4, 8, and 16.

7. Main results

T-CHO and HDL-C decreased significantly in Arm 1 and 3. In Arm 2, T-CHO and TG showed a trend toward decrease, while HDL-C showed no change. Apoprotein A-I decreased in Arm 1, increased in Arm 2, and tended to decrease in Arm 3. There was no change in Apoprotein A-II and B in any group. Analysis according to disease type revealed that 1) for patients with type IIa hyperlipidemia, T-CHO decreased significantly in Arm 1 and 3 and HDL-C did not decrease in Arm 2 and 3; 2) for patients with type IIb and IV hyperlipidemia who had high TG levels, T-CHO decreased significantly in Arm 1 and 3 and tended to decrease in Arm 2 (–8.5% at week 16), while TG decreased significantly in only Arm 3.

8. Conclusions

The combination of daisaikoto and probucol for patients with hyperlipidemia is effective in inhibiting the reduction of HDL-C and reducing TG.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In patients with high T-CHO, probucol monotherapy decreases not only T-CHO but also HDL-C (i.e., "good" cholesterol). In this study, the combination with daisaikoto in these patients suppressed the reduction of HDL-C. In hyperlipidemic patients with high TG, their TG levels were decreased significantly by only the combination therapy. Therefore, the benefit of combination therapy with daisaikoto was shown in both types of hyperlipidemia. In addition to probucol, a number of statins with HDL-C-elevating ability have been developed, lessening the importance of inhibiting the reduction of HDL-C. However, HDL-C-increasing and TG-lowering effects, which are less with statin, are still useful. From this perspective, the combination therapy with statins and daisaikoto may still be significant and worthy of further evaluation.

The article by Yamamoto (1995) also describes a basic study using human cultured hepatocytes to evaluate the reducing effect of daisaikoto on lipid levels.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Sasaki J, Matsunaga A, Handa K, et al. Effect of daisaikoto on hyperlipidemia - comparison with clinofibrate -*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1991; 68: 3861-71 (in Japanese). Ichushi Web ID: 1992128245

1. Objectives

To evaluate the efficacy and safety of daisaikoto (大柴胡湯) in patients with hyperlipidemia.

2. Design

Randomized controlled trial (RCT).

3. Setting

University hospitals and community hospitals, Japan.

4. Participants

Sixty patients with fasting serum total cholesterol ≥ 220 mg/dl and/or triglyceride ≥ 150 mg/dl.

5. Intervention

Arm 1: administration of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 2.5 g t.i.d. for 16 weeks (n=27).
Arm 2: administration of clinofibrate 200 mg t.i.d. for 16 weeks (n=18).
Arm 3: administration of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 2.5 g t.i.d. plus clinofibrate 200 mg t.i.d. for 16 weeks (n=15).

6. Main outcome measures

Levels of serum lipids (including total cholesterol, LDL cholesterol, HDL cholesterol, and serum triglyceride), and apoprotein.

7. Main results

There was a significant reduction in serum triglyceride (P<0.05), apo A-1 (P <0.05), apo E (P <0.05), and lipid peroxide (P<0.01) in the daisaikoto monotherapy group. In contrast, there was no significant change in the clinofibrate monotherapy and clinofibrate with daisaikoto groups.

8. Conclusions

Daisaikoto monotherapy was effective for hyperlipidemia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although no patient had severe adverse effects, five had diarrhea and loose stool, one had tachycardia and menorrhagia, and one had the elevation of γ-GTP level in the daisaikoto monotherapy group. One in clinofibrate with daisaikoto group had mild adverse effects including diarrhea and abdominal pain.

11. Abstractor's comments

The low follow-up rate (20 of 60 enrolled patients dropped out of the study, leaving only 40 included in the analysis) is a limitation of this study.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Muramatsu N, Okayasu M. Clinical study on hyperlipidemia at bezafibrate and da-chai-hu-tang (dai-saiko-to) for the combination therapy (Clinical study of hyperlipidemia after combination therapy with bezafibrate and da-chai-hu-tang (dai-saiko-to)). *Shigaku* (*Odontology*) 1993; 81: 94-9 (in Japanese with English abstract).

1. Objectives

Efficacy and safety of daisaikoto (大柴胡湯) combined with bezafibrate in patients with hyperlipidemia.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Ten patients with hyperlipidemia (mean age, 55.4 years) (3 with type IIa and 7 with type IIb according to WHO classification, and 4 with *jitsu-sho* [実証, excess pattern] and 6 with *chukan-sho* [中間証, intermediate pattern]).

5. Intervention

Arm 1: combination of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 7.5 g/day and bezafibrate 400 mg/day for 12 weeks (n=5).
Arm 2: bezafibrate 400 mg/day for 12 weeks (n=5).

6. Main outcome measures

Total cholesterol (TC) and triglyceride (TG) were measured every 4 weeks and their rate of decline was calculated.

7. Main results

The rate of decline in TC was not different between arms and that in TG tended to be greater in arm 1 than arm 2.

8. Conclusions

Daisaikoto (大柴胡湯) enhances the blood TG-lowering effect of bezafibrate.

9. From Kampo medicine perspective

Deficiency-Excess Pattern Identification according to *jitsu-sho* score was adopted as a patient characteristic; 3 and 1 patient in arm 1, and 1 and 4 patients in arm 2, had *jitsu-sho* and *chukan-sho*, respectively. However, the article does not discuss *sho* (証, pattern).

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor's comments

This study compared the efficacy of bezafibrate monotherapy with that of bezafibrate and daisaikoto combination therapy. For lowering TG, the combination therapy may be more effective than monotherapy; however, this study was small and no statistical analysis was performed. Since there are few effective agents for lowering TG by a mechanism of action different from that of bezafibrate, investigation of combination therapy with such agents (e.g., daisaikoto) would be meaningful. Studies with larger sample size are needed.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

4. Metabolism and Endocrine Diseases

Reference

Yamano S, Sawai F, Hashimoto T, et al. Comparative effects between dai-saiko-to and elastase on lipid metabolism and cerebral circulation in patients with hyperlipidemia. *Kampo to Saishin-chiryo* (*Kampo & The Newest Therapy*) 1995; 4: 309-13 (in Japanese).

1. Objectives

To evaluate the effects of daisaikoto (大柴胡湯) on serum lipid level and cerebral circulation.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital, Japan.

4. Participants

Sixty-five outpatients with hyperlipidemia (i.e., serum cholesterol ≥ 200 mg/dL or serum triglyceride ≥ 150 mg/dL) on 3-month diet therapy.

5. Intervention

Arm 1: administration of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 2 g t.i.d. for 12 months (n=27).
Arm 2: administration of elastase 5,400 elastase unit (EL.U.) per day for 12 months (n=38).
Arm 3: healthy controls matched for age and sex (n=27).

6. Main outcome measures

Determination of serum lipids (including total cholesterol [TC], high density lipoprotein-cholesterol [HDL], and triglyceride [TG] levels) before treatment and after 6 and 12 months.
Hemodynamic parameters in the common carotid artery were also measured.

7. Main results

In within-group comparisons, in arm 1, TC and TG levels decreased significantly after 6 and 12 months and HDL level increased significantly after 12 months, relative to baseline (pretreatment level). In arm 2, TC and HDL showed no change but TG decreased significantly. In between-group comparisons, improvement in TC was greater in the daisaikoto arm than the elastase arm (245.2±64.5 ng/dL *vs*. 228.5 ±48.7 ng/dL), whereas between-arm improvements in HDL and TG were similar. Hemodynamic parameters of the common carotid artery, blood pressure, and heart rate were unaffected in both arms.

8. Conclusions

In patients with hyperlipidemia, daisaikoto and elastase improves serum cholesterol but not cerebral circulation. The effect of daisaikoto is greater than that of elastase.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The control group consisted of healthy subjects (matched for age and sex). This study was therefore a randomized controlled trial with two arms.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

4. Metabolism and Endocrine Diseases

References

Takagi S. Mitigation of hyponatremia after operation for cholelithiasis or gallbladder polyp by preoperative administration of wu-ling-san. *Saitama Ikadaigaku Zasshi* (*Journal of Saitama Medical School*) 1990; 17: 145-50 (in Japanese with English abstract).

Seki M, Fujioka M, Hatano T, et al. Analysis of regulatory effects of gorei-san on circulatory, metabolic and diuretic function - especially in relation to endothelial activation and increase of urinary 6-keto-prostaglandin $F_{1}\alpha$ level-. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1992; 42: 313-22 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy and safety of goreisan (五苓散) in the treatment of postoperative hyponatremia for cholelithiasis or gallbladder polyps.

2. Design

Randomized controlled trial (RCT).

3. Setting

A university hospital (Saitama Medical University Hospital), Japan.

4. Participants

Fifty-eight females undergoing surgery for cholelithiasis or gallbladder polyps (without evidence of inflammation).

5. Intervention

Arm 1: administration of TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. on an empty stomach for a mean treatment duration of 7.9 days before surgery (n=17).

Arm 2: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. on an empty stomach for a mean treatment duration of 6.3 days before surgery (n=13).

Arm 3: control group, bed rest in the hospital (n=28).

6. Main outcome measures

Morning fasting levels of blood sodium (Na), potassium (K), and chloride (Cl), white blood cell, red blood cell, and platelet counts, 24-hour urinary prostaglandin (PGE1), and 24-hour urinary excretion of 6-keto prostaglandin F1 alpha (6-keto-PGF1α) were assessed beginning before administration to 14 days after surgery.

Blood urea nitrogen (BUN) was also measured in the related article indicated below.

7. Main results

At postoperative days 0 and 1, blood sodium (Na) but not K and Cl was higher in Arm 1 than in Arms 2 and 3. There was no among-group difference in white blood cell count, whereas at postoperative days 8–14, red blood cell count was lower in Arm 1 than in Arm 3, and at postoperative day 1, platelet count was higher in Arms 1 and 2 than in Arm 3. There was no among-group difference in PGE1. But 6-keto-PGF1α increased significantly in only Arm 1 for up to 14 days after surgery.

8. Conclusions

In patients planned for gallbladder surgery, preoperative administration of goreisan significantly increased postoperative urinary PGF1α and urine output. In addition, postoperative hyponatremia was mitigated and associated with a shorter duration.

9. From Kampo medicine perspective

No significant among-group difference was observed in the number of patients with *netsu-sho* (熱証, heat pattern) or *kan-syo* (寒証, cold pattern) according to Kampo diagnosis.

10. Safety assessment in the article

Goreisan has no adverse effects, according to the related article indicated below.

11. Abstractor's comments

The interim report of this study described the effect of preoperative administration of goreisan on edema in patients planned for gallbladder surgery. This study further examined that effect in terms of its mechanism. Notably, the diuretic effect of preoperatively administered goreisan persisted after surgery. The authors speculate that this effect was caused by increased production of PGI2 (associated with an increase in urine PGF1α, a 6-keto-PGI2 metabolite), which in turn resulted in renal vasodilatation and the anti-ADH effect of 6-keto-PGF1α leading to increased diuresis. Therefore, the administration before common elective surgery (not just gallbladder surgery) may result in significant increase of urine volume or reduced postoperative hyponatremia, as well as shorten duration of hospitalization. Further evaluation of goreisan may expand its applicability to other surgeries in the future.

The article by Takagi (1990) is the interim report of the article by Seki et al (1992).

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

References

Uebaba K, Xu F. Association between the SNP in sympathetic β3-adrenergic receptor gene and the efficacy of bofutsushosan* *Nihon Toyo Igaku Zasshi* (*Kampo medicine*) 2003; 54: S225.

Kamohara S, Kawakami T, Uebaba K, et al. A study on the development of individualized medicine for the prevention, diagnosis, and treatment of metabolic syndrome using an integrative approach*. *Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku* (*Research Papers of the Suzuken Memorial Foundation*) 2009; 26: 399–403.

Xu FH, Uebaba K, Ogawa H, et al. Personalized effects of a Kampo herbal formulation on metabolism — A randomized, double-blind, placebo controlled study of bohutusei-san — — *Toho Igaku* (*Eastern Medicine*) 2012; 28: 37-59 (in Japanese).

1. Objectives

To evaluate whether bofutsushosan (防風通聖散) reduces obesity.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Medical institutions in Toyama Prefecture, Japan.

4. Participants

Invitation letters were sent to 2000 residents aged 55–65. Totally 120 subjects without diarrhea, cardiac disease, and serious hepatic or renal disease (as determined by history-taking, blood test, and electrocardiography data) were selected from obese individuals (BMI≥25) who consented to participate.

5. Intervention

Arm 1: Kanebo Bofutsushosan (防風通聖散) Extract Fine Granules 3.75 g b.i.d. at least 1 hour after meals for 2 months (n=70).

Arm 2: Indistinguishable placebo containing 5% Kanebo Bofutsushosan (防風通聖散) Extract Fine Granules with the same taste, smell, and color, and administered in the same manner as arm 1 (n=50).

6. Main outcome measures

WHOQOL-26, Oriental medicine questionnaire, serum biochemical indices, IRI (immunoreactive insulin), and homeostasis model assessment-insulin resistance (HOMA-R) were measured at baseline, 2, 4, and 8 weeks.

7. Main results

The data from 112 subjects (67 in arm 1 and 45 in arm 2) who completed the study were included in the analysis. The male/female ratio was 19/48 and 11/34 for arms 1 and 2, respectively. A total of 36 subjects (18 in arm 1 and 18 in arm 2; 32.1%) had a single nucleotide polymorphism (SNP) in β3-adrenergic receptor gene (18 Arg hetero in arm 1 and 15 Arg hetero and 3 Arg homo in arm 2). There was a significant between-arm difference ($P<0.05$) with demonstrated weight loss of 0.8 kg in arm 1 versus 0.1 kg in arm 2. Comparison of the responders (15 subjects: weight loss ≥ 1.5 kg) with the non-responders (16 subjects: weight loss ≥ 0.1 kg) in arm 1 demonstrated higher blood pressure and serum total protein before administration in arm 1 than arm 2, with 140 mm Hg the threshold for high blood pressure classification. This indicates that multiple regression analysis of initial blood pressure values and serum total protein values can be used to predict weight loss attributable to Bofutsushosan. Decreases in total cholesterol values at eight weeks compared to values before administration in arm 1 demonstrated a significant difference ($P<0.05$) in the high cholesterol group only. No differences in weight loss by the presence or absence of SNP were found.

8. Conclusions

Bofutsushosan appears to reduce body weight in obese individuals aged 55–65.

9. From Kampo medicine perspective

The results suggest that bofutsushosan is effective for obese individuals with high blood pressure and high serum total protein. This presumably equates to excess pattern and supports the classical literature..

10. Safety assessment in the article

None.

11. Abstractor's comments

An important DB-RCT that tested the effectiveness of bofutsushosan for obese individuals. The original paper on which was based the brief paper published as Kamohara at al. (2009) and Uebaba et al. (2003). It deserves recognition for following the CONSORT recommendations. An RCT of bofutsushosan examining excess pattern holds promise, as suggested in 'From Kampo medicine perspective'.

12. Abstractor and date

Tsuruoka K, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Lee S J, Bose S, Seo J-G, et al. The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: A randomized double-blind controlled clinical trial. *Clinical Nutrition* 2014; 33: 973-81. Pubmed ID: 24411490

1. Objectives

To evaluate the effects of co-administration of probiotics with bofutsushosan (防風通聖散) on obesity.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

One university hospital in Seoul, the Republic of Korea.

4. Participants

Fifty females aged 19 to 65 years with BMI of >25 kg/m^2 and waist circumference of >85 cm. Exclusion criteria were hypothyroidism, Cushing's syndrome, heart diseases, cancer, lung diseases, severe renal dysfunction (Cr >2.0 mg/dL), hepatic dysfunction, non-insulin dependent diabetes mellitus (fasting blood sugar level [FBS] >140 mg/dL), eating disorders, pregnancy, breast feeding, and body weight decrease by 10% within 6 months of the study.

5. Intervention

Arm 1: TSUMURA Bofutsushosan (防風通聖散) Extract Granules 3 g b.i.d. + probiotics twice daily (Duolac7 capsules) for 8 weeks (n=25).

Arm 2: TSUMURA Bofutsushosan (防風通聖散) Extract Granules 3 g b.i.d. + placebo twice daily (identical to Duolac7 capsules) for 8 weeks (n=25).

6. Main outcome measures

The main outcome measures were body weight and gut permeability. The secondary outcome measures were BMI, blood pressure, blood parameters (e.g., lipid levels), fecal bacteria count, endotoxin level, body fat level (as measured by bioelectrical impedance), and quality of life (as measured using the Korean version of obesity-related quality of life [KOQOL] scale). In the article, parameters including body weight, waist circumference, BMI, and body fat level (bioelectrical impedance) were termed “body composition parameters,” while other parameters including blood parameters, fecal bacteria count, and endotoxin level were termed “metabolic biomarkers.”

7. Main results

Although body weight and waist circumference were significantly decreased in both arms (P=0.000), no inter-arm difference in the body composition parameters or metabolic biomarkers were found. Correlation analysis revealed that change in body composition was positively correlated with endotoxin level (γ=0.441, P<0.05 for body weight; γ=0.350, P<0.05 for fat mass) and lactic acid bacteria count (γ=0.425, P<0.05 for body weight; γ=0.407, P<0.05 for BMI). The body composition parameters, waist circumference and total cholesterol level were positively correlated with Gram negative bacteria count (γ=0.359 and γ=0.393, respectively; P<0.05 for both) and *Bifidobacterium breve* count was negatively correlated with endotoxin level (γ=−0.350, P<0.05).

8. Conclusions

Correlation between gut microbiota and change in body composition shows that probiotics affect energy metabolism in obese subjects. Correlation between endotoxin level and body weight decrease suggests that probiotics play a role in preventing the growth of endotoxin-producing bacteria in gut microbiota that promote obesity-associated dysbiosis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This DB-RCT was conducted in the Republic of Korea and evaluated the effects of co-administration of bofutsushosan and probiotics on obesity. This study was a registered clinical trial of the Korean National Institute of Health (NIH) and seems to be a well-designed study. Although body weight was decreased in both arms, the body weight decrease was not significantly different between arms. Therefore, the efficacy of adding bofutsushosan to probiotics remains unknown. In the article, the authors focused mainly on the results of correlation analyses rather than the effectiveness of probiotics. Research questions posed at the time of the study’s design seem to remain unanswered. The significance and effects of co-administration of bofutsushosan were poorly described. More explanation is needed. Further development of this research is anticipated.

12. Abstractor and date

Tsuruoka K, 31 March 2017.

5. Psychiatric/Behavioral Disorders

References

Shimada Y, Terasawa K, Yamamoto T, et al. A well-controlled study of choto-san and placebo in the treatment of vascular dementia. *Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)* 1994; 11: 246–55. Ichushi Web ID: 1996055624

Shimada Y, Terasawa K, Yamamoto T, et al. Efficacy of choto-san on vascular dementia: A well, placebo-controlled study. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 370–1 (in Japanese) Ichushi Web ID: 1996075788

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) in the treatment of vascular dementia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Multicenter clinical trials involving Toyama Medical and Pharmaceutical University Hospital, Kagoshima University, and three general hospitals, Japan.

4. Participants

Sixty patients (9 males and 51 females; mean age, 78.9 years, including both inpatients and outpatients) who satisfied the DSM-III-R criteria for dementia, were diagnosed with cerebrovascular dementia, had Carlo Loeb modified ischemic scores of ≥ 5 points, were in stable general health, and participated in the study with the consent of one or more family members.

5. Intervention

Arm 1: TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g t.i.d. after meals for 12 weeks (6 males and 26 females).

Arm 2: TSUMURA-manufactured placebo composed of such ingredients as lactose, dextrin, maltose, and cellulose, indistinguishable in appearance (color) and taste from chotosan (釣藤散), as determined before the trial, 2.5 g t.i.d. after meals for 12 weeks (3 males and 25 females).

6. Main outcome measures

Subjective symptoms, neurological manifestations, psychiatric manifestations, severity, and improvement in impaired activities of daily living; dementia status evaluated using the Revised Hasegawa Dementia Scale (HDS-R), every 4 weeks; overall safety and usefulness, evaluated at 12 weeks after the start of treatment.

7. Main results

Of 60 patients, 57 completed treatment (31 with chotosan and 26 with placebo). The following measures were significantly improved in patients receiving chotosan: global improvement rating ($P<0.05$, $P<0.01$, and $P<0.01$ at 4, 8, and 12 weeks, respectively); usefulness ($P<0.01$ at 12 weeks); subjective symptoms ($P<0.05$, $P<0.01$, and $P<0.01$ at 4, 8, and 12 weeks, respectively); psychiatric manifestations ($P<0.05$, $P<0.01$, and $P<0.01$ at 4, 8, and 12 weeks, respectively); and activities of daily living ($P<0.05$, $P<0.05$ at 4 and 12 weeks, respectively). Improvement of neurological manifestations did not significantly differ between arms at 4, 8, and 12 weeks. Subjective symptoms (“dizziness,” “shoulder muscle stiffness,” and “palpitations”) and psychiatric manifestations (“interest in TV programs and books,” “lack of expression,” and “disorientation”) were significantly improved in the chotosan group. Chotosan significantly improved HDS-R from 15.34±3.76 at baseline to 16.65±4.43 at 4 weeks ($P<0.05$), 17.94±4.79 at 8 weeks ($P<0.01$), and 19.39±5.71 at 12 weeks ($P<0.01$), although there was no significant difference between arms.

8. Conclusions

Chotosan is effective for cerebrovascular dementia.

9. From Kampo medicine perspective

Chotosan has traditionally been used to treat headache and dizziness in patients who are past middle age and relatively weak physically. These symptoms are considered to be indicators of cerebral arteriosclerosis and cerebrovascular disorder by modern medicine. The present study succeeded in objectively evaluating the clinical efficacy of chotosan for cerebrovascular dementia.

10. Safety assessment in the article

Treatment was discontinued in 1 patient receiving chotosan (3.1%) who had a history of hepatopathy and whose oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) levels increased during treatment and returned to normal after treatment discontinuation. Another patient receiving chotosan (3.1%) had a decrease in potassium that was too mild to affect treatment. There was no significant difference in overall safety between arms.

11. Abstractor’s comments

This is a well-designed RCT that generated high-quality evidence. There is much to learn from this study, which included blinding, included a placebo arm, considered dropouts, and analyzed safety and usefulness in an intent-to-treat population. A larger-scale RCT performed later to re-evaluate efficacy (Terasawa K, Shimada Y, Kita T, et al. Choto-san in the treatment of vascular dementia: A double blind, placebo-controlled study. *Phytomedicine* 1997; 4: 15–22.) is also informative.

12. Abstractor and date

Tsuruoka K, 22 September 2008, 31 December 2013.

5. Psychiatric/Behavioral Disorders

References

Terasawa K, Shimada Y, Kita T, et al. Choto-san in the treatment of vascular dementia: A double blind, placebo-controlled study. *Phytomedicine* 1997; 4: 15-22.
Terasawa K. Chotosan in the treatment of vascular dementia. *Pharma Medica* 2007; 25: 57-9 (in Japanese). Ichushi Web ID: 2008035997 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) for vascular dementia using more objective criteria.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Nine hospitals including university hospitals of Toyama Medical and Pharamaceutical University, Kagoshima University, Tohoku University, etc., Japan.

4. Participants

A total of 139 patients (50 males and 89 females with a mean age of 76.6 years) who were diagnosed with vascular dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R criteria for dementia and who fulfilled the following guidelines (Carlo Loeb modified ischemic score of ≥ 5 points; stable physical condition; informed consent obtained).

5. Intervention

Arm 1: treatment with TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g t.i.d. after meals for 12 consecutive weeks (n=69; 28 males and 41 females).

Arm 2: treatment with placebo consisting of lactose, dextrin, maltose, cellulose, etc., which was manufactured by Tsumura & Co. and not distinguishable from chotosan in terms of color or taste, at the same dose and frequency as in arm 1 (n=70; 22 males and 48 females).

6. Main outcome measures

The rating of severity and improvement in subjective symptoms, neurological symptoms, psychiatric symptoms, and disturbance in activities of daily living (ADL) as well as cognitive function using the Revised Hasegawa's Dementia Scale (HDS-R) assessed every 4 weeks. The overall safety rating and utility rating assessed at Week 12.

7. Main results

In the chotosan group compared with the placebo group, the scores for overall improvement (P<0.01 at Week 8, P<0.001 at Week 12), utility (P<0.001 at Week 12), improvement in subjective symptoms (P<0.05 at Week 8, P<0.01 at Week 12), psychiatric symptoms (P<0.05 at Week 4, P<0.001 at Week 8, P<0.001 at Week 12), and ADL (P<0.05 at Week 12) were significantly higher. No significant between-group difference was observed in neurological symptoms. The following symptoms improved significantly in the chotosan group compared with the placebo group: spontaneity of conversation; lack of facial expression; decline in simple arithmetic ability; global intellectual ability; nocturnal delirium; sleep disturbance; hallucination or delusion. The HDS-R score tended to be higher in the chotosan group.

8. Conclusions

These results suggest that chotosan may be effective in the treatment of vascular dementia.

9. From Kampo medicine perspective

Chotosan has traditionally been used in physically weak, middle-aged or older patients with symptoms such as headache, heaviness of head, vertigo, hot flashes, sleeplessness, or tinnitus. Since these symptoms may also be associated with cerebrovascular disorder, the clinical efficacy of chotosan for vascular dementia was objectively evaluated in this study.

10. Safety assessment in the article

While adverse drug reactions occurred in 5 patients in the chotosan group (rash, diarrhea, appetite loss, heartburn, and hypertension), there was no difference in the overall safety rating between the two groups.

11. Abstractor's comments

This RCT evolved from a prior larger study that evaluated the efficacy of chotosan for vascular dementia (Shimada Y, Terasawa K, Yamamoto T, et al. A well-controlled study of Chotosan and placebo in the treatment of vascular dementia. *Wakan Iyakugaku Zasshi* [*Journal of Traditional Medicines*] 1994; 11: 246-55.). It was well designed and produced high-quality evidence. The results were generally similar to those of the previous study, with a few differences in the symptoms that showed improvement (refer to the above reference). In the future, chotosan should be compared to the gold standard treatment in modern medicine. The article by Terasawa (2007) is the Japanese digest of the paper by Terasawa et al (1997).

12. Abstractor and date

Tsuruoka K, 22 April 2008, 31 December 2013.

5. Psychiatric/Behavioral Disorders

Reference

Iwasaki K, Kanbayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "ba wei di huang wan" in the treatment of dementia. *Journal of the American Geriatrics Society* 2004; 52: 1518-21. CENTRAL ID: CN-00491098, Pubmed ID: 15341554

1. Objectives

To evaluate the efficacy of hachimijiogan (八味地黄丸) for dementia.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Single hospital (long-term care facility), Japan.

4. Participants

Thirty-three anticholinergic-untreated dementia patients with an MMSE score of 0 – 25.

5. Intervention

Arm 1: oral administration of Uchida Hachimijiogan (八味地黄丸) 2.0g t.i.d. after meals for 8 weeks (n=16).

Arm 2: oral administration of 2.0 g of honey-mixed black rice powder as placebo t.i.d.after meals for 8 weeks (n=17).

6. Main outcome measures

Mini-Mental State Examination (MMSE) score, Barthel Index, and internal carotid artery pulsatility index at baseline, 8 weeks after start of dosing, and 8 weeks after completion of dosing.

7. Main results

After 8 weeks of dosing, in arm 1, a significant improvement over baseline was observed in MMSE score, from 13.5±8.5 to 16.3±7.7, Barthel Index, from 61.8±34.6 to 78.9±21.1, and pulsatility index, from 2.5±1.7 to 1.9±0.5, whereas no changes were noted in these variables in arm 2. At 8 weeks after completion of dosing (16 weeks after start of dosing), MMSE score and Barthel Index of arm 1 returned to control (arm 2) levels.

8. Conclusions

Hachimijiogan improves cognitive function, activities of daily living, and internal carotid arterial blood flow in dementia patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the study period, no adverse drug reactions occurred in either group. After completion of dosing, a hospital change due for personal reasons, and urinary tract infections and upper respiratory tract infections occurred in 1 and 2 patients in arm 1, respectively.

11. Abstractor's comments

This study, which investigated the efficacy of hachimijiogan for preserving or restoring cognitive function and activities of daily living in elderly dementia patients in a double-blind RCT, provides high-quality evidence. At week 16, MMSE scores of the hachimijiogan group had a large standard deviation (SD), indicating wide inter-individual variation in dementia severity. Even in the placebo group, MMSE score and Barthel Index did not worsen, though the study population included patients with Alzheimer's disease, suggesting disease progression may have been slower in these very old patients (aged 83 to 85 years, on average). In addition, whether the hachimijiogan-induced improvement (a mean of 2.8 points) in the dementia score of the MMSE led to clinical improvement will require further investigation. It is recommended that investigation separate patients with cerebrovascular disorders from those with Alzheimer's disease. To further elucidate the efficacy of hachimijiogan, longer-term observation of a larger sample is expected.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

5. Psychiatric/Behavioral Disorders

Reference

Suzuki T, Futami S, Igari Y, et al. A Chinese herbal medicine, choto-san, improves cognitive function and activities of daily living of patients with dementia: A double-blind, randomized, placebo-controlled study. *Journal of the American Geriatrics Society* 2005; 53: 2238-40. CENTRAL ID: CN-00554102, Pubmed ID: 16398922

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) for improvement of cognitive function and activities of daily living in dementia patients.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Not mentioned (authors belong to Department of Geriatric Medicine, Nippon Medical School Hospital, and another hospital), Japan.

4. Participants

Thirty patients with mild or moderate dementia: 13, Alzheimer type dementia (MMSE[1] score 14 – 25) and 17, Alzheimer disease (MMSE score 10 – 21) or cerebrovascular disorders (MMSE score not indicated). All were included in the analysis population.
[1]MMSE: Mini-Mental State Examination

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Chotosan (釣藤散) Extract Granules t.i.d. before meals for 8 weeks (n=10).
Arm 2: oral administration of 2.5 g of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules t.i.d. before meals for 8 weeks (n=10).
Arm 3: oral administration of 2.5 g of placebo t.i.d. before meals for 8 weeks (n = 10).

6. Main outcome measures

Cognitive function evaluated by the MMSE; activities of daily living, by Barthel Index (BI); and caregiver burden, by Zarit Caregiver Burden Scale (Z score).

7. Main results

In arm 1, a significant improvement over baseline was observed in MMSE score, from 15.5±4.0 to 17.5±4.9, and BI, from 67.5±34.6 to 71.5±35.8, whereas no such improvement was seen in arm 2 or 3. There was no significant difference in Z score among the 3 arms.

8. Conclusions

Chotosan improves cognitive function and activities of daily living in dementia patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned

11. Abstractor's comments

This study, which investigated the efficacy of chotosan and goshajinkigan for cognitive function and activities of daily living in elderly patients with dementia in a double-blind RCT, provides high-quality evidence. Although the sample size was small and no statistically significant difference between the arms was found, cognitive function and activities of daily living were significantly improved over baseline in the chotosan group. However, no baseline characteristics except for age and sex are indicated, the underlying disease is not mentioned, and MMSE scores of patients with cerebrovascular disorders are not given. Patient characteristics and each score should be provided. Furthermore, MMSE score in the chotosan group was improved over baseline, but the level after 8-week dosing was almost equal to that in the placebo group (presumably because there was a significant difference in MMSE score at baseline between 2 groups). A future investigation of the efficacy of chotosan for improving cognitive function and activities of daily living is expected with a larger sample size and for a longer period.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Iwasaki K, Satoh-Nakagawa T, Maruyama M, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine yi-gan san for improvement of behavioural and psychological symptoms and activities of daily living in dementia patients. *Journal of Clinical Psychiatry* 2005; 66: 248-52. CENTRAL ID: CN-00502716, Pubmed ID: 15705012

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for treating behavioral disorders and improving activities of daily living in dementia patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Three hospitals (long-term care facilities), Japan.

4. Participants

A total of 60 patients with dementia due to Alzheimer's disease, cerebrovascular disorder, or Lewy body disease, having a Mini-Mental State Examination (MMSE) score of <24 and a neuropsychiatric inventory (NPI) score of >6; of these, 52 patients were included for analysis.

5. Intervention

Arm 1: oral administration of 7.5 g/day of TSUMURA Yokukansan (抑肝散) Extract Granules in 3 divided doses before meals for 4 weeks (n=27).
Arm 2: untreated control group (n=25).

6. Main outcome measures

MMSE score, Barthel Index, and NPI score.

7. Main results

No changes were found in MMSE score in either group. Significant improvements (compared with baseline) were observed in Barthel Index, from 56.4±34.2 to 62.9±35.2, and NPI score, from 37.9±16.1 to 19.5±15.6, in arm 1. In NPI subscales for hallucination, anxiety/excitement, etc., significant improvements over baseline were noted in arm 1. Additional treatment with tiapride hydrochloride, a dopamine D_1 selective neuroleptic, was required in 11 patients in arm 2 but in none in arm 1.

8. Conclusions

Yokukansan is effective for improvement of behavioral disorders and activities of daily living in dementia patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Dizziness and impaired postural sway were reported in 6 patients (54.5%) treated with tiapride hydrochloride. Two patients (7.4%) who continued yokukansan after the end of the observation period became oversedated but recovered with a reduced dose.

11. Abstractor's comments

This study, which investigated the efficacy of yokukansan for cognitive function and activities of daily living in elderly dementia patients in an RCT, provides high-quality evidence. However, the same nurses who rated MMSE and NPI scores, and Barthel Index may also have administered yokukansan, suggesting the possibility of a lack of blinding, which may have affected evaluations. In future, the effects of yokukansan in dementia patients are expected to be studied over a longer term.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Mizukami K, Asada T, Kinoshita T, et al. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. *The International Journal of Neuropsychopharmacology* 2009; 12: 191-9. CENTRAL ID: CN-00704589, Pubmed ID: 19079814

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) in the treatment of behavioural and psychological symptoms of dementia.

2. Design

Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting

Twenty medical institutions (the first author belongs to the faculty of the Department of Clinical Neuroscience, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba), Japan.

4. Participants

One hundred and six patients aged 55–85 years and diagnosed with Alzheimer's disease, including mixed-type dementia or dementia with Lewy bodies. There were 59 outpatients (20 males and 39 females, mean age 78.7±5.4 years) and 47 inpatients (19 males and 28 females, mean age 78.5±6.7 years).

5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散) Extract Granules 2.5 g t.i.d. orally for 4 weeks, followed by observation with no treatment for 4 weeks (n=54).

Arm 2: No treatment with observation for 4 weeks, followed by TSUMURA Yokukansan (抑肝散) Extract Granules 2.5 g t.i.d. orally for 4 weeks (n=52).

6. Main outcome measures

Behavioural and psychological symptoms of dementia (BPSD) and cognitive functions were evaluated using the Neuropsychiatric Inventory (NPI) and Mini-Mental State Examination (MMSE), respectively. Activities of daily living were evaluated using the Instrumental Activities of Daily Living (IADL) in outpatients and the Barthel Index in inpatients. Patients were evaluated at baseline, 4 weeks, and 8 weeks.

7. Main results

In both arms, total scores on the NPI significantly improved after 4 weeks of yokukansan treatment (P<0.01), but not during the no-treatment period. Among the NPI subscales, delusion, hallucination, agitation/aggression, and irritability/lability (P<0.01 for each) improved in arm 1 and agitation/aggression (P<0.01), depression, anxiety, and irritability/lability (P<0.05 for each) improved in arm 2 after the yokukansan treatment.

8. Conclusions

Oral administration of yokukansan improves behavioural and psychological symptoms associated with dementia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions were reported in 6 patients. Gastrointestinal symptoms including vomiting, diarrhea, nausea, and epigastric pain developed in 3 patients. When yokukansan treatment was discontinued, these symptoms promptly resolved. Hypokalemia was reported in 2 patients, one of whom experienced oversedation. When yokukansan treatment was discontinued, serum potassium levels returned to normal in both patients. Another patient developed lower leg edema. No serious adverse reactions, such as extrapyramidal symptoms and hallucination, were observed.

11. Abstractor's comments

This is a very meaningful clinical study that demonstrated the efficacy of yokukansan for improving BPSD in a multicentre setting. In both arms, symptoms improved during yokukansan treatment compared with the no-treatment period. The results would be more valuable if the data had been analyzed rigorously as a cross-over design. In the future, larger-scale multicentre placebo-controlled studies and clinical studies of longer-term treatment with yokukansan are needed to further demonstrate the efficacy of this agent.

12. Abstractor and date

Goto H, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Fujita H, Yoshida M, Yomoda S. Effects of Yokukansankachimpihange on cognitive ability, an open randomized controlled trial. *Psychiatry* 2013; 23: 130-8 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy and safety of yokukansankachimpihange (抑肝散加陳皮半夏) on cognitive function.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Residents or users and staff of 3 institutions in Toyama Prefecture, Japan.

4. Participants

Forty-one adult males and females aged 55 years or older with moderate strength, slightly weak gastrointestinal system, easy fatigability, aggressiveness, irritability, insomnia, and mild psychiatric symptoms

5. Intervention

Arm 1: Kracie Yokukansankachimpihange (抑肝散加陳皮半夏)Extract Granules 7.5 g/day (3.75 g b.i.d) for 4 weeks (n=20)

Arm 2: no administration of yokukansankachimpihange (n=21)

6. Main outcome measures

Prior to and 4 weeks after the study, the Mini-Mental State Examination (MMSE), Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-J cog.), and assessments of behavioral and psychological symptoms of dementia (BPSD) and activities of daily living (neuropsychiatric inventory [NPI] and disability assessment for dementia [DAD]) were performed. In addition, changes in oxyhemoglobin concentration (ΔO_2Hb) were measured using an infrared oxygen monitor to determine cerebral blood flow during execution of the following tasks: standard clinical assessment for attention, tapping span, memory updating test, digit span, and compound digit cancellation test.

7. Main results

Three subjects in arm 1 dropped out of the study. There was no significant between-group difference in MMSE score, NPI score, or DAD score The amount of change in ADAS-J cog. was –2.9 ± 3.5 in arm 1 and 0.22 ± 2.6 in arm 2, indicating a significant improvement in arm 1 compared to arm 2 (P<0.01). The ΔO_2Hb value in the left hemisphere during task execution was significantly higher in arm 1 than in arm 2 (P<0.05). Of the tasks executed during measurement of cerebral blood flow, the standard clinical assessment for attention showed a significantly larger difference in total number of answers between the baseline and 4 weeks after the study in arm 1 than in arm 2 (P<0.05).

8. Conclusions

Yokukansankachimpihange improves ADAS-J cog. for core symptoms and oxygen metabolism in the brain during task execution.

9. From Kampo medicine perspective

The inclusion criteria for the study are the *sho* (証, pattern) for yokukansankachimpihange.

10. Safety assessment in the article

Treatment was discontinued in 2 subjects receiving yokukansankachimpihange due to increased blood pressure and vomiting. Changes in blood components were within the normal range in both groups.

11. Abstractor's comments

This landmark clinical study has clarified the effects of yokukansankachimpihange on cognitive function, based on clinical symptoms (including core symptoms, BPSD and activities of daily living), and changes in cerebral blood flow in the frontal lobe. On the other hand, the authors state only that residents and staff of institutions were included in the study without providing detailed information on them; that is, effects in dementia patients and those in normal persons are mixed in study results. The authors also state that subjects were stratified and randomized by sex, age, and MMSE score, although the number of the subjects was small and other measurements may be biased. In fact, there was no between-group difference in mean baseline ADAS-J cog. score, but the yokukansankachimpihange group included many subjects with high ADAS-J cog. scores. For this reason, the amount of change in score may have been larger in the yokukansankachimpihange group. Moreover, as described in the Discussion section, the amount of change in oxyhemoglobin concentration (ΔO_2Hb), which was measured to determine brain metabolism during task execution, was less in the control group than in the yokukansankachimpihange group after 4 weeks, thereby contributing to the significant difference between the two groups. However, these laborious investigations and evaluations of cerebral blood flow will play an important role in determining the effects of Kampo medicines on cognitive function. It is hoped that clinical studies in dementia patients will be continued.

12. Abstractor and date

Goto H, 6 June 2015

5. Psychiatric/Behavioral Disorders

Reference

Egawa H, Hamaguchi S. Clinical applications of Kampo medications – Clinical applications of Kampo medications for Postoperative Cognitive Dysfunction (POCD) – Yokukansan and perioperative management of fracture of the proximal femur in the elderly.* *Nou* 21 (*Brain 21)* 2015; 18: 271-4.

1. Objectives

To evaluate the effectiveness of yokukansan (抑肝散) for cognitive dysfunction after surgery for fracture of the proximal femur/ in the elderly.

2. Design

Randomized controlled trial (RCT).

3. Setting

Centers not mentioned. (The authors are from the Pain Clinic and Department of anaesthesiology), Japan

4. Participants

Forty patients, 70-years or older scheduled for femoral neck fracture surgery.

5. Intervention

Arm 1: Yokukansan (抑肝散) 7.5g/day (manufacturer and administration frequency not mentioned) taken orally for 7-14 days then surgery and a further 3 weeks administration (n=20).

Arm 2: No administration (n=20).

6. Main outcome measures

Cognitive function test (Mini-Mental State Examination: MMSE) combined with 3-item Nishimura Mental State Scale for the Elderly (NMS); days hospitalized (before surgery); and cognitive function on days 1, 3, 5, 7, 10, 14, and 21 after surgery.

7. Main results

MMSE was 3.3±1.0 and NMS was 5.6±1.2 on day 1 after surgery in both Arms 1 and 2, which was a significant decrease compared to presurgery (P<0.01). MMSE improved significantly from day 3 to 7 after surgery in arm 1 compared to arm 2 (P<0.05), but there was no difference in NMS between groups. A significant improvement was found in arm 1 compared to arm 2 for both MMSE and NMS from day 7 to 21 after surgery (P<0.05).

8. Conclusion

Yokukansan suppresses the decrease in cognitive function after surgery for fracture of the proximal femur in elderly patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This is a very interesting clinical study of the application of yokukansan, which is frequently used for elderly dementia patients, to decreased cognitive function after surgery in the elderly. However, perhaps because it is a short paper, the authors did not mention any background factors in either group such as gender or primary disease, and they did not describe the administration methods or details of whether there were any dropouts, etc. In addition, it would appear that there was a difference in MMSE on day 1 after surgery, while the authors asserted that taking yokukansan improved MMSE from day 3 after surgery compared to the non-administration group. There is the possibility that administration of yokukansan before surgery affected this difference, so, to clarify the postsurgery effects, the authors would have preferably measured MMSE and NMS immediately before surgery. Nevertheless, the study suggests that yokukansan improves cognitive function after surgery for fracture of the proximal femur, so hopefully those details will be clearly articulated and it will be widely used in clinical practice.

12. Abstractor and date

Goto H, 31 December 2016

5. Psychiatric/Behavioral Disorders

References

Takase S. The efficacy of Yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 132‐4 (in Japanese).

Takase S, Yokoyama H. Using a Kampo medication in the perioperative period – The preventative effects of yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly*. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2013; 22: 113–19 (in Japanese).

1. Objectives

To evaluate the efficacy of yokukansan (抑肝散) for postoperative delirium after cardiovascular surgery in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Cardiovascular Surgery, Fukushima Medical University Hospital, Japan.

4. Participants

Thirty patients who underwent cardiovascular surgery since April 2009.

5. Intervention

Arm 1: Administration of TSUMURA Yokukansan (抑肝散) Extract Granules 2.5 g t.i.d. from 5-7 days prior to surgery until the day of discharge except for the day of surgery (n=15).

Arm 2: No administration of yokukansan (n=15).

6. Main outcome measures

Each item on the 10-item Delirium Rating Scale-J (DRS-J) (orientation, hallucination, delusions, agitation, motor restraints, perceptual disturbances, physical disorders, sleep-wake cycle disturbance, lability of mood, fluctuation of symptom severity). Assessment by physicians of 10 items of the DRS-J at 3 days prior to surgery, and 3 and 10 days after surgery. Assessment by nurses of 6 items of the DRS-J (hallucination, agitation, motor restraints, perceptual disturbances, sleep-wake cycle disturbance, lability of mood) at 3 days prior to surgery and 1–5, 7, 10, 12, 14, and 16 days after surgery.

7. Main results

In the assessments by physicians, there were significant between-arm differences in orientation (P=0.0033), delusion (P=0.021), agitation (P=0.0011), and lability of mood (P=0.0044). In the assessments by nurses, there were significant between-arm differences in hallucination (P=0.0383), agitation (P=0.0049), and lability of mood (P=0.0364). Overall assessments (the total sum of the scores for all items) both by physicians and by nurses tended to improve in arm 1 more than arm 2.

8. Conclusions

Yokukansan is effective for preventing delirium after cardiovascular surgery in elderly patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Using diuretics after cardiovascular surgery makes patients susceptible to hypokalemia; however, no impacts from yokukansan administration were observed.

11. Abstractor's comments

This is an innovative clinical trial evaluating the efficacy of yokukansan for delirium after cardiovascular surgery in the elderly. It is significant that the authors used yokukansan to solve an actual clinical problem such as post-operative delirium and demonstrated its effectiveness. On the other hand, the control group included three cerebrovascular disorder patients and one patient with preoperative dementia, so the mean surgical risk score was significantly high, a circumstance that might have meant greater susceptibility to delirium. Considering that the envelope method was used to allocate participants, it may have been better if the allocation was randomized more rigorously. Nevertheless, this interesting clinical study provides a helpful perspective for a future large-scale study assessing the efficacy of yokukansan for preventing postoperative delirium in the elderly.

12. Abstractor and date

Goto H, 25 December 2010, 31 December 2013, 6 June 2015.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
5. Psychiatric/Behavioral Disorders

References

Sugano N, Aoyama T, Sato T, et al. Randomized phase II study of TJ-54 (Yokukansan) for postoperative delirium in gastrointestinal and lung malignancy patients. *Molecular and Clinical Oncology*. 2017; 7: 569-73.
CENTRAL ID: CN-01421749, Pubmed ID: 28855990

1. Objectives

To evaluate the efficacy and safety of yokukansan（抑肝散）for postoperative delirium in patients with gastrointestinal or lung cancer

2. Design

Randomized controlled trial (RCT)

3. Setting

Nine hospitals, including one university hospital, Japan

4. Participants

A total of 186 patients aged 70 years or older who underwent surgery for gastrointestinal or lung cancer with an Eastern Cooperative Oncology Group Performance Status score of 2 or less, who underwent a mini-mental state examination (MMSE), and who had normal hepatic, renal, and bone marrow functions. Patients were excluded if they had a history of severe hypersensitivity to drugs, had serious constipation, were pregnant, or were lactating.

5. Intervention

Arm 1: TSUMURA Yokukansan（抑肝散）Extract Granules 7.5 g/day (2.5 g t.i.d.) administered orally for 7 days preoperatively and 4 days postoperatively, excluding the operation day (n=93)
Arm 2: Control group (n=93)

6. Main outcome measures

Primary endpoints were the incidence of postoperative delirium and safety. Secondary endpoint was the length of hospital stay. Delirium was assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, independently by two physicians.

7. Main results

The incidence of delirium was 6.5% in Arm 1 (n=6) and 9.7% in Arm 2 (n=9), showing no significant difference between the two arms. A subgroup analysis showed that, among patients with MMSE scores of ≤26, the incidence of postoperative delirium was 9.1% in Arm 1 and 26.9% in Arm 2 (risk ratio, 0.338; 95% CI, 0.078–1.462, *P*=0.115). Among patients with MMSE scores of ≥27, the incidence of postoperative delirium was 6.8% in Arm 1 and 3.6% in Arm 2 (risk ratio, 1.864; 95% CI, 0.356–9.778, *P*=0.453). The length of hospital stay was 16 days in Arm 1 and 15 days in Arm 2, showing no difference between the arms.

8. Conclusion

In patients with MMSE scores of ≤26, yokukansan reduces the risk of delirium after surgery for gastrointestinal or lung cancer.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Occurrence of adverse reactions did not differ between the two arms. No adverse reactions appeared to be related to yokukansan.

11. Abstractor's comments

Postoperative delirium is an important postoperative management issue. With a focus on this, and using yokukansan, which has been widely used recently for delirium in patients with other behavioral and psychological symptoms of dementia (BPSD), the authors conducted this interesting clinical study evaluating the effects of yokukansan on postoperative delirium in patients with gastrointestinal or lung cancer. Analysis of the primary endpoint failed to show an intergroup difference, partly because the incidence of delirium in the control group was lower than expected, as stated by the authors in the Discussion section, for which further studies in larger samples would be needed. The subgroup analysis showed reduction in the risk of delirium after yokukansan administration in those with MMSE scores of ≤26. This indicates that yokukansan may be effective in suppressing delirium in patients with lower cognitive function. However, regarding those with MMSE scores ≥26, the article does not provide details such as the number of the patients. Furthermore, the article does not provide any basis for the MMSE cutoff score of 26, and therefore the efficacy may not be convincing. Given that this was a phase 2 study, a phase 3 clinical study based on these data is awaited to further clarify the disease conditions for which yokukansan is indicated.

12. Abstractor and date

Goto H, 1 June 2020.

5. Psychiatric/Behavioral Disorders

Reference

Miyaoka T, Furuya M, Yasuda H, et al. Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia: An open-label study. *Clinical Pharmacology* 2009; 32: 6–9.

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Psychiatry, Shimane University School of Medicine, Japan.

4. Participants

Patients diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) who met treatment-resistance criteria as follows:

a) no satisfactory response to antipsychotic drugs from at least 2 different classes, in a dose equivalent to at least 1000 mg/d of chlorpromazine for at least 6 weeks during the course of illness;
b) no period of good functioning within the preceding 2 years;
c) positive and negative syndrome scale (PANSS) scores in the 70th percentile or higher, based on normative data for patients with chronic schizophrenia.

5. Intervention

The study was brief (4 weeks) and had an open-label design.

Arm 1: administration of Yokukansan (抑肝散) 6.7 ±2.5 g (range, 2.5–7.5 g)/day (n=34).

Arm 2: no administration of Yokukansan (抑肝散) (n=25).

All patients were taking conventional and/or atypical antipsychotic medications, including olanzapine, risperidone, quetiapine, aripiprazole, perospirone, haloperidol, levomepromazine, and zotepine.

6. Main outcome measures

PANSS and drug-induced extrapyramidal symptom scale (DIEPSS) were assessed at baseline, and after 2 and 4 weeks of treatment.

7. Main results

In Arm 1, treatment with Yokukansan significantly reduced the PANSS positive symptoms subscale score of 27.7±6.1 at baseline by 68.2% at 2 weeks (means score 18.9±5.0) (P<0.001) and 43.0% at 4 weeks (mean score, 11.9±3.7) (P<0.001), the PANSS negative symptom subscale score of 30.4±5.8 at baseline by 73.7% at 2 weeks (mean score, 22.4±4.3) (P<0.001) and 59.9% at 4 weeks (mean score, 18.2±2.2) (P<0.001), and the PANSS general psychopathology subscale score of 65.1±5.4 at baseline by 70.5% (mean score, 45.9±9.0) (P<0.001) at 2 weeks and 60.8% (means score, 39.6±6.9) (P<0.001) at 4 weeks. In the control group, each PANSS subscale remained unchanged. There was no significant difference in the DIEPSS scores in both groups.

8. Conclusions

In this pilot study, statistically significant improvement in clinical assessment scale was observed after yokukansan treatment, suggesting that yokukansan has efficacy for treatment-resistant schizophrenia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

DIEPSS corresponds to the safety assessment, and no serious adverse effects of yokukansan were reported. A few mild and transient adverse events included 2 cases of nausea and 1 case of tiredness.

11. Abstractor's comments

This RCT was designed to evaluate the efficacy of yokukansan for schizophrenia, as it has been shown to be effective in treating psychiatric disorders such as dementia. The idea is great and the result is clinically significant. As the authors discuss, the absence of blinding may have introduced bias into the outcome assessment. The total number of the participants of the two arms is 59. However, the Figure 1 legend states that 54 completed a 4-week trial, making unclear the number of subjects who dropped out. Because of the small sample size, the number of subjects used as denominator for analyses is a concern. More precise design for the main trial is anticipated.

12. Abstractor and date

Tsuruoka K, 2 January 2011.

5. Psychiatric/Behavioral Disorders

References

Miyaoka T, Furuya M, Horiguchi J, et al. Efficacy and safety of yokukansan in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled trial (a Positive and Negative Syndrome Scale, five-factor analysis). *Psychopharmacology* 2015; 232: 155-64.

Miyaoka T, Furuya M, Horiguchi J, et al. Efficacy and safety of yokukansan in treatment-resistant schizophrenia: a randomized, multicenter, double-blind, placebo-controlled trial. 2015 *Evidence-Based Complementary and Alternative Medicine* 2015; 1-11.

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

34 psychiatric hospitals (The authors belong to the Department of psychiatry, University Hospital), Japan.

4. Participants

One hundred and twenty hospitalized patients aged between 20 and 59, who were diagnosed with treatment-resistant schizophrenia (DSM-IV-TR), diagnosed at least 3 years previously, had taken at least 2 types of antipsychotic (equivalent to at least 600mg/day chlorpromazine) for 4 weeks but scored at least 4 on 2 or more subscales for positive psychiatric symptoms on the Positive and Negative Syndrome Scale (PANSS) or a total score greater than 60, a Clinical Global Impression (CGI) score more than 4, and were suitable for the clozapine USA multicenter trial. Patients 6-months pregnant or less, patients in an unstable condition, and patients who have abused alcohol or drugs were excluded.

5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散) Extract Granules 7.5g/day (2.5g t.i.d.) for 4 weeks (n=56).
Arm 2: Placebo 2.5g t.i.d. for 4 weeks (n=64).

6. Main outcome measures

The clinical effects used were 5 PANSS scores (excitement/hostility, depression/anxiety, cognition, positive, negative), CGI-S and Global Assessment of Functioning (GAF). Overall adverse effects and motor disorder were assessed, and motor disorder was assessed with the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS). Effects and tolerability were assessed by the principle researcher. The primary results were measured by changes in the 5 PANSS scores, and then by measuring changes in CGI-S.

7. Main results

For *Psychopharmacology*, mITT was used for statistical analysis, 3 participants dropped out of arm 2, leaving 56 participants in arm 1 and 61 in arm 2 for analysis. Excitement/hostility subscale PANSS scores improved significantly in arm 1 compared to arm 2 (P=0.018). For *Evidence-Based Complementary and Alternative Medicine*, PPS was used for statistical analysis, 48 participants in arm 1 were analyzed and 50 in arm 2. This analysis resulted in significant differences between arm 1 and arm 2 for lack of spontaneity and flow of conversation, tension, and poor impulse control (P<0.018, P<0.045, P<0.037).

8. Conclusion

Yokukansan for treatment-resistant schizophrenia improves PANSS excitement and hostility, etc. subscores.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effect from administration of yokukansan was observed.

11. Abstractor's comments

This is a very interesting clinical study that sheds light on the efficacy of yokukansan for treatment-resistant schizophrenia using the Positive and Negative Syndrome Scale. Two papers were written using the differing mITT and PPS analytical methods, which is why the numbers of dropouts differed and the results were described differently. However, the authors have therefore identified a new indication for yokukansan and further evaluations of its effectiveness for similar pathological conditions are anticipated.

12. Abstractor and date

Goto H, 27 January 2017.

5. Psychiatric/Behavioral Disorders

Reference

Arai YC, Kawanishi J, Sakakima Y, et al. The effect of the kampo medicine yokukansan on preoperative anxiety and sedation levels. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-4. doi: 10.1155/2014/965045 Pubmed ID: 24799947

1. Objectives

To evaluate the effectiveness and safety of yokukansan (抑肝散) in preoperative sedation.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (hospital surgery department).

4. Participants

Seventy patients whose physical status was rated I or II (American Society of Anesthesiologists) before hemicolectomy (ages: 30-85; 23 females and 47 males).

5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散) extract granules (2.5 g) taken orally 1.5 hours before general anesthetic (n=36).

Arm 2: Diazepam (5 mg) taken orally 1.5 hours before general anesthetic (n=34).

6. Main outcome measures

Intensity of anxiety immediately prior to anesthesia, using a verbal rating scale (VRS); Level of sedation using the modified Observer's Assessment of Alertness/Sedation Scale (OAA/S).

7. Main results

There was no significant difference between arms 1 and 2 in the intensity of anxiety on the VRS. The levels of sedation on the OAA/S showed statistically significant sedation in arm 2 compared to arm 1 ($P<0.05$).

8. Conclusions

Compared to diazepam, yokukansan does not excessively sedate patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse drug reactions in either the yokukansan group or the diazepam group.

11. Abstractor's comments

This clinical trial evaluated the significance of using yokukansan in sedation prior to hemicolectomy. The authors concluded that sedation with yokukansan prior to surgery under general anesthesia is not excessive. However, because the trial was not designed as a non-inferiority study, it does not clarify whether diazepam and yokukansan have the same level of effectiveness in suppressing anxiety. Hopefully the authors will conduct a trial that indicates non-inferiority by comparing yokukansan administration with diazepam administration for the suppression of anxiety prior to surgery under general anesthesia, and indicates the effectiveness of yokukansan administration for the suppression of anxiety prior to surgery under general anesthesia in comparison with the use of placebo or no preoperative drugs prior to surgery, as the next stage of their research.

12. Abstractor and date

Koike H, 31 March 2017.

5. Psychiatric/Behavioral Disorders

Reference

Ishida H, Otake T, Kurihara H, *et al*. Clinical study on augmentative effect of saiboku-to for anxiolytic and antidepressive action of diazepam. *Pain Clinic*, 1999; 20: 395-9 (in Japanese).

1. Objectives

To evaluate the efficacy of saibokuto (柴朴湯) as a potentiator of the anxiolytic and antidepressant effects of diazepam.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single clinic (pain clinic), Japan.

4. Participants

Fifteen patients with chronic anxiety or depression were included for analysis.

5. Intervention

Arm 1: oral administration of 7.5 g/day of saibokuto (柴朴湯) extract granules (manufacturer, not specified; frequency, not specified) for 2 weeks followed by 6 mg/day of diazepam for 2 weeks. (n=7)

Arm 2: oral administration of 6 mg/day of diazepam for 2 weeks. (n=8)

6. Main outcome measures

Hamilton Rating Scale (HS) score, diazepam and desmethyldiazepam blood levels, motor nerve conduction velocity (MCV)

7. Main results

Mean HS scores were 11.0, 7.4, and 4.1 before and after saibokuto and after diazepam, respectively, in Arm 1, while 8.9 and 5.5, respectively, before and after diazepam in Arm 2. Significant improvement in HS score was observed after diazepam in both arms. No between-arm difference was seen in diazepam and desmethyldiazepam blood levels or MCV.

8. Conclusions

Administration of saibokuto followed by diazepam, compared with diazepam monotherapy, has at least an equal anxiolytic and antidepressant effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The study comparing diazepam monotherapy with saibokuto and subsequent diazepam for anxiolytic and antidepressant treatment in patients with anxiety neurosis in a randomized controlled trial provides a high quality of evidence. The statement concluding that administration of saibokuto was likely to be associated with clinical improvement of symptoms was in the Discussion, although not in the Results. Despite the small sample size, it is likely that the effect of diazepam was enhanced by prior saibokuto treatment, so studies with larger sample size are needed. A trend towards clinical improvement of symptoms in the saibokuto arm was presented as a conclusion in the Discussion, but the measures of clinical symptoms are not mentioned. Providing details of these measures would improve the quality of this study.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Numata T, Gunfan S, Takayama S, et al. Treatment of posttraumatic stress disorder using the traditional Japanese herbal medicine saikokeishikankyoto: A randomized observer-blinded controlled trial in survivors of the great East Japan earthquake and tsunami. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-6. doi:10.1155/2014/683293 CENTRAL ID: CN-00988474, Pubmed ID: 24790634

1. Objectives

To evaluate the efficacy and safety of saikokeishikankyoto (柴胡桂枝乾姜湯) for posttraumatic stress disorder (PTSD).

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Forty-three patients aged 20 years or older who survived the Great East Japan Earthquake and tsunami and had a diagnosis of PTSD according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (text revision) (DSM-IV TR), with an Impact of Event Scale-Revised Questionnaire (IES-R) score of ≥25. The patients meeting any of the following four criteria were excluded from the study: 1) major medical illness such as neoplastic disease, acute inflammation, and any other disease precluding successful completion of the study; 2) psychosis due to other disorders such as schizophrenia, depression, and dementia; 3) delirium due to drugs, alcohol; and 4) use of neuroleptics, antianxiety drugs, antiepileptic drugs, antidepressants, or herbal remedies during the past 2 months.

5. Intervention

Arm 1: TSUMURA Saikokeishikankyoto (柴胡桂枝乾姜湯) Extract Granules 2.5 g t.i.d. for 2 weeks orally (n=21).

Arm 2: No administration (n=22).

6. Main outcome measures

The primary outcome measure was severity of PTSD as measured on the total IES-R scale. The secondary outcome measures were scores on three IES-R subscales: the intrusion subscale of 8 items, Questions 1, 2, 3, 6, 9, 14, 16, and 20; the avoidance subscale of 8 items, Questions 5, 7, 8, 11, 12, 13, 17, and 22; and the hyperarousal subscale of 6 items, Questions 4, 10, 15, 18, 19, and 21.

7. Main results

Twenty-one subjects in Arm 1 and 22 subjects in Arm 2 were included in the analysis. One subject in Arm 1 dropped out of the study due to cough on Day 3. Changes in total IES-R scores were significantly different between the two arms ($P<0.001$). Total IES-R scores were significantly improved from baseline to the completion of the study in Arm 1 ($P<0.001$) but not in Arm 2. The between-arm differences in all three subscales were significant ($P=0.025$ for avoidance subscale; $P=0.005$ for hyperarousal subscale; $P<0.001$ for intrusion subscale). From baseline to the completion of the study, there was a significant improvement in three subscale scores in Arm 1 ($P=0.003$ for avoidance sub-scale; $P<0.001$ for hyperarousal subscale; $P<0.001$ for intrusion sub-scale) and a significant improvement in one subscale score in Arm 2 ($P=0.032$ for avoidance subscale). There were significant inter-arm differences in the scores on Questions 1, 3, 6, 14, 19, 20, and 21 ($P<0.001$ for Question 1; $P=0.005$ for Question 3; $P<0.001$ for Question 6; $P=0.003$ for Question 14; $P=0.001$ for Question 19; $P=0.002$ for Question 20; $P=0.001$ for Question 21).

8. Conclusions

Saikokeishikankyoto is effective for alleviation of PTSD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One subject in the saikokeishikankyoto arm was withdrawn from the study on Day 3 due to mild cough.

11. Abstractor's comments

This was an innovative clinical study evaluating the efficacy of a Kampo product for treatment of post-disaster PTSD, and a valuable study given the rarity of this type of disaster. However, as mentioned by the authors, the small number of subjects, the influence of placebo effect, and the absence of control drugs for comparison seems to preclude adequate evaluation of the efficacy. Although there are many limitations to the conduct of this type of study, based on this study's findings, further development of clinical studies with longer follow-up and inclusion of positive and negative controls for comparison is anticipated.

12. Abstractor and date

Goto H, 31 March 2017.

5. Psychiatric/Behavioral Disorders

Reference

Yamagiwa M, Sakakura Y, Harada T, et al. Therapeutic response to various drugs in patients with continuous or periodic discomfort in the throat. *Jibiinkoka Rinsho* (*Practica Otologica*) 1990; 83: 1687–92 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of saibokuto (柴朴湯) for relieving discomfort in the throat.

2. Design

Randomized controlled trial (RCT).

3. Setting

The departments of otorhinolaryngology of Mie University Hospital and of related hospitals (not identified), Japan.

4. Participants

Four-hundred and ninety-four patients seen in the above hospitals with a chief complaint of discomfort in the throat, diagnosed with and treated for laryngopharyngeal discomfort without adverse drug reactions and with available efficacy data.

5. Intervention

Arm 1: placebo (sugar-coated tablet indistinguishable from Alprazolam tablets 0.4 mg), 3 tablets/day for 2 weeks (n=73).
Arm 2: lysozyme chloride granules, 270–300 mg/day for 2 weeks (n=91).
Arm 3: tiaprofenic acid, 6 tablets/day for 2 weeks (n=99).
Arm 4: Alprazolam 0.4 mg, 3 tablets/day for 2 weeks (n=72).
Arm 5: dosulepin hydrochloride, 1–2 capsules/day for 2 weeks (n=59).
Arm 6: saibokuto (柴苓湯) extract granules (manufacturer unknown), 7.5 g/day for 2 weeks (n=100).

6. Main outcome measures

The percentage of patients whose discomfort in the throat disappeared, evaluated at weeks 0, 1, 2, and 3 after the start of treatment in patients with “constant discomfort” and patients with “frequent discomfort” in arms 1–6.

7. Main results

In arms 1, 2, and 5, “frequent discomfort” disappeared in a higher percentage of patients than did “constant discomfort,” showing that frequent discomfort is more tractable. In arms 3 and 6, there was no difference between the percentage of patients whose “frequent discomfort” disappeared and the percentage of patients whose “constant discomfort” disappeared. In arm 4, “frequent discomfort” disappeared in a higher percentage of patients than did “constant discomfort” during treatment, but “frequent discomfort” recurred in these patients at week 3.

8. Conclusions

“Constant discomfort” is not necessarily more intractable to treatment than “frequent discomfort.”

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This clinical trial is unique because it investigated the rate of response to each treatment separately in patients with “constant discomfort” and patients with “frequent discomfort,” but did not evaluate the efficacy of the investigational product over placebo. However, the number of participants varied among groups, and the method of allocation described in the paper as “randomly” allocated to treatment is not clear. Furthermore, the analysis population included only patients without adverse drug reactions and with available drug efficacy data. Indicating the method used to allocate the original medicines, reporting the number of dropouts, and evaluating the efficacy of the investigational product over placebo, would have improved this clinical trial.

12. Abstractor and date

Goto H, 17 August 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Yamagiwa M, Fujita K. Effect of treatment using lansoprazole on patients with an abnormal sensation in the throat and concomitant heart burn. *Jibi to Rinsho* (*Otologia Fukuoka*) 2007; 53: 109-15 (in Japanese with English abstract). Ichushi Web ID: 2007166411

1. Objectives

To evaluate the efficacy of lansoprazole in patients with pharyngolaryngeal paresthesia and acid reflux symptoms (compared with rikkunshito (六君子湯) as a control).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Two institutions including Matsusaka Chuo General Hospital, Japan.

4. Participants

Eighty-six patients with pharyngolaryngeal paresthesia and acid reflux symptoms who presented to the participating institutions between May 2003 and November 2005.

5. Intervention

Arm 1: administration of TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 2 weeks in 38 patients who started treatment on odd-numbered days.

Arm 2: administration of lansoprazole 15 mg/day for 2 weeks in 48 patients who started treatment on even-numbered days.

6. Main outcome measures

Pharyngolaryngeal discomfort and reflux symptoms.

7. Main results

Rates of excellent, moderate, mild, and no improvement in pharyngolaryngeal discomfort after 2 weeks of treatment were 29, 34, 11, and 26%, respectively, in arm 1 and 33, 27, 19, and 21%, respectively, in arm 2. The respective rates of improvement in heartburn/acid reflux symptoms were 57, 30, 3, and 10% in arm 1 and 89, 9, 0, and 2% in arm 2.

8. Conclusions

No conclusions were drawn from this data (the authors say they will publish a new paper describing the outcomes in detail for rikkunshito-treated patients).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This paper describes the efficacy of lansoprazole (compared with rikkunshito as a control) in patients with pharyngolaryngeal paresthesia and acid reflux symptoms. But, since the two treatment arms were not compared, the analysis seems to be incomplete. As the authors say they will publish a new paper describing the outcomes in detail for rikkunshito-treated patients, a follow-up report is anticipated.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of combination treatment of hatimi-zio-gan and Red Ginseng powder on unidentified clinical complaints - estimation of double blind comparative study in many hospitals -. *Therapeutic Research* 1989; 10:4951–65 (in Japanese). Ichushi Web ID: 1991057823 MOL, MOL-Lib

1. Objectives

To clinically evaluate the symptom-relieving effects of hachimijiogan (八味地黄丸) alone, kojin (紅参) alone, or in combination in elderly patients with underlying chronic disease.

2. Design

Double-blind randomized controlled trial using sealed envelopes for allocation (DB-RCT-envelope).

3. Setting

Eleven facilities belonging to the Matsuyama Red Ginseng Research Group, mainly including Kaneko Heart Clinic, Japan.

4. Participants

Fifty-four inpatients or outpatients at the above facilities with underlying hypertension, cerebrovascular disorder, arteriosclerosis, diabetes mellitus, hyperlipidemia, etc.

5. Intervention

Arm 1: KOTARO Hachimiganryo (八味丸料) Extract Granules 1 sachet (3.0 g) t.i.d. (after meals) (8 males, 9 females).

Arm 2: CHEONG-KWAN-JANG Kojin (正官庄紅参) Powder 1 sachet (1.0 g) t.i.d. (after meals) (4 males, 15 females).

Arm 3: combination (mixture of 6.0 g of KOTARO Hachimiganryo (八味丸料) and 3.0 g of CHEONG-KWAN-JANG Kojin Powder), 3 g t.i.d (after meals) (4 males, 14 females).

Two weeks of observation followed by 12 weeks of treatment.

6. Main outcome measures

Improvement in clinical symptoms: evaluation on a seven-point scale using a check sheet at baseline and 4, 8, and 12 weeks of treatment.

Relationship between clinical symptom improvement rating and *kyojitsu* (虚実, excess or deficiency) *sho* (証, pattern): comparison of therapeutic improvement rating with *kyojitsu* rating evaluated using an original *sho* scoring table.

Laboratory tests: hematology (red blood cell [RBC] count, hemoglobin, hematocrit value, etc.), serum biochemistry (glutamate oxaloacetate transaminase [GOT], glutamate pyruvate transaminase [GPT], lactate dehydrogenase [LDH], blood urea nitrogen [BUN], etc.) evaluated at baseline, and 4, 8, and 12 weeks of treatment.

7. Main results

Symptoms improved significantly or tended to improve in arm 2 and arm 3. Particularly, the combination therapy had the earliest and greatest therapeutic effect. Only the combination therapy had a significant therapeutic effect on cold limbs, numbness, and lightheadedness. In association with *kyojitsu sho*, *sho* tending towards *jitsusho* (実証, excess pattern) was associated with significantly higher subjective symptom improvement in the combination group ($r=0.61$, $P<0.05$). There were no changes in laboratory values or adverse drug reactions.

8. Conclusions

Both hachimijiogan and kojin, particularly their combination, are useful for improving unidentified complaints in elderly patients with various chronic diseases. Furthermore, *sho* tending towards *jitsusho* is associated with the greater effect of the combination.

9. From Kampo medicine perspective

The larger effect of hachimijiogan and kojin, which are intended for *kyosho* (虚証, deficiency pattern) and *jitsusho*, suggests that the empirically/traditionally defined rule does not apply in some cases.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

Underlying chronic diseases in the 54 patients enrolled in this study vary but all impair quality of life. This paper demonstrates that hachimiijiogan/kojin combination therapy can improve unidentified complaints in these patients. In this study, analysis was appropriately performed through symptom evaluation on a 7-point scale using a detailed health check list and data collection using a *sho* determination table reflecting the theory of Kampo medicine, and thus made the conclusion highly credible. Further valuable clinical studies on how to use *hojin* (補腎, kidney-tonifying) medicinals in the elderly are expected.

12. Abstractor and date

Ushiroyama T, 6 August 2008, 1 June 2010, 31 December 2013.

5. Psychiatric/Behavioral Disorders

Reference

Tanaka H. Problems and approaches to treatment of psychosomatic disease by an otorhinolaryngologist, and Kampo treatment for psychosomatic cases with depressive tendency – Focusing on kamikihito (加味帰脾湯) –. *Phil Kampo* 2014; 47: 20-2. Ichushi Web ID: 2014238207

1. Objectives

To evaluate the efficacy and safety of kamikihito (加味帰脾湯) and kamishoyosan (加味逍遙散) for otorhinolaryngological symptoms with a strong psychosomatic element.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Single facility (hospital otorhinolaryngology department).

4. Participants

Thirty patients who presented at the otorhinolaryngology department with dizziness, tinnitus or hypopharyngeal globus sensation; who scored at least 11 points on the Toho University Self-Rating Questionnaire for Depression, SRQ-D; and whose psychosomatic factors appeared to aggravate symptoms.

5. Intervention

Arm 1: Kamikihito (加味帰脾湯) (manufacturer and dose unknown) taken for four weeks then kamishoyosan (加味逍遙散) (manufacturer and dose unknown) taken for four weeks (n=15).

Arm 2: Kamishoyosan (加味逍遙散) (manufacturer and dose unknown) taken for four weeks then kamikihito (加味帰脾湯) (manufacturer and dose unknown) taken for four weeks (n=15).

6. Main outcome measures

Change in chief complaint following the change of Kampo medication.

7. Main results

Efficacy was relatively high in 6.7% and low in 33.3% of patients in arm 1 after the change of Kampo medication. Efficacy was not high in any and it was low in 50.0% of the 10 patients who scored 16 or more on the SRQ-D, which is an indicator of possible depression. Of the 5 patients who scored 11-15 on the SRQ-D, which is on the borderline of depression, efficacy was high in 20.0% and it was not low in any patient. In arm 2, efficacy was high in 26.7% and low in 6.7% of patients. Of the 10 patients who scored 16 or more on the SRQ-D, efficacy was high in 40.0% and it was not low in any patient. Of the 5 patients who scored 11-15 on the SRQ-D, efficacy was not high in any and it was low in 20.0%.

8. Conclusions

Kamikihito was more effective than kamishoyosan for dizziness, tinnitus and hypopharyngeal globus sensation aggravated by psychosomatic factors in patients with an SRQ-D score of 16 or more and kamishoyosan was more effective than kamikihito in patients with an SRQ-D score of 11-15.

9. From Kampo medicine perspective

Kamikihito appears to be more appropriate than kamishoyosan for patients with severe depressive tendency.

10. Safety assessment in the article

No adverse effect induced by kamishoyosan or kamikihito was observed.

11. Abstractor's comments

This study was a cross-over comparison to evaluate whether kamikihito or kamishoyosan is more effective for otorhinolaryngological symptoms in which psychosomatic factors exist. The study suggests that kamikihito is effective for patients with severe depression and that kamishoyosan is effective for patients with slightly mild depression. It suggests that the SRQ-D could be a tool when selecting these two prescriptions. However, this study alone does not conclusively prove that kamikihito and kamishoyosan are effective for otorhinolaryngological symptoms. As the next stage of research to clarify which patient group responds to kamikihito and kamishoyosan, the author should prospectively study in a randomized controlled trial whether kamikihito is effective for patients with severely depressive otorhinolaryngological symptoms and whether kamishoyosan is effective for patients with mild depressive otorhinolaryngological symptoms.

12. Abstractor and date

Koike H, 31 March 2017.

5. Psychiatric/Behavioral Disorders

Reference

Sato Y, Horita H, Adachi N, et al. Effect of oral administration of prostaglandin E1 on erectile dysfunction. *British Journal of Urology* 1997; 80: 772-5.

1. Objectives

To compare the efficacy and safety of limaprost, an oral prostaglandin E1 derivative, with those of goshajinkigan (牛車腎気丸) in the treatment of erectile dysfunction.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Not mentioned (the authors belong to Department of Urology, Sapporo Medical University and Sanjukai Hospital), Japan.

4. Participants

Fifty patients with mild erectile dysfunction.

5. Intervention

Arm 1: treatment with goshajinkigan (牛車腎気丸; manufacturer, not specified) 2.5 g t.i.d. for 8 weeks (n=25; of these 24 were included for analysis).
Arm 2: treatment with limaprost 10 μg t.i.d. for 8 weeks (n=25; of these 24 were included for analysis).

6. Main outcome measures

Achievement of two consecutive vaginal penetrations, nocturnal penile tumescence measurements, and self-reported penile rigidity (0-5 points) and maintenance of erection (0-5 points).

7. Main results

Four of 24 analyzable patients in arm 1 and 11 of 24 in arm 2 achieved at least two consecutive vaginal penetrations; the rate of response was significantly higher in arm 2 than in arm 1 ($P<0.05$). However, not all patients who achieved vaginal penetrations experienced full erection. The mean increase of penile circumference was 6.0±6.6 mm for 23 patients who had measurements in arm 2 and only 2.3±5.8 mm for 21 patients in arm 1. The increase of penile circumference was significantly greater in arm 2 than in arm 1. There were no significant between-arm differences in the penile rigidity and maintenance of erection.

8. Conclusions

Limaprost, an oral prostaglandin E1 derivative, is more effective than goshajinkigan in the treatment of mild erectile dysfunction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One limaprost-treated patient developed facial flush.

11. Abstractor's comments

This study demonstrated that limaprost, an oral prostaglandin E1 analogue, was more effective than goshajinkigan in the treatment of mild erectile dysfunction. All patients in this study had achieved full erection after local injection of prostaglandin E. Limaprost resulted in a response in 45.1% of patients, but not in full erection. In this study, treatment assignment was in the order of patient presentation, but a randomized assignment is preferred.

12. Abstractor and date

Okabe T, 19 August 2008, 1 June 2010, 31 December 2013.

5. Psychiatric/Behavioral Disorders

Reference

Nishimatsu H, Kitamura T, Yamada D, et al. Improvement of symptoms of aging in males by a preparation LEOPIN ROYAL containing aged garlic extract and other five of natural medicines-comparison with traditional herbal medicines (Kampo). *Aging male* 2014; 17: 112-6. CENTRAL ID: CN-00992899, Pubmed ID: 24844765

1. Objectives

To compare the efficacy of LEOPIN ROYAL with that of Kampo medicines for aging in males.

2. Design

Randomized controlled trial (RCT).

3. Setting

One department of urology in a university hospital and one department of urology in a hospital, Japan.

4. Participants

Forty-nine males who complained of aging symptoms and underwent physical examinations at the Department of Urology, Faculty of Medicine, University of Tokyo.

5. Intervention

Arm 1: LEOPIN ROYAL for 6 months (n=24).

Arm 2: Kamishoyosan (加味逍遙散) (n=20), hangekobokuto (半夏厚朴湯) (n=1), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) (n=1), hochuekkito (補中益気湯) (n=1), goshajinkigan (牛車腎気丸) (n=1), and hachimijiogan (八味地黄丸) for 6 months (n=1) (manufacturers unknown).

6. Main outcome measures

Aging Males' Symptoms (AMS) scale; International Index of Erectile Function with 5 questions (IIEF-5); Androgen Deficiency in the Aging Male (ADAM) score; Self-Rating Questionnaire for Depression (SRQ-D) score; and serum levels of the following hormones: total testosterone, free testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and estradiol (E2).

7. Main results

In the LEOPIN ROYAL arm compared to the Kampo arm, somatic and phycological subscores and the total score in the AMS scale were significantly lower (P<0.01 for somatic sub-score; P<0.01 for phycological subscore; P<0.01 for total score), and the AMS somatic score and IIEF-5 score were significantly improved (P<0.01 for somatic subscore; P=0.019 for IIEF-5 score). Blood levels of total testosterone, free testosterone, FSH, LH, PRL, or E2 remained unchanged in the two arms.

8. Conclusions

LEOPIN ROYAL is more effective than kamishoyosan for symptoms of aging in males.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No special problems were noted.

11. Abstractor’s comments

In this study, kamishoyosan was the control for LEOPIN ROYAL, but hangekobokuto, saikokaryukotsuboreito, hochuekkito, goshajinkigan, and hachimijiogan were also used as controls in one subject each, depending on their symptoms. For symptoms such as decreased libido, hachimijiogan was presumably more effective than LEOPIN ROYAL; therefore, presenting in this article information about each Kampo formulation, rather than information about the group of Kampo formulations, would have been more valuable.

12. Abstractor and date

Nakata H, 31 March 2017.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Satoh T, Takahashi T, Iwasaki K, et al. Traditional Chinese Medicine on four patients with Huntington's disease. *Movement Disorders* 2009; 24 453-5.

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) in patients with Huntington's disease.

2. Design

Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting

Not mentioned (the first author belongs to the faculty of Yonezawa National Hospital), Japan.

4. Participants

Four female patients with Huntington's disease (aged 48, 51, 52, and 68 years).

5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散; dose, not specified) Extract Granules for 8 weeks, followed by 4 weeks of wash-out, then TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯; dose, not specified) Extract Granules for 8 weeks (n=2).

Arm 2: TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯; dose, not specified) Extract Granules for 8 weeks, followed by 4 weeks of wash-out, then TSUMURA Yokukansan (抑肝散; dose, not specified) Extract Granules for 8 weeks (n=2).

6. Main outcome measures

Motor functions, cognitive functions, and activities of daily living were evaluated using the Unified Huntington's Disease Rating Scale - motor assessment (UHDRS-m), Mini-Mental State Examination (MMSE), and Barthel Index, respectively, at the start and end of yokukansan and saikokaryukotsuboreito treatments in both arms.

7. Main results

The UHDRS-m was decreased significantly during yokukansan treatment in all 4 patients (from 106.3±4.7 to 89.6±5.8; P=0.0004), but not significantly during saikokaryukotsuboreito treatment in 3 out of 4 patients (from 105.5±3.8 to 101±2.9). There were no changes in MMSE and Barthel Index after either treatment.

8. Conclusions

Yokukansan may improve motor function (UHDRS-m score) in patients with Huntington's disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no abnormal findings in hematology and blood biochemistry after the yokukansan or saikokaryukotsuboreito treatment.

11. Abstractor's comments

In this clinical study, the effects of yokukansan on Huntington's disease, an intractable disease, were objectively evaluated using the UHDRS-m. Videos are also available on this Journal website, thus the article may have a powerful impact on readers. Notably, the authors attempted to evaluate the effects of yokukansan in a cross-over design, despite the difficulties in collecting cases of this rare disease. However, in one of the four participants, improvement was greater during the saikokaryukotsuboreito treatment than during the yokukansan treatment. The results would be more valuable if the data had been analyzed rigorously as a cross-over design. Because there is no established treatment, it might be difficult to have a control group. Yet the use of non-Kampo medicine as a control should be considered. As the authors noted, in the future, a controlled trial with a larger number of patients should be conducted. Still, this study is meaningful in that it provided findings that suggest, albeit hypothetically, the efficacy of yokukansan for this rare disease with no remedy at present.

12. Abstractor and date

Goto H, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Yakabi K, Yamaguchi N, Ono S, et al. Open label trial of the efficacy and safety profile of rikkunshito used for the treatment of gastrointestinal symptoms in patients with Parkinson's disease: a pilot study. *Current Therapeutic Research* 2017; 87: 1-8. Pubmed ID: 28912900

1. Objectives

To evaluate the efficacy and safety of rikkunshito（六君子湯）for anorexia and dyspepsia in patients with Parkinson’s disease

2. Design

Randomized controlled trial (cross over) (RCT- cross over)

3. Setting

One university hospital, Japan

4. Participants

Fourteen patients with Parkinson’s disease aged between ≥20 and ≤85 years, with Hoehn-Yahr stage I to III, and symptoms of anorexia or dyspepsia

Exclusion criteria were intolerance to oral administration of medication, use of drugs that could not be used concomitantly with rikkunshito, current presence of cardiac, hepatic, renal, or hematological disease or malignancy, and history of allergy to Kampo medicines.

5. Intervention

Arm 1: TSUMURA Rikkunshito（六君子湯）Extract Granules 7.5 g/day administered orally (2.5 g t.i.d. 4-week treatment, followed by 4-week off treatment) (n=7)

Arm 2: TSUMURA Rikkunshito（六君子湯）Extract Granules 7.5 g/day administered orally (2.5 g t.i.d. 4-week off treatment, followed by 4-week treatment) (n=7)

6. Main outcome measures

Primary endpoint was the change in appetite score on a 100-mm visual analog scale (VAS). Secondary endpoints were the changes in gastric emptying, plasma acylated ghrelin level, depression as assessed using the self-rating depression scale (SDS), and gastrointestinal quality of life (QOL) as assessed using the Gastrointestinal Symptom Rating Scale (GSRS).

7. Main results

Rikkunshito treatment produced a significant increase in the appetite VAS score (1.84 [2.34]), compared to a decrease in the score over the off-treatment period (−1.36 [2.94]) (P=0.041). The SDS score significantly decreased with rikkunshito treatment (P=0.026). No effects of rikkunshito were determined on the GSRS score, plasma acylated ghrelin level, or gastric emptying.

8. Conclusion

Rikkunshito may improve anorexia in patients with Parkinson’s disease.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Throughout the study period, no adverse events or abnormal changes were identified with rikkunshito treatment.

11. Abstractor’s comments

Rikkunshito is known to be effective for gastrointestinal symptoms (anorexia and dyspepsia). Since gastroparesis and constipation commonly occur in patients with Parkinson’s disease, this report indicating improvement of anorexia by rikkunshito in Parkinson’s disease patients is important. In addition, the study suggested that the positive effects of rikkunshito on depression and anorexia in Parkinson’s disease patients may improve their QOL. However, as stated by the authors, the sample size in each arm was limited and did not permit multiple comparisons. Validation of the results using a randomized, double-blind, controlled trial in a larger sample size is awaited.

12. Abstractor and date

Kato Y, 1 June 2020.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Ota T, Miura I, Kanno-Nozaki K, et al. Effects of shakuyaku-kanzo-to on extrapyramidal symptoms during antipsychotic treatment: a randomized, open-label study. *Journal of Clinical Psychopharmacology* 2015; 35: 304-7.

1. Objectives

To evaluate the effectiveness and safety of shakuyakukanzoto (芍薬甘草湯) on extrapyramidal symptoms during antipsychotic treatment.

2. Design

Randomized controlled trial (RCT).

3. Setting

Centers not described. (The authors belong to the Department of Neuropsychiatry and the Hospital), Japan.

4. Participants

Twenty-two psychiatric patients who had been taking antipsychotic drugs other than anti-Parkinson drugs for at least 4 weeks before the start of the study, who scored at least 2 for general severity on the Drug-Induced Extrapyramidal Sympton Scale (DIEPSS), and at least 2 for one subscale score or more. Patients with organic brain impairment and patients with drug or alcohol abuse problems were excluded.

5. Intervention

Arm 1: Shakuyakukanzoto (芍薬甘草湯) 7.5g/day (manufacturer name and administration frequency not mentioned) for 2 weeks (n=11).

Arm 2: Biperiden 3mg/day for 2 weeks (n=11).

6. Main outcome measures

Psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI). Extrapyramidal symptoms were evaluated using DIEPSS and the Barnes Akathisia Rating Scale (BARS). All evaluations were carried out at the start of the study and at its end, after 2 weeks of treatment. Blood samples were taken at those same times: plasma homovanillic acid (HVA) and serum prolactin (PRL) were measured.

7. Main results

One participant in arm 1 decided to stop taking the shakuyakukanzoto, one participant in arm 2 stopped taking biperiden due to dry mouth, so the results for 20 participants were analyzed. Overall DIEPSS scores improved significantly in arms 1 and 2 compared to the start of the study ($P<0.001$). No changes were observed in PANSS, CGI scale, BARS, plasma HVA, or serum PRL levels. Analysis of DIEPSS items found the time-drug interaction was significant for dystonia in arm 1 ($P=0.0059$). Although there was a significant difference between arms 1 and 2 for slowness of movement and dystonia at the start of the study ($P<0.05$), the dystonia score in the shakuyakukanzoto group had improved significantly at the study end compared to the start ($P=0.0038$).

8. Conclusion

Shakuyakukanzoto is effective for extrapyramidal symptoms during antipsychotic treatment and has an especially strong effect for dystonia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No shakuyakukanzoto-induced adverse effects, including hypokalemia, were observed.

11. Abstractor's comments

This is an excellent clinical study verifying that shakuyakukanzoto is effective in generally improving extrapyramidal symptoms during antipsychotic treatment, especially dyskinesia. In regard to dyskinesia in particular being found to respond effectively to shakuyakukanzoto, considering that the scores in the shakuyakukanzoto group were significantly higher than the biperiden group at the start of the study, it is possible that it had an effect in comparing it with the effects of biperiden. On the other hand, the paper attempts consideration of the mechanism of action, not just effectiveness, so the authors have demonstrated an excellent approach to their research and their clinical study is praiseworthy.

12. Abstractor and date

Goto H, 8 January 2017.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Monji A, Takita M, Samejima T, et al. Effect of yokukansan on the behavioral and psychological symptoms of dementia in elderly patients with Alzheimer's disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2009; 33: 308-11. 33: 308-11. Pubmed ID: 19138715

Monji A, Kanba S. Effectiveness of yokukansan (抑肝散) on BPSD in Alzheimer's disease — Results of a long-term antipsychotic combination trial at a department of neuropsychiatry in Kyushu*. *No 21* (*Brain 21*) 2009; 12: 446-51 (in Japanese). Ichushi Web ID: 2010037668, MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) in the treatment of behavioral and psychological symptoms of dementia (BPSD) in elderly patients with Alzheimer's disease

2. Design

Randomized controlled trial (RCT)

3. Setting

Kyushu University and its affiliated hospitals (number of institutions, not specified), Japan

4. Participants

Fifteen patients (2 males and 13 females, mean age 80.2±4.0 years) who were diagnosed with dementia and Alzheimer's disease based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and National Institute of Neurological and Communicative Disorders and Stroke / the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, respectively, and had a Mini-Mental State Examination (MMSE) score of 6 to 23 and a Neuropsychiatric Inventory (NPI) score of 6 or higher after 2 weeks of pre-study treatment with sulpiride 50 mg/day

5. Intervention

Arm 1: Continuation of oral sulpiride 50 mg/day plus treatment with oral yokukansan (抑肝散; manufacturer, not specified) 2.5 g (containing 1.5 g of extracts) t.i.d. for 12 weeks (n=10)

Arm 2: Continuation of oral sulpiride 50 mg/day alone (n=5).

During the evaluations performed every 4 weeks, the dose of sulpiride was increased when any NPI subscore was 8 or higher and decreased when all NPI subscores were below 4.

6. Main outcome measures

BPSD and cognitive functions were evaluated using the NPI and MMSE, respectively. The Barthel Index was used for the evaluation of activities of daily living. Patients were evaluated at baseline, 4, 8, and 12 weeks.

7. Main results

One patient in arm 2 was excluded due to severe edema. NPI was significantly improved at 8 and 12 weeks compared with the baseline in arm 1 ($P<0.001$), whereas no change was observed in arm 2. The dose of sulpiride at 12 weeks was less, but not significantly less, in arm 1 than in arm 2. There were no changes in MMSE and Barthel Index from the baseline in both arms.

8. Conclusions

Yokukansan improves BPSD in elderly patients with Alzheimer's disease and can reduce the dose of antipsychotics.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Hypokalemia was reported in 2 patients in arm 1. In addition, extrapyramidal symptoms developed and the dose of sulpiride was decreased from 150 mg/day to 100 mg/day in one patient in arm 1.

11. Abstractor's comments

This is a valuable clinical study that evaluated the efficacy of yokukansan in elderly patients with Alzheimer's disease over 12 weeks from various aspects, including behavioral and psychological symptoms, cognitive functions, and activities of daily living. Because patients in both arms were prescribed sulpiride at baseline and yokukansan was evaluated in an add-on design, there is a possibility that the efficacy of yokukansan alone was not adequately evaluated. The differences in NPI and MMSE score from those in arm 2 were not significant owing to the small number of patients. However, the trend in these scores over time suggests that significant improvements over baseline might be found if more patients were included. Even in a small population, it is suggested that yokukansan may improve NPI and reduce the dose of antipsychotics. In the future, the efficacy of yokukansan in the field of psychiatry could be more convincingly demonstrated by increasing the number of patients and selecting the appropriate control agent**.**

12. Abstractor and date

Goto H, 1 June 2010, 1 February 2011, 31 December 2013

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Okahara K, Ishida Y, Hayashi Y, et al. Effects of yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 2010; 34: 532–6. CENTRAL ID: CN- 00752183, Pubmed ID: 20170698

1. Objectives

To investigate the efficacy and safety of yokukansan (抑肝散) as a common treatment for behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Hospitals and Clinics in Miyazaki and Kagoshima prefecture, 12 institutions, Japan.

4. Participants

Sixty-three outpatients were registered from July 2006 to December 2008 and met the following inclusion criteria: 1) have dementia and a diagnosis of Alzheimer's disease (including mixed-type dementia), 2) show at least one symptom score ≥4 in the Neuropsychiatric Inventory (NPI) subscales, 3) aged ≤85 years, 4) taking donepezil hydrochloride for at least 4 weeks.

5. Intervention

Arm 1: administration of TSUMURA Yokukansan (抑肝散) Extract Granules, 2.5 g t.i.d. for 4 weeks (n=30).

Arm 2: no administration (n=33).

6. Main outcome measures

Evaluations of BPSD using the NPI subscales (delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor activity), cognitive function by the Mini-Mental State Examination (MMSE), activities of daily living (ADL) by the Disability Assessment of Dementia (DAD), burden of caregivers by the Zarit Burden Interview, caregiver's depression by the Self-rating Depression Scale (SDS) at the start and at 4 weeks of the study.

7. Main results

One patient in arm 1 and one patient in arm 2 withdrew, and the efficacy analysis set included 29 patients in arm 1 and 32 patients in arm 2. Inter-group comparison revealed significantly more improvement in arm 1 compared with arm 2 in the total NPI score after 4 weeks of treatment ($P<0.05$). On analysis of individual NPI subscale scores, significant improvement was observed for agitation and irritability in arm 1 compared to arm 2 ($P<0.05$). Intra-group comparison of values at the start and at 4 weeks of treatment identified a significant improvement in the NPI total score in arm 1 ($P<0.05$). Analysis of each NPI subscale scores at baseline and after 4 weeks of treatment demonstrated significant improvement in delusions, agitation, dysphoria, anxiety, apathy, or irritability in arm 1 ($P<0.05$), and in apathy in arm 2 ($P<0.05$). Inter-group and intra-group comparisons found no changes in MMSE, DAD, Zarit Burden Interviews, or SDS.

8. Conclusions

Yokukansan significantly accelerates improvement in BPSD in patients with Alzheimer's disease treated with donepezil.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None of the patients had any adverse reactions to yokukansan such as decreased serum potassium or edema.

11. Abstractor's comments

This is a clinical trial to determine the efficacy of yokukansan for dementia in patients with Alzheimer's disease treated with donepezil by evaluating its effect on behavioral and psychological symptoms. The result of the clinical trial can be applied immediately to daily practice. Despite improvement in NPI scores, scores reflecting the burden of caregivers were not improved. To assess this effect, further studies with larger sample size and longer study period would be necessary. However, as no drugs effective for peripheral symptoms of dementia are presently available, demonstration of the efficacy of yokukansan is a great achievement.

12. Abstractor and date

Goto H, 27 December 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Furuhashi Y. Comparative efficacy of risperidone versus yokukansan (抑肝散) on behavioral and psychological symptoms of dementia in patients with Alzheimer's disease*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 120–1 (in Japanese).

1. Objectives

To evaluate the efficacy of yokukansan (抑肝散) and risperidone in the treatment of behavioral and psychological symptoms of dementia (BPSD)

2. Design

Randomized controlled trial (RCT).

3. Setting

Asahi Hospital, units of psychiatry, psychosomatic internal medicine, and geriatric psychiatry, Japan.

4. Participants

Twenty patients admitted to the hospital between January 2008 and January 2009 who met Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) or International Classification of Diseases (ICD) criteria for Alzheimer's disease.

5. Intervention

Arm 1: yokukansan (抑肝散) (manufacturer not specified) 7.5 g/day for 4 weeks (n=10
Arm 2: risperidone 0.5 mg/day for 4 weeks (n=10

6. Main outcome measures

Neuropsychiatric Inventory (NPI; for psychological symptoms) and the Cohen-Mansfield Agitation Inventory (CMAI; for behavioral symptoms) were used for evaluation.

7. Main results

Significant improvements in NPI scores and CMAI scores were observed in both the risperidone arm and yokukansan arm (P<0.01).

8. Conclusions

Both yokukansan and risperidone have a similar effect on BPSD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Sedation, malaise, drowsiness, and constipation were reported in arm 2, but no adverse events were reported in arm 1.

11. Abstractor's comments

This paper discusses the effect of yokukansan on the peripheral symptoms of Alzheimer's disease. More and more patients with dementia are being treated with yokukansan, and this paper reflects this recent trend. From the viewpoint of Kampo medicine, yokukansan is expected to reduce anger. Most anticipated is the efficacy of yokukansan on peripheral symptoms, especially on agitation, which should alleviate the burden on caregivers. Though no data were shown, this paper stated that yokukansan significantly improved CMAI scores for aggressive behaviors such as beating, kicking, grabbing, scratching, and breaking, and unaggressive behaviors such as repeating the same action over and over and asking questions continuously. These seem to be the exact effects of yokukansan. A precise report with details is awaited.

12. Abstractor and date

Nakata H, 12 January 2011, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Teranishi M, Kurita M, Nisiho S, et al. Efficacy and tolerability of risperidone, yokukansan, and fluvoxamine for the treatment of behavioral and psychological symptoms of dementia: A blinded, randomized trial. *Journal of Clinical Psychopharmacology* 2014; 33: 600-7.

Kurita M, Efficacy and tolerability of yakukansan for behavioral and psychological symptoms of dementia (BPSD) – A 3-way comparative trial of risperidone and fluvoxamine. *Brain 21* 2015; 18: 249-52.

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for behavioral and psychological symptoms of dementia (BPSD).

2. Design

Randomized controlled trial (RCT).

3. Setting

One psychiatric hospital, Japan.

4. Participants

Eighty-two patients who met the diagnostic criteria of dementia according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) with total score on the Mini-Mental State Examination (MMSE) of <19 and at least one symptom score of >4 in the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). Patients meeting any of the following criteria were excluded from the study: participation in any other drug study within 4 weeks of the study; hypersensitivity to risperidone, yokukansan, or fluvoxamine; evidence of chronic and/or severe disease that could interfere with the study.

5. Intervention

Arm 1: Yokukansan (抑肝散) (manufacturer unknown) 2.5 to 7.5 g/day for 8 weeks (n=27).
Arm 2: Risperidone 0.5 to 2.0 g/day for 8 weeks (n=27).
Arm 3: Fluvoxamine 25 to 200 mg/day for 8 weeks (n=28).
The study was initiated after a 1-week washout of drugs used for treatment of BPSD. The dose of each drug was adjusted at the discretion of the investigator and based on his/her analysis of NPI-NH subscales.

6. Main outcome measures

At baseline and Weeks 2, 4, 6, and 8, an assessment was made of neuropsychiatric symptoms using the NPI-NH, cognitive function using the MMSE, and daily life function using the Functional Independence Measure (FIM). To evaluate drug tolerability, blood and other tests and the Drug-induced Extra-pyramidal Symptoms Scale (DIEPSS) were performed.

7. Main results

Of the 82 subjects, 76 were included in the analysis. NPI-NH scores were significantly improved from baseline to Week 8 in all arms ($P=0.034$ in Arm 1; $P=0.022$ in Arm 2; $P<0.001$ in Arm 3), but with no significant difference among the three arms. MMSE and FIM scores did not change significantly in the three arms.

8. Conclusion

Yokukansan is as effective as risperidone and fluvoxamine for BPSD but safer to use than risperidone.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

DIEPSS scores were similar between the yokukansan and fluvoxamine arms, but significantly higher in the risperidone arm than in the yokukansan and fluvoxamine arms. One subject in the risperidone arm died suddenly during the study.

11. Abstractor's comments

BPSDs are important symptoms to treat, but there are no good drugs for BPSD treatment at this time. This clinically meaningful study evaluated the efficacy and safety of risperidone and yokukansan, which are frequently used in clinical settings, and fluvoxamine used by the authors. However, as acknowledged by the authors, no placebo was used in this study; the investigator's assessment might have been affected by this omission. In addition, since hospitalized patients were included in this study, care by staff members might have improved NPI-NH scores in all arms. However, the intent of this study was to improve the state of current treatment. It is anticipated that similar future studies will be conducted to establish the guidelines for treatment of BPSD with Kampo medicines.

12. Abstractor and date

Goto H, 31 March 2017.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Furukawa, K, Tomita N, Une K, et al. Randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's disease. *Geriatrics and Gerontology International* 2017; 17: 211-8. CENTRAL ID: CN-01337019, Pubmed ID: 26711658

1. Objectives

To evaluate the efficacy and safety of yokukansan（抑肝散）for behavioral and psychological symptoms of dementia (BPSD) in Alzheimer’s disease

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

Twenty-two sites (clinics, hospitals, and nursing homes), Japan

4. Participants

A total of 145 patients with probable Alzheimer’s disease, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Main inclusion criteria were age 55–84 years, total score of greater than 4 on the Neuropsychiatric Inventory Brief Questionnaire (NPI-Q), the sum of the NPI-Q subcategory scores for “agitation/aggression” and “irritability/lability” greater than 2, and the Mini-Mental State Examination (MMSE) score within the range of 10–26. Patients were excluded if they had cerebral infarction possibly affecting cognitive function, or they had depression, bipolar disorder, malignant tumor, or other life-threatening disease within the previous 2 years. Patients were also excluded if they had received typical or atypical neuroleptics, tricyclic or tetracyclic antidepressants, or Kampo medicines other than yokukansan.

5. Intervention

Arm 1: TSUMURA Yokukansan（抑肝散）Extract Granules 7.5 g/day (2.5 g t.i.d.) administered orally for 12 weeks (n=75)

Arm 2: Matching placebo (3 times daily) administered orally for 12 weeks (n=70)

The first 4 weeks of the treatment were double-blinded for comparison of the effects, and the following 8 weeks were non-double-blinded for safety assessment.

6. Main outcome measures

The primary outcome measure was the 4-week change in the NPI-Q total score. The secondary outcome measures were 12-week changes in NPI-Q total score, NPI-Q subcategory scores, MMSE total score, rescue drug dose, and safety.

7. Main results

The 4-week change in NPI-Q total score, which was the primary outcome measure, and the changes in NPI-Q subcategory scores did not differ significantly between the two arms. The NPI-Q total score significantly decreased from baseline at Week 4 in both arms (P <0.001 for both). Among the secondary outcome measures, the 12-week changes in NPI-Q total score and MMSE total score did not differ between the arms. However, a subgroup analysis showed that the agitation/aggression score significantly decreased after 4 weeks of treatment in Arm 1 compared with Arm 2 among patients with baseline MMSE <20 and patients aged ≤74 years (P =0.007 and P =0.049, respectively). Also, among patients with hallucinations at baseline, NPI-Q total score significantly decreased in Arm 1 compared with Arm 2 (P =0.019).

8. Conclusion

Yokukansan improves symptoms including agitation/aggression and hallucinations with low frequencies of adverse reactions.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Hypokalemia was observed in 4 of the 72 patients in the yokukansan group. However, there were no significant differences between the two arms.

11. Abstractor’s comments

This is a valuable clinical study that evaluated the efficacy and safety of yokukansan for BPSD in Alzheimer’s disease, conducted as a multicenter, double-blind, randomized, controlled trial. Although primary and secondary outcome measures did not demonstrate efficacy of yokukansan, the subgroup analysis revealed some significant findings. Further clinical studies based on these findings are awaited, to further clarify the disease conditions for which yokukansan is indicated.

12. Abstractor and date

Goto H, 1 June 2020.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Higashi K, Rakugi H, Yu H, et al. Effect of kihito extract granules on cognitive function in patients with Alzheimer's-type dementia. *Geriatrics & Gerontology International* 2007; 7: 245-51. Ichushi Web ID: 2008113647

1. Objectives

To evaluate the efficacy and safety of kihito (帰脾湯) for Alzheimer-type dementia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Hanwa Daini Senboku Hospital, Japan.

4. Participants

Seventy-five elderly patients diagnosed with Alzheimer's disease according to DSM-IV criteria, with Hachinski ischemic score of ≤4 points and Mini-Mental State Examination (MMSE) score of 10–26 points. Patients with marked hypertension, diabetes, hypercholesterolemia, heart disease, renal failure, or depression, or MRI findings of marked cerebral infarction were excluded.

5. Intervention

Arm 1: no treatment, n=20.
Arm 2: oral administration of 2.5 g of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules t.i.d. after meals for 3 months, n=24.
Arm 3: Oral administration of 2.5 g of TSUMURA Kihito (帰脾湯) Extract Granules t.i.d. after meals for 3 months, n=20.

6. Main outcome measures

MMSE score, activities of daily living (ADL) evaluated in all patients at baseline and 3 months. Brain blood flow measured by single photon emission computed tomography (SPECT) in 6 patients in arm 2 and 4 patients in arm 3 at baseline and 3 months (selection criteria for performing SPECT not indicated).

7. Main results

Of 75 participants, 64 were included in the analysis population. MMSE score in arm 3 was significantly improved from baseline at 3 months and was also significantly improved compared with arm 1 and arm 2. In particular, disorientation and attentiveness were markedly improved. There were no among-arm differences in ADL and between baseline and 3 months. SPECT revealed no obvious changes in brain blood flow.

8. Conclusions

Kihito is an effective treatment for Alzheimer-type dementia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient in arm 2 experienced diarrhea and 1 patient in arm 3 increased blood pressure, leading to discontinuation of treatment.

11. Abstractor's comments

This excellent clinical study investigated and demonstrated the efficacy of kihito for Alzheimer's dementia using a non-Kampo-treatment and goshajinkigan as controls. The authors selected goshajinkigan as a control because of its *onji*-free composition and the lack of reports showing an effect on cognitive function. However, since the efficacy of hachimijiogan, containing goshajinkigan ingredients other than gohitsu and shazenshi, for elderly dementia has already been reported (Iwasaki K, Kanbayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "Ba wei di huang wan" in the treatment of dementia. *Journal of the American Geriatrics Society* 2004; 52: 1518-21.), goshajinkigan was considered inappropriate for a control, although the results showed significantly improved MMSE score only with kihito. Furthermore, although they attribute, in the discussion, the absence of a difference in brain blood flow to the small sample size, information on selection criteria for performing SPECT would be necessary. The number of dropouts in arm 1 should be indicated. Although these details were omitted, this clinical research demonstrated the efficacy of kihito for treatment of dementia, and investigation of the mechanism of action and long-term effect using a larger sample size is expected.

12. Abstractor and date

Goto H, 28 November 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Maruyama T. Goshuyu-to versus lomerizine hydrochloride in the prophylactic treatment of migraine headaches: an open crossover trial.. *Itami to Kampo* (*Pain and Kampo Medicine*) 2006; 16: 30-9 (in Japanese with English abstract). Ichushi Web ID: 2006303125

1. Objectives

To evaluate the efficacy and safety of goshuyuto (呉茱萸湯) for treatment of migraine.

2. Design

A crossover randomized controlled trial (RCT-crossover).

3. Setting

No description of the setting is available; the authors belong to the Department of General Medicine, Iida Municipal Hospital, Japan.

4. Participants

Fourteen patients with at least a 1-year history of migraine and suffering a mean of 3 or more migraine attack events monthly.

5. Intervention

Arm 1: Oral administration of lomerizine hydrochloride 5 mg 5 mg b.i.d. for 28 days, followed by a wash-out period of two weeks, and then oral administration of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules 2.5 g t.i.d. for 28 days (n=7).

Arm 2: Oral administration of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules 2.5 g t.i.d. for 28 days, followed by a wash-out period of two weeks, and then oral administration of lomerizine hydrochloride 5 mg b.i.d. for 28 days (n=7).

Oral triptans to treat migraine attacks were allowed.

6. Main outcome measures

Frequency of migraine attacks, visual analogue scale (VAS) score, number of triptan oral tablets used, response to a triptan (time to relieve attacks), evaluated in the pretreatment period (28 days), course 1 (28 days), withdrawal period (14 days), course 2 (28 days), and final period (28 days).

7. Main results

Differences in measures of drug efficacy (i.e., frequency of migraine attacks, VAS peak value, and number of triptan oral tablets used) were greater in goshuyuto group than in lomerizine hydrochloride group.

8. Conclusions

Goshuyuto is more effective for migraine attacks than lomerizine hydrochloride.

9. From Kampo medicine perspective

As indications of goshuyuto, the following *shoe*s were identified: *genchimyaku* (弦遅脈, string-like, slow pulse), *katsuhakutai* (滑白苔, slippy white tongue coating), *shinsuion* (振水音, splashing sounds in the stomach), *shinkahikou* (心下痞鞭, stuffiness and rigidity below the heart), *shishikanrei* (四肢厥冷, reversal cold of the limbs) in 71.4, 57.1, 64.3, 85.7, and 100% of patients.

10. Safety assessment in the article

While 2 patients receiving lomerizine hydrochloride experienced sleepiness, none receiving goshuyuto experienced any adverse drug reactions.

11. Abstractor's comments

This excellent clinical study investigated the effect of goshuyuto on migraine using lomerizine hydrochloride as the control and demonstrated that it prevented migraine attacks. However, the author stated in the discussion of his paper that lomerizine hydrochloride used as the control was weaker than reported in previous clinical research. Therefore, it would be necessary to determine whether migraine was correctly diagnosed in participants and whether response to previous oral treatment with lomerizine hydrochloride was poor. Furthermore, in arm 2, goshuyuto was received in course 1, and the frequency and severity of migraine attack had not returned to baseline levels by the start of lomerizine in course 2, suggesting that the pace of withdrawal was too rapid. This may explain the stronger effect of goshuyuto in arm 1 (patients who received goshuyuto in course 2). Moreover, compliance with goshuyuto treatment (74%) was significantly lower than compliance with lomerizine hydrochloride treatment (93%), warranting improvement in future compliance. Nevertheless, this research demonstrated that goshuyuto prevented migraine, and further investigation of its efficacy is expected with various prescriptions.

12. Abstractor and date

Goto H, 17 November 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Matsushita M, Saito M, Katayama S, et al. Clinical evaluation of DS-4773 on sedative effect: a cross-over trial. *Yakuri to Chiryo* (*Japanese Pharmacology & Therapeutics*) 1994; 22: 2371–82 (in Japanese). Ichushi Web ID: 1995083169

1. Objectives

To evaluate the efficacy and safety of DS-4773 for sedation versus sansoninto (酸棗仁湯) used as control.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

The Department of Neurology and Psychiatry, University of Tokyo Hospital, departments of psychiatry of 5 hospitals, and 2 clinics, Japan.

4. Participants

Seventy-nine male and female patients (≥ 15 years old) with medical histories taken by specialists in the fields of internal medicine, psychosomatic medicine, or psychiatry and any of the following five complaints: insomnia, daytime irritability, daytime bad mood, daytime hypobulia, and lack of refreshing sleep.

5. Intervention

Arm 1: oral administration of DS-4773 (containing 0.5 g dried extract of sansonin [酸棗仁], 0.1 g dried extract of bukuryo [茯苓], and 0.2 g of sanshishi [山梔子]) granules 1 sachet (1 g) b.i.d. before breakfast and before bedtime for 2 weeks (n=79).

Arm 2: oral administration of sansoninto (酸棗仁湯) extract granules for medical use (manufacturer unknown) 1 sachet (3.75 g) b.i.d. before breakfast and before bedtime for 2 weeks (n=79).

6. Main outcome measures

Ease of falling asleep, depth of sleep, mood on awakening, daytime mood, daytime physical condition, daytime motivation, anorexia, constipation and diarrhea, rated on a 4-point scale.

7. Main results

After exclusions and withdrawals, 59 patients were included in the analysis population. Slight or more improvement was reported in 63.5%/51.9% of patients (arm 1/arm 2) for ease of falling asleep, 63.6%/45.5% for depth of sleep, 64.9%/50.9% for mood on awakening, 50.0%/37.5% for daytime mood, 47.4%/38.6% for daytime physical condition, 35.8%/26.4% for daytime motivation, 27.8%/23.2% for anorexia, 41.2%/35.3% for constipation, and 100%/75.0% for diarrhea. Group comparison revealed a significant improvement in the ease of falling asleep, depth of sleep, mood on awakening, daytime physical condition, and daytime motivation in arm 1 compared with arm 2.

8. Conclusions

DS-4773 is more efficacious than sansoninto extract granules for sedation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Safety was evaluated in 68 patients. No adverse reactions were noted in 64 patients receiving DS-4773 (94.1%) and 61 patients receiving sansoninto (89.7%). Adverse reactions requiring treatment discontinuation were palpitations, dizziness, and anxiety, each occurring in 1 patient.

11. Abstractor's comments

This is a well-designed clinical study with a cross-over design. It investigated the efficacy of DS-4773 using sansoninto extract granules as control. However, lack of a washout period between treatments may have resulted in carry-over effects of the first drug. Furthermore, 7 patients receiving DS-4773 and 1 patient receiving the control drug were noncompliant at the time of either inclusion or exclusion after 2 weeks of treatment, suggesting that more participants received DS-4773 first and this may have contributed to the greater efficacy of DS-4773. In the section on concomitant drugs, combinations with hypnotics were used to treat persistent sleep disorder, suggesting that the hypnotic may have improved the efficacy of the investigational product. The contribution of concomitant drugs to the efficacy of DS-4773 should be evaluated to better determine the actual efficacy of this Kampo medicine.

12. Abstractor and date

Goto H, 18 August 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Zhuang H.Y., Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation of normal young adults. *Shinkei Seishin Yakuri* (*Japanese Journal of Neuropsychopharmacology*) 1992; 14: 319–25 (in Japanese with English abstract). Ichushi Web ID: 1994094031

Hagino H, Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation with quantitative EEG method. *Noha to Kindenzu* (*Japanese Journal of Electroencephalography and Electromyography*) 1995; 23: 361–7 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of kakkonto (葛根湯) on sleepiness after sleep deprivation.

2. Design

Double blinded randomized cross-over controlled trial (DB-RCT-cross over).

3. Setting

Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital, Japan.

4. Participants

Seven healthy female students (aged 20 or 21 years).

5. Intervention

Arm 1: oral administration of Kanebo Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals on day 2 of the experiment. After one month of washout, oral administration of placebo (lactose) 2.5 g t.i.d. before meals on the second day of the experiment (n=3).

Arm 2: oral administration of placebo (lactose) 2.5 g t.i.d. before meals on day 2 of the experiment After one month of washout, oral administration of Kanebo Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals on day 2 of the experiment (n=4).

6. Main outcome measures

Subjective sleepiness (Sleepiness Scale), Critical Flicker Frequency (CFF), Multiple Sleep Latency Test (MSLT), blood pressure, heart rate, body temperature, and electroencephalogram (EEG).

7. Main results

An hourly comparison revealed significantly less subjective sleepiness in arm 1 than in arm 2 at 10:00 a.m. on day 2 of the experiment (P<0.05). No between-arm differences were found in the mean values for CFF, MSLT, subjective sleepiness, blood pressure, heart rate, and body temperature. The mean latency in the MSLT value was significantly longer in kakkonto group than in placebo group (P<0.05). The calculated relative power contribution ratio at each frequency band was reported significantly lower %δ at 16:00 and 18:00 and significantly higher %α at 16:00 in the kakkonto group than in the placebo group.

8. Conclusions

Kakkonto is effective for relieving sleepiness after sleep deprivation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an excellent clinical study report by Zhuang et al (1992) investigating the effect of kakkonto on sleepiness after sleep deprivation using a cross-over design and subjective sleepiness and objective measures, e.g., EEG, for evaluation. However, as discussed by the authors, kakkonto was deemed effective on the basis of different measures at different hours, making sleepiness difficult to evaluate. In addition, the attempts to blind the participants to treatment allocation, including administration with a soft drink, were inadequate. Ideally, encapsulation should have been used. Significant differences in some measures have been shown in a larger sample size. Nevertheless, this is an interesting report elucidating the efficacy of a Kampo medicine. The original article by Hagino et al (1995) included an analysis of EEG results..

12. Abstractor and date

Goto H, 19 August 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Murase K, Toyama Y, Harada Y, et al. Evaluation and comparison of the effect of two Chinese herbal medicines (Bofu-tsusho-san and Dai-saiko-to) on metabolic disorders in obstructive sleep apnea patients. *American Journal of Respiratory and Critical Care Medicine* 2013; 187: A5694. CENTRAL ID: CN-00870751

1. Objectives

To evaluate the lipid lowering and antihypertensive effects of bofutsushosan (防風通聖散) and daisaikoto (大柴胡湯) for patients with obstructive sleep apnea as a complication of obesity and hypertension.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the corresponding author belongs to the Faculty of Medicine, Kyoto University, Japan).

4. Participants

One hundred and twenty-eight obstructive sleep apnea patients with hypertension and obesity remaining after at least six-month CPAP treatment.

5. Intervention

Arm 1: Bofutsushosan (防風通聖散) (manufacturer unknown) for six months (n=65).
Arm 2: Daisaikoto (大柴胡湯) (manufacturer unknown) for six months (n=63).

6. Main outcome measures

Body mass index (BMI), blood pressure.

7. Main results

The patients who completed the study were 44 in arm 1 and 41 in arm 2. BMI decreased significantly in arm 1 from 34.6±6.3 kg/m^2 before treatment to 33.7±6.6 kg/m^2 after six months of treatment, while in arm 2 the scores were 34.9±7.9 kg/m^2 before administration and 34.9±8.1 kg/m^2 after six months. Although in statistical terms no antihypertensive effect with a significant difference between groups was found, a decrease in morning systolic blood pressure was observed in home blood pressure measurements in arm 1 (from 143.3±13.4 mmHg to 138.7±13.9 mmHg, P=0.03) and a decrease in diastolic blood pressure was observed in arm 2 (from 84.3±10.4 mmHg to 80.2±11.1 mmHg, P<0.01). A decrease in sleep onset latency was observed.

8. Conclusions

The results suggest bofutsushosan (防風通聖散) and daisaikoto (大柴胡湯) have lipid lowering and antihypertensive effects for patients with obstructive sleep apnea as a complication of obesity and hypertension.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Having evaluated the lipid-lowering and antihypertensive effects of bofutsushosan and daisaikoto for patients with obstructive sleep apnea as a complication of obesity and hypertension, the authors' interim report suggests that bofutsushosan has a BMI-lowering action. While no significant antihypertensive effect was observed between the two groups, blood pressure measurements taken in the morning with a home sphygmomanometer suggest a decrease in systolic blood pressure in the bofutsushosan group, and a decrease in diastolic blood pressure in the daisaikoto group. As this paper is an interim report, completion of the trial must be awaited for the final results.

12. Abstractor and date

Okabe T, 6 June 2015.

6. Nervous System Diseases (including Alzheimer's disease)

Reference

Yamada K, Kanba S, Ohnishi K, et al. Clinical effectiveness of oren-gedoku-to for sleep disorder associated with acute schizophrenia and other psychotic disorders. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1997; 47: 827-31 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the efficacy of orengedokuto (黄連解毒湯) for sleep disorder associated with acute psychotic disorder.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

No study site was specified (authors belonged to the Kampo Clinic, School of Medicine, Keio University and/or Department of Neuropsychiatry, School of Medicine, Keio University), Japan.

4. Participants

Eighteen untreated male patients who were diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, or brief psychotic disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, and had sleep disorder among their chief complaints.

5. Intervention

Arm 1: standard therapy with haloperidol in combination with oral treatment with TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. for 4 weeks (n=9).

Arm 2: only standard therapy with haloperidol for 4 weeks (n=9).

6. Main outcome measures

Dose of nitrazepam used as needed for insomnia; assessment of schizophrenic symptoms by the Brief Psychiatric Rating Scale (BPRS).

7. Main results

In assessment of schizophrenic symptoms, there was no between-arm difference. In addition, there was no significant between-arm difference in the oral dose of nitrazepam.

8. Conclusions

In patients with sleep disorder associated with acute schizophrenia and other psychotic disorders, orengedokuto used in combination with the antipsychotic tends to improve thought disorder and decrease the dose of nitrazepam.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

This is an interesting clinical study comparing the effect of antipsychotic in combination with orengedokuto for sleep disorder associated with acute schizophrenia, etc. with the effect of antipsychotic alone. While it was stated in the Methods section that "in both groups, haloperidol was the only antipsychotic used, and biperiden was the only anti-parkinson agent used", the number of patients treated with each drug was not specified. In addition, it was stated that "the attending physician initiated standard therapy with haloperidol in the presence or absence of concomitant orengedokuto", failing to provide information on patients treated with each of these two drugs. Moreover, the statement "tended to improve schizophrenic thought disturbance and decrease the dose of nitrazepam" indicating that there was no significant difference between the orengedokuto group and control group, was inconsistent with the statement in the Abstract that "additional treatment with orengedokuto may be effective for sleep disorder". Nevertheless, this is a meaningful clinical study in determining the efficacy of Kampo medicine in this field because it suggests the possibility that the efficacy of orengedokuto for sleep disorder could be demonstrated by a larger study.

12. Abstractor and date

Goto H, 11 September 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Aizawa R, Kanbayashi T, Saito Y, et al. Effects of yoku-kan-san-ka-chimpi-hange on the sleep of normal healthy adult subjects. *Psychiatry and Clinical Neurosciences* 2002; 56: 303-4 CENTRAL ID: CN-00444122, Pubmed ID: 12047606, Ichushi Web ID: 2003024669

1. Objectives

To evaluate the efficacy of yokukansankachimpihange (抑肝散加陳皮半夏) for sleep disorders.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Not mentioned (probably the Akita Red Cross Hospital), Japan.

4. Participants

Of 20 normal healthy men receiving yokukansankachimpihange before the start of the study, 7 with sleep disorders favorably affected were selected for the study.

5. Intervention

Arm 1: oral administration of yokukansankachimpihange (抑肝散加陳皮半夏) extract (manufacturer, dosage, and dosing frequency unknown) for 3 days followed by 1-week withdrawal and then by oral administration of anchusan (安中散) extract for 3 days.

Arm 2: oral administration of anchusan (安中散) extract (manufacturer, dosage, and dosing frequency unknown) for 3 days followed by 1-week withdrawal and then by oral administration of yokukansankachimpihange (抑肝散加陳皮半夏) extract product for 3 days.

(The grouping method for the 7 subjects is not indicated).

6. Main outcome measures

Sleep time, sleep latency, sleep depth, and rapid eye movement (REM) sleep time.

7. Main results

Total sleep time was significantly prolonged in arm 1 (438±13 min *vs* 371±19 min in arm 2).

8. Conclusions

Yokukansankachimpihange increases sleep time.

9. From Kampo medicine perspective

Seven subjects responding to yokukansankachimpihange were selected for the double-blind study.

10. Safety assessment in the article

No adverse drug reactions occurred in either group.

11. Abstractor’s comments

This study, which investigated the efficacy of yokukansankachimpihange for sleep in a double-blind RCT, provides high-quality evidence. However, giving participants yokukansankachimpihange as pretreatment and using anchusan (which has a similar taste) as the control may have compromised blinding. Nevertheless, the research content is advantageous in that it involved objective evaluation of sleep using all-night polysomnography. Investigation with a larger sample size is expected.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Kimura H, Otake T, Ishikura H. Efficacy of shakuyakukanzoto for relieving facial spasm*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1991; 79: 2505–8 (in Japanese).

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) for relieving facial spasm.

2. Design

Randomized controlled trial (RCT).

3. Setting

Outpatient department of anesthesia of one hospital, Japan.

4. Participants

Twenty patients visiting hospital with facial spasm (3 males and 17 females; mean age, 58.3 years), all receiving a centrally-acting muscle relaxant (afloqualone, tolperisone hydrochloride, and tizanidine hydrochloride in 15, 3 and 2 patients, respectively) and minor tranquilizer (diazepam and etizolam in 11 and 9 patients, respectively).

5. Intervention

Arm 1: administration of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 7.5 g/day in 9 patients and 5.0 g/day in 1 patient (2 males and 8 females).
Arm 2: no administration of shakuyakukanzoto (芍薬甘草湯) (1 male and 9 females).

6. Main outcome measures

Severity of spasm rated before and 4, 8, 12, and 16 weeks after the start of treatment on a 4-point scale (disappeared, rare, repetitive, persistent).

7. Main results

There was no difference in baseline severity between arms. The severity in both arms decreased with time resulting in no significant between-arm differences at 4 and 8 weeks and significantly larger decrease in severity in arm 1 at 12 and 16 weeks (12 weeks, $P<0.05$; 16 weeks, $P<0.05$).

8. Conclusions

Combination of shakuyakukanzoto with a centrally-acting muscle relaxant and minor tranquilizer significantly decreases severity of facial spasm.

9. From Kampo medicine perspective

The authors state that "shakuyakukanzoto can be used without considering *sho* (証, pattern), which should be usually taken into account in prescribing a Kampo formulation, suggesting its usefulness for facial spasma."

10. Safety assessment in the article

No adverse drug reactions suspected to be attributable to shakuyakukanzoto occurred.

11. Abstractor's comments

First, this study is respectable for conducting an RCT of a Kampo medicine in 1991, when the term evidence-based medicine had only just emerged. From the perspective of CONSORT statement, however, this study raises some concerns; the drugs and their doses differed between arms, suggesting that the study may have been biased. It is not known whether the study was blinded. A study with a more rigorous design to re-evaluate efficacy is expected.

12. Abstractor and date

Tsuruoka K, 23 September 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Sekine R, Watanabe H, Mimura M, et al. The effects of gosha-jinki-gan on the low back pain and lower limb pain caused by the lumbar spine: A comparison of Gosha-jinki-gan with Benfotiamine. *Itami to Kampo* (*Pain and Kampo Medicine*) 2003; 13: 84-7 (in Japanese with English abstract). Ichushi Web ID: 2006247217

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) for treatment of lumbar (low back) and leg pain.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One general hospital and one university hospital, Japan.

4. Participants

Twenty patients with lumbar degeneration (aged 60 years or older) with a chief complaint of low back and leg pain persisting over 6 months.

5. Intervention

Arm 1: oral administration of 7.5 g/day of goshajinkigan (牛車腎気丸) extract granules for 4 weeks, followed by oral administration of 75 mg/day of benfotiamine for 4 weeks (n=10).

Arm 2: oral administration of 75 mg/day of benfotiamine for 4 weeks, followed by oral administration of 7.5 g/day of goshajinkigan (牛車腎気丸) extract granules for 4 weeks (n=10).

In each group, one patient experienced gastrointestinal symptoms following administration of goshajinkigan (牛車腎気丸) and was excluded from the statistical analysis.

6. Main outcome measures

Subjective symptoms (low back pain at rest, low back pain with motion, leg pain at rest, leg pain with motion, leg numbness, and leg fatigue), and clinical laboratory tests (hematology, blood biochemistry, and urinalysis).

7. Main results

Subjective symptoms – low back pain at rest, low back pain with motion, and leg numbness – were significantly improved after administration of goshajinkigan, compared with benfotiamine.

8. Conclusions

Goshajinkigan is more effective than benfotiamie, a vitamine B1 derivative, in the treatment of lumbar (low back) and leg pain.

9. From Kampo medicine perspective

In each arm, 6 patients with *jinkyo* (腎虚, kidney deficiency) were included. No difference was observed in the efficacy between patients with and without *jinkyo*.

10. Safety assessment in the article

Of 20 patients receiving goshajinkigan, 2 experienced gastrointestinal symptoms, which led to discontinuation of treatment. Hematology/biochemistry tests and urinalysis revealed no abnormalities in either arm.

11. Abstractor's comments

This study suggests the efficacy of goshajinkigan for low back and leg pain. To confirm that efficacy is not influenced by the presence of *jinkyo*, a clinical trial with a larger sample size is recommended.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Fukumura N, Yamamoto H, Kitahara M, et al. Hochuekkito reduced the incidence of inflammatory complications in patients with sequelae of cerebrovascular disease in convalescent rehabilitation wards: a randomized multicenter study. *Japanese Journal of Rehabilitation Medicine* 2017; 54: 303-14 (in Japanese with English abstract). Ichushi Web ID: 2017298884, UMIN ID: UMIN000021801 J-STAGE

1. Objectives

To evaluate the efficacy and safety of hochuekkito（補中益気湯）to address reduced activities of daily living (ADL), nutritional status, and immunity in patients undergoing rehabilitation for hemiplegia as a sequela of cerebrovascular disease

2. Design

Randomized controlled trial (RCT)

3. Setting

Four hospitals (departments of rehabilitation)

4. Participants

Thirty-one patients with hemiplegia as a sequela of cerebrovascular disease who were treated between April 2013 and March 2015. Participants had to be 50 years of age, have started their recovery period in a rehabilitation setting within the past 1 week, have a Functional Independence Measure (FIM) total score of ≤40, and be able to orally take medication. Patients were excluded if they had insufficient nutritional intake (<1200 kcal/day), blood C-reactive protein (CRP) ≥10 mg/dL, Physical Disability Certificate Grade ≥2 or Long-term Care Requirement Level ≥3 since before the onset of cerebrovascular disease, taken any Kampo medicine within 4 weeks before participation in this study, had any hepatic, renal, cardiac, hematologic, or metabolic disease that was considered serious, or other conditions not suitable for this study in the opinion of the investigator.

5. Intervention

Arm 1: oral administration of TSUMURA Hochuekkito（補中益気湯）Extract Granules 7.5 g/day (in 2 or 3 divided doses) for 24 weeks, starting at the initiation of rehabilitation (n=11)
Arm 2: no administration of hochuekkito (n=17)

6. Main outcome measures

Primary endpoints were FIM total score, FIM motor subscale score, and FIM cognitive subscale score, and these scores upon admission were compared with those at discharge. Secondary endpoints were albumin, body weight, Body Mass Index (BMI), % ideal body weight, total lymphocyte count, hemoglobin, CRP, and incidence of inflammatory complications.

7. Main results

The analysis excluded 3 patients who did not fulfill the inclusion criteria. The FIM total score significantly improved in both arms (P<0.001), without significant difference between the arms. Albumin significantly increased in both arms (P<0.001 for Arm 1, P=0.01 for Arm 2). CRP significantly decreased after the treatment only in Arm 1 (P=0.04). Other endpoints showed no significant differences. Among the patients with an FIM motor subscale score of ≤20, the total lymphocyte count tended to increase in Arm 1 compared with Arm 2. The incidence of inflammatory complications was 9.1% in Arm 1 and 41.2% in Arm 2, and significantly lower in Arm 1 (P=0.049).

8. Conclusion

Oral administration of hochuekkito was not shown to improve ADL in patients with hemiplegia as a sequela of cerebrovascular disease. Oral administration of hochuekkito significantly reduces occurrence of inflammatory complications.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Adverse events occurred in 5 patients (8 events) in Arm 1 and 10 patients (14 events) in Arm 2. No adverse reactions to hochuekkito were noted.

11. Abstractor’s comments

This article reports an interesting clinical study that evaluated the efficacy and safety of hochuekkito in patients with severe sequelae of cerebral infarction who started their recovery period in a rehabilitation setting. No ADL-improving effects were shown, possibly because of the limited sample size. However, an exploratory analysis showed a significantly reduced incidence of inflammatory complications in the hochuekkito group. Future clinical studies are awaited that have larger sample sizes to re-evaluate the presence or absence of the ADL-improving effect of hochuekkito in the setting of rehabilitation, or that are designed to test new hypotheses, for example using prevention of inflammatory diseases as a primary endpoint.

12. Abstractor and date

Koike H, 1 June 2020.

7. Eye Diseases

Reference

Takama N, Fujiwara T. The Efficacy of hainou-san-kyu-to for internal hordeolum. *Ganka Rinsho Iho* (*Japanese Review of Clinical Ophthalmology*) 2006; 100: 9-11 (in Japanese). Ichushi Web ID: 2006117653

1. Objectives

To evaluate the efficacy of hainosankyuto (排膿散及湯) for internal hordeolum in the acute phase.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two hospitals, Japan.

4. Participants

Twenty-six patients with internal hordeolum not complicated with other ophthalmopathy or diabetes who received basic treatment with 4 doses of antibiotic eye-drops (0.3% ofloxacin) + steroid eye-drops (0.1% fluorometholone) per day.

5. Intervention

Arm 1: basic treatment +oral administration of 2.5 g of TSUMURA Hainosankyuto (排膿散及湯) Extract Granules t.i.d. before meals (n=16).
Arm 2: basic treatment alone (n=10).

6. Main outcome measures

Duration of treatment (in days) required to achieve improvement in subjective symptoms, need for adjunctive treatment.

7. Main results

Duration of treatment in days required to achieve symptom improvement was significantly shorter in arm 1 (2.2±0.9) than in arm 2 (5.5±4.1) (P<0.001). The number of subjects requiring adjunctive treatment was not significantly different in arm 1 (1/16; 6.3%) and arm 2 (3/10; 30%). One patient in arm 1 healed 3 days after the start of treatment but had a recurrence 4 days after treatment discontinuation.

8. Conclusions

TSUMURA Hainosankyuto Extract Granules induced proliferation and differentiation of pluripotent stem cells and activity of granulocyte colony stimulating factor, strongly suggesting its suppressive effect on neutropenia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events were observed in either arm.

11. Abstractor's comments

In western medicine, antibiotics are concomitantly used with anti-inflammatory drugs. Kampo medicine, which preceded the discovery of the antibiotics used in the modern medicine, targets pathogenic microorganisms by an entirely different mechanism.

12. Abstractor and date

Hoshino E, 15 March 2009, 31 December 2013.

7. Eye Diseases

References

Nagaki Y, Hayasaka S, Hayasaka Y, et al. Effects of goshajinkigan on corneal sensitivity, superficial punctate keratopathy and tear secretion in patients with insulin-dependent diabetes mellitus. *The American Journal of Chinese Medicine* 2003; 31: 103-9. CENTRAL ID: CN-00437062, Pubmed ID: 12723759

Nagaki Y. Effects of goshajinkigan on diabetic keratopathy*. *Kampo Igaku* (*Kampo Medicine*) 2004; 28: 63-5 (in Japanese).

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) for corneal sensitivity, superficial keratitis, and tear secretion in patients with insulin-dependent (type 1) diabetes mellitus.

2. Design

Double-blined randomized controlled trial (DB-RCT).

3. Setting

Toyama Medical and Pharmaceutical University Hospital (now Toyama University Hospital), Department of Ophthalmology, Japan.

4. Participants

Fifty patients with insulin-dependent diabetes mellitus complicated with keratopathy. Participants met the following selection criteria: (1) 5 years or longer duration of insulin dependence; (2) simple or preproliferative diabetic retinopathy; (3) diffuse superficial keratitis revealed by fluorescein staining; (4) no history of eye disease other than diabetic retinopathy; and (5) no treatment with eye drops in the past 3 months.

5. Intervention

Arm 1: treatment with TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. (30 minutes before meals) for 3 months in 25 patients (age 25.5±6.9 years; male:female = 10:15; 14 with simple retinopathy and 11 with proliferative retinopathy; disease duration 11.6±5.7; group A).

Arm 2: treatment with placebo granules (lactose granules not containing extract powder) 2.0 g t.i.d. (30 minutes before meals) for 3 months in 25 patients (age 26.6±5.2 years; male:female = 13:12; 14 with simple retinopathy and 11 with proliferative retinopathy; disease duration 11.6±5.7; group B).

Arm 3: treatment with goshajinkigan (牛車腎気丸) for 3 months in 25 healthy volunteers (age 26.2±5.4 years; male:female = 11:14; group C).

6. Main outcome measures

Corneal sensitivity, fluorescein staining score, and Schirmer score were evaluated before and after the treatment.

7. Main results

Corneal sensitivity significantly improved from the pre-treatment value of 2.47±1.1 to the post-treatment value of 2.03±0.63 in group A (P<0.05) but not in group B (2.36±1.35 and 2.33±1.02, respectively). Schirmer score markedly improved from the pre-treatment value of 9.3±3.5 to the post-treatment value of 11.0±3.3 in group A (P<0.01) but not in group B (9.0±3.8 and 9.0±4.0, respectively). Fluorescein staining score markedly improved from the pre-treatment value of 1.32±0.56 to the post-treatment value of 0.64±0.49 in group A (P<0.01) but not in group B (1.40±0.64 and 1.36±0.68, respectively). Corneal sensitivity, Schirmer score, and fluorescein staining score all remained within their normal ranges in group C.

8. Conclusions

Goshajinkigan improves reduced corneal sensitivity, increases tear secretion, and markedly repairs damage to the corneal surface, thereby improving keratopathy without affecting the progression of diabetes mellitus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were observed.

11. Abstractor's comments

This study was a double-blind RCT involving 50 diabetic patients (groups A and B). It is a well-designed clinical trial in which both prescribing physician and patients were blinded. If more details, such as data on withdrawals, had been described, intention-to-treat (ITT) analysis data and more reliable results could have been obtained. Further studies are expected to determine effects of goshajinkigan on ocular complications of type 2 diabetes mellitus as a lifestyle-related disease.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

7. Eye Diseases

Reference

Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of traditional Sino-Japanese herbal medicines on aqueous flare elevation after small-incision cataract surgery. *Journal of Ocular Pharmacology and Therapeutics* 2001; 17: 59-65. CENTRAL ID: CN-00347524, Pubmed ID: 11322638

1. Objectives

To evaluate the efficacy of Kampo medicines for aqueous flare elevation after small-incision cataract surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

Toyama Medical and Pharmaceutical University Hospital (now Toyama University Hospital) and an affiliated hospital, Japan.

4. Participants

Fifty-four patients undergoing surgery for age-related cataract. Patients with complications (such as diabetes mellitus and autoimmune disease), a history of uveitis, or use of anti-inflammatory drugs were excluded.

5. Intervention

Arm 1: no medication in 20 patients (8 males and 12 females; 9 right eyes and 11 left eyes; mean age, 73.1 years [48-85 years]) as a control group.

Arm 2: treatment with TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 7.5 g/day for 3 days before surgery, on the day of surgery, and for 7 days after surgery in 14 patients (5 males and 9 females; 8 right eyes and 6 left eyes; mean age, 74.5 years [56-90 years]).

Arm 3: treatment with TSUMURA Kakkonto (葛根湯) Extract Granules7.5 g/day on the same schedule as arm 2 in 10 patients (3 males and 7 females; 6 right eyes and 4 left eyes; mean age, 75.5 years [68-83 years]).

Arm 4: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 9.0 g/day on the same schedule as arm 2 in 10 patients (5 males and 5 females; 4 right eyes and 6 left eyes; mean age, 73.8 years [61-84 years]).

Cataract surgery in all patients was performed by a single surgeon according to a standard small-incision procedure.

6. Main outcome measures

Aqueous flare intensity (in photon counts/msec) was measured preoperatively and on postoperative days 1, 3, 5, and 7.

7. Main results

Preoperatively, no differences were observed in aqueous flare intensity among the groups. Aqueous flare intensity on postoperative days 1, 3, and 5 was significantly lower in the orengedokuto group ($P<0.05$) and kakkonto group ($P<0.01$) than in the control group. There was no difference between the saireito and control groups.

8. Conclusions

Orengedokuto and kakkonto reduce aqueous flare elevation after small-incision cataract surgery.

9. From Kampo medicine perspective

Evaluation of *sho* and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic (now Department of Japanese Oriental Medicine) in the above-mentioned university hospital.

10. Safety assessment in the article

No adverse drug reactions were observed.

11. Abstractor's comments

Aqueous flare intensity was used in this RCT as a measure of intraocular inflammation after cataract surgery. Since aqueous flare is a surrogate outcome, results from clinical trials examining other outcomes such as reduction of treatment duration and dosage of commonly used postoperative medication are anticipated. See the article "Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of Kakkon-to and Sairei-to on aqueous flare elevation after complicated cataract surgery. *The American Journal of Chinese Medicine* 2002; 30: 347-53", as a follow-up of the present study.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

7. Eye Diseases

Reference

Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of kakkon-to and sairei-to on aqueous flare elevation after complicated cataract surgery. *The American Journal of Chinese Medicine* 2002; 30: 347-53. CENTRAL ID: CN-00434525, Pubmed ID: 12230023

1. Objectives

To evaluate the efficacy of Kampo medicines for aqueous flare elevation after complicated cataract surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (one department of ophthalmology), Japan.

4. Participants

Twenty-seven patients with bilateral cataracts (54 eyes were eligible) associated with idiopathic or sarcoid uveitis. Of these patients, 5 were excluded from analysis.

5. Intervention

No Kampo formulation was administered in right eye surgeries. In left eye surgeries, one of the following Kampo formulations was administered for 3 days before surgery, on the day of surgery, and for 7 days after surgery.

Arm 1: treatment with TSUMURA Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. in 12 patients (mean age, 64.2 years [48-75 years]; 6 males and 6 females; 9 with idiopathic uveitis and 3 with sarcoid uveitis).

Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. in 10 patients (mean age, 73.8 years [61-84 years]; 7 males and 8 females; 12 with idiopathic uveitis and 3 with sarcoid uveitis).

Cataract surgery in all patients was performed by a single surgeon following a standard procedure.

6. Main outcome measures

Aqueous flare intensity (in photon counts/msec) was measured preoperatively and on postoperative days 1, 3, 5, and 7.

7. Main results

Preoperatively, aqueous flare intensity was not different between the two groups. For right eyes, flare intensity was 99.1 in the kakkonto group and 89.6 in the saireito group on postoperative day 1, and then gradually decreased in both groups. For left eyes, compared with the untreated right eyes, aqueous flare intensity was significantly decreased in the kakkonto group on postoperative days 1, 3, and 5 ($P<0.001$ for each). In contrast, there was no difference between left and right eyes in the saireito group.

8. Conclusions

Kakkonto inhibits the elevation in aqueous flare intensity after complicated cataract surgery.

9. From Kampo medicine perspective

Evaluation of *sho* and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic（now Department of Japanese Oriental Medicine）in the above-mentioned university hospital.

10. Safety assessment in the article

No adverse drug reactions were observed.

11. Abstractor's comments

This study was conducted as a follow-up to the preceding study "Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of traditional Sino-Japanese herbal medicines on aqueous flare elevation after small-incision cataract surgery. *Journal of Ocular Pharmacology and Therapeutics* 2001; 17: 59-65". Participants in the present study were different from those in the preceding study, and patients with both cataracts and uveitis were examined. Also, kakkonto, which had been more effective than orengedokuto in the preceding study, was used as a test Kampo drug. These studies were conducted by the same investigators and the blinding was not described in either article; suggesting that these might have been single-blind studies.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Inoue H. Rapid effect of combination therapy with shoseiryuto and eppikajutsuto for acute otitis media with effusion in adults*. *Jibi to Rinsho* (*Otologia Fukuoka*) 2001; 47: 361-6 (in Japanese). Ichushi Web ID: 2002064379

1. Objectives

To evaluate the efficacy of shoseiryuto (小青竜湯) combined with eppikajutsuto (越婢加朮湯) for otitis media with effusion (OME) in adults.

2. Design

A quasi-randomized controlled trial (quasi-RCT).

3. Setting

A clinic (otorhinolaryngology), Japan.

4. Participants

Thirty-four patients aged 16 years or older with acute OME.
Diagnostic criteria: eligible patients were those who complained chiefly of aural fullness, hearing loss, and autophony in the preceding three weeks at interview, and who had tympanic effusion evident under a binocular microscope.

5. Intervention

Arm 1: treatment with shoseiryuto (小青竜湯) extract 1 pack t.i.d. and eppikajutsuto (越婢加朮湯) 1 pack t.i.d. (after meals).
(a total of 28 ears of 20 patients; 11 males and 9 females; aged 38.1±16.9 years).
Arm 2: treatment with carbocisteine 500 mg t.i.d. and clarithromycin 200 mg b.i.d. (after meals).
(a total of 18 ears of 14 patients; 10 males and 4 females; aged 37.9±11.5 years).
Patients in both arms were treated for 7 days. If excellent or good response was obtained and subjective symptoms disappeared at 4 days, treatment was stopped at 4 days.

6. Main outcome measures

Main variables were symptoms (assessed on interview) and eardrum findings (under a microscope) at 4 and 7 days after the first visit. Symptoms were evaluated on a 4-point scale as follows: 'excellent response,' 'good response,' 'minimal response,' and 'no response.' Eardrums were checked primarily for tympanic effusion. Tympanogram was recorded at the first visit and 7 days later (or at 4 days in patients who showed improvement at that point).

7. Main results

'Excellent or good response' with normalization or improvement of the tympanogram and with disappearance of tympanic effusion was achieved in 38.9% of the control group (arm 2) *vs* 75.0% of the Kampo group (arm 1); the outcome was significantly better in the Kampo group (P=0.02, Wilcoxon rank sum test). In patients with abnormal tympanogram at the first visit, therapeutic response tended to be more pronounced in the Kampo group. Time to the onset of improvement of subjective ear symptoms was significantly shorter in arm 2 than arm 1 (P=0.05).

8. Conclusions

In acute OME in adults, combination therapy with shoseiryuto extract and eppikajutsuto extract results in rapid disappearance of the effusion and improvement of ear symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Nausea was observed in one patient in arm 2, while no adverse drug reactions occurred in arm 1.

11. Abstractor's comments

This report is clinically relevant. Since patients were randomly assigned to each arm, based on odd- or even chart number, this study was strictly a randomized clinical controlled trial (CCT), not an RCT, and is classified as a quasi-randomized trial. Results from larger rigorously-designed trials are awaited.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Machii K, Ikezono T, Utasato S, et al. Comparative study of the efficacy of saireito monotherapy versus antiallergic agent plus carbocysteine combination therapy for otitis media with effusion*. *Kampo Igaku* (*Kampo Medicine*) 1992; 16: 200-3 (in Japanese).

1. Objectives

To compare the efficacy of saireito (柴苓湯) monotherapy versus antiallergic agent plus S-carboxymethyl-L-cysteine (S-CMC; carbocysteine) combination therapy for otitis media with effusion.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (outpatient clinic in the department of otorhinolaryngology), Japan.

4. Participants

Twenty patients with otitis media with effusion who had conductive hearing loss defined as air-bone gap (A-B GAP) of 15 dB or more (at 3 frequency average hearing levels). Otitis media with effusion was diagnosed based on eardrum findings, audiometry, and tympanogram.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 9 g/day for patients weighing ≥40 kg, 6 g/day for patients weighing 20–40 kg, and 3 g/day for patients weighing <20 kg for 4 weeks (n=10 [5 males and 5 females]; age, 7–64 years).

Arm 2: Ketotifen 1.2–2.0 mg/day or oxatomide 1 mg/kg/day for children and 60 mg/day for adults plus S-CMC 30 mg/kg/day for children and 1500 mg/day for adults for 4 weeks (n=10 [5 males and 5 females]; age, 4–60 years).

6. Main outcome measures

"Good response" was defined as hearing improvement of 10 dB or greater (at 3 frequencies) as measured by pure-tone audiometry, and improvements in tympanogram and eardrum findings; "minimal response" as 1–10 dB improvement (at 3 frequency average hearing levels) and improvements in tympanogram and eardrum findings; "no response" as no change by pure-tone audiometry; "worsening" as loss of hearing by pure-tone audiometry.

7. Main results

In arm 2 and arm 2, respectively, about 50% and 60% of patients achieved moderate or mild improvement, with the response to treatment characterized as "moderate improvement" in 2 and 3, "mild improvement" in 3 and 3, "no change" in 2 and 2, and "worsening" in 3 and 2 patients, respectively. There was no statistically significant between-group difference in the percent and number of responders and in pure-tone audiogram, tympanogram, and eardrum findings.

8. Conclusions

Saireito is effective for the treatment of otitis media with effusion as standard combination therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Notable adverse reactions were not observed.

11. Abstractor's comments

This is a valuable RCT of the efficacy of saireito for otitis media with effusion. Comparing a monotherapy with combination therapy may make blinding of patients difficult because the number of drug(s) used is obviously different. In addition, since age range of patients was wide, the treatment regimen varied accordingly. Readers might have been confused by the change of terms for assessment from "response" as defined in the outcome measures section, to "improvement" as used in the results. Reassessment using a higher-quality study design is desirable.

12. Abstractor and date

Tsuruoka K, 27 September 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Sato H, Nakamura H, Honjo I, et al. Clinical evaluation of Tsumura-Saireito in children with otitis media with effusion - A comparative randomized controlled study of cepharanthine -. *Jibiinkoka Rinsho* (*Practica otologica*) 1988; 81: 1383–7 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) compared with cepharanthine for otitis media with effusion.

2. Design

Randomized controlled trial (RCT)

3. Setting

Outpatient clinic at the Department of Otolaryngology, Kyoto University Hospital, Japan.

4. Participants

Sixty-four ears of 42 children diagnosed with otitis media with effusion as evidenced by type B tympanogram who had mean hearing level of 20 dB or more (at 3 frequency average levels: 500, 1000, and 2000 Hz).

5. Intervention

Arm 1: Thirty-two ears of 21 children aged 4–7 years (mean 5.2) were treated with TSUMURA Saireito (柴苓湯) Extract Granules 1.5 g b.i.d. for 4 weeks.

Arm 2: Thirty-two ears of 21 children aged 4–7 years (mean 5.0) were treated with cepharanthine 5.0–7.5 mg b.i.d. for 4 weeks.

6. Main outcome measures

Pure-tone audiogram and tympanogram were obtained before and after the treatment. In pure-tone audiometry, “improved” hearing after tympanoplasty was defined as an increase of 15 dB or more in mean hearing level, and “not changed” as an increase of less than a 15 dB. The otitis media with effusion was judged to be “improved” when the tympanogram changed to type A or C1, and “not changed” when it was type C2 or B. Patients were considered “responders” if either test indicated improvement and “non-responders” if neither test indicated improvement.

7. Main results

After treatment, mean hearing level increased 7.2 dB (the percentage of ears with improvement: 28.1%) in arm 1 and 3.8 dB (15.6%) in arm 2; the between-arm difference was not significant. The tympanogram was improved in 18.8% of ears in arm 1 and 3.1% of ears in arm 2; the between-arm difference was also not significant. In all, 43.8% of the saireito-treated and 18.8% of the cepharanthine-treated ears were classified as responders; the response rate was significantly higher in arm 1 (χ^2 test, $P<0.05$).

8. Conclusions

Saireito is an effective conservative treatment for otitis media with effusion in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No notable adverse reactions were observed.

11. Abstractor’s comments

This is an RCT of the efficacy of saireito for otitis media with effusion in children. Although it was published in 1988, which was before the term “EBM (evidence-based medicine)” became popular, this clinical study is well-designed. The inclusion and exclusion criteria and the outcome variables were clearly defined, and the results took into account participants who used other drugs as well. The authors also discussed the difficulty of blinding subjects to the intervention when the drugs could be identified by their respective odors. It may have been the best possible study design under the circumstances at that time.

12. Abstractor and date

Tsuruoka K, 28 September 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Yoshizaki T. A multicenter, double-blind, randomized controlled trial on the usefulness of juzentaihoto in children with recurrent otitis media* (2009−clinical study−general—007) *Chozai to Joho* (*Dispensing and Information*) Health Labour Sciences Research Grant, General Research Program for Practical Application of Medical Technology, 2009, General Research Report in 2011. 2012: 1-23 (in Japanese).

Ito M, Maruyama Y, Kitamura K, et al. Randomized controlled trial of juzen-taiho-to in children with recurrent acute otitis media *Auris Nasus Larynx* 2017; 44: 390-7. Ichushi Web ID: 2018007858, Pubmed ID: 278101268

1. Objectives

To evaluate the efficacy and safety of juzentaihoto (十全大補湯) in children with recurrent otitis media.

2. Design

Randomized controlled trial (RCT).

3. Setting

Seven university hospitals, 8 hospitals, and 11 otorhinolaryngological clinics, Japan.

4. Participants

Eighty-seven children aged ≥six months and <4 years with otitis media, recurrences of otitis media that were difficult to treat with standard therapy, a diagnosis of recurrent otitis media "acute otitis media occurring three times or more within the past 6 months, or four times or more within the past 12 months," and any of the following symptoms: a decrease in physical strength, fatigue and malaise, anorexia, night sweat, cold extremities, or anemia.

5. Intervention

Arm 1: Juzentaihoto (十全大補湯) (manufacturer unknown) administered orally at 0.05 to 0.125 g/kg b.i.d and standard therapy for 3 months (n=39).

Arm 2: Standard therapy alone (n=48).

6. Main outcome measures

Primary outcome: The mean number of recurrences with acute otitis media per month during the study.

Secondary outcome: The mean number of recurrences with coryza per month, mean frequency of antibiotic use per month, number of subjects treated by eardrum ventilation tube insertion during the study and the period of treatment.

7. Main results

A total of 70 subjects were included in the analysis: 31 subjects in the juzentaihoto arm and 39 subjects in the standard therapy alone arm. For the primary outcome, a significant decrease in the mean number of acute otitis media recurrences was observed in Arm 1 (0.61±0.54 recurrences/month) compared to Arm 2 (1.07±0.72 recurrences/month) (P=0.005). For the secondary outcomes, significant improvements were observed for both the mean number of coryza recurrences per month and the mean frequency of antibiotic use per month (P=0.015, P=0.024) in Arm 1 compared to Arm 2.

8. Conclusions

Juzentaihoto decreases the incidence of recurrent otitis media in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One subject in the juzentaihoto arm experienced skin rash, leading to suspension of treatment. No significant inter-arm difference in blood chemistry was found throughout the study.

11. Abstractor's comments

This clinical study, which evaluated the efficacy of juzentaihoto in pediatric patients with recurrent otitis media, a widely prevalent and refractory disease, is highly valuable with regard to clinical significance, setting, and study methods. Initially the study was presented in the form of a report, but in 2017 the details were clearly described and was published as a research paper. The report issued in 2012 mentioned that juzentaihoto showed efficacy in the subjects showing indications of "decreased physical strength after illness, fatigue, loss of appetite, night sweats, coldness in the extremities, and anemia". Furthermore, the authors also investigated overall physical condition, including nutritional status and whether or not there was any improvement in anemia, and reported that there was no difference between the Arms. As the authors mentioned, this clinical research is fully expected to generate evidence for the efficacy of juzentaihoto in the treatment of childhood recurrent otitis media in the future.

12. Abstractor and date

Goto H, 31 March 2017, 1 June 2020.

8. Ear Diseases

Reference

Kaneko T. Comparison of saireito and isosorbide in efficacy against low-frequency sensorineural hearing loss. *Kampo to Saishin Chiryo* (*Kampo and the Newest Therapy*) 2010; 19: 233–9 (in Japanese with English abstract). Ichushi Web ID: 2010304850

1. Objectives

To compare the effectiveness of saireito (柴苓湯) and isosorbide for low-frequency sensorineural hearing loss.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

An otorhynolaryngology clinic (Tochigi prefecture), Japan

4. Participants

One hundred and fifty-five patients with low-frequency sensorineural hearing loss who presented with ear blockage sensation as chief complaint between June 2008 and October 2009.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. (n= 76).
Arm 2: isosorbide (Kowa Pharmaceutical Co., Ltd., Isobide) 30 mL t.i.d. (n=75).

6. Main outcome measures

Two measures: pure tone audiometry and subjective symptoms. Assessment by pure tone audiometry was divided into four stages: recovered (hearing threshold levels for three low frequencies [125, 250, and 500 Hz] all found within 20 dB, or no left/right difference detected), improvement (restored to 10 dB or more, but not full recovery), no change (less than 10 dB), and worsening. Four-stage subjective assessment: improved, somewhat improved, no change, worsened.

7. Main results

The number of tested patients was 51 in arm 1 (10 males and 41 females; ages 19–76; mean age 47.8 years) and 53 in arm 2 (16 males and 37 females; ages 11–78; mean age 47.1 years). Arm 1 showed a slightly stronger tendency for improvement in the hearing test compared to arm 2, but no statistically significant difference was observed. The subjective measures “no change” and “worsened” tended to be more common in arm 2, but no significant difference was observed. Comparison of initial occurrences with recurrences showed that improvement tended to be more difficult after recurrence in both groups, but no significant difference was observed. Recovery tended to be poor in subjects with dizziness symptoms in both groups, but no significant difference was observed.

8. Conclusions

Saireito and isosorbide are similarly effective for low-frequency sensorineural hearing loss.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

Low-frequency sensorineural hearing loss is frequently encountered in daily practice, nevertheless, its causes remain unknown. A finding of the study that is significant in clinical and pathological terms is that Saireito and isosorbide have equal effectiveness. Unfortunately, the trial amounted to a quasi-RCT because allocation of participants to receive one of the treatments was in the order of diagnosis. The reliability of the results could have been improved if patients who did not return to the clinic for determination of the effects of treatment could have been followed up. Participants might not have returned because their symptoms improved or because they visited another clinic. This greatly affected the results. Hopefully the researcher will properly randomize the trial and improve the follow-up rate in the next stage of his research. In this study a doctor at the frontline of community health care has attempted an RCT to verify a medical practice that has concerned him in the clinic. It is praiseworthy for its contribution to the development of Kampo medicine.

12. Abstractor and date

Tsuruoka K, 31 December 2012.

8. Ear Diseases

Reference

Tanaka H. Efficacy of a Kampo preparation combined with tranquilizers in patients with tinnitus. *Jibiinkoka Rinsho* (*Practica otologica*) 1996; suppl 89: 8 (in Japanese).

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) combined with tranquilizers for tinnitus.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single institution (Department of Otorhinolaryngology, Koseiren Nagaoka Chuo General Hospital), Japan.

4. Participants

Two hundred and twelve tinnitus patients with symptoms of Eustachian tube dysfunction. (The paper mentions 212 participants, however, there are 222 in arms 1 and 2 combined.)
Inclusion criteria were: tinnitus that is 1) worsened by the common cold, nasal allergy, or sinusitis; 2) relieved by Eustachian tube insufflation; 3) still present after myringotomy for otitis media with effusion; 4) complicated by chronic otitis media and relieved by the patch test; or 5) associated with sequelae of otitis media.

5. Intervention

Arm 1: treatment with tranquilizer alone for more than 4 weeks, then combined with Kanebo Saireito (柴苓湯) Extract Fine Granules (n=104).
Arm 2: treatment with Kanebo Saireito (柴苓湯) Extract Fine Granules + tranquilizer combination for 2 weeks, then tranquilizer alone (n=118).

6. Main outcome measures

Changes in the symptoms (measured using a 3-point scale corresponding to improvement, no change, and worsening).

7. Main results

Efficacy was observed in around 60% of patients treated with the combination (69/104 in arm 1 and 58/118 in arm 2) and in 62.6% and 57.1% of patients treated with 8.1 g and 5.4 g of saireito, respectively. Even the lower-dose administration was effective.

8. Conclusions

Saireito combined with tranquilizers was effective for treating tinnitus. Current Kampo extract preparations contain large amounts of ingredients. Considering the possibility of poor drug compliance, the treatment with 5.4 g of saireito was suggested to be useful.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study was referred to as a RCT-cross over study, based on the mention of "cross-over trial" in the paper. But it was a short paper and information was scarce. Basic information, including age and sex of participants, names of tranquilizers used, and when, how, and by whom the outcomes were measured, is absent and therefore assessment of this study is difficult. The development of future studies on this topic is expected.

12. Abstractor and date

Tsuruoka K, 22 April 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Suzuki T. *Clinical efficacy of chotosan for tinnitus. Pathology and treatment of tinnitus and dizziness*[*]. The 28th Chiba Symposium of Japanese Traditional Medicine Tokyo: Kudansha; 2001:8-20 (in Japanese). Ichushi Web ID: 2003129990

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) for tinnitus.

2. Design

A crossover randomized controlled trial (RCT-crossover).

3. Setting

A community hospital (department of otorhinolaryngology), Japan.

4. Participants

Fifty-eight patients with tinnitus.

5. Intervention

Arm 1: oral administration of TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g, t.i.d. for 4 weeks, followed by mecobalamin 0.5 mg, t.i.d. for 4 weeks (n=29).

Arm 2: oral administration of mecobalamin 0.5 mg, t.i.d. for 4 weeks, followed by TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g, t.i.d. for 4 weeks (n=29).

6. Main outcome measures

The intensity (loudness level) and duration of tinnitus, and tinnitus-associated annoyance was evaluated on a 6-point scale (from 0 = disappearance to 5 = maximum) according to the diagnosis criteria established by a study group of the Japan Audiological Society. Scores of these three measures were summed before and after each treatment, and the degree of improvement was measured by reduction in the summed score from the pre-treatment value. 'Disappearance' was defined as reduction to zero, 'marked improvement' as reduction of 8 or more points, 'moderate improvement' as reduction of 4 to 7 points, 'mild improvement' as reduction of 1 to 3 points, 'no improvement' as no change in score, and 'worsening' as increase in score.

7. Main results

In the chotosan-first group (arm 1), scores were significantly reduced after 4 weeks of chotosan treatment, but significantly increased after the switch to mecobalamin treatment. In mecobalamin-first group (arm 2), scores did not change at 4 weeks, and significantly increased after the switch to chotosan treatment. The degree of improvement in tinnitus was significantly different between groups at 4 weeks, then similar at 8 weeks. Improvements were significant, as compared with the pre-treatment baseline values, in both groups. Tinnitus had disappeared in 5 ears, was markedly improved in 8 ears, and was moderately improved in 14 ears. Moderate-to-marked improvement was seen in 39.8% of ears and mild-to-marked improvement in 80.9%. There was no case of 'worsening' tinnitus. Regarding background factors, there were no between-group differences in sex, age, diagnosis, disease duration, side of diseased ear, and medical history. Chotosan showed significant efficacy for tinnitus with heaviness of head/ headache or shoulder stiffness, compared with other accompanying symptoms.

8. Conclusions

Chotosan is more effective than mecobalamin in improving tinnitus.

9. From Kampo medicine perspective

Although specific results were not provided, the author concluded that the treatment would be more effective when they took into account on the patient's condition.

10. Safety assessment in the article

Serious adverse drug reactions were not reported in either group.

11. Abstractor's comments

This study provided high-quality evidence that chotosan is efficacious for tinnitus, which is often difficult to treat. Chotosan tended to improve, though not significantly, Meniere's disease and tinnitus without hearing loss, but not C5dip-type sensorineural hearing loss. These points are helpful when the efficacy of chotosan is determined, and also provide useful insights in its mechanism. In addition, unlike previous reports showing that patients with shorter disease duration were more likely to respond, this study described striking improvement in some cases, such as 'marked improvement' in a patient with disease for 30–40 years and complete recovery in several patients with disease for 4–5 years. The problems of this study are as follows: 1) The presentation of the results is inconsistent. For example, results are presented on a patient basis at first, and then on an affected-ear basis. 2) The report is incomplete because results from a Kampo medicine perspective are not presented. And 3) there is no description of the randomization step or the method of assignment to arm 1 and arm 2. The randomization step may have been omitted because of the crossover design. Nevertheless, an accurate description is desired. However, the article presents future challenges, and further developments are expected.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010.

8. Ear Diseases

Reference

Onishi S. Kampo treatment for tinnitus and hearing impairment*. *JOHNS* 1990; 6: 535-9 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for tinnitus.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Otolaryngology Department, Kanto Teishin Hospital, Japan.

4. Participants

Thirty-nine patients who presented with tinnitus as their chief complaint (22 males and 17 females, age ranging from the 20s to 80s).

5. Intervention

Arm 1: goshajinkigan group. TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (7.5 g/day) for 8 weeks (n=22).

Eight participants from arm 2 were included in arm 1 for a total of 30 after experiencing no effect from treatment in arm 2.

Arm 2: chotosan group. TSUMURA Chotosan (釣藤散) Extract Granules (7.5 g/day) for 8 weeks (n=24).

Six participants from arm 1 were included in arm 2 for a total of 30 after experiencing no effect from treatment in arm 1.

Participants were allocated to arm 1 or arm 2 in the order of presentation, regardless of their Kampo pattern.

6. Main outcome measures

Tinnitus severity, duration, and how it becomes concerning classified into five grades: remarkable improvement, improvement, slight improvement, no change, and deterioration.

7. Main results

Although there was no significant difference between groups, effectiveness of goshajinkigan for tinnitus tended to be greater (50% with grade 'improvement' or better) than that of chotosan (30% with grade 'improvement' or better). Three out of seven participants with tinnitus following sudden hearing loss in arm 1 and one of the five such participants in arm 2 scored 'improvement' or better. In both groups, most patients experienced an effect within two months of the start of treatment.

8. Conclusions

Goshajinkigan may be effective for tinnitus. Its efficacy is at least equivalent to chotosan.

9. From Kampo medicine perspective

While the Kampo medications were administered regardless of the patient's Kampo pattern, tinnitus is a major symptom within the goshajinkigan-pattern (by stratified analysis), and no relation between effectiveness and the existence of lower limb pain, numbness, and swelling could be identified.

10. Safety assessment in the article

Diarrhea was observed in one participant in each group, however it was not severe enough to discontinue administration.

11. Abstractor's comments

This is a clinically significant study in that it compared and analyzed the clinical effects of goshajinkigan for tinnitus to those of chotosan in a controlled clinical trial. Its clinical significance would be improved by analyzing effectiveness in patients administered goshajinkigan and chotosan in a crossover manner with a required washout period after demonstrating ineffectiveness in each group. Further research is anticipated.

12. Abstractor and date

Kogure T, 31 December 2013.

8. Ear Diseases

Reference

Ino T, Odaguchi H, Wakasugi A, et al. A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of hangekobokuto in adult patients with chronic tinnitus. *Journal of Traditional Medicines* 2013; 30: 72-81. Ichushi Web ID: 2013310385 J-STAGE

1. Objectives

To evaluate the effects of hangekobokuto (半夏厚朴湯) on chronic tinnitus.

2. Design

Double-blind, placebo-controlled, randomized controlled trial (DB-RCT).

3. Setting

Department of Otorhinolaryngology, Kitasato University Hospital, Japan.

4. Participants

Seventy-six adults aged at least 20 years with tinnitus persisting for at least three months, the impairment rated at least 18 points on the Tinnitus Handicap Inventory score (THI score), or between mild and severe. The five exclusion criteria were: (1) objective tinnitus, intermittent tinnitus, or pulsatile tinnitus; (2) conductive hearing impairment; (3) acoustic nerve tumor confirmed by MRI or clinically related nerve impairment, psychiatric disorder, or systemic disease (e.g. cardiac disease, malignant tumor, renal failure, hepatic failure); (4) administration of a Kampo medication within 4 weeks before the trial; and (5) currently pregnant or breastfeeding.

5. Intervention

Arm 1: Kracie Hangekobokuto (半夏厚朴湯) Extract Tablets, 6 tablets b.i.d. for 12 weeks (n=38)

Arm 2: Placebo, 6 tablets b.i.d. for 12 weeks (n=38). The placebo tablets were made of cornstarch and lactose to resemble the Hangekobokuto (半夏厚朴湯) Extract Tablets in color, form, weight, smell and taste.

6. Main outcome measures

The main outcome was the difference between baseline and final THI scores. Secondary outcomes: changes in the visual analog scale (VAS), Hospital Anxiety and Depression Scale (HADS), and Short-Form 36-Items Health Survey scores (SF36).

7. Main results

There was no significant difference between arms in THI scores (total: P =0.73, functional: P=0.99, emotional: P=0.78, catastrophic: P=0.59). There was no significant difference in the secondary outcome measures. There was no difference between arms in THI score among participants with no anxiety or depression. THI scores tended to improve in the hangekobokuto arm compared to the placebo arm among participants with dizziness (total: P=0.006). The authors did a hangekobokuto pattern subgroup analysis (16 participants in the hangekobokuto arm and 26 in the placebo arm), but there was no significant difference between groups.

8. Conclusions

While there were no significant differences between arms, hangekobokuto tended to improve THI scores for participants with dizziness more than the placebo.

9. From Kampo medicine perspective

As mentioned in the results, a hangekobokuto pattern subgroup analysis was carried out.

10. Safety assessment in the article

Itchiness and worsened tinnitus were observed in the placebo arm. Neither was sufficiently severe to discontinue the trial.

11. Abstractor's comments

This is a well-designed RCT. The randomization, delineation between the inclusion and exclusion criteria, participant recruitment, flow diagram, and outcomes were clear and readily comprehensible. It is an exemplary paper with much to teach new learners of EBM. Although unfortunately the results did not demonstrate significant differences, as the authors mention in their considerations, they will take the next step forward by finding the definitive factors that lead to Kampo medication prescribing, and formulating a study design that fully reflects the particular features of Kampo. Further development of this research is anticipated.

12. Abstractor and date

Tsuruoka K, 6 June 2015.

9. Cardiovascular Diseases

References

Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitoring. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 282-3 (in Japanese).

Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitoring*. *Kampo Shinryo* 1996; 15: 34-5 (in Japanese).

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) and orengedokuto (黄連解毒湯) for hypertension using ambulatory blood pressure monitoring.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Eight hypertensive patients who visited the hospital for the first time.

5. Intervention

Arm 1: Tsumura Chotosan (釣藤散) Extract Granules (TJ-47) 7.5 g/day (n=3).
Arm 2: Tsumura Orengedokuto (黄連解毒湯) Extract Granules (TJ-15) 7.5 g/day (n=5).
The period of administration was 15–265 days.

6. Main outcome measures

Blood pressure (BP) was measured using an ambulatory blood pressure monitor (ABPM) before and after treatment, and the following BP values were determined: 1) the 24-hour average systolic BP (sBP) and diastolic BP (dBP), 2) the average daytime sBP and dBP, 3) percentage of ambulatory dBPs more than 90 mm Hg during 24 hours (diastolic pressure load), and 4) BP values analyzed by a cosinor method. Hypertensive patients with or without accessory symptoms were separately assessed.

7. Main results

1) A 24-hour antihypertensive effect on sBP was observed in 3 patients in arm 2, and a 24-hour antihypertensive effect on dBP was observed in 1 patient in arm 1. 2) Daytime sBP decreased in 1 patient in arm 1 and 3 patients in arm 2, and daytime dBP decreased in 1 patient in arm 1 and 1 patient in arm 2. 3) Reduction in diastolic pressure load was noted in 2 patients in arm 1 and 1 patient in arm 2. 4) Cosinor analysis revealed efficacy in 1 patient in arm 1 and 2 patients in arm 2.

In patients with accessory symptoms, headache and heaviness of the head improved in 1 patient in arm 1, headache and shoulder stiffness improved in 1 patient in arm 1, but no indices of hypertension for these patients was affected. Lightheadedness in 1 patient in arm 2 was accompanied by decrease in BP.

8. Conclusions

Kampo monotreatment has a satisfactory hypotensive effect in some cases.

9. From Kampo medicine perspective

It is noted that in two patients with *sho* (証, pattern) for chotosan, treatment was effective (all indices) for 1 patient but not for the other. Also in a patient with *sho* for orengeokuto, no effect was observed.

10. Safety assessment in the article

In the “result” and “discussion” sections of the related article, it is noted that the Kampo diagnosis of “*sho* (証, pattern)” may not be associated with a hypotensive effect of Kampo treatment, which may not be observed even when *sho* is compatible with the Kampo prescription.

11. Abstractor’s comments

Despite the small number of the subjects, this is an important report that evaluates (using ABPM) the hypotensive effect of Kampo drugs. The results of many multicenter trials of orengedokuto for treatment of hypertension suggest its efficacy for accessory symptoms but not for high BP. However, I have the clinical impression that orengedokuto is effective in some cases, and these data support that impression. Analysis found no association between the accessory symptoms and *sho*. How goals *sho* for use of Kampo drugs are set (e.g., trial and error) should be further investigated.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Sasaki J, Matsunaga A, Kusuda M, et al. Efficacy of daisaikoto and chotosan in patients with essential hypertension. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1993; 70: 1965-75 (in Japanese). Ichushi Web ID: 1994042619

1. Objectives

To evaluate the efficacy and safety of daisaikoto (大柴胡湯) and chotosan (釣藤散) in patients with essential hypertension.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Five hospitals (1 university hospital and 4 clinics), Japan.

4. Participants

A total of 94 patients who met the following 4 criteria: 1) essential hypertension with unidentified complaints, 2) inadequate control of hypertension by other antihypertensive agents, 3) mild hypertension, and 4) judged to be appropriate for the study. Of these, 83 patients were included for analysis.

5. Intervention

Jitsu-sho Arm 1: thirty patients with *jitsu-sho* (実証, excess pattern). Tsumura Daisaikoto (大柴胡湯) Extract Granules (TJ-8) 2.5 g t.i.d. for 8 weeks (n=14); *jitsu-sho* arm 2: no administration (n=15).

Kyo-sho Arm 1:Sixty-two patients with *kyo-sho* (虚証, deficiency pattern).Tsumura Chotosan (釣藤散) Extract Granules (TJ-47) 2.5 g t.i.d. for 8 weeks (n=24); *kyo-sho* arm 2: no administration (n=30).

6. Main outcome measures

Blood pressure (BP). Pulse rate. Subjective symptoms assessed in 3 grades (improved, no change, or worse); headache, heaviness of the head, dizziness, shoulder stiffness, palpitation, hot flashes, irritation, tinnitus, insomnia, anxiety/restlessness, cold or hot feelings in the limbs, numbness in the limbs, loss of appetite, constipation, diarrhea, nausea, dry mouth, eye fatigue, and lassitude. Global improvement. The results of laboratory tests.

7. Main results

Diastolic BP in *jitsu-sho* arm 1 and BP in *kyo-sho* arm 1 were significantly decreased in the treatment group when compared to the untreated group after 8 weeks. Tinnitus was significantly improved ($P<0.05$) and global improvement was better in chotosan-treated arm (*kyo-sho arm 1*). The results of laboratory tests remained within normal limits.

8. Conclusions

In *kyo-sho* patients, chotosan has a significant antihypertensive effect.

9. From Kampo medicine perspective

In this study, patients were grouped into *jitsu-sho* and *kyo-sho* using a questionnaire, and were treated with Kampo drugs appropriate for their *sho* (証, pattern).

10. Safety assessment in the article

Fifteen patients in arm 1 and 26 patients in arm 2 were assessed. In the daisaikoto treatment group, 1 patient experienced watery diarrhea and withdrew from the study. In the chotosan treatment group, 1 patient discontinued treatment because of abdominal discomfort and bloating and withdrew from the study.

11. Abstractor's comments

This is an important report on the Kampo treatment of hypertensive patients based on body constitution (*sho*). In this study, a significant antihypertensive effect of chotosan in *kyo-sho* patients was observed. On the other hand, this paper did not elucidate the hypotensive effect of daisaikoto in *jitsu-sho* patients and was therefore consistent with other papers reporting that orengedokuto (黄連解毒湯) used for *jitsu-sho* or *chukan-sho* has no direct hypotensive effect ("Arakawa K, Saruta T, Abe K, et al. Double-blind placebo-controlled trial of TSUMURA Orengedokuto (TJ-15) for the treatment of accessory symptoms of hypertension*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Study*) 2003; 80: 354-72 (in Japanese)" Ichushi Web ID: 2003184342 MOL, MOL-Lib). It might be that blood pressure is more closely associated with symptoms in *kyo-syo* patients. It would be interesting to know whether the effects can still be observed when the *sho* of the patients is not considered. Efficacy of chotosan for tinnitus has been previously reported, and this study confirmed this effect in *kyo-sho* patients.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010.

9. Cardiovascular Diseases

Reference

Saku K, Hirata K, Zhang B, et al. Effects of Chinese herbal drugs on serum lipids, lipoproteins, and apolipoproteins in mild to moderate essential hypertension. *Journal of Human Hypertension* 1992; 6: 393-5. CENTRAL ID: CN-00089422, Pubmed ID: 1464897

1. Objectives

To evaluate the effects of daisaikoto (大柴胡湯) and saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) on serum lipid levels in patients with mild to moderate hypertension.

2. Design

Randomized controlled study (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Thirty patients with mild to moderate hypertension.

5. Intervention

Arm 1: daisaikoto (大柴胡湯) (manufacturer not specified) 2.5 g t.i.d. for 3 months (n=15).
Arm 2: saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) (manufacturer not specified) 2.5 g t.i.d. for 3 months (n=15).

6. Main outcome measures

Blood pressure, pulse rate, total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), HDL2-C, HDL3-C, low density lipoprotein cholesterol (LDL-C), lecithin-cholesterol-acyltransferase (LCAT), apolipoprotein (apo-AI, AII, B, CII, CIII, and E).

7. Main results

In both arms, blood pressure was unchanged, but pulse rate was significantly decreased in arm 2 after 3 months of administration. In arm 1, levels of HDL-C, LCAT, and apo-AII were significantly increased, but others were unchanged. In arm 2, the level of HDL-C was significantly increased.

8. Conclusions

Both daisaikoto and saikokaryukotsuboreito affect serum lipid levels but not blood pressure.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

By studying patients before and after administration, it was shown that both daisaikoto and saikokaryukotsuboreito increase HDL-C (also known as beneficial cholesterol), which will help patients with dyslipidemia. Further studies with larger sample size and control group are warranted.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

9. Cardiovascular Diseases

References

Arakawa K, Saruta T, Abe K, et al. Double-blind placebo-controlled trial of TSUMURA Orengedokuto (TJ-15) for the treatment of accessory symptoms of hypertension*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Study*) 2003; 80: 354-72 (in Japanese). Ichushi Web ID: 2003184342 MOL, MOL-Lib

Arakawa K, Saruta T, Abe K, et al. Improvement of accessory symptoms of hypertension by TSUMURA Orengedokuto Extract, a four herbal drugs containing Kampo-Medicine Granules for ethical use: a double-blind, placebo-controlled study. *Phytomedicine* 2006; 13: 1-10. [CENTRAL ID: CN-00553637, Pubmed ID: 16360926

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) in patients with hypertension symptoms.

2. Design

Double-blind, randomized, controlled trial (DB-RCT).

3. Setting

A total of 116 university hospitals and community hospitals, Japan.

4. Participants

A total of 265 patients with hypertension who met the inclusion and exclusion criteria; 204 included and 61 not included for analysis.

5. Intervention

Arm 1: administration of TJ-15 (containing 0.25 g of TSUMURA Orengedokuto (黄連解毒湯) Extract Granules) capsules, 2 cap, t.i.d. (n=103).

Arm 2: administration of placebo capsules, 2 cap, t.i.d. (n=101).

Oral administration before each meal. Duration of treatment: 8 weeks.

6. Main outcome measures

Reduction in blood pressure was evaluated by comparing blood pressure measurements (systolic, diastolic, and mean) obtained after the run-in period and after the treatment period, and the antihypertensive effect was classified into 5 grades. Improvement in five major accessory symptoms – irritability (feeling irritated), anxiety, sleep disorder, hot flushes, and facial flushing – and other subjective symptoms – headache/heavy-headedness, shoulder stiffness, dizziness, and malaise – were graded from –3 to 3.

7. Main results

There was no significant difference in blood pressure decrease, or antihypertensive effect, between the TJ-15 group and placebo group. Significant efficacy against hot flushes and facial flushing was observed in the treatment group. Irritability, anxiety, and sleep disorder were also improved in the treatment group as compared with the placebo group. Scores of the other subjective symptoms improved significantly. There was no significant between-group difference in the overall safety rating.

8. Conclusions

This study demonstrates the efficacy and safety of orengedokuto for the treatment of hypertension symptoms.

9. From Kampo medicine perspective

The inclusion criteria were high blood pressure and presence of hypertension symptoms (irritability, anxiety, sleep disorder, hot flushes, and facial flushing) indicating orengedokuto "*sho* (pattern)". Also 'patients with "*kan-sho*" (寒証, cold/yin pattern) or "*kyo-sho* (虚証, deficiency pattern)" in Kampo medicine' were excluded. Although "*sho*" is not fully equivalent to body-mass index (BMI), patients with thin physique were excluded from this study, resulting in the mean BMI of 24.3. Thus, the focus of this study was on the patients who were most likely to respond to and benefit from orengedokuto.

10. Safety assessment in the article

Adverse effects were observed in eight patients (6.3%) in the placebo group and 15 patients (11.5%) in the TJ-15 group. Nausea (n=2), abnormal laboratory data such as liver dysfunction (elevated liver enzymes) (n=7), and generalized rash (n=1) might be associated with orengedokuto.

11. Abstractor's comments

Orengedokuto, a typical Kampo medicine for hypertension, was reevaluated in this original article. This study targets the symptoms related to stress or hyper-activation of sympathetic nervous system such as anger, stress, anxiety, and fear. In this multicenter double-blind clinical trial, blood pressure tended to decrease, but did not significantly decrease, in response to treatment. However, significant improvement in some accessory symptoms is a milestone. Compared with benzodiazepine anxiolytics in a study of essential hypertension, Orengedokuto seemed to show more efficacy. However, simple comparison cannot be done owing to different criteria used in selecting study participants. This study suggests that treatment based on "*sho*" may be effective.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 13 March 2009, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Azushima K, Tamura K, Haku S, et al. Effects of the oriental herbal medicine Bofu-tsusho-san in obesity hypertension: a multicenter, randomized, parallel-group controlled trial (ATH-D-14-01021.R2) . *Atherosclerosis* 2015; 240: 297-304.

1. Objectives

To verify the effectiveness of the combined use of bofutsushosan (防風通聖散) with Western medical treatments for obesity hypertension patients using Ambulatory Blood Pressure Monitoring (ABPM).

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital nephrology/hypertension department, 3 hospital nephrology departments, 1 clinic, Japan.

4. Participants

One hundred and six obesity hypertension patients with a BMI of at least 25kg/m^2, aged between 20 and 79 years, who underwent antihypertensive treatment including diet and exercise therapy for at least 4 weeks before the start of the trial.

5. Intervention

Arm 1: Antihypertensive treatment including diet and exercise therapy in addition to bofutsushosan (2.5g/day at first taken orally between or before meals, with the dosage titrated as appropriate according to symptoms, up to a maximum of 7.5g/day. Manufacturer's name not mentioned) for 24 weeks (n=54).

Arm 2: Antihypertensive treatment including diet and exercise therapy without bofutsushosan (n=52).

6. Main outcome measures

The primary endpoints were hypotensive effect (using ABPM, means and short-term variability of systolic and diastolic phases and BPM at daytime and nighttime), and the secondary endpoints were the between-group differences in BMI, etc. at weeks 12 and 24.

7. Main results

After excluding dropouts, the authors analyzed 93 participants at week 12 and 88 at week 24. There was no significant difference in ABPM at week 12. In week 24, the mean diastolic phase blood pressure in daytime was significantly lower in the control group (P=0.045), and systolic blood pressure variability in daytime was significantly lower in the bofutsushosan group (P=0.006). BMI was significantly lower in the bofutsushosan group in both weeks 12 and 24 (P=0.005 and P=0.029 respectively).

8. Conclusion

Adding bofutsushosan to an anti-hypertensive agent improves short-term blood pressure variability and has an anti-obesity effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

2 out of 54 participants (3.7%) who took the additional bofutsushosan experienced an adverse effect.

11. Abstractor's comments

This paper verified the effectiveness of adding bofutsushosan to a usual anti-hypertensive drug for patients with hypertension associated with obesity and reasons that short-term variability in blood pressure decreases with bofutsushosan. However, the authors listed 24 primary endpoints and compared 2 groups, indicating a difference of P<0.05 in effectiveness for systolic phase blood pressure variability in the daytime in the group that took additional bofutsushosan, and on the other hand, effectiveness in the control group for mean blood pressure in the diastolic phase in daytime for the other group of P<0.05, although coming to an overall conclusion for the paper that bofutsushosan is effective, is not statistically possible. It is also unclear in this study whether bofutsushosan affected blood pressure, as the authors do not describe any anti-hypertensive drug coordination. The study is significant as an exploratory study, so further research to verify that bofutsushosan decreases short-term blood pressure variability is anticipated. The paper also indicates an anti-obesity effect for bofutsushosan, although as a secondary endpoint. Further research examining its effectiveness with greater reliability is anticipated.

12. Abstractor and date

Koike H, 15 February 2017.

9. Cardiovascular Diseases

Reference

Tamano M, Toyoda S, Kato S, et al. Clinical investigation of the combined effect of goreisan and tolvaptan in tolvaptan-responder elderly patients with heart failure. *Progress in Medicine* 2018; 38: 751-6 (in Japanese). Ichushi Web ID: 2018339804

1. Objectives

To investigate combined effect of goreisan（五苓散）in elderly tolvaptan-responder patients with heart failure.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the author belongs to the University of Tsukuba Hospital and Kyowa Chuo Hospital, Oriental Medical Center), Japan.

4. Participants

Twenty patients admitted with acute exacerbation of chronic heart failure who were assessed as tolvaptan-responders, after receiving intravenous furosemide at an average dose of 40–80 mg/day for 2 days without improvement in symptoms or physical findings, followed by addition of tolvaptan 7.5 mg/day from Day 3, resulting in an increased urine output compared with the previous day.

5. Intervention

Arm 1: TSUMURA Goreisan（五苓散）Extract Granules 5–7.5 g/day for 1 year (n=10).
Arm 2: Control (without goreisan) (n=10).

6. Main outcome measures

Changes in the frequency of re-hospitalization due to exacerbation of heart failure within 1 year after discharge, the New York Heart Association (NYHA) class one year after discharge, B-type natriuretic peptide (BNP), and renal function (estimated glomerular filtration rate [eGFR]) were compared.

7. Main results

The measures that significantly decreased or improved in Arm 1 compared with Arm 2 included frequency of re-hospitalization due to exacerbation of heart failure within 1 year after discharge (mean ± standard deviation) (0.7±0.5 times vs 1.6±0.6 times, respectively, $P<0.05$), BNP at 1 year after discharge (186±156 pg/mL vs 332±321 pg/mL, respectively, $P<0.05$), and change in BNP at 1 year (853±371 pg/mL vs 540±422 pg/mL, $P<0.05$). The NYHA class at 1 year was 1.3±0.4 in Arm 1 and 2.2±0.7 in Arm 2, showing significant improvement in Arm 1 compared with Arm 2 ($P<0.05$).

8. Conclusions

In tolvaptan-responder elderly patients with heart failure, add-on goreisan may prevent further exacerbation of heart failure.

9. From Kampo medicine perspective

The pathological condition of heart failure can be regarded as "*Suidoku*（水毒）(water intoxication [fluid congestion]", for which goreisan is considered to be indicated.

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

This is a valuable clinical study that followed elderly patients with heart failure for one year. Moreover, this study is unprecedented in that it looked at the effectiveness of goreisan in tolvaptan-responder elderly patients with heart failure, attempting to reveal unknown benefits of Kampo medicine. The article states that no cardiac deaths occurred in either group during the follow-up period, but does not mention anything about dropouts. Given that the study followed elderly patients with severe heart failure for one year, there could be deaths other than cardiac deaths. Deaths of patients with severe heart failure could affect the analysis results in this study with a small sample size. In addition, since this was an open-label study, use of "frequency of re-hospitalization" as an endpoint required establishing the criteria for hospitalization. It is also important to state other details as to whether or not other drugs were additionally used. Despite some limitations, this clinical study is valuable in that it suggested possible efficacy of goreisan in elderly patients with heart failure, and further results on this topic from more patients by the authors are awaited.

12. Abstractor and date

Goto H, 2 September 2019.

9. Cardiovascular Diseases

Reference

Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of the effect of ohrengedoku-toh and ohrengedoku-toh-Red Ginseng mixture on chronic cardiovascular disorders in middle and aged patients. *The Ginseng Review* 1991; 12: 89-93 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy and safety of orendokuto (黄連解毒湯) plus red ginseng combination therapy for relieving symptoms associated with hypertension.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Five clinics, Japan.

4. Participants

A total of 40 out-patients with stable symptoms were recruited, 29 of whom were included for analysis (hypertension, n=14; atherosclerotic disease, n=6; ischemic heart disease, n=4; others, n=5).

5. Intervention

Arm 1: Kotaro Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. between meals (n=15).
Arm 2: Kotaro Orengedokuto (黄連解毒湯) Extract Granules 2.0 g t.i.d. plus CHEONG-KWAN-JANG kojinmatsu powder (正官庄紅参末) 1.0 g t.i.d. between meals (n=14).

6. Main outcome measures

Subjective symptoms (insomnia, numbness of the limb, palpitation, tinnitus, vertigo, orthostatic syncope, stiff shoulder, headache/heaviness of head, and amnesia), overall improvement, and general effect were evaluated. Blood pressure, pressure rate product (PRP: blood pressure×heart rate), echocardiogram (resting coronary flow velocity [RFV] and left ventricular [LV] mass) were also determined.

7. Main results

Only numbness of the limbs was significantly improved in arm 1, whereas vertigo, stiff shoulder, headache/heaviness of head and general effect were significantly improved in arm 2. When subjects in both arms were further subgrouped according to *jitsu-sho* (実証, excess pattern) and *kyo-syo* (虚証, deficiency pattern), in arm 1, improved items were observed only in subjects with *kyo-sho*. In arm 2, improvement in shoulder stiffness and vertigo was found in *jitu-syo*-type patients, and headache improved in *kyo-syo*-type patients. Improved cardiovascular hemodynamics (decreased blood pressure, increased RFV, decreased LV mass, and lower PRP) were observed in arm 2.

8. Conclusions

When compared with single administration of orengedokuto, combination therapy with kojinmatsu effectively improved subjective symptoms as well as cardiovascular hemodynamics.

9. From Kampo medicine perspective

Subjects in both arms were further classified on the basis of *jitsu-sho* and *kyo-syo* for evaluation, which demonstrated more efficacy in arm 2 regardless of *sho*.

10. Safety assessment in the article

None.

11. Abstractor's comments

The result here is surprising in that even after short-term (12-week) administration, combination therapy with koujinmatsu was more effective than administration of orengedokuto alone. Orengedokuto is generally used for subjects with intermediate- or *jitsu-sho*; however, the result here demonstrating more efficacy in *kyo-syo*-type patients than in *jitsu-sho*-type patients should serve as a useful reference. Combination of the two drugs increased the effectiveness even in patients with *jitsu-sho*, suggesting its usefulness (suitability for a wider range of patients) and efficacy (improvement in cardiovascular hemodynamics). Further studies with a larger sample size are awaited.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010.

9. Cardiovascular Diseases

Reference

Yoshikawa T, Munakata S, Okuma H. Effectiveness of goreisan for recurrence prevention in elderly cases of chronic subdural hematoma surgery— Interim report on a comparative trial*. *Noshinkei Geka to Kampo* (*Neurosurgery and Kampo*) 2010: 16 (in Japanese).

1. Objectives

To evaluate the effectiveness and safety of goreisan (五苓散) after chronic subdural hematoma surgery in elderly people.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Neurosurgery, Kuroishi General Hospital, Japan.

4. Participants

Forty-three elderly people over 70 years who underwent surgery (trephining) for symptomatic chronic subdural hematoma between January and August 2009.

5. Intervention

Administration continued for 1 month from the day after surgery.

Arm 1: goreisan (五苓散) (manufacturer not identified) 7.5 g/day (administration frequency not indicated) (n=22).

Arm 2: no treatment (n=21).

Steroids, glyceol, or hemostatics were not used in combination.

6. Main outcome measures

Changes in the hematoma were compared using CT scan 7, 14, and 28 days after surgery.

7. Main results

The age range was 73–89 years, and the between-group differences in gender or age were insignificant. The rate of hematoma shrinkage was greater in arm 1 than arm 2, especially between the 7th and 14th days (statistical significance not specified). Repeat surgery was required for 2 of the 22 participants in arm 1 (9%) and 5 of the 21 participants in arm 2 (24%), however, there was no significant between-group difference.

8. Conclusions

Goreisan may be effective for prevention of recurrence following chronic subdural hematoma surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No complications from goreisan were observed.

11. Abstractor's comments

This is a novel clinical study that investigated the effects of goreisan in preventing recurrence in elderly after chronic subdural hematoma surgery. The study was conducted to investigate goreisan's effects in preventing recurrence of postoperative chronic subdural hematoma, because it had been suggested that goreisan was effective for non-surgical cases of the condition. However, the study was presented as an abstract at a seminar, so unfortunately no details of the methods and results are included. In addition, it is an interim report, as the title indicates, so at the time it was written, it could report no significant difference recurrence rate between the goreisan group and the control group. The authors will hopefully continue with their research because the possibility remains that enlarging the sample groups will elucidate the effectiveness of goreisan, as the authors mention in their abstract. Goreisan has few adverse effects, so once it is established that it is effective for the prevention of recurrence after surgery in elderly cases of chronic subdural hematoma, a new therapeutic domain will have opened up for Kampo medicines in the field of neurosurgery. This is, therefore, a very important clinical study that holds much interest.

12. Abstractor and date

Goto H, 31 December 2012

9. Cardiovascular Diseases

Reference

Katayama K, Matsuda N, Kakuta K, et al. The effect of goreisan on the prevention of chronic subdural hematoma recurrence: multi-center randomized controlled study. *Journal of Neurotrauma* 2018; 35: 1537-42. CENTRAL ID: CN-01611342, Pubmed ID: 2944611, UMIN ID: UMIN000015970

1. Objectives

To investigate the preventative effect of goreisan（五苓散）on post-operative recurrence of chronic subdural hematoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Five neurosurgical institutions (university hospital and other hospitals)(the author belongs to the Department of Neurosurgery, Hirosaki University Graduate School of Medicine), Japan.

4. Participants

Two-hundred and eight patients over 60 years old with chronic subdural hematoma presenting neurological deficits and undergoing burr hole surgery. Exclusion criteria were severe liver dysfunction, severe renal dysfunction, and prior use of goreisan or corticosteroids before surgery.

5. Intervention

Arm 1: TSUMURA Goreisan（五苓散）Extract Granules 2.5 g three times daily orally for 12 weeks, starting within 72 hours after surgery (n=104).

Arm 2: Control (without goreisan) (n=104).

6. Main outcome measures

Neurological assessment and CT were performed pre-operatively and on Days 1, 7, and 14 and Weeks 4, 8, and 12 post-surgery. These assessments were performed by two site investigators blinded to the allocation. The primary endpoint was recurrence of chronic subdural hematoma, which was defined as increased hematoma volume with neurological deficits and need for re-operation. The secondary endpoint was hematoma volume reduction rate, calculated as "(1−A/B)*100 [%] (where A was post-operative hematoma volume and B was the preoperative hematoma volume).

7. Main results

Since 12 patients in Arm 1 and 16 patients in Arm 2 were lost to follow-up, the analysis was conducted on 92 patients in Arm 1 and 88 patients in Arm 2. In overall subjects, post-operative recurrence occurred in 9 patients (9.8%) in Arm 1 and 11 patients (12.5%) in Arm 2, without significant difference between the two groups. Among the subjects under 75 years of age, post-operative recurrence occurred in 1 patient (3.0%) in Arm 1 and 6 patients (17.4%) in Arm 2, and in significantly fewer patients in Arm 1 than in Arm 2 (P=0.04). Among the subjects over 75 years of age, the number of post-operative recurrences did not significantly differ between the two groups. The hematoma volume reduction rates showed no significant differences between the two groups at any time points of evaluation. Even when the subjects were divided by age (i.e., under or over 75 years), the hematoma volume reduction rate did not significantly differ between the two groups. Multivariate analyses were performed to evaluate factors associated with post-operative recurrence and the preventive efficacy of goreisan. As confounding factors, those reported to have an influence on the postoperative recurrence, such as use of goreisan, age, use of anticoagulant, and bilateral chronic subdural hematoma were selected. Bilateral chronic subdural hematoma was the only independent risk factor for the recurrence.

8. Conclusions

This preliminary study showed that goreisan did not reduce the recurrence of chronic subdural hematoma or the hematoma volume reduction rate.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

This was a multicenter randomized study of goreisan in the prevention of recurrence of chronic subdural hematoma, and is unprecedented in that it attempted to determine the effectiveness of goreisan on chronic subdural hematoma. However, the study showed no significant differences compared with the control group. This could be due to the inadequate sample size, as the authors stated. However, the study revealed that goreisan can be effective in patients aged under 75 years with relatively less brain atrophy and patients with unilateral chronic subdural hematoma. Future studies are awaited to collect data from more patients, determine the conditions indicated for goreisan, and characterize the efficacy of goreisan in preventing recurrence of chronic subdural hematoma.

12. Abstractor and date

Goto H, 10 September 2019.

9. Cardiovascular Diseases

Reference

Ito E, Takahashi A, and Kazuya F. Clinical effectiveness of TSUMURA Orengedokuto in the treatment of cerebral infarction. *Geriatric Medicine* 1991; 29: 303-13 (in Japanese).* Ichushi Web ID: 1991179676

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) in the treatment of cerebral infarction.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifteen hospitals (two departments of a university hospital and 14 hospitals), Japan.

4. Participants

A total of 109 clinically stable patients with cerebral infarction (thrombosis, embolism) (57 men and 51 women, and 1 patient who withdrew consent).

5. Intervention

Arm 1: administration of Tsumura Orengedokuto (黄連解毒湯) Extract Granules (TJ-15) 2.5 g t.i.d. orally before meals for 12 weeks (n=56).

Arm 2: no administration of Kampo medicines for 12 weeks (n=52).

6. Main outcome measures

Overall severity, subjective symptoms, neurological symptoms, improvement in activities of daily living (ADL), general improvement, safety, and usefulness were evaluated before administration and 4, 8, and 12 weeks after administration. Clinical parameters were examined (blood pressure, pulse rate, blood count, standard biochemical parameters, blood coagulation and fibrinolytic activity).

7. Main results

No significant changes were observed in overall severity and in general improvement. Patients were evaluated to be “more than slightly improved” in subjective symptoms significantly more frequently in arm 1 than arm 2 ($P<0.05$). Among subjective symptoms, improvement in dull headache, vertigo, hot flashes ($P<0.05$), and cold feeling and numbness of the limbs and stiff shoulders ($P<0.01$) occurred significantly more frequently. Significant change occurred in usefulness ($P<0.05$) but not in mental symptoms, neurological symptoms, and ADL. Significant difference in the clinical parameters was observed only in blood coagulation and fibrinolytic activity.

8. Conclusions

Orengedokuto was suggested to be effective in improving subjective symptoms (hot flashes, headaches, stiff shoulders, and cold feeling and numbness of the limbs) in patients with cerebral infarction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects were observed in 3 patients in arm 1 (lightheadedness or dizziness) and 1 patient in arm 2 (loose stool and vomiting).

11. Abstractor’s comments

By around 1990, at the time when this article was published, efficacy of orengedokuto for cerebral infarction had been surmised from basic research, accumulation of clinical cases, and comparison with the other medicines. This is a high-quality controlled-trial demonstrating that orengedokuto improves some of the subjective symptoms in clinically stable patients with cerebral infarction.

Reported pharmacological activities of orengedokuto include increase in local blood flow in the hippocampal region, inhibition of platelet aggregation by baicalein which is a component of ogon (黄芩) present in this Kampo medicine. And these reported activities are consistent with the present study result revealing the improvement in blood coagulation and fibrinolytic activity. They observed no effect on blood pressure, which is also the result of other large-scale trials studying its efficacy against high blood pressure. Therefore, orengedokuto seems to have little effect on decreasing blood pressure.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Nakae Y. Effectiveness of saireito in acute ischemic stroke. *Kampo to Saishin Chiryo (Kampo & the Newest Therapy)* 2013; 22: 329-32. Ichushi Web ID: 2014077192

1. Objectives

To evaluate the effectiveness of saireito (柴苓湯) for acute ischemic stroke.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (hospital neurology department).

4. Participants

Ninety-nine patients who gave verbal consent out of the acute ischemic stroke patients hospitalized between December 2010 and December 2011.

5. Intervention

Arm 1: Saireito administration group: TSUMURA Saireito (柴苓湯) Extract Granules (3g t.i.d.) administered after each meal for two weeks (n=43).
Arm 2: Non-administration group (n=56)

6. Main outcome measures

NIHSS (National Institutes of Health Stroke Scale) and mRS (modified Rankin Scale) comparison.

7. Main results

The results of a questionnaire taken after the first week of hospitalization showed that symptoms had been significantly alleviated in the saireito administration group. The NIHSS scores showed significant improvement in the saireito administration group compared to the non-administration group after the second week of hospitalization (P=0.020). The mRS scores showed significant improvement in the saireito administration group compared to the non-administration group after the first week (P=0.020) and the second week (P=0.011) of hospitalization.

8. Conclusions

Saireito is effective for acute ischemic stroke.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study used the NIHSS and the mRS to evaluate the effectiveness of saireito in acute ischemic stroke. It showed that saireito has a certain effect on symptoms after stroke. Much of saireito's mechanism of action has not been elucidated, so comparing the scores for each item may provide clues to its mechanism of action, such as whether it is more effective for lower or upper limb symptoms.

12. Abstractor and date

Nakata H, 31 March 2017

9. Cardiovascular Diseases

Reference

Otomo E, Togi H, Kogure K, et al. Clinical usefulness of TSUMURA Orengedokuto for the treatment of cerebrovascular disease: a well-controlled study comparing TSUMURA Orengedokuto versus Ca hopantenate, using sealed envelopes for allocation*. *Geriatric Medicine* 1991; 29: 121–51 (in Japanese). Ichushi Web ID: 1991224400

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) for relieving psychiatric symptoms in patients with late effects of cerebrovascular disease.

2. Design

Randomized controlled trial used sealed envelopes for allocation (RCT-envelope).

3. Setting

Thirty university hospitals (including departments of neurology of Iwate Medical University, Tohoku University School of Medicine, and Gunma University Faculty of Medicine) and 20 general hospitals, Japan.

4. Participants

One hundred and forty-eight post-stroke patients with psychiatric symptoms due to cerebral infarction, cerebral hemorrhage, or stoke with unknown origin.

5. Intervention

Arm 1: TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. orally after meals for 12 weeks (n=81).

Arm 2: calcium hopantenate 500 mg t.i.d. orally after meals for 12 weeks (n=67).

The treatment was discontinued at the time of disappearance of symptoms.

6. Main outcome measures

Psychiatric symptoms (apathy; problematic behaviors; emotional, intellectual, and mental disturbances), subjective symptoms (heaviness of head, headache, hot flush, etc.), neurological symptoms (aphasia, dysarthria, motor paralysis, etc.), and impairment in activities of daily living (sitting up, standing, walking, etc.) were evaluated at baseline and after 4, 8, and 12 weeks of treatment. Hasegawa's dementia scale and laboratory tests were performed at baseline and after 12 weeks of treatment.

7. Main results

Five patients in arm 1 (1 with concomitant cancer, 3 lost to follow-up after the initial treatment, and 1 who acted contrary to envelope method) were excluded from the study. The safety analysis included 76/67 patients (arm 1/arm 2) and efficacy analysis included 74/67. The percentages of patients who achieved moderate-or-greater and mild-or-greater overall improvement in psychiatric symptoms were significantly higher in arm 1 than in arm 2 at 8 and 12 weeks. There were no between-arm differences in each of the global improvement scores for subjective symptoms, neurological symptoms, and impairment in activities of daily living. The percentages of patients who achieved moderate-or-greater improvement in abulia at 4 weeks and moderate-or-greater and mild-or-greater improvements at 8 and 12 weeks were significantly higher in Arm 1 than in arm 2. Among other items of spontaneity, reduced expression of desires, decreased interest in others, decreased interest in performing activities of daily living, decreased interest in housekeeping, leisure activities, hobbies, etc., and inability to communicate with others were significantly improved at 12 weeks compare with at baseline in both arms to a similar extent.

8. Conclusions

Orengedokuto is effective for relieving psychiatric symptoms in patients with cerebrovascular disease and its efficacy is comparable to that of cerebral metabolic activator.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Three patients in arm 1 (3.9%) discontinued treatment, respectively, because of nausea and abdominal distention, chest discomfort, and headache. In arm 2, one patient (1.5%) discontinued treatment due to fever and disturbances in consciousness. Changes in laboratory data were within normal range in both arms.

11. Abstractor's comments

This clinical study revealed the effects of orengedokuto on psychiatric symptoms in patients with late effects of cerebrovascular disease in a controlled trial using sealed envelopes for allocation. As noted by the authors, the evaluation of the efficacy of orengedokuto may have been influenced by the following two factors: i) the designation of calcium hopantenate as a powerful drug around the same time as this study was performed, which biased selection of cases; and ii) lower efficacy of calcium hopantenate in the present trial than in other clinical trials. Despite the limitations on evaluation, this clinical study was excellent and demonstrated comparable efficacy of orengedokuto and a cerebral metabolic activator.

12. Abstractor and date

Goto H, 12 September 2008.

9. Cardiovascular Diseases

Reference

Shimada Y. Efficacy of tokishakuyakusan for hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder*. *Kosei Rodo Kagaku Kenkyuhi Hojokin Choju Kagaku Kenkyu Jigyo Koreisha no Nokekkan Shogai no Shinten Yobo wo Mokuteki to Shita Kampoyaku niyoru Tailor-made Iryo no Kaihatsu - Heisei 18 Nendo Buntan Kenkyu Hokokusho* (*Ministry of Health, Labour and Welfare, Science Research Grant, Comprehensive Studies on Science of Aging, Development of Personalized Medicine using Kampo Medicines to Prevent Progression of Cerebrovascular Disorders in the Elderly: Working-group Research Report Fiscal Year 2006*) 2007: 22-30 (in Japanese)

1. Objectives

To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for treatment of hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder.

2. Design

Randomized controlled trial (RCT) (assigned by randomized allocation in 20 cases and chosen by the patient in 6 cases), Japan.

3. Setting

University hospital and community hospital.

4. Participants

Thirty-one patients with sequelae of cerebrovascular disorder.

5. Intervention

Arm 1: administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules between meals (n=16) (for 12 months**)**.
Arm 2: no administration of Kampo medicines (n=15).

6. Main outcome measures

The Stroke Impairment Assessment Set (SIAS), Functional Independence Measure (FIM), body weight and *oketsu* (瘀血, static blood), *qikyo* (気虚, qi deficiency), *qiutsu* (気鬱, qi movement stagnation) and *jinky*o (腎虚, kidney deficiency), evaluated on a 5-point scale at baseline and every 3 months thereafter.

7. Main results

Both SIAS and FIM scores remained at baseline levels in arm 1 but decreased significantly in arm 2 at 12 months, resulting in a significant between-arm difference. In arm 2, stroke recurred at 9 or 12 months.

8. Conclusions

Tokishakuyakusan suppresses hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder requiring an intermediate level of care.

9. From Kampo medicine perspective

At 12 months, *oketsu* and *jinkyo* significantly improved in arm 1, but *oketsu* remained unchanged and *jinkyo* worsened in arm 2, resulting in a significant between-arm difference. In contrast, there was no significant difference in *qikyo* and *qiutsu* between arms.

10. Safety assessment in the article

One patient in arm 1 felt numbness in hands and feet. Since the cause (tokishakuyakusan, amantadine hydrochloride, or captopril) was unclear, all these drugs were discontinued in this patient.

11. Abstractor's comments

In this valuable report about the 1-year follow-up of patients with sequelae of cerebrovascular disorder, tokishakuyakusan was shown to suppress the hypofunction and decreased independence observable in the control group at 12 months. Since the sample size is small (15 or 16 patients), a study with a larger sample size is expected in the future. Further exploration of Kampo medicines potentially able to improve this condition is also expected.

12. Abstractor and date

Namiki T, 12 March 2009, 1 June 2010.

9. Cardiovascular Diseases

References

Goto H, Satoh N, Hayashi Y, et al. A Chinese herbal medicine, tokishakuyakusan, reduces the worsening of impairments and independence after stroke: A 1-year randomized, controlled trial. *Evidence-based Complementary and Alternative Medicine* 2009: 1–6 (2011: 1-6. doi: 10.1093/ecam/nep026).
Evidence-based Complementary and Alternative Medicine 2009: 1-6. (2011: 1-6. doi: 10.1093/ecam/nep026) Pubmed ID: 19332457

1. Objectives

To evaluate the effectiveness of tokishakuyakusan (当帰芍薬散) in reducing impairment and increasing independence in post-stroke patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Tonami General Hospital and Yoshimi Hospital, Japan.

4. Participants

Thirty-one post-stroke patients hospitalized between October 2005 and January 2006 with a history of cerebral bleeding, infarction, or subarachnoid hemorrhage as well as paralysis due to cerebral lesions. (cerebral infarction, 23 cases; cerebral bleeding, 7 cases; subarachnoid hemorrhage, 1 case). The patients were in the post-acute phase of recovery.

5. Intervention

Arm 1: Tokishakuyakusan (Tsumura Tokishakuyakusan [当帰芍薬散] Extract Granules [TJ-23] 7.5 g/day for 12 months).
Arm 2: no tokishakuyakusan treatment.

6. Main outcome measures

Impairments were assessed using the Stroke Impairment Assessment Set (SIAS). Independence status was assessed using the Functional Independence Measure (FIM).

7. Main results

SIAS scores for several items such as finger-function and knee-extension decreased significantly in arm 2 ($P<0.05$), whereas no significant change was observed in arm 1. Likewise, FIM scores indicated a worsening of functional status in arm 2 and prevention of that worsening in arm 1.

8. Conclusions

Tokishakuyakusan reduces the increase in impairment after stroke.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient in the tokishakuyaku arm withdrew because of numbness in his limbs, which was not attributable to tokishakusyakusan.

11. Abstractor's comments

This protocol of post-stroke tokishakusakusan administration was not expected (from the *Kampo* way of thinking) to prevent impairment. Suffice it to say that tokishakusakusan administration might reduce *kan-kekkyo*（肝血虚, liver blood deficiency）. The authors conducted this study on the basis of the reports suggesting the efficacy of tokishakuyakusan for the treatment of cognitive impairment due to Alzheimer's disease. As evidence-based medicine (EBM) becomes widely accepted, there will be more reports of applications that transcend classical *Kampo* theory. As societies age, the importance of preventing post-stroke impairment will increase, and therefore the result obtained in this study is meaningful.

12. Abstractor and date

Nakata H, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Akiyama Y, Ohno S, Asaoka T, et al. The combination therapy with sarpogrelate hydrochloride and Kampo medicine (oren-gedoku-to or toki-shakuyaku-san) for Raynaud's phenomenon. *Japanese Journal of Oriental Medicine* 2001; 51: 1101-8 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the effectiveness of orengedokuto (黄連解毒湯) in improving peripheral circulation in Raynaud's phenomenon.

2. Design

Quasi-RCT.

3. Setting

Two departments (Department of Rheumatology and Department of Oriental Medicine) in Saitama Medical School, Japan.

4. Participants

Twenty patients with Raynaud's phenomenon who consulted at the above two departments between October and March from 1994 to 1997 (3 men and 17 women).

5. Intervention

Arm 1: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals.
Arm 2: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals, and orengedokuto (黄連解毒湯) 2.5 g t.i.d. before meals.
Arm 3: oral administration of sarpogrelate hydrochloride (100 mg) in three divided doses after meals, and tokishakuyakusan (当帰芍薬散) 2.5 g t.i.d. before meals.

6. Main outcome measures

Raynaud's phenomenon – subjective symptoms (cold sensation, numbness, pain) and increase in skin temperature assessed by thermography (increase of more than 0.6°C in the mean temperature of all 10 fingertips of both hands) – were evaluated before and after 12-week treatment. The efficacy was compared among subjects with different "*sho*" (証, pattern) (*jitsu -sho* [実証, excess pattern], *chukan -sho* [中間証, intermediate pattern], and *kyo -sho* [虚証,deficiency pattern]) in Kampo medicine.

7. Main results

After 12-week treatment, the combination with orengedokuto had significantly higher efficacy than sarpogrelate hydrochloride alone (90% *vs.* 52.5%; $P<0.02$), while the combination with tokishakuyakusan had similar efficacy to sarpogrelate hydrochloride alone. Skin temperature at the fingertips was significantly increased in arm 3 (1.8±1.9°C; $P<0.02$) compared with arm 1 (0.6±0.8°C), and also significantly elevated in arm 2 (4.1±2.1°C; $P<0.005$) compared with arm 3. Combination therapy with Kampo formulations was effective in patients with *jitsu-sho,* but not in patients with *kyo-sho*.

8. Conclusions

Orengedokuto combined with sarpogrelate hydrochloride has higher efficacy in the treatment of Raynaud's phenomenon. However, *kyo-sho* patients did not respond to this combination therapy and had higher incidence of adverse drug reactions (ADRs), suggesting the importance of prescriptions according to the patient's "*sho.*"

9. From Kampo medicine perspective

In this study, 72.7% of the subjects were regarded as *kyo-sho* type. No subject was identified as the so-called orengedokuto-*sho* type – having conditions that are expected to respond to orengedokuto therapy. In *kyo-sho* subjects, the efficacy of the orengedokuto combination therapy was similar to that of sarpogrelate hydrochloride monotherapy, and a higher dropout rate was observed because of ADRs from the bitherapy. Therefore we suggest that administration of sarpogrelate hydrochloride plus orengedokuto should be withheld from *kyo-sho* subjects.

10. Safety assessment in the article

ADRs of the orengedokuto combination occurred in *kyo-sho* patients, including nausea (n=2) and diarrhea (n=2), neither of which was serious. No serious ADRs due to the tokishakuyakusan combination were noted.

11. Abstractor's comments

Sarpogrelate hydrochloride in combination with orengedokuto, which has been reported to improve peripheral circulation, improved more efficiently peripheral circulation in Raynaud's phenomenon when compared with sarpogrelate hydrochloride monotherapy as positive control in this study. It is interesting that improvement was greater with this combination than with the tokishakuyakusan combination, even when more than 70% of subjects were *kyo-sho*. Further scientific evaluation with a larger number of subjects is awaited.

12. Abstractor and date

Ushiroyama T. 1 April 2008, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Uchida N. A Randomized controlled trial of the Chinese herbal medicine keisi-bukuryo-gan (gui-zhi-fu-ling-wan) in the treatment of deep vein thrombosis. *Jomyakugaku* (*The Japanese Journal of Phlebology*) 2009; 20: 1-6 (in Japanese with English abstract). Ichushi Web ID: 2009139345

1. Objectives

To evaluate the effect of keishibukuryogan (桂枝茯苓丸) on swelling in patients with deep vein thrombosis (DVT) of the lower limb.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Surgery, Mito Red Cross Hospital, Japan.

4. Participants

Twelve patients diagnosed with DVT of the lower limb by ultrasonography at the above-mentioned institution between January 2003 and December 2007.

5. Intervention

Arm 1: heparin (10,000 units/day) and urokinase (240,000 units/day), followed by oral warfarin plus TSUMURA Keishibukuryogan (桂枝茯苓丸) 2.5 g t.i.d. before meals for 6 months (n=6).
Arm 2: heparin (10,000 units/day) and urokinase (240,000 units/day), followed by oral warfarin (n=6).
There were no differences in age, gender, and status of the affected limbs between the two arms.

6. Main outcome measures

Difference in the lower-leg circumference between the healthy and affected limb over the 6-month period of keishibukuryogan administration.

7. Main results

The difference in the lower-leg circumference decreased significantly in both arms (P<0.05), while the rate of improvement ([pre-treatment circumference difference – post-treatment circumference difference]/pre-treatment circumference difference × 100%) was significantly higher in arm 1 (66.1±20.5%) than in arm 2 (34.0±13.7%; P=0.05).

8. Conclusions

The administration of keishibukuryogan combined with warfarin following heparin and urokinase appears to be effective for reducing swelling associated with DVT of the lower limb.

9. From Kampo medicine perspective

Keishibukuryogan is a therapeutic agent for *oketsu* (瘀血, static blood) and appears to be effective for the treatment of DVT of the lower limb stemming from pathological conditions such as changes in blood coagulability, reduced blood fluidity, and microcirculatory disturbance. Patient selection and outcome from the perspective of Kampo medicine, such as the *bensho* (弁証, Kampo diagnosis) of *qi-ketsu-sui* (気血水, *qi*, blood, and water) or *gozou roppu* (五藏六府, five viscera and six bowels)（気血水、五藏六府弁証）, are not mentioned in this paper.

10. Safety assessment in the article

Adverse reactions to keishibukuryogan were not reported.

11. Abstractor's comments

This study evaluated the effects of keishibukuryogan, a *kuoketsuzai* (駆オ血剤, blood stasis-expelling formula), on swelling associated with DVT of the lower limb. This swelling may be caused by venous system dysfunction, impaired circulation through lymph vessels, or inflammation. While the site of action of keishibukuryogan is unknown, the paper suggests that *oketsu* may be involved in the pathogenesis of the swelling. The findings in this paper have introduced a new treatment for refractory DVT of the lower limb that appears to be valuable for clinical practitioners. I hope that, in the future, the mechanism (or mechanisms) of action of keishibukuryogan will be elucidated by the accumulation of cases and investigational approaches from different directions.

12. Abstractor and date

Ushiroyama T, 6 January 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Kato N, Kato K, Hosoi Y. Effects of Otsuji-to in patients with hemorrhoid using ALTA and LE combined therapy. *Igaku to Yakugaku* (*Journal of Medicine and Pharmaceutical Science*) 2008; 60: 747-53 (in Japanese). Ichushi Web ID: 2009068979 MOL, MOL-Lib

1. Objectives

To evaluate the clinical efficacy of otsujito (乙字湯) combined with aluminum potassium sulfate/tannic acid (ALTA) sclerotherapy, the latest treatment for hemorrhoids.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two institutions: Furudate Kato Proctology & Surgery Clinic and Hosoi Surgery Clinic, Japan.

4. Participants

Twenty patients with hemorrhoids (stage III or IV according to the Goligher classification) who underwent ALTA alone or ALTA-LE (ligation and excision) at the above-mentioned two institutions between March and September 2008.

5. Intervention

Arm 1: ALTA alone or ALTA-LE, followed by treatment with Kanebo Otsujito (乙字湯) Extract Fine Granules 3 g b.i.d. orally before meals from postoperative day 1 for 4 weeks (n=10).

Arm 2: ALTA alone or ALTA-LE (n=10).

Non-steroidal anti-inflammatory drugs (NSAIDs) were used as needed for pain relief in both arms.

6. Main outcome measures

Spontaneous pain, pain during defecation, and blood C-reactive protein (CRP) level at weeks 1, 2, and 4 of the otsujito treatment; and usage of analgesics up to postoperative week 2.

7. Main results

The effects on blood CRP level at week 1, pain during defecation at week 2, and spontaneous pain at weeks 1 and 2 were significantly greater in arm 1 than in arm 2 ($P<0.05$). The usage of analgesics tended to be reduced in arm 1 than in arm 2 (median, 2 *vs.* 10 tablets; $P=0.09$). Although the incidence of induration and hemorrhoid shrinkage after ALTA was similar between arms, the period of induration-persistence（time to disappearance of induration）was significantly reduced in arm 1 (11.3 weeks) than in arm 2 (15.3 weeks; $P<0.05$).

8. Conclusions

Otsujito relieves postoperative spontaneous pain, pain during defecation, and persistent induration in patients who undergo ALTA with or without LE.

9. From Kampo medicine perspective

This study revealed that otsujito (unlike common Kampo medicines) has a rapid onset of action. The prevention of constipation seemed to mainly result from the purging effect of daio (大黄) and the intestine-moistening effect of toki (当帰). Unfortunately, postoperative pain relief from the perspective of Kampo medicine was not discussed in this paper.

10. Safety assessment in the article

Adverse reactions to otsujito were not reported in this study.

11. Abstractor's comments

Hemorrhoids are highly prevalent in the general population and can sometimes cause great discomfort and social embarrassment. This study demonstrated that otsujito, a traditional treatment for hemorrhoids, combined with ALTA sclerotherapy, the latest Western medical treatment for hemorrhoids, relieves pain after surgery and reduces the period of induration persistence. This study indicates the integration of modern Western therapy with oriental therapy (i.e., otsujito, long known, by itself, to be effective treatment for hemorrhoids) can enhance efficacy. The findings of this study have important implications for the future direction of hemorrhoids treatment. Otsujito may enhance the effects of tannic acid, such as inhibition of sterile inflammation and reduction of tissue damage. Further studies are expected to elucidate the mechanism of action of otsujito.

12. Abstractor and date

Ushiroyama T, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

References

Abe Y. The efficacy of goshajinkigan against lymphedema*. *Kampo Igaku* (*Kampo Medicine*) 2002;25:284-7 (in Japanese). Ichushi Web ID: 2002140795

Abe Y, Kosugi I, Kasashima F, et al. Lymphedema and Kampo*. *Progress in Medicine* 2003; 23: 1538-9 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in the treatment of lymphedema.

2. Design

Randamized controlled trial (RCT).

3. Setting

One hospital (department of cardiovascular surgery), Japan.

4. Participants

A total of 80 patients with lymphedema of the upper limbs (n=40) and lower limbs (n=40).

5. Intervention

Arm 1: oral administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (TJ-107) 2.5g t.i.d for 1 month in combination with compression therapy (n=40).

Arm 2: compression therapy without administration for 1 month (n=40).

6. Main outcome measures

Percentage reduction in edema: reduction in limb circumference assessed between the first visit (baseline) and after 1-month treatment was divided by baseline limb circumference, and expressed in percentage.

7. Main results

For lymphedema of the upper limbs, there was significant percentage reduction in arm 1 (15±3.4%) compared with arm 2 (5.7±1.2%; $P<0.05$). For lymphedema of the lower limbs, the percentage reduction was also significant in arm 1 (17.5±2.8% *vs* 6.7±0.8% in Arm 2; $P<0.05$).

8. Conclusions

Edema is significantly reduced in both patients with lymphedema of the upper limbs and those with lymphedema of the lower limbs by TSUMURA Goshajinkigan Extract Granules (TJ-107).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The indications for goshajinkigan are chronic nephritis, nephritic syndrome, low back pain, edema in the lower extremity, and oliguria. This RCT assessed the efficacy of goshajinkigan for the treatment of lymphedema secondary to surgical procedures. Secondary lymphedema is generally intractable in many cases despite combined treatments including lymph drainage massage, compression skin care, exercise therapy under compression, and administration of anticoagulants. It is very meaningful that goshajinkigan was shown to be efficacious. The problem is that this paper is published in a business periodical without peer review, and information on patients' background and so on is therefore insufficient. Also, since the efficacy of goshajinkigan plus compression was assessed, the effect of goshajinkigan alone will need to be evaluated by comparison with placebo and positive control drugs in the future.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Nakamura H, Nakamura T, Nakagawa S et al. Efficacy of goreisan in treatment of orthostatic hypotension in patients with diabetes mellitus*. *Diabetes Frontier* 2000; 11: 561-3 (in Japanese). Ichushi Web ID: 2001041016 MOL, MOL-Lib

1. Objectives

To evaluate the safety and efficacy of goreisan (五苓散) in the treatment of orthostatic hypotension in patients with diabetes mellitus.

2. Design

Randomized controlled trial (crossover design) (RCT- crossover).

3. Setting

One internal medicine clinic, Japan.

4. Participants

Ten patients with diabetes mellitus (type 1, 2; type 2, 8) associated with orthostatic hypotension diagnosed according to McDowell's criteria.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: Kanebo Goreisan (五苓散) Extract Tablets (EKT-17) 18 tablets/day, for 1 month, n=10.

Arm 2: placebo 18 tablets/day, for 1 month, n=10.

6. Main outcome measures

Body weight, subjective symptoms, and response to orthostatic challenge (change in blood pressure, plasma adrenaline noradrenaline, and aldosterone concentrations, and plasma renin activity) were evaluated at baseline, and 1 and 2 months after the start of treatment; adverse drug reactions (ADRs) were checked during the study.

7. Main results

There was no difference in body weight between the goreisan and placebo groups. The subjective symptom of orthostatic dizziness improved in 9 of 10 patients in the goreisan group, whereas no change was reported in all 10 subjects in the placebo group. Results of orthostatic challenge: Before standing, no significant difference was found in blood pressure between at baseline and after administration of goreisan or placebo. After standing, systolic and diastolic pressures increased significantly in the goreisan group ($P<0.05$), while no significant change was observed in the placebo group. There were no changes in the concentration of adrenaline, noradrenaline, or aldosterone, nor in plasma renin activity at orthostatic challenge after administration of goreisan or placebo.

8. Conclusions

In diabetic patients with orthostatic hypotension, goreisan improves subjective symptoms and normalized the decrease in blood pressure on standing.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no observed adverse drug reactions.

11. Abstractor's comments

General indications for goreisan are edema, nausea, vomiting, dizziness in subjects with thirst and decreased urine output. Authors applied this to diabetic orthostatic hypotension, which is neuropathic and intractable/ resistant to therapies in most cases. Modern medicine can prevent the decline in blood pressure on standing; however, problems such as adverse increase in supine blood pressure remain. In contrast, goreisan causes no increase in supine blood pressure, suggesting this Kampo formulation as an ideal therapeutic agent for orthostatic hypotension in diabetic patients. It is very meaningful that this randomized controlled trial demonstrated that goreisan has efficacy.

It is thought that further investigation with increased case numbers and multicenter trials will improve the reliability of data.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Homma Y. Kampo treatment of patients with common cold syndrome associated with fever. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1995; 46: 285–91 (in Japanese with English abstract). CiNii

1. Objectives

To compare the efficacy of Kampo treatment and fenoprofen as antipyretics in patients with common cold syndrome associated with fever.

2. Design

Randomaized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Medical Administration Center, Hokkaido University, Japan.

4. Participants

Out of 246 patients with common cold, 80 patients with a temperature of 37°C or higher (Hokkaido University students) were included.

5. Intervention

Arm 1: administration of Kampo extracts (manufacturers, not specified): kakkonto (葛根湯; n=18), maoto (麻黄湯, n=9), keimakakuhanto (桂麻各半湯, n=3), chikujountanto (竹筎温胆湯, n=2), shoseiryuto (小青竜湯, n=1), keishikashakuyakuto (桂枝加芍薬湯, n=1), or kososan (香蘇散, n=1) 2.5 or 3.0 g t.i.d. according to *sho* (証, pattern) (total n=35).

Arm 2: adminstration of fenoprofen 400 mg t.i.d. (n=45).

6. Main outcome measures

Duration of fever, percentage of patients with fever during the course of treatment, rebound of fever, and duration of cold symptoms.

7. Main results

The duration of fever was significantly shorter in arm 1 (1.5±1.9 days) than in arm 2 (2.6±1.7 days; $P<0.001$). The percentage of patients with fever was significantly higher and the duration of cold symptoms was longer in arm 2 than in arm 1.

8. Conclusions

Kampo treatment is more effective than fenoprofen, an antipyretic used for fever associated with common cold.

9. From Kampo medicine perspective

Kampo prescriptions were administered according to *sho* in patients with fever associated with common cold.

10. Safety assessment in the article

None.

11. Abstractor's comments

This paper describes an interesting randomized controlled clinical trial that demonstrated the higher efficacy of Kampo treatment than fenoprofen (an antipyretic used for fever associated with common cold). In this trial, 246 patients with common cold were allocated to two groups using sealed envelopes. Of these, 80 patients with fever were selected as subjects in the trial. Allocation using sealed envelopes is often associated with poor maintenance of randomization, and, furthermore, a two-step selection process was used in this trial. Future studies are expected to improve randomization and include a placebo group.

12. Abstractor and date

Okabe T, 18 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Homma Y, Takaoka K, Yozawa H, et al. Effectiveness of mao-bushi-saishin-to in treating common cold syndrome - controlled comparative study using the sealed envelope method -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1996; 47: 245–52 (in Japanese with English abstract). Ichushi Web ID: 1997025451 CiNii

Homma Y. Treatment of common cold by a Kampo medicine - Maobushisaishin-tou-. *Pharma Medica* 2007; 25: 19–21 (in Japanese). Ichushi Web ID: 2008035988 MOL, MOL-Lib

1. Objectives

To evaluate the effectiveness of maobushisaishinto (麻黄附子細辛湯) in relation to that of a generally available cold drug in treating common cold syndrome and in shortening the duration of symptoms.

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

Nineteen hospitals in Hokkaido, Japan.

4. Participants

Inpatients and outpatients aged 3 years or older who were diagnosed as having common cold syndrome (n=171).

5. Intervention

From November 1992 until March 1993.

Duration of administration was for 3 days from the onset of the symptoms or visit to the hospital, or, in cases where the symptoms persisted, until the symptoms were relieved.

Arm 1:TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules, 2.5 g t.i.d. (n=83).

Arm 2: general common cold drug (contains salicylamide, acetaminophen, anhydrous caffeine, and promethazine methylenedisalicylate), 1.0 g q.i.d. (n=88).

6. Main outcome measures

Overall improvement, overall safety (adverse effects), overall usefulness, and duration (time to relief of each symptom).

7. Main results

Overall improvement

The percent of patients with moderate or greater improvement was 81.9 in arm 2 and 60.3 in arm 1. The between-group difference by *U*-test was significant ($P<0.01$).

Average days until the relief of symptoms

	Arm 1	Arm 2	$P<$(*U*-test)
Fever	2.8±1.5 (29)	1.5±0.7 (27)	0.001
Feeling feverish	2.5±1.5 (36)	1.8±1.4 (29)	0.021
Cough and phlegm	3.5±1.7 (20)	2.5±1.2 (29)	0.034

Time to relief of symptoms

Using Kaplan-Meier method, 4 symptoms (fever, pain or discomfort in the throat, coughing, and phlegm) were relieved in significantly less time in arm 2.

8. Conclusions

Maobushisaishinto has significantly better efficacy in treating common cold syndrome than a generally available cold drug.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Blood urea nitrogen was mildly elevated in 1 patient in arm 1.

11. Abstractor's comments

Few RCTs have evaluated treatment for the common cold, even though it is a familiar and frequently occurring condition. This RCT appropriately uses average number of days until alleviation of fever, heat sensation, cough, and sputum secretion as the endpoints. In the early 1990s, researchers did not generally distinguish between primary and secondary endpoints. Hopefully future research will include comparative analysis of other Kampo prescriptions for the common cold, and include the Kampo pattern concept.

12. Abstractor and date

Fujisawa M, 9 March 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kaji M, Kashiwagi S, Yamakido M, et al. A double-blind, placebo-controlled study of TSUMURA Shosaikoto (TJ-9) for common cold*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Study*) 2001; 78: 2252-68 (in Japanese). Ichushi Web ID: 2002145787 MOL, MOL-Lib

1. Objectives

To assess the efficacy and safety of shosaikoto (小柴胡湯) in patients with common cold.

2. Design

Double-blind randomized controlled trial (DB-RCT)

3. Setting

From September 1995 until March 1999.
Ten university hospitals, 42 community and other hospitals, and 2 clinics, Japan.

4. Participants

Patients with persistent symptoms for more than 5 days after the onset of common cold, age from 25 to 75 years, and complaints of at least one of the following symptoms: oral discomfort (bitter taste, sticky sensation, dysgeusia), anorexia, or malaise.

5. Intervention

The placebo had similar appearance and properties. Concomitant drug use was basically prohibited, except for dimemorfan phosphate (Astomin tablets) after day 3.
Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules (TJ-9) 2.5g t.i.d., n=131.
Arm 2: placebo 2.5 g t.i.d., n=119.
Duration of administration: 1 week or less

6. Main outcome measures

Global improvement rating (comprehensive evaluation based on improvement rating of each symptom and patient's impression), improvement rating of each symptom**]**, and safety evaluation.

7. Main results

At baseline, the patients allotted to arm 1 were not matched to those allotted to arm 2 in the severity of headache, and the amount and viscosity of sputum. General improvement was significantly better in arm 1 than in arm 2, with the percentage of patients rated 4 (improved) or 5 (markedly improved) on a 5-point scale being 64.1% and 43.7% in arm 1 and arm 2, respectively. Individual symptoms (throat pain and malaise at day 3-4, clearance of sputum, appetite, joint pain and muscular pain at the end of study) all were significantly better in arm 1.

8. Conclusions

For patients with persistent common cold associated with oral discomfort (bitter taste, sticky sensation, dysgeusia), decreased appetite, and/or malaise, shosaikoto is effective and useful.

9. From Kampo medicine perspective

Subject selection was made on the basis of persistent symptoms and discomfort in the mouth, which indicate "shosaikoto-*sho*"

10. Safety assessment in the article

Ten (7.4%) of 136 subjects in arm 1 and 15 (11.4%) of 132 subjects in arm 2) experienced adverse effects. However, there were no serious adverse drug reactions.

11. Abstractor's comments

This study is a large-scale DB-RCT on Kampo therapy fitted to "*sho*" in Kampo medicine.

12. Abstractor and date

Fujisawa M, 15 June2007, 1 April 2008.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Fujimori K, Suzuki E, Simojo F. Comparison between bakumondoto (mai men dong tang) and dextromethorphan hydrobromide in terms of effect on postinfectious cough: a pilot study. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 2001; 51: 725-32. Ichushi Web ID: 2001145417 CiNii

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for postinfectious cough.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Medicine, Niigata University Medical and Dental Hospital., and a general hospital (internal medicine department), Japan.

4. Participants

Non-smoking patients with postinfectious cough for whom other causes for cough were ruled out, n=25.

5. Intervention

Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules (TJ-29) 9g/day for 7 days, n=13.

Arm 2: administration of dextromethorphan hydrobromide 60mg/day for 7 days, n=12.

6. Main outcome measures

Cough scores (cough frequency and intensity) were self-assessed everyday on a scale ranging from 0 to 9.

7. Main results

Arm 1: the cough score of 5.4±1.7 at baseline decreased significantly to 1.5±1.3 on day 7.

Arm 2: the cough score of 4.1±2.0 at baseline decreased significantly to 1.8±1.3 on day 7.

The antitussive effect developed more rapidly in arm 1 than in arm 2.

8. Conclusions

Bakumondoto is effective for postinfectious cough in non-smoking patients, and the antitussive effect is prompt.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No serious adverse drug reactions were observed in either group.

11. Abstractor's comments

The cough in all patients resolved within 4 weeks. Dextromethorphan hydrobromide suppresses cough; however, it may adversely lead to delay in the healing process. Therefore, whether bakumondoto is effective for postinfectious cough in non-smoking patients should be studied by comparing arm 1 with an untreated/placebo control group (postinfectious cough in a natural course). As cough score is a subjective measure, assessment with objective measures is also necessary. In terms of Kampo medicine, postinfectious cough can be caused in a variety of pathologies (In: *Shanghanlun* [傷寒論, *Treatise on Cold Damage Diseases*]). There are different formulae for different pathologies. For some of these, bakumondoto is not effective.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nagano F, Yamada M, et al. A randomized comparison of cough-improvement effects between mao-bushi-saishin-to and western drugs for cold in common patients with allergic cold syndrome. *Kampo to Meneki Arerugi* (*Kampo and Immuno-Allergy*) 2005; 18: 56-67 (in Japanese with English abstract).

1. Objectives

To compare the cough-improvement effect of maobushisaishinto (麻黄附子細辛湯) and western drugs in patients with the common cold.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two hospitals and four clinics, Japan.

4. Participants

Patients with the common cold.

5. Intervention

The study duration was 15 years.
Arm 1: Tsumura Maobushisaishinto (麻黄附子細辛湯) Extract Granules (TJ-127), n=879.
Arm 2: Western drugs for the common cold, n=879.

6. Main outcome measures

Various subjective symptoms (i.e. fever, headache, chill etc.).

7. Main results

In various assessments, maobushisaishinto was more effective than western drugs.

8. Conclusions

Administration of maobushisaishinto is efficacious for the common cold syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

The methodology and the subjects in this randomized controlled trial were not described. "Cough-improvement effect" is mentioned only in the title, but not in the text. Considering the short time course of the common cold syndrome, it is unclear why the randomized controlled study has been conducted for the past 15 years and continues even now.

12. Abstractor and date

Fujisawa M, 22 February 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku* (*Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine*) 1993; 10: 19–23 (in Japanese).

Abe K, Takagi K, Comparison of treatment results between Kampo medicine-treated group and Western medicine-treated group for upper respiratory tract inflammation in children, *Kampo medicine* 1993; 43: 509-15. J-STAGE

1. Objectives

To compare the efficacy of treatment (Kampo medicine vs. Western medicine) for upper airway inflammation in children.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One pediatric internal medicine clinic.

4. Participants

Four hundred and nineteen children who presented with summer-time cold at the same clinic between 1 and 31 July 1991 were allocated to two groups in the order of presentation. High frequency rates of Coxsackie A2 and Coxsackie A4 were detected in the region at the time.

5. Intervention

Arm 1: Kampo medicine group (manufacturer not specified; n=212): including those treated with keimakakuhanto (桂麻各半湯) (n=76), maoto (麻黄湯) (n=63), keishinimaoitto (桂枝二麻黄一湯) (n=14), keishinieppiitto (桂枝二越婢一湯) (n=9), gingyosan (銀翹散) (n=8), saikokeishito (柴胡桂枝湯) (n=5), shoseiryuto (小青竜湯) (n=4), and shoseiryutogohangekobokuto (小青竜湯合半夏厚朴湯) (n=4).

Arm 2: Western medicine group (n=207). The drugs administered were not mentioned.

6. Main outcome measures

Number of consultations, and outcome assessed by the quantity of antibiotics used (oral and drip infusion), and incidence of asthmatic bronchitis, acute bronchitis, and pneumonia.

7. Main results

The numbers of consultations were one (159 patients), two (37), three (12), four (3), and five (1) in arm 1 and one (132 patients), two (44), three (14), four (7), five (6), six (2), seven (1), and eight (1) in arm 2. There were fewer consultations in arm 1. Eleven patients in arm 2 and 179 patients in arm 2 used oral antibiotics. No patients in arm 1 and 12 patients in arm 2 used intravenous drip antibiotics. Nine patients in arm 1 and eight in arm 2 suffered asthmatic bronchitis. One patient in arm 1 and 10 in arm 2 suffered acute bronchitis. No cases of pneumonia were observed in either group.

8. Conclusions

There were fewer consultations for upper airway inflammation in arm 1, which suggests that Kampo medicine accelerates recovery. There was less antibiotics use and fewer cases of acute bronchitis in arm 2.

9. From Kampo medicine perspective

The author discusses Kampo *sho* (証, pattern) in hypothetical terms, but appears to make no mention of the criteria used in this study for the selection of Kampo medicines for each patient.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Allocating participants by order of consultation made this a quasi-randomized controlled trial. This clinical trial was conducted before evidence-based medicine became widespread in Japan and before the introduction of the Consolidated Standards of Reporting Trials Statement. It is difficult to interpret the results because participants' ages or genders, details of the Western medicine interventions, or the criteria for administration of the Kampo medicines are not clearly specified. For its time, it was an advanced undertaking and may be considered a valuable report.

12. Abstractor and date

Tsuruoka K. 31 December 2013, 31 March 2017.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. *Nihon Shoni Toyo Igakkaishi* (*Journal of the Japan Pediatric Society for Oriental Medicine*) 2003; 19: 46–52 (in Japanese).

1. Objectives

To compare the efficacy of two different treatments, Western medicine and byakkokaninjinto (白虎加人参湯), on summertime cold.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A pediatric and internal medicine clinic in Shimane prefecture, Japan.

4. Participants

One hundred and sixty-four children who presented with fever of at least 38.5°C between 18 June and 17 August 2001 were allocated to two groups in order of presentation. Coxsackie A2, A4, A6, and A8, as well as adenovirus were detected in the region at the time.

5. Intervention

Arm 1: Kampo medicine group (manufacturer not specified). Among 75 patients received byakkokaninjinto (白虎加人参湯), 37 patients returned their fever logs. Dosage and administration frequency are not mentioned (n=37).

Arm 2: Western medicine group. Among 89 patients received antibiotic PL granules for children (Cefzon®), 43 patients returned their fever logs. Dosage and administration frequency are not mentioned (n=43).

6. Main outcome measures

Fever duration defined as time from presentation (at least 38.5°C) to decline in body temperature to 37.5°C or less.

7. Main results

In arm 1 and arm 2, mean fever duration was 27.0 and 33.8 hours, respectively, and standard deviation was 18.3 and 28.0 hours. Fever lasted for 40 hours or more in three patients in arm 1 and 12 patients in arm 2. The longest fever duration was 106 hours in arm 1 and 144 hours in arm 2. No statistically significant differences were observed between the groups for any measure; however, fever duration, number of patients with fever duration of 40 hours or more, and longest fever duration were all less in arm 1 compared to arm 2.

8. Conclusions

Results suggest that byakkokaninjinto tends to shorten fever duration in comparison to Western medicine.

9. From Kampo medicine perspective

The characteristic symptoms of summer-time colds such as herpangina, fever, and sore throat are suggestive of the warm diseases (温病) of Kampo medicine. In Chinese traditional medicine, gingyosan (銀翹散) is the first choice for warm diseases, while byakkokaninjinto is the first choice under the cold damage approach. Since gingyosan is not covered by health insurance, byakkokaninjinto was used in this study because it is covered.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This trial is similar to the trial published by the author in 1993 (Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku* [*Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine*] 1993; 10: 19–23 [in Japanese]). This is a quasi-randomized controlled trial (i.e., participants were allocated in the order of consultation). Limiting the intervention drug to byakkokaninjinto gives the study design lucidity and facilitates interpretation of the results. Differences in the fever duration results may depend on how the time of fever onset was determined, so development of further research is anticipated.

12. Abstractor and date

Tsuruoka K, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Okabayashi S, Goto M, Kawamura T, et al. Non-superiority of Kakkonto, a Japanese herbal medicine, to a representative multiple cold medicine with respect to anti-aggravation effects on the common cold: a randomized controlled trial. *Internal Medicine* 2014; 53: 949-56. Ichushi Web ID: 2015097387, Pubmed ID: 24785885

1. Objectives

To evaluate the efficacy of Kakkonto (葛根湯) for alleviating early cold symptoms.

2. Design

Randomized controlled trial (RCT).

3. Setting

Nine university hospitals and 6 clinics, Japan.

4. Participants

A total of 407 cold patients aged 18 to 65 years with throat discomfort, mild chills, but no sweating who underwent a physical examination within 48 hours of onset. (The patients meeting any of the following criteria were excluded from the study: moderate or severe subjective symptoms, body temperature of 37.5°C or higher, any prior oral treatment or serious underlying disease.)

5. Intervention

Arm 1: Kracie Kakkonto (葛根湯) Extract Granules administered orally at 2.0 g t.i.d. for four days or until the symptoms disappeared (n=209).

Arm 2: Western-style multiple cold medicine (Pabron Gold-A) at 3.6 g/day for four days or until the symptoms disappeared (n=198).

6. Main outcome measures

Worsening of cold symptoms (yes or no) (i) within five days after oral administration and (ii) within seven days after oral administration.

7. Main results

In the Kakkonto arm, 41 subjects dropped out and 168 subjects were included in the analysis. In the Pabron arm, 26 subjects dropped out and 172 subjects were included in the analysis. Worsening occurred by five days in 38 subjects (22.6%) in the Kakkonto arm and 43 (25.0%) in the Pabron arm. The percentage was lower in the Kakkonto arm, but the difference between arms was not significant. Worsening occurred by seven days in 41 subjects (24.4%) in the Kakkonto arm and 52 (30.2%) in the Pabron arm. Again, the percentage was not significantly lower in the Kakkonto arm.

8. Conclusions

There is no significant difference in efficacy between Kakkonto and the multi-symptom cold medicine.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No serious adverse drug reactions were noted in the two arms. The incidence of mild adverse drug reactions including sleepiness and gastrointestinal disorder was lower in the Kakkonto arm (7 subjects [4.2%] vs 12 subjects [7.0 %]), but not significantly so.

11. Abstractor's comments

This is an important study evaluating the efficacy of Kakkonto, which is frequently used for daily treatment of cold symptoms in clinical settings, as compared with a multi-symptom cold medicine. Although the anti-aggravation effects of Kakkonto on cold symptoms were evaluated in the present study with sample size based on the previous study, a significant efficacy was not demonstrated. One of the limitations of the study, according to the authors, was the difficulty with demonstrating evidence based on subjective evaluation. In this study, the efficacy was evaluated in terms of cold symptom prevention, but not symptom improvement in actual clinical settings. The inclusion of patients with mild symptoms may have affected the study's ability to detect a significant difference. Although the study design seemed to be appropriate for determining Kakkonto's efficacy as a self-medication and its safety, more studies are anticipated after re-examining the existing severity classification rules or outcome measures to be evaluated.

12. Abstractor and date

Koike H, 31 March 2017.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Itagaki K, Efficacy of shimpito for treatment of cough associated with cold syndrome.* *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2013; 70: 813-6 (in Japanese). Ichushi Web ID: 2014063683 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of shimpito (神秘湯) for treatment of cough associated with cold syndrome.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One clinic, Japan.

4. Participants

Sixteen patients (3 males and 13 females) who visited the clinic between January 2011 and May 2011 and had a diagnosis of cold syndrome with severe or persistent cough.

5. Intervention

Arm 1: Kracie Shimpito (神秘湯) Extract Granules administered orally at 3.0 g b.i.d. before or between meals for 7 days and lysozyme hydrochloride 90 mg t.i.d. + carbocysteine 500 mg t.i.d. after meals for 7 days (n=9).

Arm 2: Lysozyme hydrochloride 90 mg t.i.d. + carbocysteine 500 mg t.i.d. after meals for 7 days (n=7).

6. Main outcome measures

The severity of cough was assessed on the following 4-point scale: 0, none; 1, mild; 2, moderate; 3, severe. Subjects recorded the severity scores in a cough diary. The scores on each day were compared to those on Day 1 using the Wilcoxon signed-rank test.

7. Main results

The scores improved significantly after Day 4 ($P<0.05$) in Arm 1 and after Day 6 in Arm 2 ($P<0.05$).

8. Conclusions

Shimpito is effective for the treatment of refractory cough associated with cold syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events were noted.

11. Abstractor's comments

This is a meaningful clinical study because the author, a physician at the study site, conducted the study, in the midst of daily busy clinical practice, to evaluate the efficacy of a Kampo medicine in patients with cough due to cold, which is a common symptoms. However, since some subjects with persistent cough were assigned to the control arm, the inter-arm difference in the period from onset to the start of the study investigation was large: 4.7±1.7 days in the shimpito arm and 16.7±18.4 days in the control arm. Persistent cough might be refractory and affect the results of the study. In addition, intra-arm (but not inter-arm) cough severity scores were compared; therefore, the efficacy of shimpito compared with that of control drugs remains unknown. Since it is very important to make a continuous effort to elucidate the efficacy of Kampo medicine against common symptoms in daily clinical settings, a larger number of such clinical studies are anticipated..

12. Abstractor and date

Fujisawa M, 31 March 2017; Goto H, 31 March 2017.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kato S, Tamano M, Okamura A, et al. Clinical Research The preventive effects of Kampo medications for common cold syndrome in the elderly*.*Kampo Igaku* (*Science of Kampo Medicine)* 2015; 39: 183-6.

1. Objectives

To verify the effectiveness of Kampo medications for the prevention of common cold syndrome in the elderly.

2. Design

Randomized controlled trial (RCT).

3. Setting

Health facility for the elderly (number of centers not mentioned), Japan.

4. Participants

Sixty elderly people staying at a health facility for the elderly, aged at least 75-years, who can orally take a Kampo medication unaided, and who do not have underlying pulmonary diseases (39 females and 21 males).

5. Intervention

Arm 1: A Kampo medication selected on the basis of Kampo medical diagnosis, taken for 6 months (n=30) (TSUMURA Rikkunshito [六君子湯] Extract Granules [n=6], TSUMURA Hochuekkito [補中益気湯] Extract Granules [n=4], TSUMURA Juzentaihoto [十全大補湯] Extract Granules [n=7], TSUMURA Ninjinyoeito [人参養栄湯] Extract Granules [n=3], TSUMURA Rokumigan [六味丸] Extract Granules [n=3], TSUMURA Hachimijiogan [八味地黄丸] Extract Granules [n=2]), and TSUMURA Goshajinkigan [牛車腎気丸] Extract Granules [n=5]).

Arm 2: No Kampo medication (n=30).

6. Main outcome measures

NK-cell activity (^{51}Cr) before trial start and in month 3; frequency of common cold syndrome occurring from months 3 to 6.

7. Main results

The results for 60 participants were analyzed. NK-cell activity increased by a statistically significant amount in month 3 in arm 1, but it did not increase in arm 2 (P<0.01). Frequency of common cold syndrome was lower by a statistically significant amount in arms 1and 2 (P<0.01).

8. Conclusion

Taking a deficiency-pattern treating Kampo formula activates NK-cells, improves appetite, stimulates metabolism, and prevents common cold syndrome.

9. From Kampo medicine perspective

Kampo medical diagnoses were made when selecting the specific Kampo medication in arm 1.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an important paper evaluating the preventive effects of Kampo medications on common cold syndrome. Although it is described as a randomized controlled trial, some doubt is raised about whether it was truly randomized by the fact that the group of 30 participants in the Kampo administration group were further divided by Kampo medical diagnosis into 3 groups (10 participants per group) and then administered 7 Kampo formulae: it is advisable to describe allocation methods in detail. The authors mention that ANOVA analysis was carried out, however, the graphs show repeated testing comparing 2 items, trial start and trial end data, in one group, so it is difficult to determine that ANOVA analysis testing between 3 or more groups was carried out. The authors also do not describe the criteria for diagnosing a cold. This paper is an important underpinning for further elucidation of the effectiveness of Kampo medications in preventing common cold syndrome, and hopefully the authors will continue with a paper that explicitly states the allocation method and diagnosis criteria.

12. Abstractor and date

Koike H, 23 April 2018

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kuwamura A, Komasawa N, Takahashi R, et al. Preoperative oral administration of kikyo-to, a Kampo medicine, alleviates postoperative score throat: a prospective, double-blind, randomized study. *Journal of Alternative and Complementary Medicine* 2016; 22: 294-7. CENTRAL ID: CN-01153279, Pubmed ID: 27028745

1. Objectives

To evaluate the effectiveness of kikyoto (桔梗湯) for postoperative sore throat.

2. Design

Double-blind randomized controlled trial (DB-RCT)

3. Setting

One hospital

4. Participants

Seventy adult female patients, either healthy or with slight underlying disease, who underwent surgery under general anesthetic.

5. Intervention

Arm 1: TSUMURA Kikyoto (桔梗湯) Extract Granules 2.5g taken before sleep on the night before surgery, and in the morning on the day of surgery (n=35).

Arm 2: Non-administration group (n=35)

6. Main outcome measures

Sore throat and nausea, immediately after and at 3 and 24 hours after waking from anesthesia recovery.

7. Main results

A significant reduction in the occurrence of sore throat immediately after anesthesia recovery (p=0.02), and a declining trend in sore throat 3 hours after (p=0.16) were observed in the kikyoto group. A reduction in sore throat intensity was also found immediately after recovery (p=0.02) and 3 hours after (p=0.05) in the kikyoto group. No significant difference in nausea was observed in the 2 groups during monitoring.

8. Conclusions

Sore throat from surgery under anesthesia may be alleviated by administering kikyoto before surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No significant difference between the 2 groups in critical events or nausea, etc. was observed.

11. Abstractor's comments

Alleviating wound pain and sore throat after surgery is a very important matter. This is an interesting clinical study designed to alleviate sore throat after surgery under anesthesia by administering kikyoto before surgery. Given that the participants in this study were female patients, further research into the effects of kikyoto on sore throat in male patients is advisable.

12. Abstractor and date

Kato Y, 18 May 2020.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Kubo T. The effect of maoto for treatment of influenza infection in children. (from Presentation C-41 of the Japan Society for Oriental Medicine, 56th Annual Meeting) *Medicament News* 2005 Sep 5; 1846: 15 (in Japanese)

Kubo T, Nishimura H. Antipyretic effect of mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children. *Phytomedicine* 2007; 14: 96-101. CENTRAL ID: CN-00577142, Pubmed ID: 17141491

1. Objectives

To evaluate the effect of maoto (麻黄湯) in combination with oseltamivir on the duration of fever.

2. Design

Randomized controlled trial (RCT) (partly).

3. Setting

A hospital screening patients from January to May 2004, Japan.

4. Participants

Children (aged 0–13 years; n=60) suffering from influenza-like illness with fever of ≥38°C.

5. Intervention

Oseltamivir 2 mg/kg b.i.d., TSUMURA Maoto (麻黄湯) Extract Granules 0.06 g/kg t.i.d

Influenza infection was screened with a rapid diagnosis test, and diagnosis was confirmed by isolation of the virus or viral detection using RT-PCR

Arm 1: oseltamivir and maoto (麻黄湯); influenza A; n=14..

Arm 2: oseltamivir; influenza A; n=18

Arm 3: maoto (麻黄湯); influenza A; n=17.

(Influenza-positive patients [by the rapid test] were randomly assigned to arm 1 and arm 2. Arm 3 included influenza-positive patients under the age of 1 year, who did not meet the criteria for oseltamivir treatment, and influenza-negative patients aged 1 year or older. Patients [n=11] without confirmed influenza virus infections were excluded.)

6. Main outcome measures

Time to becoming afebrile after initiation of the treatment.

7. Main results

Body temperature was recorded every 6 hours in patients not treated with acetaminophen. The median period from commencement of treatment to alleviation of fever was 18 h, 24 h, and 15 h in arms 1, 2, and 3, respectively. Using the Wilcoxon rank sum test, significant differences were observed in arm 1 (P<0.05) and 3 (P<0.01) when compared with arm 2.

8. Conclusions

Maoto effectively reduces the duration of fever in children with influenza.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse events in any group.

11. Abstractor's comments

This RCT consisted of 3 arms: arms 1 and 2 (patients randomly allocated) but not arm 3 (patients not randomly allocated) were compared. Hopefully the authors will conduct an RCT with all three arms, and if possible, use a placebo in a fourth arm. Given that maoto (麻黄湯) has adverse effects, future research would preferably include cohort studies and an RCT with a design that takes into account the predicted frequency of such adverse effects, as mentioned by the authors.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 22 February 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kimoto H, Kuroki H. Efficacy of combined administration of oseltamivir phosphate and maoto in treating influenza. *Kampo Igaku* (*Kampo Medicine*) 2005; 29: 166-9 (in Japanese). Ichushi Web ID: 2005292428

1. Objectives

To evaluate the efficacy of maoto (麻黄湯) in combination with oseltamivir phosphate in treating pediatric influenza.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

An internal medicine clinic screening patients from January to March 2004, Japan.

4. Participants

Adult patients (n=37) positive for influenza (rapid diagnostic test), and having fever (≥38°C) within 48 hours of onset.

5. Intervention

Nineteen out of 37 subjects were included in the sample. Eighteen subjects were excluded because of body temperature not more than 38°C (n=5), being on a drip (n=1), preference for Kampo formulae only (n=5), preference for Western drugs only (n=2), cognitive impairment (n=1), refusal to give consent to participate in the study (n=1), and regular use of Kampo formulae (n=3).
Oseltamivir phosphate (75 mg b.i.d. for 5 days), TSUMURA Maoto (麻黄湯) Extract Granules 2.5 g t.i.d. for 3 days), and Western medicines (an antihistamine [cyproheptadine hydrochloride] with either a bronchodilator [clenbuterol hydrochloride] or expectorant [carbocysteine]) were administered for 3 days.
Treatment assignment was chronological according to examination date.
Arm 1: oseltamivir phosphate and maoto (麻黄湯), n=10.
Arm 2: oseltamivir phosphate and Western medicines, n=9.

6. Main outcome measures

Body temperature.
The magnitude and time course of symptoms such as appetite, fatigue, and dizziness/light-headedness.

7. Main results

All subjects studied were infected with influenza A. Patients in arm 1 tended to become afebrile 12 hours earlier than patients in arm 2. There were no significant between-group differences in anorexia, fatigue, and dizziness/light-headedness, though patients in arm 1 tended to improve more rapidly than patients in arm 2.

8. Conclusions

Compared with oseltamivir plus Western formulations, oseltamivir plus Kampo formulation (maoto) tended to shorten the duration of fever and allowed patients to maintain normal activity.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse events in any group.

11. Abstractor's comments

The graph shows that 12 hours after administration, fever dropped below 38°C in the maoto (麻黄湯) group, and temperature was a little above 38.5°C in the Oseltamivir phosphate-only group, which was a significant difference. After 24 hours, body temperature was about 37.5°C in both groups. However, no other clear differences in symptoms were observed between the two groups. Most of the adult participants commented that they felt more comfortable on the day after taking Oseltamivir phosphate, but adults are commonly prescribed acetaminophen in single doses as an antipyretic analgesic, and significantly, the study found that patients experienced fever as part of the natural course after administration. Exceptional cases may be excluded from the total number of cases.

12. Abstractor and date

Fujisawa M. 15 June 2007, 1 April 2008, 9 March, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and mao-to for influenza – 3rd report-. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 2006; 19: 17-25 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of combined oseltamivir phosphate and maoto (麻黄湯) for the treatment of influenza in paediatric patients.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

February to March 2005.
One hospital and one clinic, Japan.

4. Participants

One hundred and seven children who presented within 48 hours of symptom onset, were febrile (body temperature, 38°C or higher), and were positive for influenza by the rapid diagnostic test.

5. Intervention

Treatment assignment was chronological according to examination date.
Oseltamivir phosphate was administered at a dose of 4mg/kg/day in two divided doses or 75 mg, b.i.d. for 5 days. TSUMURA Maoto (麻黄湯) Extract Granules were administered at a dose of 0.1-0.2kg/day in three divided doses or 2.5 g, t.i.d. for 3 days.
Arm 1: treatment with oseltamivir phosphate + maoto (麻黄湯) (n=57).
Arm 2: treatment with oseltamivir phosphate alone (n=55).

6. Main outcome measures

Clinical symptoms (appetite loss, myalgia, throat soreness, insomnia, cough, nasal discharge, vomiting), physical activity (kindergarten/school attendance, play), urination characteristics/frequency, fluid intake (quantity/frequency), body temperature (measured morning, noon, and night), and spasms.

7. Main results

Time to fever alleviation tended to be longer in arm 2 than arm 1.
Although there was no significant between-arm difference in appetite loss, fatigue, or dizziness, all outcome measures were slightly better in arm 1 than in arm 2.

8. Conclusions

Maoto can be administered safely and its combination with western medicine seemes to improve symptoms further. Maoto seems to be a viable treatment for influenza in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

The study compared an Oseltamivir plus maoto (麻黄湯) group with an Oseltamivir-only group and found that the former had slightly shorter fever duration and slightly improved clinical symptoms. The sample size is larger and the combined use of Oseltamivir and maoto appears to have provided slightly greater efficacy. It is hoped that in a future paper, the authors will explain more clearly the analysis of their results, clarify their sampling methods, and present the evidence in terms of RCTs, not just for conference presentation purposes. Furthermore, the 2004 study (91 participants), which was carried out under the same conditions as this paper, was unclear on several points, including group allocation, and was not treated as an RCT.

12. Abstractor and date

Fujisawa M, 8 March 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Iwasaki K, Taguchi M, Cyong JC, et al. Effect of mao-bushi-saishin-to on influenza vaccination in elderly subjects: a randomized controlled study. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2004; 17: 97-103 (in Japanese with English abstract).

Iwasaki K. Influenza and Kampo in the elderly*. *TSUMURA Mail Magazine* 2008; Suppl: 22-3 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of maobushisaishinto (麻黄附子細辛湯) as an adjuvant for influenza vaccination in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Not documented, Japan.

4. Participants

Eighteen patients with antibody titers of <1:10 to two types of influenza A antigens (H1N1, H3N2) as measured using an hemagglutination inhibition (HI) assay.

5. Intervention

Arm 1: oral administration of TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules ([TJ-127]), 7.5 g/day, from 7 days before influenza vaccination until 14 days after vaccination; n=10.

Arm 2: no administration of TJ-127; influenza vaccination only; n=8.

6. Main outcome measures

Rise in antibody titer from baseline was measured at 4 weeks after vaccination and the rate of rise was compared between arms.

7. Main results

There was no significant between-arm difference in anti-H1N1 antibody titer. Anti-H3N2 antibody titer increased on average 4.9-fold in arm 2 (when compared with baseline) and 57.3-fold in arm 1 which was significant (P<0.04) when compared with arm 2. During the observation period, 2 patients in arm 2 but none in arm 1 became infected with influenza A virus.

8. Conclusions

The rise in anti-H3N2 antibody titer (but not anti-H1N1 antibody titer) was significantly greater in arm 1 than arm 2, suggesting that maobushisaishinto enhances the anti-H3N2 antibody titer induced by influenza vaccination and enhances specific immunity.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Influenza infection complicated with infections such as pneumonia contributes substantially to mortality in the elderly. Therefore, boosting the production of anti-influenza virus antibody would have an important preventive effect and reduce the cost of influenza treatment. From these points of view, this study investigated whether administration of maobushisaishinto can increase antibody level, with the expectation that maobushisaishinto acts as an adjuvant of the humoral immune response in the elderly with low influenza-antibody level. This report focuses on strategies for the prevention of influenza in the elderly with low response to influenza vaccine. Further studies are needed to determine why only anti-H3N2 antibody titer is significantly increased compared with control group whereas no significant difference was observed in anti-H1N1 antibody, and whether maobushisaishinto can promote production of specific antibodies.

The small number of patients was a problem in this study. Further analyses with an increased number of cases are necessary. Also studies on other Kampo medicines with adjuvant effects in subjects with low antibody production against influenza virus, and on methods of administration, are awaited.

Iwasaki (2008) reported that the number of the participants is higher, i.e., 18 in arm 1 (the maobushisaishinto group) and 15 in arm 2 (the control group). The results were almost the same, revealing elevated anti-H3N2 antibody titer in arm 1.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 12 March 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Yaegashi H. Efficacy of coadministration of maoto and shosaikoto, a Japanese traditional herbal medicine (Kampo medicine), for the treatment of influenza A infection, in comparison to oseltamivir. *Nihon Hokan Daitai Iryo Gakkaishi* (*Japanese Journal of Complementary and Alternative Medicine*). 2010; 7: 59–62 (in English with Japanese summary). J-STAGE

1. Objectives

To evaluate the efficacy of coadministration of maoto (麻黄湯) and shosaikoto (小柴胡湯) for the treatment of influenza A infection, in comparison to oseltamivir.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single clinic, Japan.

4. Participants

Fourteen outpatients (18 years or older) who presented within 48 hours after onset of fever (body temperature above 37.5°C) with influenza-like symptoms (upper respiratory tract symptoms or systemic symptoms) and tested positive for influenza A antigen from December 2007 to March 2008.

5. Intervention

Arm 1: administration of TSUMURA Maoto (麻黄湯) Extract Granules 2.5 g t.i.d. + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for 3 days (n=6).
Arm 2: administration of oseltamivir 75 mg b.i.d. for 5 days (n=8).

6. Main outcome measures

Duration of fever, highest body temperature, and number of doses of antipyretics and cough medicines.

7. Main results

There was no significant between-arm difference in duration of fever after onset (2.8±0.8 [mean±SD] days in arm 1 and 2.9±0.7 days in arm 2), duration of fever after treatment (2.9±0.7 days in arm 1 and 2.0±0.6 days in arm 2), the highest body temperature (39.0±0.7°C in arm 1 and 38.8±0.5°C in arm 2), and the number of doses of antipyretics and cough medicines administered.

8. Conclusions

The efficacy of maoto plus shosaikoto for treating influenza A in adults was comparable to that of oseltamivir.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed in both arms.

11. Abstractor's comments

This paper reports a randomized controlled trial of maoto plus shosaikoto for treatment of influenza A. The effect of maoto combined with shosaikoto was comparable to that of oseltamivir. To strengthen the evidence, the efficacy needs to be confirmed in a study with a larger sample size. However, coadministration of maoto and shosaikoto is not logical from the viewpoint of Kampo medicine. Patients who did not respond to maoto should be treated with daiseiryuto (大青竜湯), keishinieppiichito (桂枝二越婢一湯), saikatsugekito (柴葛解肌湯), or saikokeishito (柴胡桂枝湯 according their excess or deficiency (虚実) pattern, and not with maoto plus shosaikoto.

12. Abstractor and date

Okabe T, 24 December 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Saita M, Naito T, Boku S, et al. The efficacy of ma-huang-tang (maoto) against influenza. *Kampo to Meneki Arerugi* (*Kampo and Immuno-allergy*). 2010; 23: 17–26 (in Japanese with English abstract).
Saita M, Naito T, Boku S, et al. The efficacy of *ma-huang-tang* (maoto) against influenza. *Health* 2011; 3: 300-3.

1. Objectives

To evaluate the efficacy of maoto (麻黄湯) against influenza A in adults.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital outpatient department, Japan.

4. Participants

Forty-five patients (20 years or older) visiting the hospital between November 2008 and March 2009 and testing positive for type A influenza antibody using a rapid diagnosis kit.

5. Intervention

Subjects were randomized to either of two arms, using Microsoft Excel.
Arm 1: TSUMURA Maoto (麻黄湯) Extract Granules (n=22).
Arm 2:no administration of maoto (n=23).

6. Main outcome measures

Symptoms (pyrexia [period from administration of drugs to afebrility], arthralgia, myalgia, headache, cough, and malaise) scored on a 5-point scale. Scores recorded daily for 5 days and sent by mail by each participant.

7. Main results

Records of symptoms including fever, etc., were obtained by mail. After excluding 8 patients whose data were not available, patients who provided complete data for analysis (18 patients in arm 1, of whom 9 patients taking oseltamivir concomitantly, and 19 patients in arm 2, of whom 13 taking oseltamivir and 6 taking zanamivir) were included for analysis. Of these 37 patients, 7 patients in arm 1 and 11 patients in arm 2 had received influenza vaccination. At the time of the allocation, there were no significant differences in age (arm 1, 31.1±9.77 years; arm 2, 33.6±13.1 years), the presence or absence of fever at the first visit, and duration of fever. During the period from administration of drugs to afebrility, there was no between-arm difference in duration of fever. Although the time to improvement of myalgia tended to be faster in arm 1, the time to disappearance of other symptoms was similar in both arms.

8. Conclusions

Maoto and anti-influenza agents have the same antipyretic effects in patients with influenza.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a conference presentation by Saita et al. This structured abstract is based on the paper. It is interesting that the authors found no significant differences in the effects of maoto and other agents on the clinical course of influenza infection. However, there is a source of bias in the use of anti-influenza agents, and the finding of no significant differences should be interpreted with caution. Their conclusion is based on a comparison of the efficacy of maoto and anti-influenza drugs, but the two groups cannot be compared using this study design. Saita et al. (2011) and Saita et al. (2010) are the same clinical controlled trial. The analysis groups are divided into four groups: a maoto-only group, a combined maoto and oseltamivir group, an oseltamivir-only group, and a zanamivir-only group. There was no significant between-group difference in fever duration, which points to maoto being a useful anti-influenza drug. While the study was a retrospective statistical analysis, its significance is clear.

12. Abstractor and date

Fujisawa M, 14 January 2011, 19 April 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nabeshima S, Kashiwagi K, Ajisaka K, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. *Journal of Infection and Chemotherapy* 2012; 18: 534-43. Pubmed ID: 22350323

1. Objectives

To compare the efficacy of oseltamivir, zanamivir, and maoto (麻黄湯) in adult influenza patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Outpatient Department, Fukuoka University Hospital, Japan.

4. Participants

Thirty-three outpatients examined between January and April 2009 who were rapid diagnostic test positive within 48 hours after onset of influenza symptoms (age range: 20–64 years).

5. Intervention

Participants were divided into three groups by computer randomization.
The only concomitant drug allowed was acetaminophen (400 mg), for high fever and headache.
Arm 1: TSUMURA Maoto (麻黄湯) Extract Granules group: 2.5 g t.i.d. for 5 days taken orally (n=11).
Arm 2: Oseltamivir group (2 type B patients): 75 g b.i.d. for 5 days taken orally (n=10).
Arm 3: Zanamivir group (2 type B patients): 20 mg b.i.d. for 5 days by inhalation (n=12).

6. Main outcome measures

The main endpoints were fever after commencement of treatment and period of symptom improvement. Other endpoints were viral persistence, safety, and serum levels of cytokines (IFN-α, IL-6, IL-8, IL-10, and TNF-α).

7. Main results

The data from 10 participants in arm 1, 8 in arm 2, and 10 in arm 3 were analyzed because there were dropouts. Participants recorded body temperature three times a day and symptoms for 5 days, then mailed the records to the hospital. The fever threshold was defined as 37.5°C. Fever duration was the time from drug administration till body temperature fell to 37.5°C or less. The period from onset to drug administration was 17 hours in arm 1, 22 hours in arm 2, and 26 hours in arm 3. Median fever duration was 29 hours in arm 1, 46 hours in arm 2, and 27 hours in arm 3, demonstrating a significant difference between arm 1 and arm 2 ($P<0.05$). There was no significant difference in persistence of symptoms among the three arms.

Viral tests and cytokine measurements were done on days 1 (the day of the examination), 3, and 5. The virus was a 2009 seasonal virus, its persistence in the body on days 1, 3, and 5, respectively, were 7/7, 3/7, and 1/7 in the maoto group, 6/6, 2/6, and 1/6 in the oseltamivir group, and 5/5, 3/5, and 1/5 in the zanamivir group. The surviving viruses were type A in the maoto group, and type B in the oseltamivir and zanamivir groups. There was no significant difference in cytokine levels among the three groups.

8. Conclusions

Maoto and neuraminidase inhibitors have similar effects on seasonal influenza viruses in healthy adults.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One participant in the maoto group and one in the oseltamivir group had slightly raised levels of liver function enzyme, which normalized in two weeks.

11. Abstractor's comments

The paper clearly presents the design and results of the study and is thoroughly convincing in demonstrating no significant difference in fever and symptom duration between the maoto-only group and neuraminidase inhibitor groups. The paper is also interesting for its investigation of virus survival and cytokine levels, as well as its proposition of an antiviral action unrelated to cytokines.

12. Abstractor and date

Fujisawa M, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku* (*Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine*) 1993; 10: 19–23 (in Japanese).

1. Objectives

To compare the efficacy of two different treatments (a Kampo medicine treatment and a Western medicine treatment) on influenza.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A pediatric and internal medicine clinic in Shimane prefecture, Japan.

4. Participants

Seven hundred and eighty-three children who presented with influenza at the same clinic between 1 and 28 February 1992 were allocated to two groups in the order of presentation. Hong Kong A strain was prevalent in the region at the time and Russian A strain was also present in small numbers.

5. Intervention

Arm 1: Kampo medicine group (manufacturer not specified; n=386): including those treated with maoto (麻黄湯) (n=200), keimakakuhanto (桂麻各半湯) (n=143), makyokansekito (麻杏甘石湯) (n=15), kakkonto (葛根湯) (n=8), keishinieppiitto (桂枝二越婢一湯) (n=8), keishinimaoitto (桂枝二麻黄一湯) (n=4), saikokeishito (柴胡桂枝湯) (n=4), shoseiryuto (小青竜湯) (n=3), etc.

Arm 2: Western medicine group (n=397). Details of the drugs administered are not mentioned.

6. Main outcome measures

Number of consultations, and outcome assessed by the quantity of antibiotics used (oral and drip infusion) and incidence of asthmatic bronchitis, acute bronchitis, and pneumonia.

7. Main results

The numbers of consultations were one (156 patients), two (130), three (51), four (32), five (11), six (4), seven (1), eight and nine (0), and ten (1) in arm 1 and one (190 patients), two (123), three (49), four (17), five (10), six (4), seven (3), eight (1), and nine ten (0) in the Western medicine group. There was no significant between-group difference in the number of clinic visits. Fifty-nine patients in arm 1 and 382 patients in arm 2 used oral antibiotics. Nine patients in arm 1 and 12 patients in arm 2 used intravenous antibiotics. Similar numbers of patients (9 in arm 1 and 12 in arm 2) suffered asthmatic bronchitis. The number of patients who suffered acute bronchitis was significantly lower in arm 1 than arm 2 (i.e., 12 vs 23, respectively, P=0.05). Two cases of pneumonia were diagnosed in arm 2 and none in arm 1.

8. Conclusions

There was no significant between-group difference in the numbers of consultations for influenza. The frequency of antibiotic use was lower in arm 1 while the severity and incidence of acute bronchitis was significantly higher in arm 2.

9. From Kampo medicine perspective

The author discusses Kampo *sho* (証, pattern) in hypothetical terms, but appears to make no mention of the criteria used to select Kampo medicines for each patient.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

As in the summer-time cold trial, participants were allocated in the order of consultation (i.e., this was a quasi-randomized controlled trial). This trial was conducted before evidence-based medicine became widespread in Japan and before the introduction of the Consolidated Standards of Reporting Trials Statement. It is difficult to interpret the results because participants' ages or genders, details of the Western medicine interventions, the criteria for administration of the Kampo medicines, or the statistical test details are not clearly specified. For its time, it was an advanced undertaking and may be considered a valuable report.

12. Abstractor and date

Tsuruoka K, 31 December 2013

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. *Nihon Shoni Toyo Igakkaishi* (*Journal of the Japan Pediatric Society for Oriental Medicine*) 2003; 19: 46–52 (in Japanese).

1. Objectives

To compare the efficacy on influenza of treatment with byakkokaninjinto (白虎加人参湯), maoto (麻黄湯), antibiotics, and amantadine.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A pediatric and internal medicine clinic in Shimane prefecture, Japan.

4. Participants

Children who presented with fever of at least 38.5℃ between 1 February and 20 March 2002 were allocated in the order of presentation to four groups (antibiotics, amantadine, byakkokaninjinto, and maoto).

5. Intervention

Arm 1: antibiotic group: Cefzon®. Mean age 3.2 years (n=21).
Arm 2: amantadine group: Symmetrel®. Mean age 5.0 years (n=23).
Arm 3: maoto (麻黄湯) group (manufacturer not specified): Mean age 4.8 years (n=23).
Arm 4: byakkokaninjinto (白虎加人参湯) group (manufacturer not specified): Mean age 4.2 years (n=18).
Dosage and frequency are not mentioned for any of the drugs.

6. Main outcome measures

Fever duration (defined as time from presentation [at least 38.5°C] to decline in body temperature to 37.5°C or less), and outcome (bronchitis or pneumonia onset)

7. Main results

Mean fever duration (in hours) in groups treated with antibiotics, amantadine, maoto, and byakkokaninjinto was 52.7, 46.5, 47.0, and 69.3, respectively, which indicates the duration was the same for amantadine treatment and maoto treatment. Bronchitis occurred in four antibiotic patients, two amantadine patients, one maoto patient, and three byakkokaninjinto patients. Pneumonia occurred in two antibiotic patients, one amantadine patient, two maoto patients, and one byakkokaninjinto patient.

8. Conclusions

Results suggest that maoto and amantadine have similar effects on influenza.

9. From Kampo medicine perspective

Physicians should alter their prescriptions for influenza in response to the changing course of symptoms. The author discusses the need to change the prescriptions in this trial after maoto use. The changes were made in accordance with Kampo medical principles. The paper describes the clinical course of influenza in all 23 maoto patients.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This trial is similar to the trial published by the author in 1993 (Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen KirokuNihon Shoni Toyo Igakkaishi* [*Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine*] 1993; 10: 19–23 [in Japanese]). Although not mentioned in the paper, the diagrams imply that participants contracted influenza A. Unlike the previous trial, the present trial simplifies the study design by limiting the number of intervention drugs to four. However, diversification of prescription patterns after maoto use complicates interpretation of the results. The frequency of amantadine administration also decreased, so further development of this research is anticipated.

12. Abstractor and date

Tsuruoka K, 31 December 2013

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kawamura K. No difference between two brands of maoto and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients*. *Nihon Shonika Rinsho* (*Japanese Journal of Pediatrics*) 2009; 62: 1855-61 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of two brands of maoto (麻黄湯) and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One medical clinic, Japan.

4. Participants

One hundred and seventy-two influenza patients who tested positive for type A (quick diagnostic test kit) and whose throat swabs confirmed viral clearance from the pharynx.

5. Intervention

Arm 1: TEIKOKU (麻黄湯) Maoto Extract Granules (0.13–0.20 g/kg in three divided doses) for 1–6 days (n=64).

Arm 2: TSUMURA Maoto (麻黄湯) Extract Granules (0.11–0.21 g/kg in three divided doses) for 1–6 days (n=61).

Arm 3: Oseltamivir (2.1–4.4 mg/kg in two divided doses) for 1.5–5 days (n=47).

6. Main outcome measures

Defervescence period, general symptoms.

7. Main results

The mean defervescence period (hours) after taking medication (arm 3 [30.36 ± 20.96] vs arm 1 [45.73 ± 35.51] and arm 2 [53.90 ± 39.42]; $P<0.01$), the mean fervescent period (hours) (arm 3 [45.79 ± 21.05] vs arm 1 [67.27 ± 37.88] and arm 2 [69.57 ± 39.76]; $P<0.01$), and the period until disappearance of symptoms (hours) (arm 3 [48.47 ± 26.90] vs arm 1 [70.47 ± 41.99] and arm 2 [73.95 ± 43.01]; $P<0.01$) were significantly shorter in arm 3. The period from onset to influenza virus clearance (hours) was similar in arm 1 (98.00 ± 31.83), arm 2 (101.72 ± 34.39) and arm 3 (95.91 ± 30.80) ($P>0.05$). The period from defervescence to influenza virus clearance (hours) was significantly shorter in arm 1 (31.73 ± 44.26) and arm 2 (32.15 ± 36.61) than in arm 3 (50.13 ± 32.84; $P<0.01$).

8. Conclusions

Oseltamivir clears fever and improves symptoms faster than maoto. TEIKOKU Maoto, TSUMURA Maoto, and oseltamivir have the same efficacy in clearing type A influenza virus from the pharynx. TEIKOKU Maoto and TSUMURA Maoto have the same efficacy in terms of defervescence period, symptomatic period, and period until clearance of type A influenza virus from the pharynx.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is a controlled clinical trial of the effectiveness of two brands of maoto and oseltamivir and measured the time required to clear influenza virus from the pharynx of patients with type A influenza virus. It is a quasi-randomized controlled trial in which drug treatments were allocated in the order of consultation. Oseltamivir reduced fever and improved symptoms faster than maoto. On the other hand, it is very interesting that oseltamivir and maoto had similar effectiveness in clearing influenza virus. The fact that there was no difference between the two brands of maoto verifies the homogeneity of Japanese Kampo preparations.

12. Abstractor and date

Okabe T, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and mao-to for influenza. *Kampo to Meneki-Arerugi* (*Kampo and Immunoallergy*) 2005; 18: 47-55 (in Japanese with English abstract).

1. Objectives

To compare the effect the combination of oseltamivir phosphate and Western medications with that of oseltamivir phosphate and maoto (麻黄湯) for pediatric influenza.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One center: Hospital pediatric outpatient department, Japan.

4. Participants

Ninety-one pediatric patients (1–16 years) who were examined between January and March 2004, showed flu-like symptoms within 48 hours of onset, and rapid diagnostic test positive for influenza.

5. Intervention

Treatment assignment in the order of consultation.
Oseltamivir phosphate (4 mg/kg or 150 mg in two divided doses) for 5 days, TSUMURA Maoto (麻黄湯) Extract Granules (0.1–0.2 g/kg in three divided doses) for 3 days. The Western medications were bronchial dilator, anti-histamine, and expectorant.
Arm 1: Oseltamivir phosphate plus Maoto (n=48).
Arm 2: Oseltamivir phosphate plus Western medications (n=43).

6. Main outcome measures

Clinical symptom score using the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) to assess loss of appetite, muscle ache, sore throat, insomnia, cough, nasal discharge, vomiting, activity level, and return to school/kindergarten and play; urine condition and urination frequency; fluid intake frequency and volume; body temperature (measured every eight hours: morning, noon, and evening); presence/absence of cramps; and medication as recorded by parent/guardian.
Adverse eventts were collected by query of visiting outpatients or by phone at weeks 2, 4, and 8.

7. Main results

Mean duration of fever (38°C, in hours) was similar between groups: 27.6 ± 3.6 (SE) in arm 1 and 36.2 ± 4.3 in arm 2, showing no significant difference, although duration tended to be shorter in arm 1. There was no significant between-group difference in the CARIFS score over the five-day follow-up period.

8. Conclusions

Maoto can be administered safely and has almost the same effectiveness when combined with Western medications. It appears that maoto combined with oseltamivir may be used effectively for pediatric influenza.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events were observed in the two groups.

11. Abstractor's comments

This report is from the proceedings of a symposium. The number of participants is sufficient for analysis, and the effects and safety outcomes appear to suggest that maoto may be used in place of Western medications for relief of symptoms. The authors neglected to mention (in the results) the outcomes that were indicated in the methods; however, hopefully they will formally address this in a further paper. Notably, the Western medications did not include any anti-pyretic analgesics.

12. Abstractor and date

Fujisawa M, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Saiki I, Koizumi K, Goto H, et al. The long-term effects of a Kampo medicine, juzentaihoto, on maintenance of antibody titer in elderly people after influenza vaccination. *Evidence-Based Complementary and Alternative Medicine* 2013: 1-8. doi: 10.1155/2013/568074. Pubmed ID: 24348705

1. Objectives

To evaluate the long-term effects of juzentaihoto (十全大補湯) on maintenance of the anti-influenza antibody titer in elderly people after influenza vaccination.

2. Design

Randomized controlled trial (RCT).

3. Setting

Four long-term care facilities, Japan.

4. Participants

Ninety patients aged 65 years or older who were receiving long-term care for cerebrovascular disease, dementia, bone, joint disease, etc.

5. Intervention

Arm 1: Kracie Juzentaihoto (十全大補湯) Extract Granules administered orally or through a gastrostomy tube 3.75 g b.i.d. for a total of 28 weeks (i.e., from 4 weeks before influenza vaccination to 24 weeks after influenza vaccination) (n=44).

Arm 2: No administration (n=46).

6. Main outcome measures

Antibody titer to influenza virus A (H1N1 and H3N2) and B at Weeks −4, 0, 4, 8, 12, and 24.

7. Main results

The H3N2 antibody titer was significantly higher in the juzentaihoto arm (Arm 1) than in the control arm (Arm 2) at 8 weeks after vaccination (P=0.0229), and rose still higher at Weeks 4, 12, and 24. In addition, the antibody titer from Weeks 4 to 24 was significantly higher in Arm 1 than in Arm 2 (P=0.0468). There was no significant inter-arm difference in antibody titers to H1N1 or B at any post-vaccination week.

8. Conclusions

Juzentaihoto increases and maintains the titer of influenza antibodies especially those specific for H3N2.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Epigastric discomfort was reported in one subject after administration of juzentaihoto, but improved after discontinuation of administration. There were no significant changes in serum chemistry values in the two arms.

11. Abstractor's comments

Notably, this RCT demonstrated significantly higher anti-H3N2 antibody titers at Week 8 after vaccination in elderly people, at high risk for influenza infection, treated with juzentaihoto from 4 weeks before to 24 weeks after vaccination, a total of 28 weeks. Although a previous RCT of maobushisaishinto had reported that anti-H3N2 antibody titers were significantly higher at Week 4, it did not report this effect after Week 4. In another RCT, hochuekkito did not significantly increase antibody titer. These preceding studies and the present study differed in the Kampo products selected, treatment period, target subjects, etc. Especially, the present study included subjects with the mean age of 85.6 years who had experienced the outbreaks of H3N2 in 1968 to 1969, which elicited a strong post-vaccination response. Previously, the adjuvanticity of juzentaihoto was demonstrated in a basic study. This is the first RCT to clinically evaluate the effect of juzentaihoto on enhancing production of influenza antibody.

12. Abstractor and date

Motoo Y, 31 March 2017.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Watanabe N, Miyazawa T. Comparative investigation of the antitussive effects of bakumondoto and tipepidine hibenzate in cases of mycoplasma bronchitis. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2007; 21: 31-6 (in Japanese with English abstract).

Watanabe N, Nakagawa T, Miyazawa T. Examination of effective antitussive against cough caused by mycoplasma bronchitis. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2008; 22: 63-8 (in Japanese with English abstract).

1. Objectives

To compare the efficacy of bakumondoto (麦門冬湯) with that of tipepidine hibenzate for suppressing cough in patients with mycoplasmal bronchitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

An internal medicine department in a hospital (the authors belong to the faculty of the Division of Respiratory and Infectious Diseases, Department of Internal Medicine, St. Marianna University School of Medicine), japan.

4. Participants

Twenty patients with mycoplasma bronchitis who exhibited no signs of pneumonia on chest radiographs.

5. Intervention

Arm 1: azithromycin 500 mg for 3 days and TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. for 2 weeks (n=6).

Arm 2: azithromycin 500 mg for 3 days and tipepidine hibenzate 60 mg for 2 weeks (n=8).

Arm 3: azithromycin 500 mg for 3 days, tipepidine hibenzate 60 mg for 2 weeks, and TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. for 2 weeks (n=6).

6. Main outcome measures

Cough score, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein (CRP) level.

7. Main results

In arms 1 and 3, cough score was significantly decreased on day 5 compared with day 1 after the first visit (P<0.05). In arm 2, cough score was significantly decreased on day 7 (P<0.05). The rate of cough score decline was significant on day 5 in arms 1 and 3 (P<0.05) and on day 11 in arm 2 (P<0.05). The cumulative decline in cough score from day 1 to day 14 was highest in arm 3. There were no significant differences in white blood cell count, erythrocyte sedimentation rate, and CRP level.

8. Conclusions

Combination therapy with azithromycin and bakumondoto or tipepidine hibenzate appears to be effective in the treatment of cough in patients with mycoplasma bronchitis. In addition, triple therapy with azithromycin, bakumondoto, and tipepidine hibenzate may be similarly effective.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Persistent cough in mycoplasma bronchitis is often difficult to treat. This interesting study evaluates the efficacy of azithryomycin combined with bakumondoto and/or tipepidine hibenzate in treating cough in mycoplasma bronchitis in a randomized controlled trial. However, it uses allocation by the envelope method (which likely leads to difficulty in preserving randomization) and lacks a placebo-group as control. Furthermore, to determine the differences in efficacy among the three arms, post-administration cough scores must be compared among the three arms. In addition, some participants have persistent cough even after 2 weeks in all three arms. In future studies, Kampo "*sho*" (証, pattern) should be considered for bakumondoto.

12. Abstractor and date

Okabe T, 8 December 2009, 1 June 2010, 31 December 2013.

2. Infections (including Viral Hepatitis)
10. Respiratory Diseases (including Influenza and Rhinitis)

References

Watanabe N, Makino S, Nakagawa T, et al. Efficacy of bakumondoto on cough in mycoplasma infection. *Science of Kampo Medicine* 2017; 41: 116-8 (in Japanese). Ichushi Web ID: 2017285714

1. Objectives

To evaluate the efficacy of bakumondoto（麦門冬湯）on cough in mycoplasma bronchitis

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

Study sites not stated (authors' institutions: a research center and clinics), Japan.

4. Participants

Twenty-four patients who presented with persistent cough, who underwent chest X-ray that excluded pneumonia findings such as ground-glass opacity, and who had an increased mycoplasma antibody titer (PA method) of 1:80 or above and thus were clinically considered as having mycoplasma bronchitis, and were started on treatment with azithromycin hydrate 500 mg once daily for 3 days.

5. Intervention

Arm 1: oral administration of TSUMURA Bakumondoto（麦門冬湯）Extract Granules 3 g t.i.d. for 2 weeks (n=7)
Arm 2: oral administration of tipepidine hibenzate 20 mg t.i.d. for 2 weeks (n=9)
Arm 3: oral administration of TSUMURA Bakumondoto（麦門冬湯）Extract Granules 3 g plus tipepidine hibenzate 20 mg, t.i.d. for 2 weeks (n=8)

6. Main outcome measures

Change in the cough score

7. Main results

The cough score significantly decreased on day 4 in the bakumondoto group, on day 7 in the tipepidine hibenzate group, and on day 4 in the bakumondoto + tipepidine hibenzate group ($P<0.05$ for all).

8. Conclusion

Add-on use of bakumondoto to a macrolide antimicrobial agent is effective for cough in mycoplasma bronchitis. In particular, combination use of bakumondoto plus a central antitussive agent more promptly alleviates cough in mycoplasma infection.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

This is a meaningful article on evaluation of the effect of bakumondoto on persistent cough as a common complaint in the context of mycoplasma infection. Drawbacks include lack of statement about the specific scale used for the cough scoring, which makes the symptomatic course assessments difficult. In addition, because of lack of intergroup comparison, assessment of the effect of the intervention with bakumondoto is also difficult. A question also remains whether mycoplasma infection can be diagnosed only from a mycoplasma PA antibody titer in single serum of 1:80 or above (rather than 1:320 or above) without a paired serum and without chest X-ray opacity. The authors concluded that combination use of bakumondoto plus a central antitussive agent is useful, but did not specify how the results led to this conclusion. Efficacy of bakumondoto on cough is generally discussed, but has rarely been investigated by RCTs, and such studies are meaningful. Future studies designed to compare symptomatic changes between treatment arms are awaited. Also, while determination of causative bacteria is often difficult in clinical practice, further studies with determination of causative organisms or evolutionary studies without determination of causative organisms would be warranted.

12. Abstractor and date

Koike H, 1 June 2020.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Ohya Y. Kampo treatment for allergic diseases -from the viewpoint of a general hospital-. *Progress in Medicine* 1988; 8: 604–12 (in Japanese).

Ohya Y. Efficacy of preseasonal administration of shoseiryuto for cedar pollen allergy*. Kampo Shinryo 1991; 10: 42–8 (in Japanese).

1. Objectives

To evaluate the preventive effect and safety of preseasonal administration of syoseiryuto (小青竜湯) against cedar pollen allergy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (a department of otolaryngology), Japan.

4. Participants

Patients with cedar pollen allergy of mild or less severity (n=43).

5. Intervention

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3 mg t.i.d. for 57 days (n=23).
Arm 2: ketotifen 1 g b.i.d. for 57 days (n=20).
Treatment period was from 7 February to 4 April 1987.

6. Main outcome measures

Change in subjective nasal symptoms was graded on a scale of 1–4 before and during the pollen dispersal period.

7. Main results

The data of 29 patients who completed nasal allergy diaries (15 in arm 1 and 14 in arm 2) were analyzed. There were no significant between-arm differences in moderate or better improvement effects on the following symptoms: sneezing (66.7% in arm 1, 64.3% in arm 2), nasal discharge (60% in arm 1, 57.1% in arm 2), nasal obstruction (86.7% in arm 1, 85.7% in arm 2), and overall nasal symptoms (66.7% in arm 1, 64.3% in arm 2).

8. Conclusions

Preventive effects of shoseiryuto and ketotifen on cedar pollen allergy are equivalent.

9. From Kampo medicine perspective

Among the 15 patients in the shoseiryuto arm, 1 patient had *jitsu-sho* (実証, excess pattern) and 14 patients had *chukan-sho* (中間証, intermediate pattern).

10. Safety assessment in the article

Mild diarrhea was observed in 1 patient in arm 1.

11. Abstractor's comments

This randomized controlled trial demonstrated that the clinical effectiveness of shoseiryuto for preventing mild cedar pollen allergy was equivalent to that of the oral anti-allergy drug ketotifen. The flaw in this study is that the endpoint is not objective. Change in the subjective nasal symptoms is judged from patients' nasal allergy diaries. Also the patients enrolled in this study have mild or less severity disease and therefore the results of this study should be evaluated with caution. Shoseiryuto is expected to prevent cedar pollen allergy in patients with the appropriate *sho*. However, further clinical trials considering this point are awaited.

12. Abstractor and date

Okabe T, 18 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Mori H. Comparative study of Kampo preparations sho-seiryu-to and ryokankyomishingenin-to for nasal allergy. *Therapeutic Research* 1996; 17: 3691-6 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To evaluate the effects of shoseiryuto (小青竜湯) and ryokankyomishingeninto (苓甘姜味辛夏仁湯) on spring nasal allergy (pollinosis).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital and two clinics, Japan.

4. Participants

Forty-one patients who were first diagnosed with pollinosis from January 25, 1996 to April 1, 1996.

5. Intervention

Arm 1: TSUMURA Ryokankyomishingeninto (苓甘姜味辛夏仁湯) Extract Granules 2.5 g t.i.d., 20 patients enrolled, 15 patients analyzed.
Arm 2: TSUMURA Shoseiryuto (小青竜湯) Extract Granules 3.0 g t.i.d., 21 patients enrolled, 15 patients analyzed.
Group assignment in the order of receipt; concomitant use of Intal Nasal Drops (sodium cromoglycate) for severe symptoms.

6. Main outcome measures

Improvement in sneezing, runny nose, and nasal congestion.

7. Main results

There was no significant between-arm improvement in sneezing, runny nose, or nasal congestion.
Improvement was mild or better in 66.7% and 80.0% of patients in Arms 1 and 2, respectively, indicating no significant between-arm difference.

8. Conclusions

Ryokankyomishingeninto and shoseiryuto have similar efficacy for pollinosis, but shoseiryuto has more efficacy for nasal congestion.

9. From Kampo medicine perspective

Kyo-sho (虚証, deficiency pattern) patients were excluded.

10. Safety assessment in the article

One patient treated with ryokankyomishingeninto developed leg edema and gained body weight but had no abnormal hematology findings. Shoseiryuto was not associated with any problems.

11. Abstractor's comments

Dr. Mori has published several articles comparing Kampo preparations with shoseiryuto as control in the treatment of pollinosis. Clarification of the differences in the characteristics of Kampo preparations based on these data would be a great help to those who practice Kampo medicine.

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Mori H, Shimazaki Y, Kurata H, et al. Comparative study of Kampo preparations sho-seiryu-to and eppika-jutsu-to for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1997; 18: 3093-9 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of shoseiryuto (小青竜湯) and eppikajutsuto (越婢加朮湯) for spring allergic rhinitis (pollinosis).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One clinic, Japan.

4. Participants

One hundred thirty-five patients who were first diagnosed with pollinosis from January 27, 1997 to April 5, 1997. *Kyo-sho* (虚証, deficiency pattern) patients were excluded.

5. Intervention

Arm 1: JPS Shoseiryuto (小青竜湯) Extract Granules 2.5 g t.i.d. (68 patients enrolled, 45 patients analyzed).
Arm 2: JPS Eppikajutsuto (越婢加朮湯) Extract Granules 2.5 g t.i.d. (67 patients enrolled, 49 patients analyzed).
Assignment in the order of receipt; concomitant use of Intal Nasal Drops/Eye Drops (sodium cromoglycate) for severe symptoms.

6. Main outcome measures

Measures of improvement in sneezing, runny nose, nasal congestion, periocular itching, lacrimation, eye discharge, and eye pain.

7. Main results

No significant between-arm difference was observed in any symptom except runny nose, which was significantly improved in arm 1.
Mild or better improvement was achieved in the severity of periocular itching (55.6% and 65.3%) and lacrimation (13.3% and 16.3%), and moderate or better global improvement was achieved in the severity of nasal symptoms (53.3% and 67.3%) in arms 1 and 2, respectively. There was no significant between-arm difference in the percentage of patients with improved symptoms.

8. Conclusions

Both eppikajutsuto and shoseiryuto had effects on pollen allergy without significant difference between them.

9. From Kampo medicine perspective

Since shoseiryuto is used in *chukan –sho* (中間証, intermediate pattern) to *jitsu -sho* (実証, excess pattern) patients, and eppikajutsuto is used in physically strong patients, physically weak patients were excluded. Eppikajutsuto, which contains *Sekko* (石膏, gypsum), is intended to reduce fever-related symptoms such as periocular itching, hyperemia, or skin warmth.

10. Safety assessment in the article

Epigastric pain and nausea occurred in 1 patient treated with eppikajutsuto, and rash occurred in 1 patient treated with shoseiryuto.

11. Abstractor's comments

Dr. Mori's articles on pollinosis have focused on shoseiryuto. Refer to "Baba S, Takasaka T, Inamura N et al. Efficacy of shoseiryuto for perennial nasal allergy - double-blind controlled study - *Jibiinkoka Rinsho* (*Practica otologica*) 1995; 88: 389-405".

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Mori H. Comparative study of Kampo preparations sho-seiryu-to and dai-seiryu-to for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1998; 19: 3299-307 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of shoseiryuto (小青竜湯) and daiseiryuto (大青竜湯) (keishito plus makyokansekito) (桂枝湯合麻杏甘石湯) for spring allergic rhinitis (pollinosis).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One clinic, Japan.

4. Participants

Fifty-six patients who were first diagnosed with pollinosis from January 26, 1998 to April 9, 1998. *Kyo-sho* (虚証, deficiency pattern) patients were excluded.

5. Intervention

Arm 1: Kotaro Shoseiryuto (小青竜湯) Extract Fine Granules 2.5 g t.i.d. (28 patients enrolled, 15 patients analyzed).

Arm 2: Daiseiryuto (大青竜湯) (Kotaro Keishito [桂枝湯] Extract Fine Granules 5 g + Kotaro Makyokansekito [麻杏甘石湯] Extract Fine Granules 9 g) 14.0 g/day in three divided doses (28 patients enrolled, 24 patients analyzed).

Group assignment in the order of receipt; concomitant use of Intal Nasal Drops/Eye Drops (sodium cromoglycate) for severe symptoms.

6. Main outcome measures

Measures of severity of sneezing, runny nose, nasal congestion, periocular itching, lacrimation, eye discharge, and eye pain.

7. Main results

There was no significant between-arm improvement in symptoms.

Overall improvement (in severity of nasal symptoms) was mild or better in 46.7% and 87.5% of patients in Arms 1 and 2, respectively, and significantly different between arms.

8. Conclusions

Shoseiryuto and daiseiryuto have similar efficacy for individual symptoms; daiseiryuto has significantly greater clinical efficacy than shoseiryuto for overall symptoms.

9. From Kampo medicine perspective

Since shoseiryuto is used in *chukan-sho* (中間証, intermediate pattern) to *jitsu-sho* (実証, excess pattern)patients, physically weak patients were excluded. Because “Mori H, Shimazaki Y, Kurata H, et al. Comparative study of Kampo preparations Sho-Seiryu-To and Eppika-Jutsu-To for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1997; 18: 3093-9 (in Japanese with English abstract)” showed that eppikajutsuto was effective for pollinosis, daiseiryuto (containing mao [麻黄, ephedra herb]and sekko [石膏, gypsum], constituent crude drugs of eppikajutsuto) was used in this controlled trial.

10. Safety assessment in the article

One patient treated with daiseiryuto experienced hand, foot, and eyelid edema and body weight gain, which were later found to be associated with pseudoaldosteronism.

11. Abstractor’s comments

Dr. Mori’s articles on pollinosis have focused on shoseiryuto. Refer to “Baba S, Takasaka T, Inamura N et al. Efficacy of shoseiryuto for perennial nasal allergy - double-blind controlled study - *Jibiinkoka Rinsho* (*Practica otologica*) 1995; 88: 389-405”.

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Mori H, Kurata H, Shimazaki Y, et al. Comparative study of Kampo preparations sho-sei-ryu-to and kei-ma-kakuhan-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 1999; 20: 2941-7 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To compare the efficacy of shoseiryuto (小青竜湯), and keimakakuhanto (桂麻各半湯) in treating springtime nasal allergy and allergic conjunctivitis.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

From 25 January 1999 until 10 April 1999.
One hospital and three clinics of internal medicine, Japan.

4. Participants

Eighty eight patients with springtime nasal allergy and allergic conjunctivitis. Of these patients, 65 were included for analysis.

5. Intervention

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3.0 g, t.i.d. for 2 weeks, n=32.
Arm 2: keimakakuhanto (桂麻各半湯) 8.0 g/day in three divided doses (4.0 g of TSUMURA Keishito (桂枝湯) Extract Granules [TJ-45] + 4.0 g of TSUMURA Maoto (麻黄湯) Extract Granules [TJ-27]) for 2 weeks, n=33.

6. Main outcome measures

Improvement in each symptom and global improvement.

7. Main results

Efficacy (percent improvement in arm 1 and arm 2, respectively) was observed against sneezing (68.8% and 66.7%), rhinorrhea (56.3% and 63.6%), nasal sinus obstruction (40.6% and 30.3%), and periocular pruritus (46.9% and 54.5%); there was no significant difference in between-arm improvements.
As for global improvement, 62.5% and 60.6% of patients in arm 1 and arm 2, respectively, were rated "moderately-to-markedly improved," demonstrating no significant between-arm difference in efficacy.

8. Conclusions

Keimakakuhanto is as effective as shoseiryuto in treating springtime nasal allergy and allergic conjunctivitis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In the shoseiryuto arm, two subjects reported dry mouth, one reported gastric distension, and one reported stomach discomfort leading to discontinued administration; and in the keimakakuhanto arm, one reported dry mouth and one discontinued administration because of nausea.

11. Abstractor's comments

As of 1999, no definite evidenced-based medicine (EBM) approach had been used to study the efficacy of Kampo formulations in treating springtime nasal allergy and allergic conjunctivitis. This paper presents a comparative study of the efficacies of two Kampo medicines, and further placebo-controlled analysis is awaited.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Yoshimoto T, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and maoh-bushi-saisin-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 2002; 23: 2253-9 (in Japanese with English abstract). Ichushi Web ID: 2003161479 MOL, MOL-Lib

1. Objectives

To compare the effects of shoseiryuto (小青竜湯) and maobushisaishinto (麻黄附子細辛湯) in treating springtime nasal allergy and allergic conjunctivitis.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Five clinics of internal medicine, Japan.

4. Participants

Of the patients who visited the above-mentioned clinics for the first time with springtime nasal allergy and allergic conjunctivitis (allergic rhinitis), 66 having previously diagnosed pollen hypersensitivity/pollinosis or newly diagnosed rhinitis with increased eosinophils in nasal discharge and elevated IgE level were enrolled. Exclusion criteria were: "*kyo-sho* (虚証, deficiency pattern)," sinusitis, nose disorders such as nasal septal deviation, conjunctivitis other than allergic conjunctivitis, pregnancy, and refusal to take Kampo medicines.

5. Intervention

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-019) 3.0 g t.i.d., n=34.
Arm 2: TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules (TJ-127) 2.5 g t.i.d., n=32.
Concomitant drug use was prohibited, with the exception of Intal eye drops or nasal spray for severe and intolerable symptoms.

6. Main outcome measures

Symptom improvement: Each of nose and eye symptoms after 2-week administration was rated on a 5-point scale (markedly improved, moderately improved, slightly improved, unchanged, and aggravated).
Global improvement: The severity of illness (nose and eye symptoms) after 2-week administration, compared with that before treatment, was rated on a 5-point scale (as maobushisaishinto acts rapidly, change in the symptoms was recorded beginning one week after the initiation of treatment.)
Overall safety: Adverse drug reactions after 2-week administration were evaluated on a 5-point scale.
Usefulness: The global improvement combined with overall safety was assessed on a 5-point scale (very useful, useful, slightly useful, indiscernible, and useless).

7. Main results

Slight-to-marked (or moderate-to-marked) improvement was seen in each of the following symptoms: sneezing (41.2% and 59.4% in arms 1 and 2, respectively), rhinorrhea (47.1% and 53.1%), nasal obstruction (58.8% and 37.5%), periocular pruritus (35.3% and 45.2%), lacrimation (23.5% and 19.4%), and ocular discharge (11.8% and 9.7%). The chi-square test and Mann-Whitney *U* test revealed no significant differences in improvement of any symptoms between the two arms. Also, there was no significant difference between the arms in global improvement (slight-to-marked global improvement in 67.6% and 71.9% for arms 1 and 2, respectively, and moderate-to-marked global improvement, 52.9% and 53.1%). As for usefulness, interventions were assessed to be "useful or very useful" in 50% for arm 1 and 50% for arm 2, with no significant between-arm difference.

8. Conclusions

Maobushisaishinto is suggested to be as effective as shoseiryuto in treating springtime nasal allergy and allergic conjunctivitis.

9. From Kampo medicine perspective

Maobushisaishinto is more suitable than shoseiryuto for treating subjects with "*kyo-sho*," who are frail or elderly.

10. Safety assessment in the article

No adverse drug reactions were observed in either arm.

11. Abstractor's comments

This study followed a RCT of shoseiryuto for nasal allergy and allergic conjunctivitis in spring (*Jibiinkoka Rinsho* [*Practica otologica*] 1995; 88: 389-405 [in Japanese]), and uses the same outcome measures. However, patients were allocated sequentially and not properly randomized, making this study a clinical controlled trial (CCT: quasi-RCT). Results with no significant differences in this study provide a new therapeutic option for springtime nasal allergy and allergic conjunctivitis, and can be regarded as clinically meaningful.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Shimazaki Y, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and go-ko-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 2001; 22: 2385-91 (in Japanese with English abstract). Ichushi Web ID: 2002138087 MOL, MOL-Lib

1. Objectives

To compare the effects of shoseiryuto (小青竜湯) and gokoto (五虎湯) in subjects with nasal allergy and allergic conjunctivitis in spring.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital and four clinics, Japan.

4. Participants

Patients with nasal allergy and allergic conjunctivitis in spring who had increased nasal eosinophil count and high IgE level, n=116.

5. Intervention

Patients who visited the setting of this study for the first time between 31 January 2000 and 10 April 2000 were recruited. Patients with severe symptoms were treated with Intal (sodium cromoglicate) nasal drops and eye drops. Assessments were done after two weeks of administration of one of the following.
Arm 1: Tsumura Gokoto (五虎湯) Extraction Granules 2.5 g, t.i.d., n=58.
Arm 2: Tsumura Shoseiryuto (小青竜湯) Extraction Granules 3.0 g, t.i.d., n=58.

6. Main outcome measures

Nasal symptoms: sneezing, discharge, and obstruction. Ocular symptoms: eyelid itching, tearing, eye discharge, and orbital pain.

7. Main results

Ten subjects in arm 1 and 17 in arm 2 who stopped visiting hospital/clinic and 1 subject in arm 1 who discontinued drug administration because of adverse effect were excluded. Though not significantly different between arms, the efficacy rates were higher in arm 2 for all outcome measures except eye discharge and orbital pain, which were higher in arm 1.

8. Conclusions

There was no significant between-arm difference in treatment usefulness, with usefulness in 70.8% of arm 1 and 80.5% of arm 2 was characterized as moderate or more than moderate.

9. From Kampo medicine perspective

Subjects with *kyosho* (虚証, deficiency pattern） were excluded because shoseiryuto and gokoto are used to treat subjects with *jitsusho* (実証, excess pattern) or *chukansho* (中間証).

10. Safety assessment in the article

Adverse effects included dry mouth (n=5), abdominal pain (n=1), hard stool (n=1), palpitation (n=1, excluded from analysis) in arm 1, and dry mouth (n=1) and constipation (n=1) in arm 2.

11. Abstractor's comments

The authors also compare Kampo drugs for allergic rhinitis or nasal allergy and allergic conjunctivitis in spring in several previous papers, which should be read together.

12. Abstractor and date

Fujisawa M, 15 January 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Baba S, Takasaka T, Inamura N, et al. Double-blind clinical trial of Sho-seiryu-to (TJ-19) for perennial nasal allergy. *Jibiinkoka Rinsho* (*Practica otologica*) 1995; 88: 389–405 (in Japanese with English abstract). CENTRAL ID: CN-00192055, Ichushi Web ID: 1995184251

1. Objectives

To evaluate the efficacy and safety of shoseiryuto (小青竜湯) for perennial nasal allergy.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Twenty-six university hospitals and 35 other hospitals, Japan.

4. Participants

Patients with perennial nasal allergy who visited otolaryngologists in 61 hospitals in the 8-month period from June 1993 to January 1994 (n=220).

5. Intervention

The package and appearance of the placebo were indistinguishable from those of shoseiryuto.
Duration of administration was 2 weeks. On-demand use of clemastine fumarate was permitted in case the symptoms were severe.
Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules, 3.0 g t.i.d. (n=110).
Arm 2: placebo 3.0 g t.i.d. (n=110).

6. Main outcome measures

Overall general improvement, improvements in each symptom, safety, and the relationship between body-constitution and efficacy.

7. Main results

The number of subjects analyzed was 186 for overall general improvement, 217 for general safety, and 189 for usefulness. In arm 1, general improvement was high in 12.0% of the patients and moderate in 32.6%, and was significantly greater than in arm 2 (5.3% and 12.8%, respectively). Patients in arm 1 had significantly greater improvement in sneezing, nasal discharge, and nasal obstruction.
The efficacy of shoseiryuto was significantly higher in those with “average” or “muscular and strongly built” body type, “average to pale” facial color, “average” voice, “neither hot nor cold” or “sensitive to heat” cold or hot constitution, “warm” or “average” hands and feet, and “excess” or “average” sweating, as determined from questionnaire responses.

8. Conclusions

Shoseiryuto has significantly better efficacy (overall general improvement, improvements in each symptom, and usefulness).

9. From Kampo medicine perspective

The targets of shoseiryuto are watery and foamy phlegm, watery nasal discharge, and sneezing, in other words, the symptoms of allergic rhinitis.

10. Safety assessment in the article

Adverse reactions possibly related to the administered drug were observed in 6.4% of the placebo group and 6.5% of the shoseiryuto group. Patients treated with shoseiryuto had mild symptoms (digestive symptoms, headache, and facial edema), and one patient had mild elevations in GOT and GPT, neither of which led to the discontinuance of administration.

11. Abstractor’s comments

This is a full-scale, nationwide, and large RCT.

12. Abstractor and date

Fujisawa M, 15 October 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nakai Y, Ohashi Y, Esaki Y, et al. Clinical evaluation of maobushisaishinto for nasal allergy*. *Jibi-inkouka Tenbou* (*Oto-Rhino-Laryngology*, Tokyo) 1990; 33: 655–73 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of maobushisaishinto (麻黄附子細辛湯) extract granules prepared based on *Shanghanlun* (傷寒論, *Treatise on Cold Damage Diseases*) and conventionally-prepared maobushisaishinto extract powder in the treatment of perennial nasal allergy.

2. Design

Quasi-randomized controlled trial (quasi-RCT), Japan.

3. Setting

Departments of otorhinolaryngology of 5 university hospitals and 10 general hospitals (including Osaka City University Hospital, Teikyo University Mizonokuchi Hospital, and Nagoya City University Hospital).

4. Participants

One hundred and fifty-five patients with moderate or severe perennial nasal allergy.

5. Intervention

Arm 1: oral treatment with Kotaro Maobushisaishinto (麻黄附子細辛湯) Extract Fine Granules (content of currently-available capsule formulation) 1 g t.i.d. for 4 weeks (n=74).

Arm 2: oral treatment with Kotaro Maobushisaishinto (麻黄附子細辛湯) Extract Powder (old product: currently not available) 2 g t.i.d. for 4 weeks (n=81).

6. Main outcome measures

Nasal symptoms (paroxysmal sneezing, nasal discharge, nasal congestion, olfactory disturbance, interference with activities of daily living), rhinoscopic findings, severity, and nasal allergy tests (skin reaction, nasal provocation test, eosinophil count in nasal discharge).

7. Main results

Efficacy analyses revealed marked or moderate response in 28 out of 52 patients (53.8%) included in arm 1 and 27 out of 59 (45.8%) included in arm 2 at 2 weeks, and in 33 of 44 (76.7%) in arm 1 and 33 of 52 (63.5%) in arm 2 at 4 weeks; there was no between-arm difference at both time points.

8. Conclusions

The efficacy of maobushisaishinto extract powder prepared by the conventional method for perennial nasal allergy is comparable to that of maobushisaishinto extract fine granules prepared on the basis of *Shanghanlun*.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In patients who received maobushisaishinto extract powder, 4 (6.15%) experienced adverse reactions: gastrointestinal symptoms in 3 (stomach ache, anorexia, nausea, and dysgeusia) and sleepiness in 1. In patients who received maobushisaishinto extract fine granules, 3 (5.17%) experienced adverse reactions: gastrointestinal symptoms in 2 (gastric distress, dry mouth) and headache/heaviness of the head in 1.

11. Abstractor's comments

It is noteworthy that this multicenter controlled clinical trial demonstrated equivalent efficacy of two different maobushisaishinto formulations for perennial nasal allergy. Outcomes were assessed using not only subjective symptoms but also objective measures (such as rhinoscopic findings) and the results are highly reliable. Unfortunately, the randomization in this study seems to be flawed. A randomized controlled trial including placebo and an active reference is desired.

12. Abstractor and date

Okabe T, 18 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Sakurada T, Ikeda K, Takasaka T, et al. Clinical effectiveness of Kampo medicine for chronic rhinitis and sinusitis. *Jibiinkoka Rinsho* (*Practica otologica*) 1992;85:1341–6 (in Japanese with English abstract).

1. Objectives

To determine the effectiveness of Kampo medicines for chronic rhinitis and sinusitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university and 5 hospitals, Japan.

4. Participants

Six patients with non-allergic chronic rhinitis and 61 with chronic sinusitis who first visited the participating institutions between November 1989 and June 1990.

5. Intervention

Arm 1: oral administration of TSUMURA Shin'iseihaito (辛夷清肺湯) Extract Granules 2.5 g t.i.d. before meals for 4-8 weeks (n=39).

Arm 2: oral treatment with TSUMURA Shigyakusan (四逆散) Extract Granules 2.5 g t.i.d. before meals for 4-8 weeks (n=28).

6. Main outcome measures

Severity of subjective symptoms: rhinorrhea, ease of nose blowing, postnasal drip, nasal obstruction, heaviness of head (headache), and olfactory disturbance.

Objective findings: redness and edema of the nasal mucosa, characteristics of nasal discharge.

Examinations: neutrophil count in nasal discharge, rhinomanometry.

7. Main results

Improvement in subjective symptoms was at least mild in 76.3% and 59.3% of patients in arms 1 and 2, respectively; the between-arm difference was not significant. Improvements in objective findings were not significantly different between arm 1 (60.5%) and arm 2 (70.4%). There were no significant between-arm differences in neutrophil count, nasal discharge, and rhinomanometric results.

8. Conclusions

The preceding paper was Ikeda K, Takasaka T, Kusakari J, et al. Outcome of treatment with Leftose (lysozyme hydrochloride) for chronic sinusitis – a comparison of clinical efficacy in adults versus children -. *Jibiinkoka Rinsho* (*Practica otologica*) 1984;77:1863–69. The present study revealed that Kampo medicines had efficacy comparable with that of Leftose (i.e., mild or greater improvement in 63% of patients with chronic sinusitis).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One shin'iseihaito-treated patient had chest distress, which was considered unlikely to be related to the drug.

11. Abstractor's comments

In the treatment of chronic sinusitis, long-term low-dose administration of 14-membered ring macrolide antibiotics became available around 1990 and now these antibiotics are used as standard conservative therapy. Anti-inflammatory enzymes, including Leftose, were commonly used before 1990 and otology physicians reported reasonably adequate efficacy of these drugs. Now they are combined with these antibiotics to relieve symptoms.

12. Abstractor and date

Fujisawa M, 1 June 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Suzuki S, Furukawa H, Ami H, et al. Experience with TSUMURA Saibokuto (TJ-96) in patients who underwent thyroid or parathyroid surgery*. *Progress in Medicine* 1994; 14: 2254–8 (in Japanese). Ichushi Web ID: 1995247312

1. Objectives

To determine the efficacy of saibokuto (柴朴湯) for relieving complaints after thyroid or parathyroid surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution: the outpatient clinic of the Second Department of Surgery, Fukushima Medical University, Japan.

4. Participants

Seventy-seven patients who underwent excision via a collar incision for thyroid or parathyroid disease at the above institution.

5. Intervention

Arm 1: oral treatment with TSUMURA Saibokuto (柴朴湯) Extract Granules 1 pack (2.5 g) t.i.d. before meals for 90 days after the surgery (n=40).

Arm 2: no treatment with Kampo medicines (n=37).

6. Main outcome measures

Clinical examination: flap blood flow at 4 sites on the body surface and flow index (by a laser tissue blood flowmeter) were measured before and 1, 4, 7, and 90 days after surgery.

Improvement in clinical symptom scores: neck and systemic symptoms were evaluated on a 4-point scale using a health questionnaire at 1, 2, and 3 months after surgery.

7. Main results

The improvement in neck tenderness and pain on swallowing was significantly greater in arm 1 than in arm 2 at 2 months after surgery ($P<0.01$ and $P<0.05$, respectively). The improvement in the systemic symptoms (fatigue and insomnia) tended to be greater in arm 1. The between-arm differences in improvements disappeared by 3 months after surgery. For patients who underwent subtotal thyroidectomy or parathyroidectomy, flap blood flow was increased significantly at 4 and 7 days after surgery in arm 1 ($P<0.05$), and there was a trend of increase in flow index at 90 days in arm 2. For patients who underwent total thyroidectomy or parathyroidectomy, there were no significant between-arm differences in flap blood flow and flow index after surgery.

8. Conclusions

Saibokuto is effective for relieving neck symptoms after cervical surgery, possibly by increasing not only flap blood flow at the wound site but also systemic blood flow.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

After cervical surgery, symptoms considered as targets of saibokuto treatment, including neck tenderness or discomfort and difficulty swallowing, frequently develop. The aim of the present study was to evaluate the efficacy of saibokuto for relieving those symptoms. The main feature of this study is that all the enrolled patients had undergone thyroid or parathyroid surgery. The improvements in neck symptoms were obviously greater in the saibokuto-treated group at 2 months but not 3 months after surgery. From this, it is speculated that saibokuto may accelerate healing and thereby increase blood flow. Future investigations are expected to be from an oriental medicine perspective and to include i) oriental medical pathology during the period of maximum efficacy and ii) a study of the dependence of efficacy on *sho* (証, pattern).

12. Abstractor and date

Ushiroyama T, 6 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Miyamoto T, Inoue H, Kitamura S, et al. Effect of TSUMURA Sho-seiryu-to (TJ-19) on bronchitis in a double-blind placebo-controlled study. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicine)* 2001; 17: 1189-214 (in Japanese with English abstract). Ichushi Web ID: 2002029631, MOL, MOL-Lib

Miyamoto T. Clinical effectiveness of shosei-ryuto in bronchitis. *Pharma Medica* 2007; 25: 23-5 (in Japanese). Ichushi Web ID: 2008035989 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of shoseiryuto (小青竜湯) in the treatment of bronchitis.

2. Design

Doule-blind, randomized controlled trial (DB-RCT).

3. Setting

Seventeen university hospitals, forty-two hospitals, and three clinics, Japan.
From December 1994 until March 1999.

4. Participants

Patients aged 16 to <65 years with mild to moderate bronchitis, and evaluable symptoms (any of watery sputum, rales/rhonchi, and cough).

5. Intervention

The concomitant use of other drugs was prohibited with the exception of dimemorfan phosphate (Astomin) after day 4.
Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3.0 g t.i.d. for 7 days, n=101.
Arm 2: placebo 3.0 g t.i.d. for 7 days, n=91.

6. Main outcome measures

Global improvement (rate), improvement of bronchitis symptoms (such as cough and sputum), and safety.

7. Main results

At the end of treatment, there was a trend toward higher percentage of patients with moderate-to-marked global improvement in arm 1, compared with arm 2 (57.4% in arm 1 *vs* 42.9% in arm 2; *P*=0.06. No significant difference was observed at day 3 or 4. As for improvement of each symptom, ease of raising sputum, properties of sputum (purulent, viscous, etc.), and disturbance in activities of daily living, was significantly better in arm 1 at days 3-4. At the end of treatment, there was significant improvement in frequency of coughing, intensity of coughing, ease of raising sputum, and activities of daily living, and a tendency toward improvement in sneezing and nasal obstruction in arm 1.

8. Conclusions

Shoseiryuto is effective for bronchitis with mild symptoms.

9. From Kampo medicine perspective

Inclusion criteria of patients with watery sputum, rales/rhonchi, and/or cough were chosen to adopt the "*sho* (証, pattern)" for shoseiryuto in Kampo medicine. Further subgroup analyses in patients without physical frailty and those with cough and watery sputum showed a significantly higher rate of global improvement in arm 1 than arm 2.

10. Safety assessment in the article

The incidence of adverse effects was 6.7% (7 cases) in arm 1 and 9.9% (9 cases) in arm 2, with no significant difference. No serious adverse effects were found.

11. Abstractor's comments

This is a full-scale DB-RCT that addresses Kampo patterns. The authors carry out sub-group analyses based on patterns, in accordance with the clinical guidelines for re-evaluation of Kampo formulations, as indicated in Harumi K, et al.: 1991 Report of the Kampo extract formulation clinical evaluation methods research group, *Japanese Journal of Clinical Pharmacology and Therapeutics*, 1991; 22: 781–91 (in Japanese). The study finds that improvement was greater in the group with watery sputum and cough. These guidelines for the clinical evaluation of Kampo formulations ought to be more widely known and used.

12. Abstractor and date

Fujisawa M, 15 June 2007, 22 February 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Sasaki H, Sato K, Sasaki M, et al. Usefulness of bakumondo-to in senile, chronic respiratory disease patients having difficulty in expectoration: comparison with bromhexine hydrochloride preparations. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1993; 7: 139–45 (in Japanese with English abstract).

1. Objectives

To evaluate the effectiveness of bakumondoto (麦門冬湯) in loosening phlegm in comparison with a bromhexine hydrochloride preparation.

2. Design

Randomized controlled trial using sealed envelopes for allocation method (RCT-envelope).

3. Setting

One university hospital and six hospitals, Japan.

4. Participants

Patients aged 65 years or older with difficulty in expectoration who have chronic respiratory diseases such as chronic bronchitis, emphysema, pulmonary fibrosis, bronchial asthma, bronchiectasis, old tuberculosis, and pneumoconiosis (n=19).

5. Intervention

Arm 1: dministration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules 2.5 g t.i.d. for 4 weeks (n=10).
Arm 2: administration of bromhexine hydrochloride 4 mg t.i.d. for 4 weeks (n=9).a

6. Main outcome measures

Subjective symptoms: frequency of cough, intensity of cough, stridor, volume of sputum, retention of sputum, and clearance of sputum.

7. Main results

No improvement in the frequency of cough, intensity of cough, stridor, and volume of sputum was observed in either arm. In contrast, there was significant improvement in retention of sputum after 2 weeks in arm 1, and a tendency toward improvement in arm 2. Clearance of sputum was also significantly improved after 2 and 4 weeks of treatment in arm 1, but less improved in arm 2. The percentage of patients with more than moderate general improvement was 60.0% in arm 1 and 11.1% in arm 2, but the between-arm difference was not statistically significant.

8. Conclusions

Bakumondoto can be used in the aged without adverse effects, and has significant efficacy in loosening phlegm in patients with chronic lung disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No safety issues were identified.

11. Abstractor's comments

As mentioned in the introduction of this article, "the significance of expectorants is not always recognized. For instance, there is no definite answer to the question whether we should increase or suppress the volume of sputum to improve difficulty in expectoration. In fact, expectorants are not sold in the United States." This is what I realize at the moment. Moreover, bakumondoto is an expectorant I actually prescribe.

12. Abstractor and date

Fujisawa M, 13 October 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kato S, Matsuda T, Nakajima T, et al. Clinical significance of the combination therapy of smoking cessation and seihaito for chronic obstructive pulmonary disease. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2005; 14: 260-5 (in Japanese). Ichushi Web ID: 2005292823

Kato S, Oda K, Hasumi H, et al. The combined effect of smoking cessation and Seihai-to on airway clearance on COPD patients. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-Allergy*) 2006; 19: 26-35 (in Japanese with English abstract).

1. Objectives

To assess the efficacy of smoking cessation combined with administration of seihaito (清肺湯) for chronic obstructive pulmonary disease (COPD).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT- envelope)

3. Setting

Two university hospitals, Japan.

4. Participants

Patients with GOLD stage 0, 1, or 2 COPD who had stopped smoking, but whose respiratory symptoms (cough, sputum, and dyspnea) were still present one month after smoking cessation, n=31.

5. Intervention

Arm 1: smoking cessation and administration of TSUMURA Seihaito (清肺湯) Extract Granules 9.0 g/day, for 24 months, n=16.
Arm 2: smoking cessation only, for 24 months, n=15.

6. Main outcome measures

Respiratory symptoms.
Chest radiography and chest CT findings (emphysema, organizing pneumonia, bronchial obstruction by sputum).

7. Main results

Respiratory symptoms were significantly improved in arm 1 compared with arm 2 for 1 to 6 months; however, no significant difference was found after 12 months. The imaging findings were significantly improved in arm 1 at 24 months. Diagnostic imaging showed significant improvement in organizing pneumonia and bronchial obstruction in arm 2 after 24 months and no improvement in emphysema in both arms.

8. Conclusions

Administration of seihaito for 6 months improves clinical symptoms, and administration for 24 months is necessary for improvement in imaging findings.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

The information from this RCT included guidance on how to stop smoking using Kampo medicine as an add-on treatment. Dyspnea is a respiratory symptom that can be evaluated objectively by respiratory function testing and measurement of blood oxygen saturation. Future use of these tests in the follow-up period is desired. Future developments in this area of research hold promise.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 22 February 2009, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Shinozuka N, Tatsumi K, Nakamura A, et al. Evaluation of systemic inflammation and utility of hochuekkito administration in subjects with COPD*. *Kosei Rodosho Kagaku Kenkyu Kenkyuhi Hojokin: Nanchisei Shikkan Kokufuku Kenkyu Jigyo Kokyufuzen ni Kansuru Chosa Kenkyu, Heisei 18 Nendo Buntan Kenkyu Hokokusho* [*Ministry of Health, Labour and Welfare, Science Research Grant, The Intractable Disease Treatment Research Project Research on Respiratory Failure, Working-group Research report fiscal year 2006*] 2007:94-9 (in Japanese).

Shinozuka N, Tatsumi K, et al. A traditional herbal medicine hochuekkito improves systemic imflammation in patients with COPD. *American Journal of Respiratory and Critical Care Medicine* 2007; 175: A638 CENTRAL ID: CN-00651806

Shinozuka N, Tatsumi K, Nakamura A, et al. The traditional herbal medicine hochuekkito improves systemic inflammation in patients with chronic obstructive pulmonary disease. *Journal of the American Geriatrics Society* 2007; 55: 313-4. CENTRAL ID: CN-00578499, Pubmed ID: 17302677

Fukuchi Y, Tatsumi K. Utility evaluation of Kampo in the treatment of chronic obstructive pulmonary disease*. *Kosei Rodosho Kagaku Kenkyuhi Hojokin Choju Kagaku Sogo Kenkyu Jigyo: Mansei Heisokusei Shikkan ni Taisuru Kampochiryo no Yuyosei Hyoka ni Kansuru Kenkyu, Heisei 18 Nendo Sokatsu Kenkyusho Hokokusho* (*Ministry of Health, Labour and Welfare, Science Research Grant: Study on Evaluation of Usefulness of Kampo Treatment for Chronic Obstructive Pulmonary Disease, Summary Report Fiscal Year 2006*) 2007: 1-31 (in Japanese).

Tatsumi K, Shinozuka N, Nakayama K, et al. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. *The American Geriatrics Society* 2009; 57: 169-70

1. Objectives

To investigate the effect of hochuekkito (補中益気湯) on systemic inflammation in subjects with chronic obstructive pulmonary disease (COPD).

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

Twelve university hospitals and thirteen hospitals, Japan.

4. Participants

Clinically stable patients who fulfilled the diagnostic criteria of the Japan Respiratory Society Guidelines for COPD, n=71.

5. Intervention

Assessments were done after 6 months of treatment.
Arm 1: conventional treatments with Tsumura Hochuekkito (補中益気湯) Extract Granules, 2.5 g, b.i.d. or t.i.d., n=34.
Arm 2: control: continued conventional treatments, n=37.

6. Main outcome measures

Subjective symptoms: SGRQ (St. George's Respiratory Questionnaire), symptoms related to *ki-kyo*, incidence of common cold (assessed using patients' diaries), and frequency of exacerbations (defined on the basis of Anthonisen's criteria and requirement for systemic administration of steroids).

Objective measurements: body mass index (BMI), change in body weight, respiratory function, blood gas analysis, markers of nutrition status (prealbumin, leptin, and adiponectin), and markers of inflammation (high sensitivity C-reactive protein [hsCRP], TNF-α, and IL-6).

7. Main results

SGRQ subjective symptom score was significantly improved in Arm 1. Also, incidence of the common cold and frequency of exacerbation were significantly less in Arm 1 than in Arm 2. There was no significant change in body weight in both arms during 6 months of observation. Prealbumin, a marker of nutritional status, increased significantly only in Arm 1. Leptin level remained unchanged after administration of hochuekkito. The markers of systemic inflammation (hsCRP, TNF-α, and IL-6) were negatively correlated with severity of COPD (represented by FEV_1% predicted). In Arm 1, hsCRP and TNF-α decreased significantly, but IL-6 remained unchanged. Concentration of adiponectin, secreted by adipocytes and suggested to be involved in the development of arteriosclerosis, was negatively correlated with BMI and significantly increased after treatment with hochuekkito.

8. Conclusions

Administration of hochuekkito improves systemic inflammation and nutritional status in subjects with COPD, and decreases COPD exacerbation and incidence of the common cold.

9. From Kampo medicine perspective

Among the symptoms related to *qikyo* (気虚, qi deficiency), physical lassitude, morale, fatigability, susceptibility to the common cold, and appetite improved.

10. Safety assessment in the article

There were no safety issues.

11. Abstractor's comments

Fukuchi et al. (2007) is an interim report of the findings of Shinozuka et al. (2007) and Shinozuka et al. American Journal of Respiratory and Critical Care Medicine (2007), while Shinozuka et al. Journal of the American Geriatrics Society (2007) presents only the objective outcomes of that interim report. Tatsumi et al. (2009) and Fukuchi et al. (2007) have the same intention. Airflow restriction is considered a prognostic factor that is independent of weight loss in COPD, and recognition of COPD as a systemic inflammatory disease is increasing. If numerous papers are to follow from the succession of RCTs, then each should include the clinical trial registration number to increase understanding of their interrelationships.

12. Abstractor and date

Fujisawa M, 22 February 2009, 1 June 2010, 12 October 2011, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. *Phytomedicine* 2011; 18: 625–9. CENTRAL ID: CN-00790726, Pubmed ID: 21177084

Hattori N, Mukaida K, Haruta Y, et al. A pilot study of the effects of Bakumondoto (TJ-29) on cough in chronic obstructive pulmonary disease (COPD)*. *Kampo to Meneki – Arerugi (Kampo and Immuno-Allergy)* 2011; 24: 38–45 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of bakumondoto (麦門冬湯) on cough in patients with chronic obstructive pulmonary disease (COPD).

2. Design

Crossover randomized controlled trial (RCT –cross over).

3. Setting

Hiroshima University Hospital and two general hospitals, Japan.

4. Participants

Twenty-four COPD outpatients aged over 65 who presented between May 2007 and March 2009.

5. Intervention

Treatment with or without bakumondoto (麦門冬湯) for 8 weeks in a cross-over design.

Patients taking any Kampo medicine within the previous 2 weeks were excluded. Treatment with the usual COPD drugs was continued during the trial.

Arm 1: TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. before meals for 8 weeks, then no bakumondoto (麦門冬湯) for 8 weeks (n=13).

Arm 2: No bakumondoto (麦門冬湯) for 8 weeks, then TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. before meals for 8 weeks (n=11).

One subject in arm 1 was excluded from the efficacy analysis.

6. Main outcome measures

Frequency and intensity of cough assessed on a VAS (visual analogue scale) and changes in severity as recorded in a cough diary. Quality of life (QOL) using St. George's Respiratory Questionnaire (SGRQ). Lung functions.

7. Main results

Twenty-three patients were included in the efficacy analysis. VAS scores showed significant improvement in cough intensity and frequency during the first 8-week period of treatment with bakumondoto in arm 1 (P=0.004), but the magnitude of improvement gradually declined after treatment ceased. In arm 2, however, no significant improvement was observed for the latter 8-week period of treatment with bakumondoto. The authors do not mention whether or not there was a significant difference between the bakumondoto treatment and non-treatment groups for arms 1 and 2 combined. Neither QOL nor lung functions were affected by bakumondoto.

8. Conclusions

Bakumondoto may be effective for cough in elderly COPD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Increases in ALP were observed in one participant in each of arms 1 and 2, however, they both completed the course of bakumondoto.

11. Abstractor's comments

The report by Hattori et al. (2011) was presented at a conference, so it includes questions and answers. One person asked whether cough in COPD patients was a common complaint. The presenter replied that there were many cases of exposure to toxic gas among the cases at Hiroshima University, and that some of those who complained of cough symptoms were included in the study. However, there is no mention of patients being exposed to toxic gas in the article by Mukaida et al. (2011). The authors should include such background information in their article.

12. Abstractor and date

Fujisawa M, 31 December 2012.

10. Respiratory Diseases

Reference

Hamada H, Sekikawa K, Murakami I, et al. Effects of Hochuekkito combined with pulmonary rehabilitation in patients with COPD. *Experimental and Therapeutic Medicine* 2018; 16: 5236-42. CENTRAL ID: CN-01788887, Pubmed ID: 30542479, UMIN ID: UMIN000015092

1. Objectives

To investigate the efficacy and safety of adding hochuekkito（補中益気湯）to pulmonary rehabilitation for patients with chronic obstructive pulmonary disease (COPD).

2. Design

Randomized controlled trial (RCT).

3. Setting

One university and five hospitals, Japan.

4. Participants

Moderate to severe COPD (defined by forced expiratory volume in 1 sec/forced vital capacity [FEV1/FVC] <70% and FEV1% predicted to be >30% and <80%), predicted percent of ideal body weight (%IBW) less than 100%, clinically stable disease and able to participate in pulmonary rehabilitation (PR) for 12 weeks, 40 years or older; and smoking history of more than 10 pack-years. Patients were excluded if they had any of the following: i) undergone PR within 24 weeks preceding the study; ii) a diagnosis of other pulmonary diseases or alpha1-antitrypsin deficiency; iii) diagnosis of an acute exacerbation within 4 weeks preceding the study; iv) received pulmonary transplantation; v) received herbal medicine for any problem within 4 weeks preceding the study; vi) had newly received bronchodilators or inhaled or systemic corticosteroids within 2 weeks before the study; vii) a diagnosis of other severe diseases, such as malignant tumors, autoimmune disease, liver disease, renal disease, heart disease, hematologic disease, and metabolic disease; viii) engaged in another clinical trial within 4 weeks preceding the study; ix) signs of definite or possible pregnancy; or x) inability to participate in the present study as judged by the physician (n=35).

5. Intervention

Arm 1: TSUMURA Hochuekkito（補中益気湯）Extract Granules 2.5 g three times daily orally before or between meals and pulmonary rehabilitation for 12 weeks (n=18).

Arm 2: Pulmonary rehabilitation without Hochuekkito for 12 weeks (n=17).

6. Main outcome measures

The primary endpoint was the change in the 6-minute walk distance (6MWD). The secondary endpoints were change in body weight, % ideal body weight, body mass index (BMI), modified Medical Research Council (mMRC) dyspnea scale score, visual analog scale (VAS) score for dyspnea, VAS for fatigue, COPD assessment test (CAT) score, and the number of acute exacerbations.

7. Main results

The analysis was conducted on 33 patients (18 patients in the hochuekkito group and 15 patients in the control group), after exclusion of 2 patients because of withdrawal. In both groups, the 6MWD showed no changes. Body weight (P<0.05), % ideal body weight (P<0.05), mMRC dyspnea scale score (P<0.05), VAS scores for dyspnea and fatigue (P<0.05, P<0.05), and CAT score (P<0.005) significantly improved in Arm 1, but not in Arm 2. In Arm 2, one patient experienced pneumonia requiring hospitalization, and two patients experienced acute exacerbations of COPD. In Arm 1, no patients had such an experience.

8. Conclusions

The addition of hochuekkito to pulmonary rehabilitation improved body weight, dyspnea scores, and health-related quality of life scores in patients with COPD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were noted with the use of hochuekkito.

11. Abstractor's comments

This study was conducted on a small number of patients, and the 6-minute walk distance showed no significant difference contrary to the authors' hypothesis. However, this study is important in that the hochuekkito group showed significant improvement in the general condition of COPD patients. It is desired that larger studies will follow this pilot study.

12. Abstractor and date

Koike H, 4 November 2019.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Japanese herbal medicine, saiboku-to (cai-pu-tang) on brochospasms in aspirin-induced bronchial asthmatic patients. A randomized, double-blind test. *Jibi-inkoka Tenbo* (*Oto-Rhino-Laryngology Tokyo*) 2001; 44: 5-13 (in Japanese with English abstract). Ichushi Web ID: 2002025794

1. Objectives

Development of saibokuto (柴朴湯) inhalation therapy, and to evaluate its efficacy in preventing attacks of aspirin-induced asthma.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Two clinics, Japan.

4. Participants

Patients with aspirin-induced asthma in whom the threshold dose of L-lysine-aspirin for provoking an asthma attack was determined by inhalation, n=74.

5. Intervention

Saibokuto inhalant: TSUMURA Saibokuto (柴朴湯) Extract Granules (TJ-96) were dissolved in injectable saline, sonicated for 90 minutes, and filtered through a Millipore sterile 0.22-micron filter. After adjustment to a concentration of 100 μg/mL, 5 mL of the inhalant was inhaled three times a day.
Arm 1: inhalation of saibokuto (柴朴湯) inhalant for 6 months, n=35.
Arm 2: inhalation of saline for 6 months, n=39.

6. Main outcome measures

The efficacy and safety of inhaled saibokuto for reducing the frequency of asthma attacks.

7. Main results

Saibokuto inhalant was newly developed. Prolonged inhalant usage significantly reduced the frequency of asthma attacks (0.004 times/person/6 months in arm 1 *vs* 0.120 times/person/6 months in arm 2).

8. Conclusions

Inhalation, compared with oral administration, can increase the concentration of saibokuto in the lung to the same level as achieved in experiments *in vivo* and *in vitro*, resulting in suppression of the production and release of biologically active substances in bronchoalveolar lavage fluid, and thereby of asthma attacks.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects were observed in 7 cases (20.0%) in arm 1 and 7 cases (17.9%) in arm 2, none of which led to withdrawal from the study.

11. Abstractor's comments

The preparation of saibokuto inhalant (as described above) involved more than simply dissolving the extract granules in saline.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Kampo medicine, cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on brochospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain. *Itami to Kampo* (*Pain and Kampo Medicine*) 2001; 11: 14-21 (in Japanese with English abstract). Ichushi Web ID: 2002261501

1. Objectives

To evaluate the efficacy of long-term inhaled saibokuto（柴朴湯）in alleviating psychological suffering.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One hospital and three clinics, Japan.

4. Participants

Thirty-two patients with aspirin-induced asthma.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: Saibokuto (柴朴湯) inhalation group (TSUMURA Saibokuto (柴朴湯) Extract Granules 1 mg dissolved in 1 ml of distilled water for injection, then sonicated for 90 minutes before Millipore filtration. Concentration adjusted to 100 μg/ml and 5 ml inhaled b.i.d.)

Arm 2: Placebo inhalation group (distilled water for injection inhaled b.i.d.)

Inhalation treatment lasts 6 months and is followed by washout for 4 weeks and inhalation treatment using the other liquid for 4 weeks (n=32).

6. Main outcome measures

Chronic pain (CP): Overall quality of life (QOL), visual analogue scale for pain (VAS-P), face rating score, QOL scores (quality of well-being scale [QWB] score, Modified Health Assessment Questionnaire [MHAQ], face scale)

7. Main results

In the trial of long-term inhalation, significant improvements were observed in each QOL domain and also in global QOL scores (this global QOL assessment method was developed by the authors using a visual analog scale [VAS] to assess physical [QOL-P], mental/psychological [QOL-M], social activity [QOL-S], medical economics [QOL-E], therapeutic drug [QOL-D], and individual QOL [QOL-I] incorporated items measuring the perspectives of individuals [including his/her perspectives on philosophy, thoughts, ethics, generation, policy, religion, and so on], as well as face scale and modified health assessment questionnaires)..

8. Conclusions

Inhaled saibokuto therapy improves QOL and respiratory function.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Dysguesia (or altered sensation of taste) was observed in 5 cases (15.6%) in arm 1 and in 2 cases (6.3%) in arm 2. Cacosmia (or imagining of unpleasant odors) was observed in 7 cases (21.9%) in arm 1 and in 4 cases (12.5%) in arm 2. None of these adverse effects caused withdrawal from the study.

11. Abstractor's comments

The paper also mentions a comparative study of TJ-96 immediately after inhalation; however, it did not clearly describe the sample population, method of allocation, and results. Thus, the study was not reported as an RCT. Furthermore, saibokuto (柴朴湯) inhalation liquid is not simply extract granules dissolved in distilled water for injection: it is a special medicine with an altered formulation, made using an original process.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Urata Y, Yoshida S, Irie Y, et al. Treatment of asthma patients with herbal medicine TJ-96: a randomized controlled trial. *Respiratory Medicine* 2002; 96: 469-74. CENTRAL ID: CN-00390241, Pubmed ID: 12117049

1. Objectives

To investigate the clinical effect of saibokuto (柴朴湯) for the treatment of atopic asthma.

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

One university hospital and one hospital, Japan.

4. Participants

Adult patients with atopic asthma, n=33.

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.
Cross-over design (administration of saibokuto (柴朴湯) or placebo [2.5 g, t.i.d.] for 4 weeks, and then, after a washout period of at least 4 weeks, patients crossed over to receive the alternative treatment), n=33.
Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules (TJ-96).
Arm 2: placebo.

6. Main outcome measures

Clinical symptoms, respiratory function test, methacholine provocation testing, eosinophil counts in blood and sputum, and eosinophilic cationic protein (ECP) in blood and sputum.

7. Main results

Symptom score (which employed similar severity classification according to Guidelines for Asthma Prevention and Management 2004 [JGL 2004]) before treatment was 1.65±0.38 in arm 1 and 1.66±0.43 in arm 2. After treatment, it was significantly decreased in arm 1 (0.73±0.25 in arm 1 and 1.63±0.39 in arm 2, P=0.001). Forced expiratory volume in 1 second ($FEV_{1.0}$) improved slightly but not significantly in arm 1. Response to provocation challenge with methacholine was significantly better in arm 1. Significant decreases in eosinophil counts and ECP in blood and sputum but not neutrophil counts were observed in arm 1.

8. Conclusions

Saibokuto improves clinical symptoms in patients with atopic asthma. Although $FEV_{1.0}$ and FVC were unaffected, saibokuto was able to attenuate eosinophilic inflammation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

This is a high-quality trial, a double-blind RCT with a placebo control group for evaluation of saibokuto (柴朴湯) extract granules as treatment for asthma. Although there was no between-group difference in pulmonary function (FEV 1.0 and FVC), there was a significant between-group difference in subjective symptoms. The respiratory function data obtained in this study should be useful for sample selection in future RCTs.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Chinese traditional medicine, she-bi-tang (shinpi to) on bronchospasm in aspirin-indolerant bronchial asthmatic patients – a randomized, group-paralleled comparative trial –. *Jibi-inkoka Tenbo* (*Oto-rhino-laryngology Tokyo*) 2003; 46: 3-14 (in Japanese). CENTRAL ID: CN-00451669, Ichushi Web ID: 2004041278

1. Objectives

To assess the efficacy and safety of inhaled shimpito (神秘湯) for the control of aspirin-induced asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Several clinics and others, Osaka prefecture, Japan.

4. Participants

Patients with histories of aspirin-induced asthma, whose threshold levels of inhaled lysine-aspirin are determined, n=114.

5. Intervention

Arm 1: inhalation of TSUMURA Shimpito (神秘湯) Extract Granules, 500 μg in four divided doses, n=53.
Arm 2: inhalation of cromoglycate, 5 mg q.i.d., n=61.
Duration of the study was 1 year.

6. Main outcome measures

The effect was evaluated by assessing 1) leukotrienes levels in bronchoalveolar lavage (BAL) fluid, 2) forced expiratory volume in 1 second ($FEV_{1.0}$) after lysine-aspirin inhalation, and 3) frequency of asthma attacks (or exacerbations).

7. Main results

The decrease in $FEV_{1.0}$ after lysine-aspirin inhalation was significantly greater in arm 1 than arm 2. Also, the frequency of asthma attacks and leukotriene levels in BAL fluid were decreased in arm 1 relative to arm 2.

8. Conclusions

Inhaled shimpito is more efficacious than inhaled cromoglycate for the management of aspirin-induced asthma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The frequency of both abnormal laboratory findings and adverse reactions were higher in arm 2 than in arm 1 (number of cases are unclear because the results were omitted in this paper).

11. Abstractor's comments

Despite the term "multicenter, randomized" in the title, the method of randomization is not described, and the facilities where this clinical trial was actually performed (not the research institute) are unspecified. This paper does not state the number of withdrawals and analyzed cases during the 1-year follow-up of 114 subjects. Might it mean no withdrawals during the 1-year treatment period? Aspirin-induced asthma comprises 4-10% of all asthma cases. Inhaled corticosteroids are the most commonly used asthma medications. This study implies the greater efficacy of inhaled shimpito therapy in the management of asthma when compared with that of inhaled cromoglycate therapy. Further studies are awaited to assess whether oral administration of shimpito also provides similar efficacy when used by subjects with the appropriate "*sho*."

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Goto GH, et al. A randomized, group-parallel comparative trial of the suppressiveeffect of Chinese traditional medicine, shen-mi-tang (shin-pi-to), compared to sodium oramolycate inhalation in improving subjective and objective symptoms in bronchial asthmatics. *Jibi-inkoka Tenbo* (*Oto-rhino-laryngology Tokyo*) 2004; 47: 20-7 (in Japanese with English abstract).
CENTRAL ID: CN-00496741, Ichushi Web ID: 2005016956

1. Objectives

To assess the efficacy and safety of inhaled shimpito (神秘湯) therapy for improving asthma symptoms in patients with aspirin-induced asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Several clinics and other health care facilities, Osaka prefecture, Japan.

4. Participants

Patients with aspirin-induced asthma, whose thresholds for induction of asthma (attacks) have been determined, n=161.

5. Intervention

Arm 1: inhalation of shimpito (神秘湯), 500 μg in four divided doses, n=81.
Arm 2: inhalation of cromoglycate, 5 mg q.i.d., n=80.
Duration of the study was 3 years.

6. Main outcome measures

1) Frequency of asthma attacks (or exacerbations), 2) improvement in health-related QOL, 3) improvement in chronic pain, 4) leukotriene level in bronchoalveolar lavage (BAL) fluid

7. Main results

In arm 1, frequency of asthma attacks and leukotriene level in BAL fluid were significantly reduced, and QOL and chronic pain were significantly improved when compared with arm 2.

8. Conclusions

Inhaled shimpito therapy suppresses production of leukotrienes, prevents exacerbation of aspirin-induced asthma, alleviated chronic pain, and improved QOL.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Fewer cases and subjects had abnormal laboratory findings and adverse reactions in arm 1 than in arm 2.

11. Abstractor's comments

The authors do not specify the medical facilities where this clinical trial (described as multicenter trial) actually took place. In this prospective, randomized study, the number of withdrawals and cases analyzed during the 3-year period of observation for 161 enrolled subjects is not stated. It is unclear whether there were any withdrawals during this period. Aspirin-induced asthma comprises 4-10% of all cases of asthma. Inhaled corticosteroids are the most common medications used for asthma therapy. This study implies that inhaled shimpito therapy is more efficacious in the management of asthma than inhaled cromoglycate therapy. In patients with aspirin-induced asthma, health-related QOL is generally not good because of limitation on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and inflammation. However, shimpito can improve these symptoms. Further studies are awaited to assess whether oral administration of shimpito also has similar efficacy when used in subjects with the appropriate "*sho*."

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Goto HG et al. Chronic pain in intractable and chronic internal diseases*. *Mansei Totsu* (*The Journal of the Japanese Society for the Study of Chronic Pain*), 2002; 21: 67-77 (in Japanese with English abstract). Ichushi Web ID: 2003126703 MOL, MOL-Lib

1. Objectives

To investigate the effect of saibokuto (柴朴湯) inhalation therapy in improving quality of life (QOL) in patients with aspirin-intolerant asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital and two clinics, Japan.

4. Participants

Patients with aspirin-intolerant asthma, n=214.

5. Intervention

The study duration was 3 years. For saibokuto (柴朴湯) inhalation, 500 μg of saibokuto was packed into capsules comparable to those used for sodium cromoglycate (DSCG) inhalation.
Arm 1: saibokuto (柴朴湯) (the manufacturer not identified), 500 μg q.i.d. inhalation, n=105.
Arm 2: DSCG 20 mg q.i.d. inhalation, n=109.

6. Main outcome measures

Subjective symptoms, various tests, chronic pain, and QOL were assessed using a visual analog “total disease-related symptoms” scale developed by the authors, and face rating scores.

7. Main results

Saibokuto inhalation improved various endpoints.

8. Conclusions

Symptom-related QOL of patients with exacerbated aspirin-intolerant asthma is improved.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The incidence of adverse effects was higher in arm 1, however, there was no significant difference in the number of cases. These results were omitted from the original article.

11. Abstractor’s comments

This RCT resembles two other RCTs of saibokuto inhalation therapy, “Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive Effect of Japanese Herbal Medicine, Saiboku-to (Cai-Pu-Tang) on Brochospasms in Aspirin-induced Bronchial Asthmatic Patients. A Randomized, Double-blind Test. *Jibi-inkoka Tenbo* (*Oto-Rhino-Laryngology Tokyo*) 2001; 44: 5-13 (in Japanese with English abstract)” and “Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Kampo medicine, Cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on brochospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain. *Itami to Kampo* (*Pain and Kampo Medicine*) 2001; 11: 14-21 (in Japanese with English abstract)”. The only difference between these studies is the method of administering the inhalant: inhalation of saibokuto dissolved in distilled water or saline, or as a powder using a spinhaler as mentioned in this paper. Inhalation of powder should further improve QOL because powder increases accessibility. Common to these three papers is their complicated format, poorly-described rationale, and omission of results, which makes understanding the contents more difficult.

12. Abstractor and date

Fujisawa M, 22 February 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Egashira Y, Nagano H, et al. Results of a comparative clinical study of the effect of "TSUMURA Saiboku-to" (TJ-96) against steroid dependent bronchial asthma in 2 groups, a Saiboku-to administration group and a non-administration group, divided by the envelope method. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1990; 4: 128–44 (in Japanese with English abstract).
Egashira Y, Nagano H. A multicenter clinical trial of TJ-96 in patients with steroid-dependent bronchial asthma. A comparison of groups allocated by the envelope method. *Annals of the New York Academy of Science* 1993; 685: 580-3. CENTRAL ID: CN-00095466, Pubmed ID: 8363267

1. Objectives
To evaluate the effectiveness, safety, and usefulness of saibokuto (柴朴湯) against steroid-dependent bronchial asthma.

2. Design
Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting
Twenty university hospitals and 31 hospitals, Japan.

4. Participants
Patients with bronchial asthma treated with steroids (n=112).

5. Intervention
Arm 1: administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 g t.i.d. for 12 weeks (n=64).
(The patients receiving more than 5 mg/day of prednisolone （-equivalent dose of steroids） [n=37]; patients with asthma for more than 5 years [n=48])
Arm 2: no administration (n=48).
(The patients receiving more than 5 mg/day of prednisolone （-equivalent dose of steroids） [n=25]; patients with asthma for more than 5 years [n=41])

6. Main outcome measures
Asthma score = attack score (severity) + treatment score (level of the concomitant drugs). Scores and the number of subjects who succeeded in decreasing steroid doses.

7. Main results
A larger percentage of patients in arm 2 had moderate or greater improvement (32.8% *vs.* 10.4% in arm 1) and slight or greater improvement (60.9% *vs.* 18.8% in arm 1; $P<0.001$). A larger percentage of patients in arm 2 had reduction in steroid dose of 50% or more (17.2% *vs.* 6.3% in arm 1; $P<0.01$), which showed the significant steroid sparing effect of saibokuto.

8. Conclusions
Saibokuto improves the clinical symptoms of asthma and leads to a reduction in the dosage of concomitantly administered steroids.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Stomach pain and stomach discomfort were observed in 1% of the saibokuto group.

11. Abstractor's comments
The article by Egashira et al (1993) was based on the original article by Egashira et al (1990), and it includes detailed analysis of individual cases. The RCT report published in *Ann. N.Y. Acad. Sci.* was also cited in "Huntley A, Ernst E. Herbal medicines for asthma: a systematic review, *Thorax*, 2000; 55:925-929." Future promise lies in an RCT incorporating Kampo patterns, after clinical trial registration.

12. Abstractor and date
Fujisawa M, 31 March 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Ito S, Mikawa H. Effect of "TSUMURA Saiboku-to" (TJ-96) on bronchial asthma in children. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1990; 4: 115–25 (in Japanese with English abstract).

Ito S, Mikawa H. Clinical evaluation of saibokutou in the treatment of children with bronchial asthma. *Kiso to Rinsho* (*The Clinical Report*) 1992; 26: 3993–8 (in Japanese). Ichushi Web ID: 1993226668 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of saibokuto (柴朴湯) for the treatment cedar pollen allergy in children with bronchial asthma.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Two university hospitals (Department of Pediatrics, Faculty of Medicine, Kyoto University, and Kansai Medical University Rakusai Newtown Hospital) and six other hospitals, Japan.

4. Participants

Children with mild or moderate (symptoms of) bronchial asthma (n=43).

5. Intervention

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 1.25 mg b.i.d. (for children less than 7 years old) or 2.5 g b.i.d. (for children 7 years or older) for 8–12 weeks (n=22).
Arm 2: tranilast 5 mg/kg/day in two or three divided doses for 4–12 weeks (n=21).

6. Main outcome measures

Frequency of asthma attacks (very frequent, moderately frequent, infrequent) in a week, and the severity score of the attack (severe=6, moderate=4, mild=1).

7. Main results

No severe attacks were observed in either arm after 5 weeks of treatment. Frequencies of moderate attacks were not significantly different between the two arms throughout the study period. Mild attack was less frequent in arm 2 than in arm 1. The frequency and severity scores were significantly decreased in arm 2 compared to arm 1 at 4–6 weeks of treatment ($P<0.05$), and significantly decreased in arm 1 compared to arm 2 at 11–12 weeks of treatment ($P<0.05$).

8. Conclusions

Saibokuto and tranilast have equivalent efficacy in children with mild to moderate bronchial asthma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed.

11. Abstractor's comments

Patient allocation by the envelope method makes the randomization process tenuous in this study. However, the value of this study is that it confirms the equivalent efficacy of saibokuto and tranilast as treatment for bronchial asthma in children. There is no placebo arm in this study. Use of a placebo arm may pose an ethical problem. Therefore, further randomized controlled clinical trials with cross-over design are indicated.

12. Abstractor and date

Okabe T, 19 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Tubaki T, Ebisawa M, Akimoto K, et al. Effects of shinpi-to (*shenbi-tang*) on bronchial asthma. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1994; 8: 65–71 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of shinpito (神秘湯) on exercise-induced asthma and changes in clinical symptoms in patients with moderate to severe bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Patients aged 7–15 years with moderate asthma (n=5) or severe asthma (n=7) who were treated concomitantly with theophylline, disodium cromoglycate, inhaled beclomethasone, and beta2-agonists.
Patients were excluded who received oral steroids, had a predicted FEV1 of less than 80%, or had wheezing before exercise tests.

5. Intervention

The observation period was 2 weeks, and the administration period was 12 weeks.
The administered dose was one sachet b.i.d. to patients aged less than 13 years and one sachet t.i.d. to patients aged 13 or older.
Arm 1: administration of TSUMURA Shinpito (神秘湯) Extract Granules (n=7) (dose not described).
Arm 2: EBIOS 1 g b.i.d. or t.i.d. (n=5).

6. Main outcome measures

Asthma symptom diary.
Respiratory function changes observed on ergometer exercise tests during the 2-week observation period and at the conclusion of shinpito administration.

7. Main results

In both arms, exercise lowered $FEV_{1.0}$ below standard values after 5 minutes, and $FEV_{1.0}$ gradually recovered. However, in arm 2 after administration of shinpito, the rate of this reduction was significantly inhibited immediately after and 5 minutes after exercise, and some inhibition was still observable 15, 30, and 60 minutes after exercise. In addition, a significant reduction in numbers of attacks was observed in arm 2, whereas no significant improvement was observe in arm 1.

8. Conclusions

Shinpito effectively improves the symptoms of bronchial asthma and reduces the number of exercise-induced asthma attacks.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The result that shinpito is effective for exercise-induced asthma attacks is interesting. However, random grouping in this study seems unbalanced even after taking the severity into consideration: 5/7 subjects in arm 2 and 2/5 in arm 1 were treated with inhaled beclomethasone, while 3/7 subjects in arm 2 and 0/5 in arm 1 were treated with beta2-agonists. Further studies with more patients are expected.

12. Abstractor and date

Fujisawa M, 13 October 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Nagano F, et al. Sparing effect of saibokuto inhalation on inhaled beclomethasone dipropionate to halved of reduction of inhaled beclomethasone dipropinate-dose: well-controlled comparative study of saiboku-to-inhalation and sodium cromoglycate-inhalation. *Jibi-inkoka Tenbo* (*Oto-rhino-laryngology Tokyo*) 2002; 45: 8-15 (in Japanese with English abstract).
CENTRAL ID: CN-00403706, Ichushi Web ID: 2003036732

1. Objectives

To assess the efficacy and safety of inhaled saibokuto (柴朴湯) while reducing the amount of inhaled beclomethasone during the course of treatment for bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Several clinics and others, Osaka prefecture, Japan.

4. Participants

Patients with stable bronchial asthma whose peak expiratory flow rate was maintained at more than 70% of normal for 6 months by the use of inhaled beclomethoasone (800 μg/day) , n=94.

5. Intervention

Amount of inhaled beclomethasone was reduced from 800 μg/day to 400 μg/day at 4 weeks before the intervention.
Arm 1: inhaled saibokuto (柴朴湯), 500 μg q.i.d., n=49.
Arm 2: inhaled cromoglycate, 20 mg q.i.d., n=45.
Duration of the study was 12 months.

6. Main outcome measures

1) Intensity of subjective symptoms (visual analogue scale), 2) peak expiratory flow (respiratory function test), 3) frequency of the use of β_2-agonist, 4) cytokine levels in bronchial lavage fluid, 5) nitric oxide (NO) concentrations in expired air, and so on.

7. Main results

In arm 1, subjective symptoms and respiratory function were significantly improved, and compared to arm 2, patients in arm 1 had significantly reduced frequency of β_2-agonist use, NO concentration in expired air, and cytokine levels in bronchial lavage fluid. Less than 10% decrease in the peak expiratory flow rate occurred in 67.3% of arm 1 and 13.3% of arm 2.

8. Conclusions

Inhaled saibokuto therapy is suggested to maintain the efficacy of inhaled beclomethasone as treatment for bronchial asthma despite dosage reduction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects occurred in 11 cases (22.4%) in arm 1, and in 8 cases (17.8%) in arm 2.

11. Abstractor's comments

Although they mention a multicenter study, the authors cite only one research institute, and do not specify the facilities where the clinical trials were actually conducted. The number of withdrawals during the 1-year follow-up and the percentage of the 94 enrolled patients who were actually included for analysis were not stated. Perhaps no one withdrew during the 1 year of treatment. Inhaled saibokuto therapy is assumed to be efficient compared to inhaled cromoglycate. All participants in this study should be considered adult patients with mild asthma. In terms of Kampo medicine, bronchial asthma presents a variety of "*sho* (証, pattern)." Previous studies demonstrated that oral administration of saibokuto shows only limited clinical efficiency for those who do not have "*sho*" for saibokuto.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Kampo medicine, chai-po-tang (Japanese name: saiboku-to) compared with xiao-quing-long tang (Japanese name: shoseiryu-to) in asthmatics with anxiety and depression due to asthmatic attacks. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2003; 18: 11-7 (in Japanese with English abstract). Ichushi Web ID: 2006192016

1. Objectives

To compare the efficacy of the anxiolytic-like agent saibokuto (柴朴湯) with that of shoseiryuto (小青竜湯) in patients with bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

The setting of this study is unstated; the authors of this paper work in clinics and are specialists in allergy and respiratory medicine, Japan.

4. Participants

Patients with bronchial asthma who fulfilled one of the following criteria were included (n=139): comprehensive asthma inventory score ≥20, both state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40.

5. Intervention

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 5.0 g/day in three divided doses (in capsule form) administered between meals for 24 weeks, n=71.

Arm 2: TSUMURA Shoseiryuto (小青竜湯) Extract Granules 5.0 g/day in three divided doses (in capsule form) administered between meals for 24 weeks, n=68.

6. Main outcome measures

Scores on various types of mental and psychological tests, subjective symptoms, bronchoalveolar lavage (BAL) fluid levels of hormones of the hypothalamo-pituitary-adrenal system, the assessment of suffering from chronic and intractable medical diseases, improvement in global symptoms (rated on a scale from 1 [markedly improved] to 5 [worsened], taking into account disease-related symptoms and the development of adverse reactions).

7. Main results

Various types of psychological tests, subjective symptoms, BAL fluid findings, levels of hormones of the hypothalamo-pituitary-adrenal system, chronic and intractable medical diseases, and global symptom scores showed significantly greater improvement in arm 1 than arm 2. The conditions of 66.2% of subjects in arm 1 and 7.3% in arm 2 were improved or better at the end of the study.

8. Conclusions

Saibokuto is more effective than shoseiryuto in asthma patients with anxiety symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although the authors do not offer a detailed description, adverse effects were observed in 2 cases (2.8%) and 5 cases (7.4%) in arm 1 and 2, respectively. Abnormal laboratory findings were noted in 2 cases (2.8%) in arm 1 and 6 cases (8.8%) in arm 2.

11. Abstractor's comments

Using a double-blind randomized controlled design, this study provides high-quality evidence that saibokuto and shoseiryuto are effective for asthma in patients with anxiety symptoms. As the authors refer to development of adverse reactions, the number of withdrawals and the reasons for withdrawal should have been included to make this report even better. Accumulation of the detailed comparative information about these two Kampo drugs will clarify understanding of how both drugs work.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Chinese tracitional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clotiazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2002; 17: 20-7 (in Japanese with English abstract). Ichushi Web ID: 2006192005

1. Objectives

To assess the efficacy of the anxiolytic-like agent, saibokuto (柴朴湯), in treating bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

The setting of this study is unstated; the authors of this paper work in clinics, and are specialists in allergic and respiratory medicine, Japan.

4. Participants

Patients with bronchial asthma who fulfill one of the following criteria were included (n=107): comprehensive asthma inventory score ≥ 20, both state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40.

5. Intervention

Arm 1: administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 g t.i.d. before meals for 3 years, n=51.

Arm 2: administration of clotiazepam 15-30 mg/day (mean 23.9 mg/day) t.i.d. before meals for 3 years, n=56.

6. Main outcome measures

Clinical effects, scores various types of mental and psychological tests, airway hyperreactivity, bronchoalveolar lavage (BAL) fluid, improvement in global symptoms (as assessed by a combination of the preceding measures and the development of adverse reactions indicating worsening).

7. Main results

Scores on various types of psychological tests, airway hyperreactivity, BAL fluid findings, and global symptoms showed significantly greater improvement in subjects in arm 1 than those in arm 2. The conditions of 68.6% of subjects in arm 1 and 21.3% of subjects in arm 2 were improved or better.

8. Conclusions

Saibokuto is significantly more effective than clotiazepam in reducing the severity of asthma symptoms in asthma patients with anxiety symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In arm 1, there were no adverse reactions or abnormal laboratory findings. In arm 2, there were 13 cases (23.2%) including cases of drowsiness and poor concentration.

11. Abstractor's comments

Using a double-blind randomized controlled design, this study provides high-quality evidence that saibokuto is effective for asthma in patients with anxiety symptoms. Withdrawal from the study is not documented in this paper, nor has it been stated whether bronchoscopy was performed in all cases. In the Results section, the authors often use the phrase "results omitted" and do not show the data. Because the results here indicate the efficacy of saibokuto for asthma patients with anxiety symptoms, these data should have been disclosed to further validate its efficacy. However this remains a well-designed study investigating the psychological and organic pathology of asthma and evaluating the long-term efficacy of a Kampo medicine. Further studies including other Kampo formulae are desired.

12. Abstractor and date

Goto H, 1 May 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of chai-to-tang (Japanese name: saiboku-to), a Chinese traditional herbal medicine, in patients with bronchial asthma and autonomic nerve dysfunction: A multicenter, randomized, double-blind, placebo-controlled study. *Nihon Toyo Shinshin Igaku Kenkyu* (*Journal of Japanese Association of Oriental Psychosomatic Medicine*) 2004; 19: 37-41 (in Japanese with English abstract). Ichushi Web ID: 2006203751

1. Objectives

To evaluate the efficacy and safety of saibokuto (柴朴湯) in patients with asthma exacerbations based on anticipatory anxiety.

2. Design

Randomized controlled trial (RCT).

3. Setting

The setting of this study is unstated; the authors of this paper work in clinics, and are specialists in allergic and respiratory medicine, Japan.

4. Participants Shimazaki Y, Mori H, Kurata H, et al. Comparative study of Kampo preparations

Patients with bronchial asthma who fulfill one of the following criteria were included (among 174 subjects participated, data from 172 subjects were analyzed): comprehensive asthma inventory score ≥ 20, both state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40.

5. Intervention

Arm 1: Administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 5.0 g/day three times a day before meals for 6 months, n=87.

Arm 2: Administration of lactose 5.0 g/day three times a day before meals for 6 months, n=85.

Each drug was given in indistinguishable capsule.

6. Main outcome measures

Assessment of improvement in objective and subjective symptoms concerning bronchial asthma, various types of mental and psychological tests, assessment of autonomic dysfunction, bronchoalveolar lavage (BAL) fluid, numbers of inflammatory cells in bronchial mucosa biopsy, frequency of asthma exacerbations, levels of hypothalamic, pituitary, and adrenal cortex hormones, assessment of chronic pain, and others.

7. Main results

Autonomic dysfunction, clinical symptoms, and BAL fluid analysis were significantly improved in arm 1 compared to arm 2. In arm 1, the number of subjects with asthma exacerbations decreased from 87 to 14 and the mean duration of asthma exacerbation decreased from 31.5 to 3.1 days, while both indices were increased in arm 2 (descriptions of the results in the text were imprecise).

8. Conclusions

Saibokuto is effective in improving asthma symptoms and psychiatric symptoms in patients with autonomic dysfunction due to asthma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no differences between the two arms in the incidences of adverse effects and abnormal laboratory data (no precise description in the paper).

11. Abstractor's comments

As the authors' notes in the Discussion section, this is the first clinical trial in the world to evaluate the effect of saibokuto in patients with bronchial asthma in a randomized, double-blind, controlled design. Following up a number of subjects in detail in multicenter analysis should have required substantial efforts. Declaration of the missing details such as 1) the number of withdrawals during 6 months of observation, 2) the number of subjects who underwent bronchoscopy, and 3) precise data omitted in the Result section, would be effective in making the efficacy of saibokuto widely accepted. Accumulation of such detailed studies may lead to elucidation of the action mechanisms and the efficacy of Kampo medicine, and more similar studies are awaited.

12. Abstractor and date

Goto H, 1 May 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Iwasaki K, Cyong JC, Kitada S, et al. A traditional Chinese herbal medicine, banxia houp tang, improves cough reflex of patients with aspiration pneumonia. *Journal of American Geriatrics Society* 2002; 50: 1751-2. CENTRAL ID: CN-00434022, Pubmed ID: 12366640

1. Objectives

To investigate whether hangekobokuto (半夏厚朴湯; banxia houp tang) improves cough reflex in elderly patients likely to have aspiration pneumonia.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Tokyo and Tohoku University, and their related facilities, Japan.

4. Participants

Elderly patients (mean age, 78) with cerebral atrophy and lacunar infarcts, who had at least one episode of aspiration pneumonia, n=16.

5. Intervention

Arm 1: hangekobokuto (半夏厚朴湯) extract (granules) 1.5 g t.i.d. orally for 4 weeks (n=7).
Arm 2: placebo (lactose) 1.5 g t.i.d. orally for 4 weeks (n=9)

6. Main outcome measures

Subjects inhaled nebulized citric acid solution (0.3-360 mg/mL) delivered by an ultrasonic nebulizer, and the cough threshold was defined as the concentration of citric acid at which subjects coughed at least five times.

7. Main results

In arm 1, the cough threshold decreased from 59.5 to 15.7. In arm 2, the values were 47.5 and remained unchanged.

8. Conclusions

The result suggests that hangekobokuto improves the (impaired) cough reflex in the elderly with an increased risk for aspiration pneumonia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

It has been reported that angiotensin-converting enzyme inhibitor (ACE-I) improves silent aspiration, and that capsaisin improves cough reflex. This study suggests that hangekobokuto also affects the attenuated cough reflex in older patients with cerebral atrophy and lacunar infarcts. Larger RCTs to confirm its efficacy are awaited.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)

References

Iwasaki K, Kato S, Monma Y, et al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in older adults with dementia. *Journal of the American Geriatrics Society* 2007; 55: 2035-40. CENTRAL ID: CN-00699802, Pubmed ID: 17944889
Iwasaki K, Kato S, Monma Y, et al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in brain-damaged elderly. *International Journal of Stroke* 2010; 5 suppl 2: 38-9. CENTRAL ID: CN-00782273

1. Objectives
To evaluate whether hangekobokuto (半夏厚朴湯) prevents aspiration pneumonia and pneumonia-related mortality in elderly people with dementia.

2. Design
Randomized controlled trial (RCT).

3. Setting
Two hospitals (the authors belong to Tohoku University, Dokkyo University, and two hospitals), Japan.

4. Participants
One hundred and four elderly people with cerebrovascular disease, Alzheimer's disease, or Parkinson's disease (31 males, 73 females, mean age 83.5±7.8 years).

5. Intervention
Ninety-five participants were randomly allocated to two groups for treatment.
Arm 1: Tsumura Hangekobokuto (半夏厚朴湯) Extract Granules 2.5 g t.i.d. (body weight ≥50 kg) or 2.5 g b.i.d. (body weight <50 kg) for 12 months, n=47.
Arm 2: placebo (lactose) 1.0 g t.i.d. (body weight ≥50 kg) or 1.0 g b.i.d. (body weight <50 kg) for 12 months, n=48.

6. Main outcome measures
The occurrence of pneumonia, mortality due to pneumonia, and amount of oral food intake.

7. Main results
Data from 92 of the 95 subjects were analyzed. One of four patients who developed pneumonia in arm 1 died as a result, whereas 6 of 14 patients who developed pneumonia in arm 2 died as a result. There was a significant decrease in pneumonia onset in arm 1 compared to arm 2 (P=0.008). Mortality related to pneumonia tended to be less in arm 1 than in arm 2 (P=0.05). Hangekobokuto (半夏厚朴湯) reduced the relative risk of pneumonia to 0.51 (95% CI: 0.27–0.84) and death by pneumonia to 0.41 (95% CI: 0.10–1.03). Amount of oral food intake was significantly greater in arm 1 than arm 2 (P=0.06).

8. Conclusions
Treatment with hangekobokuto (半夏厚朴湯) reduces the risk of pneumonia in elderly people with cerebral disorder. The results also suggest that hangekobokuto (半夏厚朴湯) administration is effective in sustaining food intake.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No adverse effects were observed.

11. Abstractor's comments
The findings of this well-designed randomized controlled study suggest the efficacy of hangekobokuto in preventing aspiration pneumonia in elderly people with dementia. In addition, hangekobokuto administration tended to improve activities of daily living such as self-feeding and to reduce the number of febrile days. Further studies to assess these points are expected. In Kampo medicine, hangekobokuto is a therapeutic prescription indicated for nonfebrile patients with *tan'in* (痰飲, fluid retention) pattern. However, many elderly people present with *sosho* (燥証, dryness pattern). Hopefully, the researchers will analyze the data from this study from the perspective of patterns, once the patterns of the 95 elderly participants in this study become available.

12. Abstractor and date
Okabe T, 25 November 2008, 1 June 2010, 31 December 2012.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Mikamo H, Tamaya T. Usefulness of Kampo medicine for the treatment of infections from the perspective of medical economics*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2007; 24: 105-8 (in Japanese). Ichushi Web ID: 2008050180

1. Objectives

To evaluate the efficacy, impact on recurrence rate, and medical cost efficiency of antibiotics plus Kampo combination therapy for bacterial respiratory infections.

2. Design

Randomized controlled trial (RCT).

3. Setting

Obstetrics and Gynecology, Gifu University Hospital, Japan.

4. Participants

One hundred and sixteen patients diagnosed with acute bacterial respiratory infection.

5. Intervention

Arm 1: antibiotics alone group: treatment with levofloxacin for 5–10 days, n=51.
Arm 2: antibiotics + Kampo group A: treatment with levofloxacin for 5–10 days + juzentaihoto (十全大補湯) or hochuekkito (補中益気湯) for 5–10 days, n=37.
Arm 3: antibiotics + Kampo group B: treatment with levofloxacin for 5–10 days + kakkonto (葛根湯) or keishito (桂枝湯) or kososan (香蘇散) or 1–2 days + juzentaihoto (十全大補湯) or hochuekkito (補中益気湯) for 3–6 days, n=28.
None of the manufacturers of Kampo medicines used were specified.

6. Main outcome measures

Response rate, rate of recurrence within 7 days, and total medical cost.

7. Main results

The response rates were 96.1% in arm 1, 97.3% in arm 2, and 96.4% in arm 3; no statistically significant differences were observed. The recurrence rates were 3.9% in arm 1, 2.7% in arm 2, and 0% in arm 3; there were no significant between-group differences, although the rates were lower in arms 2 and 3. High recurrence rates were observed in cases of atypical pneumonia, caused by atypical pneumonia-related organisms. Total medical costs were significantly higher in arms 2 and 3, whereas for patients with recurrence, total costs tended to be reduced in these two arms.

8. Conclusions

Antibiotics plus Kampo combination therapy reduces the recurrence of bacterial respiratory infections. In patients infected with atypical pneumonia and prone to frequent recurrence, Kampo-combined therapy might reduce the total medical cost.

9. From Kampo medicine perspective

The drugs used in the intervention groups were selected on the basis of common applications: ephedra formulations such as kakkonto, are used to help generate body heat and sweat during the acute phase; shosaikoto is used for immune enhancement during the subacute phase; and *hozai* (補剤, formulations with tonic effects) such as hochuekkito and juzentaihoto are used during the recovery phase.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a very interesting RCT evaluating total medical cost as an outcome. We guess from the setting that all the participants were women. Inclusion of background factors (such as gender, age, and underlying disease) as well as standard criteria with which to evaluate outcomes (such as response and recurrence rates) would have helped readers understand the results. Also, using more uniform regimens in the intervention groups would have increased the value of the results. Further studies are anticipated to provide more data.

12. Abstractor and date

Tsuruoka K, 6 February 2009, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Miyazaki Y, Yamada A, Saitou M. Effect of ninjin-youei-tou on xerostomia induced by oxybutynin hydrochloride. *Shinyaku to Rinsho* (*Journal of New Remedies and Clinics*) 1994; 43: 2613-7 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人参養栄湯) for improvement of xerostomia induced by oxybutynin hydrochloride.

2. Design

Randomized controlled trial (RCT).

3. Setting

The department of urology of a hospital (although not mentioned, it was probably an outpatient clinic) , Japan.

4. Participants

Sixteen patients who complained of dry mouth out of 20 patients who were diagnosed with psychogenic frequency or unstable bladder (chronic cystitis, neurogenic bladder) and received oxybutynin hydrochloride (6 mg/day) for 2 weeks (all females; mean age, 52.3 years; range, 31–72 years) were examined.

5. Intervention

Arm 1: oxybutynin hydrochloride alone for 2 weeks followed by oxybutynin hydrochloride combined with ninjin'yoeito (人参養栄湯; manufacturer, not specified) (8.1 g/day) for 2 weeks (a total of 4 weeks) (n=8).

Arm 2: oxybutynin hydrochloride alone for 4 weeks (n=8).

6. Main outcome measures

Severity of dry mouth (on a 5-point scale), chewing gum test, frequency of urination evaluated by interview at baseline, 2 weeks, and 4 weeks.

7. Main results

After 2-week treatment with oxybutynin hydrochloride, 16 out of 20 patients (80%) developed xerostomia symptoms (mild in 12 and severe in 4 patients). In arm 1, dry mouth worsened in 5 patients and remained unchanged in 3. In arm 2, dry mouth worsened in no patients, remained unchanged in 2, and improved slightly in 4, and moderately in 2. Dry mouth failed to disappear in any patient in either arm. Response, defined as mild or moderate improvement, was observed in 6 out of 8 patients, yielding a response rate of 75%. The chewing gum test was performed in 3 patients in arm 1 and 4 in arm 2. The total amount of saliva in arm 1 and arm 2 was, respectively, 8.00 mL and 7.30 mL at baseline, 1.27 mL and 1.30 mL at 2 weeks, and 1.13 mL and 2.40 mL at 4 weeks, suggesting that the amount of saliva had increased at 4 weeks. The frequency of urination was 11.875±2.125 times/day at baseline, 8.5±1.125 times/day at 2 weeks, and 8.375±1.0 times/day at 4 weeks in arm 1, and 11.75±2.75 times/day, 8.75±1.625 times/day, and 8.5±1.5 times/day, respectively, in arm 2; there was no between-arm difference.

8. Conclusions

Ninjin'yoeito improves the subjective symptoms of xerostomia induced by oxybutynin hydrochloride but not urinary frequency and therefore is considered to be effective for treating xerostomia induced by oxybutynin hydrochloride.

9. From Kampo medicine perspective

For drug-induced xerostomia, treatment with byakkokaninjinto (白虎加人参湯) or bakumondoto (麦門冬湯) has been frequently reported. Byakkokaninjinto is indicated for patients with *jitsu-sho* (実証, excess pattern) and *netsu-sho* (熱証, heat pattern). Since most patients with nonobstructive dysuria associated with frequency and incontinence are female with *kyo-sho* (虚証, deficiency pattern), ninjin'yoeito may be more effective for dry mouth induced by oxybutynin hydrochloride.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The authors said: "the study was triggered by the encounter with cases in which polydipsia had developed due to dry mouth induced by this drug (oxybutynin hydrochloride), and urinary frequency was not improved because of the increase in urine output." Clinical practice questions were transformed into research questions, and this RCT was conducted to answer them. Such a study is called a "practice-based study" and provides results that can easily be applied in clinical practice. Although there are some concerns about study design, including the small number of patients and lack of objective assessment of the oral cavity, the authors deserve praise for implementing a practice-based study. Further studies of this treatment are expected.

12. Abstractor and date

Tsuruoka K, 31 October 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Umemoto M, Nin T, Miuchi S, et al. Treatment of human dry mouth using various medicines. *Jibiinkoka Rinsho* (*Practica otologica*) 2007; 100: 145-52 (in Japanese with English abstract). Ichushi Web ID: 2007135958

1. Objectives

To compare the efficacy of bakumondoto (麦門冬湯) versus cevimeline hydrochloride hydrate (Evoxac) or nizatidine (Acinon) for treating dry mouth.

2. Design

Randomized controlled trial (RCT).

3. Setting

Gustatory Outpatient Clinic, Department of Otolaryngology, Hyogo College of Medicine, Japan.

4. Participants

One hundred patients with dry mouth (13 males and 87 females; mean age, 69.0 years). Patients with a basal salivary secretion rate of 3 mL/10 min or lower and a chewing-gum-stimulated salivary secretion rate of 10 mL/10 min or lower were included in the study. Exclusion criteria were Sjögren syndrome, diabetes mellitus, use of oral antihistamine or antipsychotic, asthma, ischemic heart disease, epilepsy, prostatic hyperplasia, and glaucoma.

5. Intervention

Arm 1: treatment with bakumondoto (麦門冬湯) (manufacturer, not specified) 3.0 g t.i.d. for 90 days in 24 patients (4 males and 20 females; mean age, 67.4 years), as the bakumondoto (麦門冬湯) group.

Arm 2: treatment with cevimeline hydrochloride hydrate 30 mg t.i.d. for 90 days in 42 patients (3 males and 39 females; mean age, 72.0 years), as the cevimeline group.

Arm 3: treatment with nizatidine 150 mg b.i.d. for 90 days in 34 patients (6 males and 29 females; mean age, 66.0 years), as the nizatidine group.

6. Main outcome measures

The basal rate and chewing-gum-stimulated salivary secretion rate after 90 days of treatment. Subjective symptoms were assessed using a questionnaire on a 4-point scale (“improvement”, “mild improvement”, “no change”, or “worsening”).

7. Main results

The rate of basal salivary secretion increased from 1.0±0.2 mL/10 min to 1.3±0.2 mL/10 min after treatment with bakumondoto, from 1.1±0.1 mL/10 min to 1.6±0.2 mL/10 min after treatment with cevimeline, and from 1.1±0.2 mL/10 min to 2.4±0.3 mL/10 min after treatment with nizatidine. The rate increases in the cevimeline and nizatidine groups were significant (P<0.001). The change in the rate of chewing-gum-stimulated salivary secretion after treatment with cevimeline and nizatidine were similarly significant (P<0.001). Both the basal rate and chewing-gum-stimulated salivary secretion rate were significantly different between the bakumondoto- and the nizatidine-treated groups (both P<0.01) but not between the bakumondoto- and the cevimeline-treated groups. Treatment with cevimeline or nizatidine led to “improvement” in subjective symptoms in 50–57% of patients and “improvement” or “mild improvement” in 85.7% of cevimeline-treated patients and 74.2% of nizatidine-treated patients. In contrast, only 4% of bakumondoto-treated patients noted “improvement”.

8. Conclusions

Cevimeline hydrochloride hydrate and nizatidine but not bakumondoto significantly increase both basal and stimulated salivary secretions and relieve subjective symptoms in patients with dry mouth.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No patients reported “worsening” of symptoms. No adverse drug reactions occurred.

11. Abstractor’s comments

This is a well-designed and well-conducted RCT. The authors speculate that saponins in ginseng, a component of bakumondoto, activate salivary cells by increasing cell membrane permeability. According to their discussion, increase in cell membrane permeability alone does not directly increase the amount of saliva. This was suggested by the fact that dry mouth in most subjects in this trial was due to age-related atrophy and impairment of salivary gland cells. Further studies are expected.

12. Abstractor and date

Tsuruoka K, 12 February 2009, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Satoh Y, Itoh H, Takeyama M. Effects of bakumondoto on neuropeptide levels in human saliva and plasma. *Journal of Traditional Medicines* 2009; 26: 122–30. Ichushi Web ID: 2010089062, J-STAGE

1. Objectives

To evaluate the effects of bakumondoto (麦門冬湯) on neuropeptide levels in human plasma and saliva.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Oita University Hospital, Japan.

4. Participants

Five non-smoking males, aged 25–30 years.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen. The washout period for each drug was four weeks.
Arm 1: a single administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules 18 g.
Arm 2: placebo (lactose + maltose).
Each subject was administered these drugs with an interval of four weeks.

6. Main outcome measures

Substance P, vasoactive intestinal polypeptide (VIP), somatostatin, and calcitonin-gene related peptide (CGRP) levels in plasma and saliva.

7. Main results

Treatment in arm 1 significantly increased saliva levels of substance P level at 40 min after administration of bakumondoto (mean±SD of 37.8±14.7 pg/mL *vs* 23.5±10.2 pg/mL in arm 2; *P*=0.0317) and CGRP at 90 min after administration (65.5±34.4 pg/mL *vs* 24.8±4.5 pg/mL in arm 2; *P*=0.0079), but not VIP, which remained unchanged. Treatment in arm 1 also significantly increased plasma levels of substance P at 90 min after administration (34.1±14.0 pg/mL *vs* 23.3±2.8 pg/mL in arm 2; *P*=0.0127), but not of CGRP and VIP. Saliva volume was increased by 37%, 26%, and 33% at 20, 40, and 60 min in arm 1, but not in arm 2. Saliva secretion was correlated with saliva level of substance P (r=0.66).

8. Conclusions

Bakumondoto increases substance P and CGRP levels in human saliva. An increase in saliva secretion by bakumondoto is partially attributable to increases in these neuropeptides.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is interesting because it evaluates the increases in substance P and CGRP secretion as a contributor to the stimulatory effect of bakumondoto on salivary secretion in a cross-over study. Considering the results of this study, which implicate neuropeptides in the mechanism of action of bakumondoto, and the reported involvement of substance P in the effect of hangekobokuto (半夏厚朴湯) on improvement of swallowing disorder, further elucidation of the pharmacological action of bakumondoto is awaited.

12. Abstractor and date

Okabe T, 27 December 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Suzuki Y, Itoh H, Yamamura R, et al. Significant increase in salivary substance P level after a single oral dose of Japanese herbal medicine Dai-kenchu-to in humans. *Biomedicine & Aging Pathology* 2012; 2: 81-4. Pubmed ID: 23589717

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on salivary secretion and salivary neuropeptide levels in humans after a single oral dose.

2. Design

Randomized controlled trial (cross-over) (RCT-cross over).

3. Setting

Department of Pharmacy, Oita University Hospital, Japan.

4. Participants

Five nonsmoking healthy male volunteers aged 25 to 31 years.

5. Intervention

Since allocation of patients to treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.
Arm 1: Single dose of TSUMURA Daikenchuto (大建中湯) Extract Granules 15 g with 200 mL of water
Arm 2: Single dose of placebo (lactose; dosage not specified) with 200 mL of water
Subjects were crossed over to the alternate arm after a 1-month interval.

6. Main outcome measures

The volume of saliva collected from subjects at rest in a relaxed state at 20, 40, 60, 90, 120, 180, and 240 minutes after administration, and salivary levels of substance P-like immunoreactive substances (SP-IS), calcitonin gene-related peptide (CGRP)-IS, and vasoactive intestinal polypeptide (VIP)-IS measured by enzyme immunoassays.

7. Main results

Although differences in salivary volume between arms 1 and 2 were not significant, the volume increased 1.2–1.5 times during the 20–120 minutes after administration. The salivary SP-IS level in arm 1 was significantly increased at 20, 40, and 60 minutes after administration, compared to that in arm 2 ($P<0.05$). The salivary volume was significantly positively correlated with the SP-IS level (r=0.42, $P=0.0062$). There were no significant differences in CGRP-IS and VIP-IS levels between arms 1 and 2.

8. Conclusions

Daikenchuto increases salivary secretion by increasing the level of substance P. Patients with xerostomia will benefit from treatment with daikenchuto.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The relevant references show that the group to which the authors belong has studied the effect of daikenchuto on neuropeptides in human plasma, effect of pilocarpine on neuropeptides in human saliva, and effect of hangekobokuto (半夏厚朴湯) on neuropeptides in human plasma and saliva since around year 2000. Therefore, this RCT is considered clinical verification of evidence from a series of their studies with an RCT design. Since the present study was conducted in healthy subjects, it is premature to conclude that daikenchuto is effective for xerostomia. This study, however, is a starting point for the verification of new beneficial effects of daikenchuto and hopefully will lead to further development of their research.

12. Abstractor and date

Fujisawa M, 6 June 2015.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Oka S. The effects of Oren-to on stomatitis. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1995; 46: 439–45 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the efficacy and safety of orento (黄連湯) in the treatment of stomatitis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Thirty patients with stomatitis.

5. Intervention

Arm 1: TAIKODO Orento (黄連湯) Extract at a dose of 4.5 g t.i.d. for acute aphthous stomatitis (n=18).
Arm 2: oral steroid ointment 2–3 applications/day for acute aphthous stomatitis (n=5).
Arm 3: no treatment for acute aphthous stomatitis (n=5).
Arm 4: TAIKODO Orento (黄連湯) Extract at a dose of 4.5 g t.i.d. for chronic stomatitis (n=2).

6. Main outcome measures

Number of days to resolution of pain and cure of stomatitis.

7. Main results

The mean number of days to resolution of pain was 2.1, 7.0, and 17.0 in arms 1, 2, and 3, respectively, showing a significant decrease in arm 1 compared even with arm 2. The mean number of days to a cure of stomatitis was 5.5, 12.0, and 17.0 in arms 1, 2, and 3, respectively, showing that time to cure was also significantly decreased in arm 1 compared even with arm 2. In arm 4, pain recurred after resolution.

8. Conclusions

Orento is effective for acute aphthous stomatitis.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

No adverse reactions were reported.

11. Abstractor's comments

This was a valuable controlled clinical trial showing that orento is effective for acute aphthous stomatitis. Despite an imbalance in the number of patients among the groups, the results definitely showed the efficacy of orento. These results suggested that acute aphthous stomatitis may be a symptom of *jitsu-sho* (実証, excess pattern). Chronic stomatitis may require treatment based on *sho*. A future randomized controlled trial should include a description of the randomization method, statistical analysis of the results, and a larger control group.

12. Abstractor and date

Okabe T, 19 August, 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Oh-oka H. The clinical usefulness of gargling with hangeshashinto for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer. *Kampo Medicine* 2018;69: 1-6 (in Japanese with English abstract). Ichushi Web ID: 2018142526 J-STAGE

1. Objectives

To evaluate the clinical usefulness of gargling with hangeshashinto（半夏瀉心湯）for treatment of oral mucositis caused by sunitinib in patients with metastatic renal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (department of urology) (the author belongs to National Hospital Organization, Kobe Medical Center), Japan.

4. Participants

Twenty-two patients (11 men and 11 women) with metastatic renal cancer whose global response to sunitinib was assessed as "stable disease (SD) or better" as of January 2016, and who had sunitinib-induced oral mucositis. These participants had onset of oral mucositis despite oral hygiene instructions (e.g., tooth brushing, gargling, caries treatment) given to all patients before the start of oral sunitinib therapy.

5. Intervention

Arm 1: Gargling with TSUMURA Hangeshashinto（半夏瀉心湯）Extract Granules 2.5 g three times daily, for 30 seconds after each meal, followed by refraining from eating and drinking for 30 minutes (n=12).
Arm 2: Non-gargling group (n=10).

6. Main outcome measures

Changes from baseline in the Karnofsky Performance Status (KPS), oral mucositis grade, body weight, albumin level, hemoglobin level, global self-assessment (GSA) of eating status, etc. in the treatment cycle with highest severity of oral mucositis were analyzed.

7. Main results

Patient baseline characteristics did not statistically differ between the two groups. In Arm 1, the KPS (P=0.046), oral mucositis grade (P=0.002), and GSA (P=0.002) significantly improved after the start of treatment, but body weight, albumin level, and hemoglobin level showed no significant changes. In Arm 2, the oral mucositis grade was not significantly improved, while GSA (P=0.005) significantly improved, but the KPS (P=0.007), body weight (P=0.005), albumin level (P=0.005), and hemoglobin level (P=0.005) significantly decreased.

8. Conclusions

Gargling with hangeshashinto is very effective for treating oral mucositis associated with sunitinib for metastatic renal cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No clinically relevant adverse effects were observed.

11. Abstractor's comments

This clinical study is of interest in that it was designed to determine the effect of gargling with hangeshashinto on oral mucositis associated with sunitinib for metastatic renal cancer. This article failed to specify whether or not the gargled hangeshashinto was ingested after gargling. This study makes us wonder whether similar results can be obtained with irinotecan or the fluorinated pyrimidine class of anticancer drugs, as with the multi-kinase inhibitor sunitinib. Further study results from more patients are awaited.

12. Abstractor and date

Kato Y, 1 September 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Moriyama S, Hinode D, Yoshioka M, et al. Impact of the use of Kampo medicine in patients with esophageal cancer during chemotherapy: a clinical trial for oral hygiene and oral condition. *Journal of medical investigation* 2018; 65: 184-90. CENTRAL ID: CN-01702631, Pubmed ID: 30282858, UMIN ID: UMIN000013183 J-STAGE

1. Objectives

To investigate the impact of daiokanzoto（大黄甘草湯）and hangeshashinto（半夏瀉心湯）on oral mucositis, tongue coating bacteria, and gingiva condition in patients with esophageal cancer undergoing chemotherapy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-four esophageal cancer patients aged 52 to 81 years started on chemotherapy between June 2012 and July 2015 and given professional oral healthcare. Patients were excluded if they had severe infection, severe complications, or drug allergy.

5. Intervention

Arm 1: Sherbet containing TSUMURA Daiokanzoto（大黄甘草湯）Extract Granules 2.5 g t.i.d. (between meals) during the chemotherapy (n=7).
Arm 2: Sherbet containing TSUMURA Hangeshashinto（半夏瀉心湯）Extract Granules 2.5 g t.i.d. (between meals) during the chemotherapy (n=7).
Arm 3: Control (no administration of Kampo medicine) (n=10).

6. Main outcome measures

The primary endpoint was oral mucositis evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4. The secondary endpoints were oral cavity condition and tongue coating bacteria. The oral cavity condition was evaluated using the salivary flow rate, plaque index (PlI), gingival index (GI), and tongue coating index (TCI). The tongue coating bacteria were quantified by counting *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *and Campylobacter rectus CFUs*.

7. Main results

One patient in the control group was excluded because of onset of aspiration pneumonia before first evaluation, and the analysis was conducted on 23 patients (7 patients in the daiokanzoto group, 7 patients in the hangeshashinto group, and 9 patients in the control group). Oral mucositis onset and severity did not significantly differ across the Arms. Among other parameters of the oral cavity condition, the salivary flow rate did not significantly differ across the three Arms. The GI for Arm 1 was significantly better than that for Arm 3 (P=0.04). The endpoint results were better in Arm 2 than in Arm 3. The bacterial counts of *F. nucleatum* and *C. rectus* were lower in Arm 1 than in Arm 3 (P=0.02 for both). Between Arm 2 and Arm 3, no significant differences were observed in bacterial counts.

8. Conclusions

Neither daiokanzoto nor hangeshashinto improves oral mucositis in esophageal cancer patients on chemotherapy receiving oral care. Daiokanzoto may attenuate gingival inflammation and reduce the numbers of periodontopathogenic bacteria, and thus may improve oral health of patients on chemotherapy for esophageal cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

This is a meaningful study that evaluated whether oral mucositis, a common adverse effect of chemotherapy, improves with daiokanzoto or hangeshashinto. The sample size of this study may have been too small to detect any effect of the Kampo intervention added to professional oral care. Future reports with more patients are awaited.

12. Abstractor and date

Koike H, 22 October 2019.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Bessho K, Okubo Y, Hori S, et al. Effectiveness of Kampo medicine (sai-boku-to) in treatment of patients with glossodynia. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 1998; 86: 682-6. CENTRAL ID: CN-00158400, Pubmed ID: 9868725

Yamada T, Bessho K, Murakami K, et al. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. *Shika Yakubutsu Ryoho* (*Oral Therapeutics and Pharmacology*) 1998; 17: 18-22 (in Japanese with English abstract) MOL, MOL-Lib

Yamada T, Bessho K. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 1999; 8: 261-5. Ichushi Web ID: 2000085045

1. Objectives

To evaluate the efficacy of saibokuto (柴朴湯) compared with tranquilizer plus vitamin B complex combination therapy for patients with glossodynia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Oral and Maxillofacial Surgery Kyoto University Hospital, Japan.

4. Participants

Two hundred patients with glossodynia.

5. Intervention

Arm 1: treatment with TSUMURA Saibokuto (柴朴湯) Extract Granules, 2.5g, t.i.d. for 3 months. (n=100)
Arm 2: treatment with diazepam, 2mg, t.i.d. plus vitamin B complex formulation, 1 tablets, t.i.d. for 3 months. (n=100)

6. Main outcome measures

Each of the subjective symptoms (pain, burning sensation, and unpleasant feeling) was evaluated on a 10-point scale. 'Excellent response' was defined as disappearance of all symptoms, 'good response' as improvement of pain, and 'no response' as no improvement of pain.

7. Main results

In arm 1, the percentage of excellent and good responses was 70% at 1 month, 85% at 2 months, and 92% at 3 months after the start of treatment. These values in arm 2 were 74%, 71%, and 69%, respectively ($P<0.05$). Pain relief was experienced in a significantly higher percentage in arm 1 than in arm 2 at 3 months ($P<0.01$).

8. Conclusions

It is suggested that saibokuto (in particular, the three-month treatment) is more effective against glossodynia than the diazepam plus vitamin B complex formulation.

9. From Kampo medicine perspective

The discussion contains some speculations.

10. Safety assessment in the article

Mild anorexia and diarrhea were reported, respectively, in 3 and 1 patient receiving saibokuto, and severe sleepiness was reported in 33 patients receiving diazepam.

11. Abstractor's comments

This study suggests that saibokuto monotherapy (for 3 months) is more effective against glossodynia than the combination therapy (tranquilizer plus vitamin B complex). Also, saibokuto treatment is safe, as indicated by the low frequency of adverse effects and the possibility of long-term treatment. Although the sample size of the study described in the two papers by Yamada et al (1998, 1999) was about half that in the present study, the results were very similar.

12. Abstractor and date

Okabe T, 17 September 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Koide A. Effect and role of TJ-43: Rikkun-shi-to from the aspects of endoscopic findings and QOL improvement in GERD patients. *Medical Tribune Online* (*Digestive Disease Week: DDW*) 2005: 6-7 (in Japanese).

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) combined with a proton pump inhibitor (PPI) for treating gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

Fifty-six patients with gastroesophageal reflux disease.

5. Intervention

Arm 1: oral administration of omeprazole (20 mg) plus TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the PPI + rikkunshito (六君子湯) group.
Arm 2: oral administration of omeprazole (20 mg), as the PPI alone group.

6. Main outcome measures

Endoscopic healing rates of reflux esophagitis and Gastrointestinal Symptom Rating Scale (GSRS) scores. The follow-up was scheduled at 8 weeks.

7. Main results

The endoscopic healing rates of reflux esophagitis at 8 weeks were not significantly different between the two groups. The PPI + rikkunshito group achieved significantly better scores on the following three GSRS domains: overall gastrointestinal symptoms, reflux, and abdominal pain.

8. Conclusions

Rikkunshito combined with PPI improves the quality of life (QOL) in GERD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Rikkunshito-combined therapy resulted in further improvement of QOL in GERD patients, especially in those with endoscopy-negative GERD (non-erosive reflux disease: NERD). On this basis, the authors concluded that PPI + rikkunshito is effective for "the improvement of QOL, particularly in NERD patients who are unlikely to respond to PPI."

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Kato S, Nakajima T, Matsuda T, et al. The effectiveness of the traditional Kampo medicine, "banxia houpu tang (hangekobokuto)" to respiratory disturbance by esophageal reflux disease. *Kampo to Saishin-Chiryo* (*Kampo & the Newest Therapy*) 2005; 14: 333-8 (in Japanese). Ichushi Web ID: 2006091322

1. Objectives

To evaluate the efficacy of hangekobokuto (半夏厚朴湯)-combined treatment in patients with respiratory symptoms associated with refractory gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

No description of the setting is available; the authors belong to the Department of Cardiology and Pneumology, Dokkyo Medical University, Japan.

4. Participants

Nineteen GERD patients whose digestive symptoms but not respiratory symptoms (including cough, sputum, throat discomfort, and mild dyspnea) were relieved by conventional western medical treatments. All patients had no history of smoking or respiratory disease.

5. Intervention

Arm 1: treatment with TSUMURA Hangekobokuto (半夏厚朴湯) Extract Granules (7.5 g/day) in 10 patients.
Arm 2: no treatment in 9 patients.
In arm 1, hangekobokuto (半夏厚朴湯) was administered in addition to the usual western medical treatment for 6 months, and then hangekobokuto (半夏厚朴湯) was discontinued. The course of respiratory symptoms was examined for a total of 12 months in both the hangekobokuto (半夏厚朴湯)-combined and no-treatment arms.

6. Main outcome measures

Cough, sputum, throat discomfort, and mild dyspnea.

7. Main results

The degree of improvement was evaluated on a 5-point scale. Respiratory symptoms were significantly improved after a month of treatment in arm 1, compared with arm 2 ($P<0.01$). This effect persisted up to 6 months after start of combined treatment ($P<0.01$) and 6 months after discontinuation of hangekobokuto ($P<0.01$).

8. Conclusions

Hangekobokuto relieves respiratory symptoms, including cough, sputum, throat discomfort, and mild dyspnea, that are unresponsive to western medical treatments in GERD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Respiratory or ear-nose-throat symptoms are reported to occur in 30–50% of GERD patients, depending on the literature. Western medical treatments combine proton pump inhibitors, H_2 blockers, or stomachics, with theophylline formulations, expectorants, antitussives, erythromycin antibiotics, or inhaled steroids. In some patients, however, these treatments fail to improve these symptoms. This study can be praised for examining these clinically difficult-to-treat patients. The study method has several problems including failure to measure inter-subject variability of GERD scores evaluated according to the Los Angeles classification, small sample size, and lack of a safety and adverse drug reactions assessment.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Koide A. Establishment of new treatment strategy for non-erosive reflux disease (endoscopy-negative gastroesophageal reflux disease) – potential of rikkunshito*. *MedicalQ* 2006; 187 (in Japanese).

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) Extract Granules for treatment of non-erosive reflux disease (NERD) unresponsive to proton pump inhibitors (PPIs).

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available; the author belongs to a clinic, Japan.

4. Participants

One hundred and eighteen patients with PPI-unresponsive NERD.

5. Intervention

Arm 1: treatment with omeprazole (200 mg), as the PPI alone group, n=37.
Arm 2: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the rikkunshito alone group, n=39.
Arm 3: treatment with omeprazole (200 mg) and TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the PPI + rikkunshito (六君子湯) group, n=42.
The duration of treatment was 4 weeks in all arms.

6. Main outcome measures

Gastrointestinal Symptom Rating Scale (GSRS) score (which includes ratings of overall gastrointestinal symptoms, reflux, abdominal pain, and dyspepsia).

7. Main results

Scores of overall gastrointestinal symptoms and reflux were significantly more improved in arm 3 than in arms 1 and 2; the scores in arms 1 and 2 were similar. The abdominal pain score was similarly improved in all three arms. Dyspepsia score was significantly more improved in arms 2 and 3 than in arm 1, but the scores in arms 2 and 3 were similar.

8. Conclusions

TSUMURA Rikkunshito Extract Granules is effective for relieving clinical symptoms of NERD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study deserves praise for conducting a RCT using TSUMURA Rikkunshito Extract Granules as a study drug in patients with treatment-unresponsive NERD. Unfortunately, the mechanism was not discussed, and endoscopic findings and other features were not mentioned. Publication of the latter is expected in the future.

12. Abstractor and date

Kogure T, 26 January 2009.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Tominaga K, Fujiwara Y, Shimoyama Y, et al. Rikkunshito improves PPI-refractory NERD: a prospective randomized multi-center trial in Japan. *Gastroenterology* 2010; 138: S655–6.
Tominaga K, Fujiwara Y, Arakawa T, et al. GERD — rikkunshito*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 2011; 99: 771–6 (in Japanese). MOL, MOL-Lib
Tominaga K, Fujiwara Y, Fujimoto K, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multi-center trial in Japan. *Journal of Gastroenterology* 2012; 47: 284-92. Pubmed ID: 22081052

1. Objectives

To evaluate the effectiveness of rikkunshito (六君子湯) for patients with proton pump inhibitor (PPI)–resistant gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Gastroenterology, Osaka City University Hospital, and four other research institutes (research groups), Japan.

4. Participants

One hundred and four PPI–resistant GERD patients who showed no improvement despite taking rabeprazole (RPZ 10 mg/day) for more than four weeks.

5. Intervention

Arm 1: combination group: Participants continued taking 10 mg/day of RPZ and also took TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for four weeks (n=53).
Arm 2: double-dose group: Participants doubled their RPZ dose to 20 mg/day for four weeks (n=51).

6. Main outcome measures

Frequency Scale for Symptoms of GERD (FSSG) score and improvement rate.

7. Main results

After allocation, three participants were excluded before administration commenced, making 50 participants in arm 1 and 51 in arm 2. There were no significant differences between participants in both groups before administration in age, gender, body mass index, or endoscopic findings after PPI monotherapy, however, FSSG scores were significantly higher in arm 1 before the trial commenced. The data for 45 participants in arm 1 and 50 in arm 2 were included for analysis after the four-week administration period concluded. FSSG total scores (arm 1, $P<0.001$; arm 2, $P<0.01$) as well as reflux and indigestion subscores improved significantly in both groups after 4 weeks of treatment compared to before administration, while the before/after improvement rates were similar in both groups. Sub-group analysis of male patients with non-erosive reflux disease (NERD) showed significant improvement in arm 1 compared to arm 2, and significant improvement in FSSG scores. Remarkably, the ectomorphic group showed similar trends for BMI.

8. Conclusions

Rikkunshito is effective for patients with PPI–resistant GERD (and especially NERD). The effects of combined treatment with RPZ and Rikkunshito are similar to treatment with double the RPZ dosage.

9. From Kampo medicine perspective

The researchers did not analyze participants' *sho* (証, patterns), but remarkable and significant effects were observed in ectomorphic males.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

There is still no clear definition of PPI–resistant GERD and no treatments have yet been established. Against that background, this RCT holds great clinical significance because it compared combined rikkunshito and RPZ with double-dosage RPZ in GERD patients who did not respond to 10 mg/day of RPZ. Participants showed similar rates of improvement; however, the exacerbation rate was lower in the rikkunshito and RPZ group, which indicates the effectiveness of rikkunshito in combination.

12. Abstractor and date

Kogure T, 31 December 2012, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. *Nikkei Medical* (*Supplement*) 2010; 8: 27 (in Japanese).

Morita T, Furuta K, Adachi K, et al. Effects of Rikkunshito (TJ-43) on esophageal motor function and gastroesophageal reflux. *Journal of Neurogastroenterology and Motility* 2012; 18: 181-6. Pubmed ID: 22523727

1. Objectives

To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.

2. Design

Randomized controlled crossover trial (RCT - cross over).

3. Setting

Shimane University Hospital, Japan.

4. Participants

Ten healthy people.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days, no administration for one week, then placebo for 7 days (number of participants not specified).

Arm 2: placebo for 7 days, no administration for one week, then TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days (number of participants not specified).

6. Main outcome measures

Lower esophageal sphincter (LES) resting pressure, esophageal peristaltic contraction pressure after drinking water, postprandial gastroesophageal reflux frequency.

7. Main results

LES resting pressure was significantly higher in supine position with rikkunshito administration compared to placebo administration (P=0.047), but there was no significant difference when in sitting position. No significant between-group difference attributable to rikkunshito administration was observed for esophageal peristaltic contraction pressure after drinking water or postprandial gastroesophageal reflux frequency.

8. Conclusions

Rikkunshito raised LES resting pressure in healthy subjects in supine position, but not in sitting position, and had no effect on esophageal peristaltic contraction pressure after drinking water or postprandial gastroesophageal reflux frequency.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Gastroesophageal reflux has been increasing in recent years, especially among the elderly, prompting hope that rikkunshito would be effective for patients in whom it could not be satisfactorily controlled with proton pump inhibitors. This study in healthy subjects is the first step toward generating that evidence base. Rikkunshito raised LES resting pressure in supine position, but there was no significant difference in sitting position, and no significant difference in any of the other outcomes: it was a study of healthy young people (mean age: 22.8 years), so the results should be accepted for what they are. However, there was no mention of the numbers of participants being allocated by a randomized process. Based on these outcomes, the authors will hopefully repeat this investigation not with healthy subjects, but with actual gastroesophageal reflux patients, as the authors themselves mention in the paper.

12. Abstractor and date

Motoo Y, 31 December 2012, 31 December 2013..

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. *Nikkei Medical* (*Supplement*) 2010; 8: 27 (in Japanese).

1. Objectives

To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.

2. Design

Randomized controlled crossover trial (RCT - cross-over).

3. Setting

No description (the author is from the Second Department of Internal Medicine, Shimane University), Japan.

4. Participants

Twenty healthy volunteers.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days, then placebo for 7 days (number of participants not specified).

Arm 2: placebo for 7 days then TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days (number of participants not specified).

6. Main outcome measures

Saliva amount, salivary epidermal growth factor (EGF), salivary bicarbonate concentration.

7. Main results

Rikkunshito caused no significant change in saliva amount, salivary EGF, or salivary bicarbonate concentration.

8. Conclusions

Rikkunshito increases lower esophageal sphincter (LES) resting internal pressure in healthy people, but does not affect saliva excretion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Saliva dilutes refluxed acid and neutralizes bicarbonate, while EGF appears to aid repair of esophageal mucous cells. Decreased saliva excretion in conditions including gastroesophageal reflux, Sjogren's syndrome, diabetes, old age, and stress facilitate the onset of reflux esophagitis. This trial was conducted on the assumption that increases in saliva excretion, and therefore in EGF and bicarbonate, by rikkunshito will improve gastroesophageal reflux disease (GERD). But the study found no significant effect on these factors, which at this point suggests that rikkunshito's main mechanism of action is the increase in LES pressure. The subjects in this study were healthy volunteers, so a further study might verify that the improvement of GERD by rikkunshito is due to increased saliva excretion. To confirm the mechanism, participants with reduced saliva excretion (e.g., elderly people, diabetics, or Sjögren's syndrome sufferers) should be compared to participants with normal saliva excretion to find the differences among them.

12. Abstractor and date

Motoo Y, , 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Tokashiki R, Okamoto I, Funato N, et al. Rikkunshito improves globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. *World Journal of Gastroenterology* 2013; 19: 5118-24. Pubmed ID: 23964146

1. Objectives

To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton-pump inhibitor (PPI)-refractory laryngopharyngeal reflux (LPR).

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (university hospital otorhinolaryngology department), Japan.

4. Participants

In total, 22 patients with PPI-refractory LPR aged 20-76, between March 2007 and December 2008.

5. Intervention

Following administration of lansoprazole (30 mg) once daily for 2 weeks, patients with LPR symptoms and at least a score of 3 for acid reflux, abdominal pain, and dyspepsia on the gastrointestinal symptom rating scale (GSRS) were assigned to two groups using the envelope method. Excluded from the study were patients taking psychoactive or other gastrointestinal drugs, during pregnancy, breastfeeding mothers, and patients with sinusitis, asthma, or organic disease.

Arm 1: TSUMURA Rikkunshito (六君子湯) (2.5 g t.i.d) alone for four weeks (n=11).

Arm 2: TSUMURA Rikkunshito (六君子湯) (2.5 g t.i.d) plus lansoprazole (30 mg/day) for four weeks (n=11).

Outcome measures were compared before and four weeks after administration.

6. Main outcome measures

(1) LPR symptoms (globus sensation, sore throat, and excessive laryngeal care) were assessed using a Visual Analogue Scale (VAS). (2) Gastrointestinal symptoms were assessed on the GSRS (comprised of five domains including abdominal and reflux symptoms). (3) Gastric emptying was assessed with a radio-opaque marker (carried out on 18 patients).

7. Main results

LPR symptoms (VAS score) decreased significantly in both groups after four weeks, but there was no significant difference between the groups. Of the LPR symptoms, sore throat decreased significantly in the rikkunshito plus PPI group compared to the rikkunshito-alone group, however, there was no significant difference between the two groups for excessive laryngeal care. Gastrointestinal symptoms decreased significantly on the GSRS in both groups. Gastric emptying improved in the rikkunshito-alone group, but there was no significant before-after difference, while significant improvement was observed in the rikkunshito plus PPI group, however, there was no significant difference between the two groups. Examination of the relation between gastric emptying and globus sensation improvement found a significant correlation between the two.

8. Conclusions

Rikkunshito is effective for PPI-refractory LPR (especially globus sensation). Gastric emptying capacity may be involved in the mechanism of action.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse event or reaction was observed during the protocol period.

11. Abstractor's comments

While PPI is effective for LPR, quite a few patients do not respond. The protocols for this study provided for a two-week PPI administration period before non-responsive patients were randomly assigned to a rikkunshito-alone group or a PPI combined with rikkunshito group for the four-week clinical trial, which made for a highly precise design. As well as obtaining significant clinical outcomes in relation to efficacy, the authors suggest the involvement of improvement in gastric emptying in the mechanism of action. Hopefully the authors will carry out further clinical trials with larger samples in future.

12. Abstractor and date

Kogure T, 31 March 2017.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Tominaga K, Kato M, Takeda H, et al. A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study. *Journal of Gastroenterology* 2014; 49: 1392-405. Pubmed ID: 24535455

Sakata Y, Tominaga K, Kato M, et al. Clinical characteristics of elderly patients with proton pump inhibitor-refractory non-erosive reflux disease from the G-PRIDE study who responded to rikkunshito. *BMC Gastroenterology* 2014; 14: 116. Pubmed ID: 24990161

1. Objectives

To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton pump inhibitor-refractory non-erosive reflux disease.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

One university hospital department of gastroenterology and 48 other medical institutions (including university hospitals, non-university hospitals, clinics), Japan.

4. Participants

Two hundred and forty-two patients with PPI-refractory (FSSG [Frequency Scale for the Symptoms of gastroesophageal reflux disease {GERD}] scores greater than 8 after treatment with regular use of rabeprazole (RPZ), omeprazole, and lansoprazole for 4 weeks or longer) for non-erosive reflux disease (NERD).

5. Intervention

Arm 1: Oral administration of RPZ 10mg/day + TSUMURA Rikkunshito (六君子湯) 7.5g/day in 3 divided doses (administration period: 8 weeks) (n=109).

Arm 2: Oral administration of RPZ 10mg/day + placebo (granules that have a taste and scent similar to rikkunshito and are packaged similarly to rikkunshito [六君子湯]) 7.5g/day in 3 divided doses (n=108).

6. Main outcome measures

FSSG, GSRS (Gastrointestinal Symptom Rating Scale), and SF-8 (Short-Form Health survey-8) scores. Each domain of the SF-8.

7. Main results

Sixteen patients in the rikkunshito-administered group and 9 patients in the placebo-administered group were excluded due to invalid results or drop out due to adverse events. Both groups showed no significant improvement in FSSG and GSRS scores at week 4 and week 8. Mental component Summary (MCS) scores improved significantly in the rikkunshito group at week 4 compared to the placebo group ($P<0.05$). In patients aged over 65, acid-related dysmotility symptoms (ARD) improved significantly in the rikkunshito group at week 8.

8. Conclusions

Administration of rikkunshito in addition to RPZ improved subjective symptoms of PPI-refractory NERD; however, the difference compared to placebo was not statistically significant.

9. From Kampo medicine perspective

None. However, the improvement in the SF-8 MCS score was prominent in patients with BMI below 22.

10. Safety assessment in the article

There were no differences in serious complications related to the treatment drugs.

11. Abstractor's comments

Conducting a multi-center placebo-controlled trial in patients with PPI-refractory NERD deserves praise. However, the improvement in subjective symptoms of PPI-refractory NERD due to administration of rikkunshito plus RPZ (when compared with placebo) was not statistically significant. A sub-analysis and supplementary paper demonstrated that rikkunshito is effective in improving MCS score and ARD (manifesting as abdominal distension, stomach feeling heavy, and indigestion after meals) in elderly patients. Future analysis of its intended use should be anticipated.

12. Abstractor and date

Kogure T, 31 March 2017

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takeuchi T, Hongo H, Kimura T, et al. Efficacy and safety of hangeshashinto for treatment of GERD refractory to proton pump inhibitors: Usual dose proton pump inhibitors plus hangeshashinto versus double-dose proton pump inhibitors: randomized, multicenter open label exploratory study. *Journal of Gastroenterology* 2019; 1-12. Pubmed ID: 31037449, UMIN ID: UMIN000021251

1. Objectives

To determine the efficacy and safety of hangeshashinto（半夏瀉心湯）in treating patients with proton pump inhibitor (PPI)-refractory gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Seven hospitals, Japan (the author belongs to Osaka Medical College Hospital Endoscopy Center).

4. Participants

Seventy-eight patients with GERD refractory to a standard regimen containing PPI for at least 4 weeks.

5. Intervention

Arm 1: Combination of rabeprazole at a standard dose (10 mg/day) plus TSUMURA Hangeshashinto（半夏瀉心湯）Extract Granules (2.5 g three times daily for 4 weeks) (n=42).

Arm 2: Rabeprazole at a double dose (20 mg/day for 4 weeks) (n=36).

6. Main outcome measures

Primary end points of efficacy were the degree of improvement in the "Frequency Scale for the Symptoms of GERD (FSSG)" score, and the change in FSSG score over time. Secondary end points included acid-related dyspepsia (ARD) score and gastrointestinal-related QOL.

7. Main results

The analysis was conducted on 70 patients (i.e., 38 patients in Arm 1 and 32 patients in Arm 2) after exclusion of dropouts, etc. The change in the FSSG score showed no significant difference between the two groups. While the total FSSG score significantly decreased in both groups ($P < 0.001$), the ARD score in the hangeshashinto-combined group significantly decreased from Week 1 of treatment ($P < 0.05$). In the hangeshashinto-combined group, compared with the double-dose PPI group, the ARD score significantly improved in the subsets of patients with BMI <22 ($P< 0.05$) and age <65 years ($P< 0.05$).

8. Conclusions

Hangeshashinto may be beneficial for patients with PPI-refractory GERD, particularly in non-obese and non-elderly patients with dyspepsia symptoms.

9. From Kampo medicine perspective

The subgroup analyses for non-obese and non-elderly patients take the Kampo medicine concept of "*Kyojitsu* (*虚実*, deficiency and excess)" into account.

10. Safety assessment in the article

Adverse events that could be causally related to the treatment occurred in 3 of 38 patients in the hangeshashinto-combined group and none of 33 patients in the control group, with no significant difference in the incidence. The adverse events noted in the hangeshashinto-combined group were soft stool, nausea, and abnormal liver function.

11. Abstractor's comments

This RCT in GERD patients refractory to the standard dose of PPI is of value in that it showed earlier onset of symptomatic relief with the addition of hangeshashinto compared with a double-dose of PPI. Although the primary endpoint of "Frequency Scale for the Symptoms of GERD" showed no difference, absence of difference between adding Kampo medicine and doubling the PPI dose is meaningful from the viewpoint of the health economy. However, since this study used an open-label design, and the assessment scale was dependent on subjective symptoms, a placebo effect cannot be excluded. If the control group also used the standard dose of PPI, the primary endpoint of efficacy also could have shown a significant difference in favor of the hangeshashinto-combined group. Hangeshashinto is indicated for symptoms including belching and heartburn, which are also symptoms of GERD. This study provides evidence that supports recommending hangeshashinto in treating PPI-refractory GERD in non-obese and non-elderly patients.

12. Abstractor and date

Motoo Y, 28 August 2019.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Nakahara A, Kashimura H, Fukutomi H. Gastric ulcer - saikokeishito or shigyakusan monotherapy -*. *Nikkei Medical* (separate-volume supplement) 1988; 17: 20-1 (in Japanese).
Fukutomi H, Nakahara A. Traditional oriental therapy of the gastric ulcer. *Shokakika* (*Gastroenterology*) 1990; 12: 159-65 (in Japanese)

1. Objectives

To compare the efficacy of saikokeishito (柴胡桂枝湯), H_2 receptor antagonist, or their combination for preventing recurrence of gastric ulcer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifty-one institutions (names are not specified; the authors belong to the Institute of Clinical Medicine, University of Tsukuba), Japan.

4. Participants

One hundred and eighty-nine patients whose gastric ulcer was healed by treatment with the combination of TSUMURA Saikokeishito Extract Granules and H_2 receptor antagonist.

5. Intervention

Arm 1: treatment with TSUMURA Saikokeishito Extract Granules (柴胡桂枝湯) 5.0 g/day (TJ-10 group; n=40).
Arm 2: treatment with H_2 receptor antagonist 400 mg/day (H_2-blocker group; n=32).
Arm 3: treatment with TSUMURA Saikokeishito Extract Granules plus H_2 receptor antagonist (combined group; n=54)
The dose was halved after month 4.

6. Main outcome measures

Recurrence of gastric ulcer.

7. Main results

The cumulative recurrence rate (calculated monthly) was around 24% at 6 months and similar for all three groups. In patients aged under 50 years, the recurrence rate was lowest after treatment with the combination, whereas in patients aged 50 years or older, the rate was around 20% and not different among the three groups.

8. Conclusions

For patients aged 50 or older, saikokeishito monotherapy is the preferred maintenance therapy for gastric ulcer because (unlike receptor antagonist) it is less associated with age-related reduction of drug metabolizing capacity and adverse reactions.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinically valuable report showed that the effectiveness of saikokeishito is comparable to that of H_2 receptor antagonist as a maintenance therapy for gastric ulcer. Because the cumulative rates of recurrence for the three groups were similar and the Kampo medication caused fewer adverse reactions, the authors concluded that Kampo therapy is a treatment of choice for patients aged 50 or older. However, the paper contains no results or discussion regarding adverse drug reactions. So the submission as an original article is desired, and descriptions of adverse drug reactions should be included.

12. Abstractor and date

Arai M, 18 October 2008, 6 January 2010, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Watanabe H. A study of peptic ulcer maintenance therapy combined with Kampo medicines*. *Kampo Igaku* (*Kampo Medicine*) 1995; 19: 18-21 (in Japanese).

1. Objectives

To evaluate the usefulness of H_2-blocker (cimetidine) combined with Kampo medicine (shigyakusan [四逆散], saikokeishito [柴胡桂枝湯]) as a maintenance therapy for peptic ulcer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Department of Gastroenterology, Matsudo City Hospital), Japan.

4. Participants

Thirteen patients who were confirmed to have peptic ulcer (8 with gastric ulcer, 5 with duodenal ulcer) by upper gastrointestinal endoscopy, and received two-month initial therapy (H_2-blocker + protective factor-enhancing agent combination) and one-year maintenance therapy.

5. Intervention

Arm 1: treatment with cimetidine 400 mg s.i.d. (before bedtime) + Kampo medicine twice daily (morning and evening) (n=7; TSUMURA Shigyakusan Extract Granules (四逆散) 2.5 g b.i.d. [n=4], TSUMURA Saikokeishito Extract Granules (柴胡桂枝湯) 2.5 g b.i.d. [n=3]).

Arm 2: treatment with cimetidine 400 mg s.i.d. (before bedtime) + sucralfate 1.0 g b.i.d. (morning and evening) (n=6).

6. Main outcome measures

Recurrence of ulcer, change in ulcer scar stage, and improvement of redness of the gastric antral mucosa.

7. Main results

The effects were evaluated by upper gastrointestinal endoscopy after a year of treatment. No recurrence was observed in either arm. In 4 of 6 patients (66.7%) in the sucralfate group and 5 of 7 (71.4%) in the Kampo group, scars had improved from stage S_1 at the start of maintenance therapy to stage S_2 at 1 year. In cases with marked redness of gastric antral mucosa, mild improvement was observed in 2 (33%), no change in 3 (50%), and worsening in 1 (17%) of 6 sucralfate-treated patients; moderate improvement was observed in 1 (25%) and mild improvement in 3 (75%) of 4 shigyakusan-treated patients.

8. Conclusions

Kampo medicine (TSUMURA Shigyakusan Extract Granules, TSUMURA Saikokeishito Extract Granules) plus H_2-blocker (cimetidine) combination therapy is likely to have remarkable efficacy for preventing recurrence of ulcer.

9. From Kampo medicine perspective

Based on the endoscopic findings, patients with marked redness and irregularity of gastric antral mucosa, which is regarded as *jitsu-sho* (実証, excess pattern), were assigned to the shigyakusan treatment, and patients with less evident findings, which is regarded as *kyo-sho* (虚証, deficiency pattern), to the saikokeishito treatment.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

With the recent advent of *Helicobacter pylori* eradication therapy for peptic ulcer, recurrence of ulcer and incidence of gastric cancer have remarkably decreased. However, some patients are reported to fail or be ineligible for the eradication therapy. This study may be, even now, very meaningful for those cases. Some points need further clarification, including incomplete statistical evaluation of the efficacy owing to the small sample size, the possibility that the patient population was atypical in that no one developed recurrence of ulcer, and the need for a description of adverse drug reactions. In addition, patients were assigned to the shigyakusan or saikokeishito treatment based on the author's empirical rule; this point also needs reconsideration. The study will be more meaningful when these points are considered and a larger number of patients are enrolled.

12. Abstractor and date

Arai M, 18 October 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Ohta Y, Nishioka M, Yamamoto Y, et al. Multicenter clinical evaluation of Kampo preparations for medical use in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - comparison with gefarnate as a control -*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1990; 78: 2935-46 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of rikkunshito (六君子湯) and hangeshashinto (半夏瀉心湯) for treating acute gastritis and acute exacerbation of chronic gastritis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Four university medical schools, including Ehime University School of Medicine (Third Department of Internal Medicine), Kagawa Medical School (Third Department of Internal Medicine), and Kochi Medical School (First Department of Internal Medicine), plus 13 hospitals (17 institutions in total), Japan.

4. Participants

Sixty-four patients who (i) visited one of the participating institutions between October 1986 and May 1987; (ii) had subjective symptoms such as abdominal pain and abdominal bloating; and (iii) were endoscopically confirmed to have gastritis lesion, diagnosed with gastritis (acute gastritis or acute exacerbation of chronic gastritis), and had indications for medical therapy. Patients with the following conditions were excluded: (i) peptic ulcer (except for scarring) or gastric cancer; (ii) so-called verrucous erosion with marginal elevations, or serious complications, particularly gastrointestinal disease (such as hepatobiliary disease); or (iii) known or suspected pregnancy.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito Extract Granules (六君子湯) 2.5 g t.i.d. (n=20).
Arm 2: treatment with TSUMURA Hangeshashinto Extract Granules (半夏瀉心湯) 2.5 g t.i.d. (n=14).
Arm 3: treatment with gefarnate 100 mg t.i.d. (n=16).
Treatment duration was 4 weeks in principle; treatment was discontinued when symptoms disappeared during this period.

6. Main outcome measures

Subjective symptoms (nausea, anorexia, epigastric pain, abdominal bloating, abdominal discomfort, heartburn, belching, and fatigue), endoscopic findings (redness, erosion, edema, and hemorrhage), and laboratory findings (routine blood test, serum biochemistry, and urinalysis).

7. Main results

No statistically significant among-arm differences in subjective symptom improvement (5-point scale) and in endoscopic improvement (5-point scale) were found. The scores for both total endoscopic improvement and overall improvement (evaluated on the basis of subjective symptoms and endoscopic findings) tended to be slightly higher in arms 1 and 2 ($P<0.1$), but showed no statistically significant differences between each two arms. Overall usefulness (5-point scale) was assessed as “useful” or better in 80.0%, 85.7%, and 56.3% of patients, respectively, in arms 1, 2, and 3. The among-arm distribution of usefulness was significantly different ($P<0.05$). Multiple comparisons between two arms showed significantly higher usefulness score in arm 2 than in arm 3 ($P<0.05$).

8. Conclusions

Both TSUMURA Rikkunshito Extract Granules and TSUMURA Hangeshashinto Extract Granules result in improvements equivalent to or better than those obtained with gefarnate in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis); thus they are clinically effective and safe agents.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions or laboratory abnormalities were not reported in any of the arms.

11. Abstractor’s comments

This report is clinically relevant in that the authors conducted a multicenter study comparing two types of Kampo preparations with an existing mucosal protectant and defining in detail the outcome measures. Recently, in western medicine, the idea of functional dyspepsia has been introduced and classification based on clinical symptoms prevails. In the future, the efficacy of Kampo formulas might be clarified using a symptoms-based method, in which subjective symptoms that respond specifically to each Kampo formula are identified by comparing responders and non-responders, and then selecting participants based on the specific symptoms. Future studies are expected.

12. Abstractor and date

Arai M, 20 October 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - a multicenter comparative study using sodium azulene sulfonate as a control -*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1991; 79: 789-810 (in Japanese).

1. Objectives

To determine the efficacy and safety of rikkunshito (六君子湯) for treating gastritis (acute gastritis and acute exacerbation of chronic gastritis).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Forty-five institutions including Shizuoka General Hospital, Japan.

4. Participants

Two hundred and thirty-six patients with gastritis (acute gastritis or acute exacerbation of chronic gastritis) in whom 3 or more indefinite complaints of epigastric distress, were observed and peptic ulcer and gastric cancer were excluded by endoscopy or radiography. Of 236 participants, 207 were included in the analysis population.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before or between meals for 4 weeks (n=109).
Arm 2: treatment with Marzulene-S Granules 2 g/day in three divided doses for 4 weeks (n=98).

6. Main outcome measures

Subjective symptoms and endoscopic findings.

7. Main results

The improvement in symptom ratings for anorexia (at 1 week), epigastric pain (at 2 and 4 weeks), abdominal discomfort (at 2 weeks), and fatigability (at 1 and 4 weeks) were significantly greater in arm 1. The improvement in endoscopically assessed erosion was significantly higher in arm 1. The overall improvement in endoscopic findings at 4 weeks, and improvements in the global symptom score and global utility rating at 4 weeks were significantly greater in arm 1.

8. Conclusions

TSUMURA Rikkunshito is clinically useful for treating gastritis (acute gastritis and acute exacerbation of chronic gastritis) as it resulted in greater improvements compared with Marzulene-S.

9. From Kampo medicine perspective

Rikkunshito tended to result in greater improvements compared with the control drug in patients who had “decreased strength and fatigability”, “choking sensation in the epigastric region”, “low tension of the abdominal wall” and “splashing sounds in the gastric region”.

10. Safety assessment in the article

Only one adverse drug reaction occurred—skin rash in one patient who consequently discontinued treatment.

11. Abstractor’s comments

This paper describes a clinical evaluation of TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis). This study triggered a series of clinical trials on rikkunshito. Notably, Kampo medical findings, such as “tension of the abdominal wall” and “splashing sounds in the gastric region”, were also included in the analysis. The experimental approach of this study may have been progressive for that time.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takemoto T, Matsuda K, Tada M, et al. Clinical evaluation of the efficacy of TJ-43 Tsumura Rikkunshi-To on gastritis with abdominal symptoms - a multicenter group study in comparison with cetraxate -. Shokakika (Gastroenterology) 1990; 12: 223-34 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy and safety of TSUMURA Rikkunshito (六君子湯) for treating gastritis in a comparison with cetraxate as a control.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Sixteen institutions including Yamaguchi University Hospital, Japan.

4. Participants

Seventy patients who were diagnosed with atrophic, superficial, or erosive gastritis by endoscopy and had epigastric complaints such as abdominal pain or bloating.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 4 weeks (n=38).

Arm 2: treatment with cetraxate hydrochloride 200 mg q.i.d. before meals and bedtime for 4 weeks (n=32).

6. Main outcome measures

Subjective symptoms and endoscopic findings.

7. Main results

The rate of improvement in fatigue was significantly higher in arm 1 than in arm 2. The rate of improvement in endoscopically evaluated erosive disease, rate of global improvement in symptoms (both subjective and endoscopically assessed), and the utility rating tended to be higher in arm 1. The overall rate of improvement in subjective symptoms was significantly higher in arm 1.

8. Conclusions

TSUMURA Rikkunshito seems to have an excellent clinical efficacy for treating gastritis with epigastric disturbance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

In the present paper, the clinical utility of TSUMURA Rikkunshito in comparison with that of cetraxate (the control) is determined as treatment for gastritis. It was a multicenter controlled trial, similar to that described in "Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - a multicenter comparative study using sodium azulene sulfonate as a control -*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1991; 79: 789-810 (in Japanese)". Both studies showed similar results, but the statistical significance of differences was weaker in the present study. This discrepancy might be due to the small number of patients enrolled.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Kawamura S, Okita K, Tada M, et al. Clinical comparison of TSUMURA Rikkunshito and sulpiride in the treatment of indefinite complaints of epigastric distress - mainly the antidepressive effect and the improvement of gastric emptying -*. *Progress in Medicine* 1992; 12: 1156-62 (in Japanese with Chinese abstract).

1. Objectives

To evaluate the efficacy and safety of TSUMURA Rikkunshito (六君子湯) compared with sulpiride for treating epigastric indefinite complaints complicated by depression.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The study appears to be multicenter, but details are not available, Japan.

4. Participants

Twenty-eight patients with indefinite complaints of epigastric distress and depression.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 4 weeks (n=15).
Arm 2: treatment with sulpiride 150 mg t.i.d. after meals for 4 weeks (n=13).

6. Main outcome measures

Subjective symptoms, gastric emptying, and score on the SRQ-D (self-rating questionnaire for depression; the test for masked depression).

7. Main results

The improvement in subjective symptoms score was greater, but not significantly greater, in arm 1 than in arm 2. The improvement in gastric emptying score was significantly greater in arm 2. The improvement in SRQ-D score tended to be greater in arm 2. The utility score was high in both arms.

8. Conclusions

TSUMURA Rikkunshito presumably has an antidepressive effect comparable to that of sulpiride in the treatment of indefinite complaints of epigastric distress complicated by depression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes a comparison of the clinical utility of TSUMURA Rikkunshito and sulpiride in the treatment of indefinite complaints of epigastric distress complicated by depression. The study is appreciated because, in addition to subjective symptoms, objective outcome measures (e.g., gastric emptying and SRQ-D scores) were adopted and analyzed. However, the inclusion criteria are somewhat ambiguous and the number of patients enrolled is small, making it difficult to draw a definite conclusion. Although the authors stated "rikkunshito has an antidepressive effect comparable to that of sulpiride", this conclusion may be an exaggeration.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Komatsuzaki O. Clinical effect of TSUMURA Rikkunshito on indefinite epigastric distress - comparison with a control agent, and assessment mainly based on the endoscopic findings and the histology of gastric mucosal biopsy specimens before and after the treatment -*. *Kampo Igaku* (*Kampo Medicine*) 1993; 17: 120-31 (in Japanese).

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) for treating indefinite complaints of epigastric distress, based on an analysis of gastric endoscopy findings and histological findings of gastric mucosal biopsy specimens before and after the treatment.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single institution (Tochigi National Hospital), Japan.

4. Participants

Thirty newly-presenting patients with gastritis who had 3 or more indefinite complaints of epigastric distress.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before or between meals for 4 weeks (n=15).

Arm 2: treatment with Marzulene-S Granules (L-glutamine plus azulene) 2 g/day in three divided doses after meals for 4 weeks (n=15).

6. Main outcome measures

Measures of subjective symptoms, endoscopy findings, and histopathology.

7. Main results

Improvement in the subjective symptom score for abdominal bloating, global improvement score, and utility rating were significantly greater in arm 1 than in arm 2. Marked improvements in endoscopic or histopathologic findings were not observed.

8. Conclusions

TSUMURA Rikkunshito has beneficial effects on gastritis with epigastric distress and is a highly useful agent.

9. From Kampo medicine perspective

Stratified analysis of global improvement ratings revealed that improvements were greater in patients aged 61 or older than in those aged 60 or younger.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

This paper describes an evaluation of the clinical effect of TSUMURA Rikkunshito on indefinite epigastric distress, using outcome measures including gastric endoscopy findings and histological findings of gastric mucosal biopsy specimens before and after the treatment. In conclusion, marked changes in endoscopic or histopathologic findings were not observed, and the efficacy of rikkunshito for symptoms and gastrointestinal function was noted. Results of other measures were very similar to those from preceding studies.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Ito J, Ito Y, Asai M, et al. Efficacy of Saireito (TSUMURA) for post-infectious dyspepsia in infants: comparison with intestinal regulators*. *Shonika Shinryo* (*Journal of Pediatric Practice*) 1992; 55: 2089-92 (in Japanese). Ichushi Web ID: 1993113987

1. Objectives

To evaluate the efficacy of Saireito (柴苓湯; TSUMURA) compared with that of intestinal regulators for treatment of post-infectious dyspepsia in infants.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Yokkaichi Municipal Hospital), Japan.

4. Participants

Eighty-seven infants (age range, 4 months to 5 years 10 months old; range of body weight, 7 to 19 kg) who visited the outpatient department with presenting symptoms of cough, fever, or diarrhea (after exclusion of thirty-nine infants who were hospitalized during the study period).

5. Intervention

Arm 1: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 1.5 g b.i.d. (n=32).
Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 1.5 g b.i.d. + albumin tannate 0.1 g/kg/day + natural aluminum silicate 0.1 g/kg/day + resistant lactobacillus preparation 0.1 g/kg/day (n=21).
Arm 3: treatment with albumin tannate 0.1 g/kg/day + natural aluminum silicate 0.1 g/kg/day + resistant lactobacillus preparation 0.1 g/kg/day (n=22).
Arm 4: no treatment with antidiarrheal drugs or intestinal regulators (n=12).

6. Main outcome measures

Symptoms (including the number of episodes and type of diarrhea) and food intake for 7 days were scored (using the 7-day questionnaire, which was distributed to and completed by the patient's mother).

7. Main results

There were no among-arm differences in age, body weight, and symptoms. Diarrhea scores were significantly higher in arm 2 than in arm 3 at 1 day; in arms 1 and 2 than in arm 3 at 2 days; and in arm 1 than in arm 3 at 3 days. The number of patients who withdrew from the study was 1 from arm 1, 0 from arm 2, 15 from arm 3, and 23 from arm 4.

8. Conclusions

Saireito was likely to be useful for treating post-infectious dyspepsia in infants.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes a determination of the efficacy of saireito for post-infectious dyspepsia in infants. Although it was a small study, the report is valuable considering the scarcity of evidence in the field of pediatric gastrointestinal diseases. Lower percentage of saireito-treated patients required hospitalization. Thus, saireito may not only improve symptoms, but also prevent aggravation of symptoms.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Tatsuta M, Iishi H. Effect of treatment with Liu-jun-zi-tang (TJ-43) on gastric emptying and gastrointestinal symptoms in dyspeptic patients. *Alimentary Pharmacology and Therapeutics* 1993; 7: 459-62. CENTRAL ID: CN-00096688, Pubmed ID: 8218760

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) compared with Combizym as a control in dyspeptic patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Osaka Medical Center for Cancer and Cardiovascular Diseases), Japan.

4. Participants

Forty-two patients who had indefinite epigastric distress persisting for at least one year; had chronic gastritis confirmed by endoscopy; and gave consent to participate in the study.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 1 week (n=22).
Arm 2: treatment with Combizym 1 tablet t.i.d. after meals for 1 week (n=20).

6. Main outcome measures

Subjective symptom scores and amount of gastric emptying (measured by acetaminophen absorption method).

7. Main results

In contrast to its absence in arm 2, significant improvement in abdominal bloating, heartburn, belching, and nausea was noted in arm 1. Significant improvement in gastic emptying measured at 30, 45, and 60 minutes was observed in arm 1 but not in arm 2.

8. Conclusions

TSUMURA Rikkunshito is useful for treating dyspeptic patients by improving gastric emptying and gastrointestinal symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes an evaluation of the clinical utility of TSUMURA Rikkunshito, compared with Combizym as a control, in dyspeptic patients. It should be mentioned that this paper may be the only original article on rikkunshito written in English at this time and that the gastric emptying test was introduced as an objective outcome measure in this study. Most Kampo medicines seem to improve "functions". Given that it will become increasingly important to demonstrate the effects of Kampo medicines using measures for evaluating "functions" and to communicate those effects to the world, this is a landmark study.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Miyoshi A, Yachi A, Masamune O, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis - a multicenter comparative study using cisapride as a control -*. *Progress in Medicine* 1991; 11: 1605-31 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of TSUMURA Rikkunshito (六君子湯), using cisapride as a control, in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifty institutions including university hospitals, Japan.

4. Participants

Two hundred and forty-eight patients who had so-called “non-ulcer dyspepsia” (e.g., chronic atrophic gastritis) with 2 or more indefinite complaints of gastrointestinal disorders, associated with possible impairment of gastric motility. Of 248 participants, 215 were included in the analysis.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 4 weeks (n=111).
Arm 2: treatment with cisapride 2.5 mg t.i.d. before meals for 4 weeks (n=104).

6. Main outcome measures

Subjective and objective symptoms.

7. Main results

The improvement in certain individual subjective symptom scores (i.e., scores for anorexia [at 3 weeks], epigastric pain [at 2, 3, and 4 weeks], abdominal discomfort [at 4 weeks], cold extremities [at 2, 3, and 4 weeks], and lightheadedness [at 2 weeks]), global score, and utility rating were significantly higher in arm 1 than in arm 2. The improvement in the ratings for belching (at 1 and 2 weeks) and tenderness (at 1 week) were significantly higher in arm 2 than in arm 1.

8. Conclusions

TSUMURA Rikkunshito is more efficacious than cisapride and is clinically useful in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis.

9. From Kampo medicine perspective

For patients aged 60 or older and those who are thin or overweight, improvement in symptom scores tended to be higher in arm 1, supporting the effectiveness of rikkunshito for *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Two patients discontinued treatment owing to leg discomfort and diarrhea, respectively. There was no significant between-arm difference in the rate of adverse drug reactions and in global safety score.

11. Abstractor’s comments

This paper describes an evaluation of the clinical utility of TJ-43 TSUMURA Rikkunshito using cisapride as a control in the treatment of gastritis. It was a large, multicenter clinical trial. It is safe to say that evidence for the efficacy of rikkunshito treatment was established by this and another paper “Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - a multicenter comparative study using sodium azulene sulfonate as a control -*. *Shindan to Chiryo* (*Diagnosis and Treatment*) 1991; 79: 789-810 (in Japanese)”. Like the the approach of the latter study, that of the present study may have been progressive for its time, since Kampo medical parameters, such as “tension of the abdominal wall” and “splashing sounds in the gastric region”, were also evaluated in the analysis.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Koide A. Adoption of rikkunshito before endoscopy in patients with upper abdominal symptoms*. *Nikkei Medical* 2002; 31: 22-3 (in Japanese).

Koide A. The improvement of QOL by rikkunshito in patients with need for endoscopy*. *Medical Tribune* 2004: 45 (in Japanese).

Yamaguchi T, Koide A. Usefulness of Rikkun-shi-to (TJ-43), a Chinese herbal medicine, for the treatment of gastro-esophageal reflux disease (GERD). *Medical Science Digest* 2007; 33: 748-52 (in Japanese).

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) as an agent to improve symptoms before endoscopy in patients with upper abdominal symptoms and need for endoscopy of the upper gastrointestinal tract.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

None; the authors are members of the Department of Medical Oncology, Graduate School of Medicine, Chiba University, Japan.

4. Participants

One hundred and twenty patients with upper abdominal symptoms and need for upper gastrointestinal endoscopy.

5. Intervention

Arm 1: treatment with H_2-receptor blocker (H2RB; ranitidine 150 mg; n=39).
Arm 2: treatment with proton pump inhibitor (PPI; omeprazole 20 mg; n=40).
Arm 3: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g (n=41).
The duration of treatment was not specified (the administration was continued until the upper gastrointestinal endoscopy was performed).

6. Main outcome measures

Acid reflux (heartburn, reflux), abdominal pains (epigastric pain, hunger, and nausea), dyspepsia (borborygmus, abdominal distention, eructation, and flatus), diarrhea (diarrhea, loose stool, and rectal urgency), and constipation (constipation, hard stool, feeling of incomplete evacuation).

7. Main results

Overall, gastrointestinal symptoms associated with impaired quality of life (QOL) were significantly improved after the treatment in all arms; the improvement was significantly greater in arm 3 than in arms 1 and 2. Also improved were acid reflux associated with impaired QOL in arm 1, acid reflux and abdominal pains associated with impaired QOL in arm 2, and acid reflux, abdominal pains, and dyspepsia associated with impaired QOL in arm 3. Significantly greater improvements were found for acid reflux in arm 3 than in arm 1; for abdominal pains in arms 2 and 3 than in arm 1; for dyspepsia in arm 3 than in arms 1 and 2. Considering only patients with reflux esophagitis, gastrointestinal symptoms were also significantly improved by treatment in all arms. Acid reflux improved in arm 1, and acid reflux, abdominal pains, and dyspepsia improved in arms 2 and 3. H2RB, PPI, and rikkunshito had similar effectiveness.

8. Conclusions

The efficacy of rikkunshito as a pre-endoscopic medication, even as monotherapy, is comparable to that of other gastric acid secretion inhibitors in patients with upper abdominal symptoms and need for upper gastrointestinal endoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned**.**

11. Abstractor's comments

The study by Yamaguchi et al (2007) is considered to be a follow-up to the two studies by Koide (2002, 2004). This clinically valuable study showed that the efficacy of rikkunshito against upper abdominal symptoms including gastroesophageal reflux disease is comparable to that of other gastric acid secretion inhibitors. The present study also deserves praise for assessing each clinical symptom objectively using the GSRS (Gastrointestinal Symptom Rating Scale). The cost-effectiveness of rikkunshito is mentioned without detail in the conclusion of this paper, but it is addressed more completely in paper 2). The present paper provides very interesting insights, but its first half is too general. Therefore, publication as an original article is desired.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 20 January 2009, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Harasawa S, Miyoshi A, Miwa T, et al. Double-blind multicenter post-marketing clinical trial of TJ-43 TSUMURA Rikkunshi-to for the treatment of dysmotility-like dyspepsia. *Igaku no Ayumi* (*Journal of Clinical and Experimental Medicine*) 1998; 187: 207-29 (in Japanese). Ichushi Web ID: 1999085057

Harasawa S. The role of rikkunshito against NUD (non-ulcer dyspepsia) – especially its efficacy in dysmotility-like NUD*. *Progress in Medicine* 1999; 19: 843-8 (in Japanese). MOL, MOL-Lib

Harasawa S. Evidence from an RCT of rikkunshito (六君子湯) for epigastric complaints*. *Kampo Igaku* (*Science of Kampo Medicine*) 2011; 35: 113-7 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of TJ-43 TSUMURA Rikkunshito (六君子湯) more objectively in patients with dyspepsia caused by dysfunction of the upper gastrointestinal tract.

2. Design

Double-blind, randomized, controlled trial (DB-RCT).

3. Setting

A total of 54 institutions obtained approval of Institutional Review Boards, Japan.

4. Participants

Two hundred and ninety-six patients (30–80 years old) with a chief complaint of persistent or intermittent (for more than 4 weeks) dysmotility-like dyspepsia, characterized by anorexia (or poor appetite), gastric distress, and heavy stomach feeling (presumably due to dysfunction of the upper gastrointestinal tract), and indicating some "*kyo-sho* (虚証, deficiency pattern)" conditions such as gastroptosis, physical weakness.

5. Intervention

Arm 1: oral administration of TSUMURA Rikkunshito (六君子湯) Extract Granules (TJ-43) 2.5 g t.i.d. before or between meals for 2 weeks (n=147).

Arm 2: oral administration of low-dose (1:40 dilution) TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before or between meals for 2 weeks (n=149).

6. Main outcome measures

Five symptoms associated with dysmotility-like dyspepsia (anorexia, abdominal distension, stomach discomfort, heavy stomach feeling, and nausea).

Three symptoms associated with ulcer-like dyspepsia (upper abdominal/epigastric pain, heartburn or pyrosis, and eructation).

7. Main results

A total of 235 subjects (TJ-43 group, n=118; low-dose group, n=117) were included for analysis of efficacy. Dysmobility-like dyspepsia symptoms were improved in 59.3% of the TJ-43 group and 40.2% of the low-dose group; overall symptoms including ulcer-like dyspepsia symptoms were also improved in 60.2% of the TJ-43 group and 41.0% of the low-dose group (both P=0.004). These indicate that efficacy is significantly higher in the TJ-43 group. Furthermore, a significantly higher percentage of the TJ-43 group than the low-dose group (58.8% versus 39.3%) deemed the treatment useful (P=0.003).

8. Conclusions

The safety and effectiveness of TJ-43 was validated for the treatment of dysmotility-like dyspepsia in this double-blind study. We therefore conclude that TJ-43 Rikkunshito is clinically useful.

9. From Kampo medicine perspective

In this study, the inclusion criteria were "deficiency pattern" symptoms (i.e., decreased tone of abdominal wall, subjective/objective splashing sound, gastroptosis tendency, and mental/physical weakness) and the exclusion criteria were "*jitsu-sho* (実証, excess pattern)" symptoms (i.e., mental and physical strength, massive and muscular body, and reddish face).

10. Safety assessment in the article

Safety problems were detected in 2 cases in the TJ-43 group (diarrhea, elevated GOT) and 2 in the low-dose group (diarrhea, elevated GOT/GPT). Adverse effects (defined as symptoms undeniably caused by the drug) occurred in 7 of the TJ-43 group and 7 of the low dose group. None were serious.

11. Abstractor's comments

Use of low-dose TJ-43 in the control group and use of Kampo diagnostic considerations when selecting the inclusion and exclusion criteria are appreciated. Improvement in "*kyo-sho*" symptoms are described in Harasawa's report (1999, mentioned above). Another report of Harasawa (2011) is a sub-group analysis (rikkunshito group [n=40] and control group [n=35]) based on the Rome III criteria (2006). Patient backgrounds were similar in both groups, and the study demonstrated significant difference in the actions of rikkunshito. However, interpretations of the study must take heed of the fact that any bias from 'unknown factors', the weakness of the subgroup analysis, is not clearly identified.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2012, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Arai M. Rikkunshito significantly enhances the secretion of ghrelin in patients with functional dyspepsia*. *Kampo Igaku* (*Kampo Medicine*) 2009; 33: 405–6.

Matsumura T, Arai M, Suzuki T, et al. The traditional Japanese medicine rikkunshito improves upper gastrointestinal symptoms in patients with functional dyspepsia. *Gastroenterology* 2010; 138: S471. CENTRAL ID: CN-00796662

Arai M, Matsumura T, Yoshikawa M, et al. Analysis of the rikkunshito efficacy on patients with functional dyspepsia*. *Nihon Yakurigaku Zasshi* (*Folia Pharmacologica Japonica*) 2011; 137: 18–21. (in Japanese). J-STAGE

Arai M, Matsumura T, Tsuchiya N, et al. Rikkunshito improves the symptoms in patients with functional dyspepsia, accompanied by an increase in the level of plasma ghrelin. *Hepato-Gastroenterology* 2012; 59: 62-6. Pubmed ID: 22260823

1. Objectives

To clarify the effect of rikkunshito (六君子湯) on ghrelin secretion and symptoms and to clarify its mechanism of action in patients with functional dyspepsia (FD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the author belongs to the Department of Gastroenterology, Graduate School of Medicine, Chiba University), Japan.

4. Participants

Twenty-seven patients with FD fulfilling the Rome III criteria.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 4 weeks (n=13).
Arm 2: domperidone 30 mg/day for 4 weeks (n=14).

6. Main outcome measures

Blood acylated ghrelin (AG) levels, serum leptin levels, gastrointestinal symptoms (assessed by Gastrointestinal Symptom Rating Scale [GSRS] score), and depressive symptoms (assessed by Self-rating Depression Scale [SDS] score) before administration and 2 and 4 weeks after administration began.

7. Main results

All symptoms improved significantly in arm 1 in Week 2 of administration, while gastric acid reflux, abdominal pain, and dyspepsia improved in Week 4. Although in arm 2 these three symptoms improved significantly in Week 2, only dyspepsia had improved in Week 4. And while blood AG levels in arm 1 had improved significantly after 2 weeks compared to before administration ($P<0.05$), no significant change was observed in arm 2. The AG increase and gastrointestinal symptom improvement in arm 1 demonstrated a significant, positive correlation. There were no significant changes in serum leptin levels in either arm. Depression scores did not change significantly in arm 1, but showed a significant improvement in arm 2 in Week 4 ($P=0.04$).

8. Conclusions

Rikkunshito increases blood acylated ghrelin levels and improves gastrointestinal symptoms in FD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The authors mention that there were no adverse effects between the start and the completion of the trial.

11. Abstractor's comments

This is a valuable clinical study that demonstrated for the first time in an RCT that rikkunshito alleviates gastrointestinal symptoms by increasing blood AG levels in FD patients. In their 2010 paper, the authors did not specify the numbers of participants in each group, and AG levels showed a rising trend only in the week-four analysis. But in their 2012 paper they did specify the numbers of participants in the groups, they excluded two participants with diabetes because insulin resistance and blood sugar levels affect AG concentrations, and analysis in week two, not week four, resulted in a significant difference. Furthermore, they found that the extent of symptomatic improvement correlates to the increase in AG concentration. On the other hand, a study of the relationship of the increase in blood AG concentration and the effects of rikkunshito to the factors relevant to rikkunshito-pattern (六君子湯の証), including presence or absence of fatigue or sensitivity to cold and whether participants exhibit *kyo-sho* or *jitsu-sho* (虚証/実証, deficiency or excess pattern), might yield even more definitive and clinically significant results.

12. Abstractor and date

Motoo Y, 1 June 2010, 1 January 2012 , 1 June 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Tominaga K, Sakata Y, Kusunoki H, et al. Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: A randomized clinical trial (the DREAM study). *Neurogastroenterology and Motility* 2018; 1-12. doi: 10.1111/nmo.13319 Pubmed ID: 29498457

1. Objectives

To evaluate the efficacy and safety of rikkunshito（六君子湯）in patients with functional dyspepsia

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

Fifty-six hospitals, Japan

4. Participants

A total of 128 patients aged >20 years who had functional dyspepsia diagnosed according to the ROME III criteria, who were *Helicobacter pylori*-negative, and who had continuous symptoms after 2 weeks of placebo administration.

5. Intervention

Arm 1: oral administration of Rikkunshito（六君子湯）Extract Granules (manufacturer unknown) 2.5 g t.i.d. for 8 weeks (n=63)

Arm 2: oral administration of placebo 2.5 g t.i.d. for 8 weeks (n=65)

6. Main outcome measures

The primary endpoint was overall treatment efficacy (OTE). The secondary endpoints were the scores from the patient assessment of upper gastrointestinal disorders-symptom severity index (PAGI-SYM), Global overall symptom (GOS), Modified frequency scale for the symptoms of GERD (m-FSSG), Hospital anxiety and depression scale (HADS), and Short-form health survey-8 (SF-8).

7. Main results

During the study period, 2 patients in the rikkunshito group and 1 patient in the placebo group dropped out of the study. The OTE after 8 weeks of treatment in the rikkunshito group was “extremely improved” in 8.2% and “improved” in 29.5%, which were significantly higher compared with 1.8% and 21.1%, respectively, in the placebo group (P=0.019). After 8 weeks of treatment, the PAGI-SYM, GOS, m-FSSG, and HADS total scores were significantly decreased in the rikkunshito group compared with the placebo group (P=0.018, P =0.009, P =0.036, and P =0.027, respectively). The SF-8 did not show significant difference.

8. Conclusion

Rikkunshito alleviates gastrointestinal and psychological symptoms in *Helicobacter pylori*-negative patients with functional dyspepsia.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Adverse events and adverse drug reactions occurred in 10.8% and 4.6%, respectively, of the patients in the rikkunshito group and 11.1% and 1.6%, respectively, of the patients in the placebo group.

11. Abstractor’s comments

This article describes an important clinical study that evaluated the efficacy of rikkunshito for functional dyspepsia. Knowing that assessment of subjective symptoms is relatively unlikely to show significant differences in RCTs, this study is particularly meaningful because it showed that a significantly higher percentage of patients in the rikkunshito group experienced relief of subjective symptoms. In addition, this study used existing scales to assess gastrointestinal and psychological symptoms, and demonstrated improvements in the rikkunshito group with significant differences, and so is a good reference for other physicians. Furthermore, since this study used Western medicine rather than Oriental medicine in diagnosing functional dyspepsia and evaluating the effect of rikkunshito on functional dyspepsia, the results from this study are usable by clinicians in Japan where Western medicine is predominant. Although clinical questions remain, such as whether rikkunshito should be continued or switched to another formula in patients with poor improvement after 8 weeks of treatment with rikkunshito, this article appears to be of great significance in that it provides a foundation for future clinical practices and studies.

12. Abstractor and date

Koike H, 1 June 2020.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Nishida T. Effect of rikkunshito on gastrointestinal function in patients after gastrectomy*. *Progress in Medicine* 2006; 26: 3224-5 (in Japanese). MOL, MOL-Lib

Takahashi T, Endo S, Nakajima K, et al. Effect of Rikkunshito, a Chinese herbal medicine, on stasis in patients after pylous-preserving gastrectomy. *World Journal of Surgery* 2009; 33: 296-302. CENTRAL ID: CN-00686725, Pubmed ID: 19082653

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) Extract Granules for delayed excretion after pylorus-preserving gastrectomy (PPG).

2. Design

Osaka University Hospital, Japan.

3. Setting

Randomized controlled trial (cross-over) (RCT cross-over).

4. Participants

Eleven patients who underwent pylorus-preserving gastrectomy.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for 4 weeks and then not treated with TSUMURA Rikkunshito (六君子湯) Extract Granules for 4 weeks (n=4).

Arm 2: not treated with TSUMURA Rikkunshito (六君子湯) Extract Granules for 4 weeks and then treated with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for 4 weeks (n=7).

6. Main outcome measures

Gastrointestinal quality of life (QOL) index (GIQLI), stasis-related symptom score, Sigstad score, gastrointestinal excretion scintigram.

7. Main results

While there was no significant between-arm difference in the GIQLI and Sigstad score (dumping syndrome), the stasis-related symptom score significantly decreased on treatment in arm 1. In the scintigram, the gastric residual rate of solids (but not liquids) excretion decreased on treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules.

8. Conclusions

Treatment with TSUMURA Rikkunshito Extract Granules is effective for delayed gastric excretion of solids after PPG.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No drug-related or protocol-defined adverse event was reported.

11. Abstractor's comments

This is a clinical trial of high clinical significance in that scintigraphy was used to objectively evaluate excretion of liquids and solids separately. However, the study design, including randomization of patients and sample size, is questionable. It is desirable to conduct a high-quality RCT using an adequate sample size. In the previous version of Evidence Reports of Kampo treatment, structured abstract for this trial was developed and published based on the article by Nishida (2006), however, this trial was subsequently published as the reference above, and structured abstract was reconstructed on the basis of this new article.

12. Abstractor and date

Kogure T, 26 January 2009, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Shiratori M, Shoji T, Kanazawa M, et al. Effect of rikkunshito on gastric sensorimotor function under distention. *Neurogastroenterology & Motility* 2011; 23: 323-9, e155–6. Pubmed ID: 21175995

1. Objectives

To evaluate the effects of rikkunshito (六君子湯) on gastric contraction and expansion.

2. Design

Crossover randomized controlled trial (RCT-cross over).

3. Setting

Tohoku University Hospital, Japan.

4. Participants

Nine healthy volunteers.

5. Intervention

Participants were randomly assigned to either arm 1 or arm 2.

Arm 1: gastric pressure measured after observation for 2 weeks without administration and then after taking 7.5 g/day of TSUMURA Rikkunshito (六君子湯) Extract Granules for 2 weeks. Number of subjects: not reported.

Arm 2: gastric pressure measured after taking 7.5 g/day of TSUMURA Rikkunshito Extract (六君子湯) Granules for 2 weeks and then after observation for 2 weeks without administration. Number of subjects: not reported.

6. Main outcome measures

Gastric pressure measurements using a gastric barostat before and after imposition of stress.

7. Main results

Reduction in gastric volume due to stress was observed before or after but not during the period of rikkunshito administration. Pressure thresholds for epigastric bloating and for pain were lower during rikkunshito administration, regardless of stress imposition.

8. Conclusions

Rikkunshito may improve changes in gastric wall tone caused by stress or anxiety.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This article demonstrates the potential of rikkunshito in helping to control overeating when stress is not present, and in preventing appetite reduction when stress is present. Unfortunately, however, the authors did not report the number of subjects in each group. It is significant that the study used the objective measure of gastric pressure to assess the specific effects of rikkunshito on gastric contraction and expansion.

12. Abstractor and date

Nakata H, , 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Suzuki H, Matsuzaki J, Fukushima Y, et al. Randomized clinical trial: rikkunshito in the treatment of functional dyspepsia - a multicenter, double-blind, randomized, placebo-controlled study. *Neurogastroenterology and Motility* 2014; 26: 950-61. CENTRAL ID: CN-00995379, Pubmed ID: 24766295

1. Objectives

To evaluate the treatment effects of rikkunshito (六君子湯) on functional dyspepsia.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Multi-center study in 20 general hospitals and 11 clinics, Japan.

4. Participants

Two hundred forty-seven patients aged 20 years or older who had diagnosis of functional dyspepsia.

5. Intervention

Arm 1: Rikkunshito (六君子湯) extract granules (manufacturer unknown) 2.5 g t.i.d. before meals for 8 weeks (n=125).

Arm 2: Placebo before meals for 8 weeks (n=122).

6. Main outcome measures

Weekly change in the global patient assessment (GPA) score and Likert scale after rikkunshito administration; change in the Gastrointestinal Symptom Rating Scale (GSRS) score, anti-*Helicobacter pylori* IgG antibody level, and blood ghrelin concentrations from baseline to post-administration.

7. Main results

The proportion of participants showing symptom improvement as reflected in the GPA score was higher in the rikkunshito arm than in the placebo arm, but not significantly (33.6% vs. 23.8%; *P*=0.09). However, stomach pain was significantly more improved in the rikkunshito arm than in the placebo arm (*P*=0.04); postprandial abdominal distension also tended to improve (*P*=0.06), with greater improvement in the *H. pylori*-positive patients (40.0%) than in *H. pylori*-negative patients (20.0%) (*P*=0.07). The change in blood ghrelin concentration from baseline to post-administration was similar between the two arms.

8. Conclusions

Eight-week administration of rikkunshito improved dyspepsia symptoms especially stomach pain and postprandial distension. This indicated that rikkunshito has strong treatment effects on functional dyspepsia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No clinically significant adverse drug reactions were reported. However, mild adverse drug reactions including diarrhea and nausea were found in 15.2% of subjects in the rikkunshito arm and 11.5% of subjects in the placebo arm (no significant difference).

11. Abstractor's comments

The main value of this study was its clinical evaluation of the treatment effects of rikkunshito for functional dyspepsia, which is widely used for upper gastrointestinal tract symptoms corresponding to *qi* (気) deficiency. In particular, certain effects of rikkunshito on stomach pain and postprandial distension will enable clinical practitioners to more effectively treat functional dyspepsia in actual clinical settings. Rikkunshito is a Kampo product essential for persons living in modern society who suffer from functional dyspepsia, a psychophysiological disorder known to be difficult to treat. In this study, blood ghrelin concentrations did not changed after rikkunshito administration. To elucidate the mechanism of rikkunshito, a formulation with tonic effects for spleen *qi* deficiency or *qi* deficiency affecting upper gastrointestinal tract symptoms, future studies will need to utilize biochemical measures such as biogenic markers and physiological markers including peristaltic movement of the gastrointestinal tract and secretory release of digestive enzymes.

12. Abstractor and date

Ushiroyama T, 31 March 2017.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takayama S, Seki T, Watanabe M, et al. The herbal medicine daikenchuto increases blood flow in the superior mesenteric artery. *The Tohoku Journal of Experimental Medicine* 2009; 219: 319–30.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) and orengedokuto (黄連解毒湯) on cardiac output (CO) and superior mesenteric artery (SMA) blood flow.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single facility (Tohoku University Hospital), Japan.

4. Participants

Fourteen healthy adults (25–44 years old) without cardiac disease.

5. Intervention

Arm 1: distilled water (50 mL, 37°C).
Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules5.0 g.
Arm 3: TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g.

6. Main outcome measures

Hemodynamic parameters including CO, blood pressure, heart rate, and SMA blood flow, measured by impedance cardiography (ICG) before and at 5, 10, 15, 20, 30, 45, 60, 75, and 90 min after administration of distilled water, daikenchuto, and orengedokuto.

7. Main results

Although neither daikenchuto nor orengedokuto affected CO, daikenchuto significantly increased SMA blood flow compared with distilled water or orengedokuto ($P<0.05$). Five grams of daikenchuto significantly increased SMA blood flow between 5 min ($P<0.01$) and 90 min after administration, with a peak reached at 20 min.

8. Conclusions

Daikenchuto increases SMA blood flow without changing CO in healthy people.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study used a physiological approach to verify the blood flow-increasing effect of daikenchuto, which is used for *kansho* (寒証, cold pattern), and the blood flow-suppressing effect of orengedokuto, which is used for *netsusho* (熱証, heat pattern). Daikenchuto is well-known for its gastrointestinal prokinetic effect and is clinically applied to subileus cases regardless of *sho* (証, pattern) with certain efficacy. This study revealed that daikenchuto increases SMA blood flow, possibly providing practicing clinicians with valuable findings. However, as this study was performed in healthy people, it not certain that the outcome of daikenchuto therapy is the same in patients in the ileus state or with *hie* (冷え, a feeling of coldness) in the pelvis. Based on the results of this study in healthy adults, future studies are expected to identify the mechanisms of action (probably more than one) of these Kampo medicines (daikenchuto in subileus cases with *kansho* [寒証, cold pattern] and orengedokuto in hypertension and insomnia cases with *netsusho* [熱証, heat pattern]) using the same study protocol.

12. Abstractor and date

Ushiroyama T, 16 January 2011, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takayama S, Seki T, Watanabe M, et al. The effect of warming of the abdomen and of herbal medicine on superior mesenteric artery blood flow – a pilot study. *Forschende Komplementär Medizin* 2010; 17: 195–201 (in English with German abstract). Pubmed ID: 20829597

1. Objectives

Comparative evaluation of the regulatory effects of thermal stimulation to the abdomen and Daikenchuto (大建中湯) on superior mesenteric artery (SMA) blood flow in healthy people.

2. Design

Randomized controlled trial (RCT).

3. Setting

Five centers, including the Center for Asian Traditional Medicine, Graduate School of Medicine, Tohoku University, Japan.

4. Participants

Forty-two healthy male volunteers with no heart disease.

5. Intervention

Arm 1: participants received 20 minutes of thermal stimulation to the paraumbilical region with a warming device (40°C), and were then observed for 50 minutes.

Arm 2: participants took TSUMURA Daikenchuto (大建中湯) Extract Granules (5.0 g) with distilled water (50 mL, 37°C) and were then observed for 50 minutes.

Arm 3: participants took distilled water (50 mL, 37°C) and were then observed for 50 minutes.

Randomization was performed only in arm 1 and arm 2 (14 subjects per arm).

6. Main outcome measures

Hemodynamic testing: SMA blood flow was measured before taking daikenchuto, before thermal stimulation with a warming device, and before taking distilled water, and then 10, 20, 30, 40, and 50 minutes after the start of each intervention.

7. Main results

SMA blood flow increased significantly between 10 and 50 minutes after daikenchuto administration ($P<0.01$) and between 10 and 40 minutes after thermal stimulation ($P<0.05$). There was no significant difference between these arms. SMA blood flow did not change after administration of distilled water.

8. Conclusions

Daikenchuto increases SMA blood flow in healthy people. That increase is similar to the increase generated by thermal stimulation using a warming device.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study employed a physiological evaluation method of verification in its investigation of blood flow increase stimulated by daikenchuto, which is used for *kansho* (寒証, cold pattern). It appears to be either a follow-up of a study in *The Tohoku Journal of Experimental Medicine* (2009; 219: 319–30) or concurrent research, as it compared the effects of thermal stimulation using a warming device (positive control) with administration of distilled water only (negative control). Daikenchuto is well known for its promotion of intestinal movement and is used clinically for sub-ileus conditions regardless of pattern: it is recognized for certain effects. This study found that increases in SMA blood flow induced by daikenchuto were similar to those induced by a thermal stimulation device, which suggests that it would be valuable to practicing clinicians. However, it should be pointed out that the subjects were healthy volunteers and the study did not clarify the question of whether the same phenomenon would be observed in people suffering from ileus conditions or conditions associated with coldness in the pelvic cavity. Based on this study of healthy people, researchers should be encouraged to use the study's protocols to further elucidate the action mechanisms (probably more than one) of Kampo medicines, specifically daikenchuto, in outpatients with cold-pattern sub-ileus conditions or habitual constipation.

12. Abstractor and date

Ushiroyama T, 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Hayakawa M, Ono Y, Wada T, et al. Effects of Rikkunshito (traditional Japanese medicine) on enteral feeding and the plasma ghrelin level in critically ill patients: a pilot study. *Journal of Intensive Care* 2014; 2: 53.

1. Objectives

To verify the effectiveness of rikkunshito (六君子湯) on gastrointestinal motility function in critically ill patients.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

One center, a university hospital advanced acute medical care center, Japan.

4. Participants

Twenty-three critically ill patients aged at least 18-years, predicted to need enteral feeding over at least 7 days (10 females, 13 males).

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5g administered every 8 hours intragastrically by tube and commencing enteral feeding at 20ml/hr, suctioning from the gastric tube every 4 hours, increasing the feeding amount up to basal metabolic expenditure if the suctioned volume is 100ml or less, or reducing the amount if suctioning of greater than 100ml continues (n=10).

Arm 2: Metoclopramide (Primperan, Astellas Pharma Inc.) 10mg every 8 hours intragastrically by tube and enteral feeding as in arm 1 (n=13).

6. Main outcome measures

The primary endpoint was the period in which it was possible to increase the enteral feeding amount up to basal metabolic expenditure in 10 days, and the secondary endpoint was the increase in activated ghrelin in 10 days.

7. Main results

No statistically significant difference was observed in the amount of stomach contents suctioned from the gastric tubes or the rate at which it was possible to increase enteral feeding up to basal metabolic expenditure. The number of days until 50% of basal metabolic expenditure was reached was significantly shorter in arm 1 compared to arm 2 (P=0.004). Activated ghrelin increased significantly in arm 1 (P=0.023).

8. Conclusion

Rikkunshito increased activated ghrelin blood concentration and gastrointestinal motility function in critically ill patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This is an important paper indicating that administration of rikkunshito for critically ill patients increases gastrointestinal motility function and raises activated ghrelin blood concentration more than when administering metoclopramide. Although there was no significant difference in the period until feeding amount reached basal metabolic expenditure, a pre-set endpoint, the figures in the paper show the tendency that the rate of increase of feeding amount was faster and the volume suctioned from patients' stomachs was lower in the rikkunshito group. The possibility of significant differences emerging seems high if a sufficient number of cases were registered. This study is also greatly significant as it indicates that the period until 50% of basal metabolic expenditure was reached was shorter in the rikkunshito group compared to the metoclopramide group, even with a small number of such cases. The authors predicted in the protocols registered with UMIN (the ID code is actually UMIN000003569, not the code that appears incorrectly in the paper) that 60 participants would be registered before commencing the trial, however, the fact that that number was not reached is problematic for this paper. In future studies it would be advisable to incorporate a sufficient number, and to make the period until 50% of requisite nutrition is achieved a primary endpoint.

12. Abstractor and date

Koike H, 20 February 2017.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takagaki Y, Kawasaki S, Komai H, et al. The effect of Chinese hearb medicine (dai-kenchu-to) on paralytic ileus after repair of abdominal aortic aneurysm. *Nihon Rinsho Geka Gakkai Zasshi* (*Journal of Japan Surgical Association*) 2000; 61: 325-8 (in Japanese with English abstract). J-STAGE

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) for improving intestinal peristalsis in patients with intestinal paralysis after surgery for abdominal aortic aneurysm (AAA).

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available (the authors are cardiovascular surgeons at community or university hospitals), Japan.

4. Participants

Twenty-one patients who underwent elective surgery for non-ruptured infrarenal AAA during the same time period.

5. Intervention

Arm 1: treatment with infusion of daikenchuto (大建中湯) dissolved in lukewarm water (5 g/20 mL) through a gastric tube, followed by clipping of the tube for 30 minutes, three times daily from the first postoperative day, in 7 patients.
Arm 2: treatment with infusion of lukewarm water (20 mL) in the same manner as arm 1 in 7 patients, as a control group.
Arm 3: treatment with infusion of lukewarm water (20 mL) and intravenous panthenol (100 mg/day) in 7 patients.

6. Main outcome measures

Degree of abdominal distension, and presence or absence of bowel sounds, passage of flatus, and small bowel gas on the abdominal X-ray.

7. Main results

Bowel sounds were heard immediately after the infusion of the study drug in all patients of arm 1, but not in any patient of arms 2 and 3. Time to the first passage of flatus after surgery was 3.1±0.8 days in arm 1, 5.1±1.3 days in arm 2, and 3.7±0.8 days in arm 3; significantly earlier passage of flatus was observed in arms 1 and 3 (P<0.05), but there was no significant difference in time to first passage of flatus between these two arms. Small bowel gas disappeared at 3.3±1.4 days after surgery in arm 1, at 6.1±1.2 days in arm 2, and at 6.3±2.8 days in arm 3; the gas disappeared significantly earlier in arm 1 than in arms 2 and 3 (P<0.05). No patients developed symptoms of ileus due to decreased intestinal peristalsis after resumption of oral intake.

8. Conclusions

Oral daikenchuto is effective for improving decreased intestinal peristalsis after surgery for non-ruptured AAA.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions associated with daikenchuto treatment were not reported.

11. Abstractor's comments

AAA is caused by arteriosclerosis and common in the elderly, for whom elective surgery is indicated and achieves good outcome. In such cases, early ambulation and early resumption of oral intake are important for the prevention of early postoperative delirium. Administration of daikenchuto promotes significantly earlier recovery of intestinal peristalsis and is therefore clinically useful. Although three arms were compared in this study, other studies commonly compare just two arms - daikenchuto and panthenol as a standard treatment. This study was also limited by the small number of patients in each group. Thus, a review of the study design and number of subjects will be needed.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Ohyabu H, Matsuda S, Kurisu S, et al. Evaluation of daikenchuto in patients with adhesive ileus in a randomized trial*. *Progress in Medicine* 1995; 15: 1954-8 (in Japanese). Ichushi Web ID:1996096061

1. Objectives

To evaluate the efficacy of daikenchuto (大建中湯) in patients with adhesive ileus.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single institution (Hyogo Prefectural Awaji Hospital), Japan.

4. Participants

Fifty-three patients who were admitted with adhesive ileus and received gastric intubation. Patients with strangulation ileus were excluded.

5. Intervention

Arm 1: treatment with infusion of daikenchuto (大建中湯; manufacturer, not specified) dissolved in lukewarm water (5 g/30 mL) through a gastric tube, followed by flush with lukewarm water (30 mL), three times daily (n=28).

Arm 2: treatment with infusion of lukewarm water (60 mL) through a gastric tube, three times daily (n=25).

6. Main outcome measures

Time to passage of flatus, resolution rate with conservative treatment, rate of placement of endoscopic long tubes, and rate of progression to surgery.

7. Main results

The resolution rate with conservative treatment was higher in arm 1 (P=0.0595). The rates of tube placement and progression to surgery tended to be lower in arm 1.

8. Conclusions

Daikenchuto is a treatment worth trying in patients with adhesive ileus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes an evaluation of the clinical efficacy of daikenchuto in patients with adhesive ileus. Although the number of patients enrolled was small and between-group differences fell slightly short of significance in this study, the clinical utility of daikenchuto seems to be demonstrated.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Ishii F, Iizuka B, Nagasako K, et al. Evaluations of the therapeutic efficacy of Saikokeishito (TJ-10) versus Keishikashakuyakuto (TJ-60) for irritable bowel syndrome and Saireito (TJ-114) for ulcerative colitis*. *Progress in Medicine* 1993; 13: 2893-900 (in Japanese).

1. Objectives

To compare the efficacy of saikokeishito (柴胡桂枝湯) and keishikashakuyakuto (桂枝加芍薬湯) for irritable bowel syndrome (IBS).

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (authors belong to the Department of Internal Medicine, Institute of Gastroenterology, Tokyo Women's Medical University), Japan.

4. Participants

Forty-six patients clinically diagnosed with IBS. Patients were excluded for the following reasons: (i) medications (e.g., anticholinergics, tranquilizers), given within the previous week, possibly influencing the evaluation; (ii) complications including organic diseases of the gastrointestinal tract and bacterial infections.

5. Intervention

Arm 1: treatment with TSUMURA Saikokeishito Extract Granules (柴胡桂枝湯) 2.5 g t.i.d. (n=23) for 2 weeks.

Arm 2: treatment with TSUMURA Keishikashakuyakuto Extract Granules (桂枝加芍薬湯) 2.5 g t.i.d. (n=23) for 2 weeks.

6. Main outcome measures

Epigastric pain, lower abdominal pain, anorexia, abdominal bloating, feeling of retension, diarrhea, constipation, alternating diarrhea and constipation, flatulence /borborygmus, and feeling of incomplete evacuation.

7. Main results

The response was evaluated on a 4-point scale (marked, moderate, mild, none) and by comparing outcome measures before and after two weeks of treatment. Marked or moderate response was observed in 9 of 23 patients (39%) in arm 1 and 17 of 23 (74%) in arm 2. Regarding the pattern of bowel movements (diarrhea, constipation, and alternating diarrhea and constipation), the rate of marked or moderate response was 50% or more for all patterns in arm 2; in particular, it was 86% in those with alternating diarrhea and constipation. In arm 2, marked or moderate response was observed in 60% of patients with saikokeishito-type symptoms (epigastric pain, lower abdominal pain, and anorexia) and in 75% of those with keishikashakuyakuto-type symptoms (diarrhea, constipation, alternating diarrhea and constipation, abdominal bloating, stasis, flatulence/borborygmus, and feeling of incomplete evacuation). In arm 1, rates of marked or moderate response were under 50% in both symptom-based groups. Regarding individual symptoms, response rates were 50% for epigastric pain and 20–30% for the other symptoms in arm 1, whereas rates were 50% or more for alternating diarrhea and constipation, lower abdominal pain, diarrhea, constipation, and abdominal bloating in arm 2.

8. Conclusions

Keishikashakuyakuto can be prescribed to provide satisfactory effects for diagnostically confirmed IBS, irrespective of *sho* (証, pattern) or types of disease. Keishikashakuyakuto seems to act similarly to the anticholinergics or anxiolytics used in the medical therapy of IBS, and is recommended especially for patients with alternating-pattern of bowel movements.

9. From Kampo medicine perspective

The original study design included random assignment to the saikokeishito or keishikashakuyakuto treatment arms. During the analysis of results, response was evaluated separately in patients with saikokeishito-type clinical symptoms and those with keishikashakuyakuto-type symptoms.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes two different clinical studies. The latter part, in which therapeutic efficacy of saireito for ulcerative colitis was evaluated, was excluded from this Structured Abstract because it was not a randomized controlled trial. Many papers have been published on the efficacy of keishikashakuyakuto for IBS. The authors of this paper deserve praise for comparing keishikashakuyakuto with saikokeishito, which needs clinical differentiation. Since IBS can be a psychosomatic disease, it may be better to evaluate not only gastrointestinal symptoms, but also psychological items and systemic symptoms as measures of response. Furthermore, since IBS can be refractory, it might be better to consider treatment history and more. Further investigation of this clinically useful theme is expected.

12. Abstractor and date

Arai M, 21 October 2008, 6 January 2010, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Sasaki D, Uehara A, Hiwatashi N, et al. Clinical efficacy of keishikashakuyakuto for irritable bowel syndrome - a multicenter, randomized, parallel-group clinical trial -*. *Rinsho to Kenkyu* (*Japanese Journal of Clinical and Experimental Medicine*) 1998; 75: 1136-52 (in Japanese). Ichushi Web ID: 1998224171 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of keishikashakuyakuto (桂枝加芍薬湯) for irritable bowel syndrome.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Twenty university medical schools (including Tohoku University [Third Department of Internal Medicine, Tohoku University Hospital]; Tokai University [Sixth Department of Internal Medicine, Tokai University Hospital]; Kyushu University [Department of Psychosomatic Medicine, Kyushu University Hospital]), 53 hospitals, and 3 clinics (76 institutions in total), Japan.

4. Participants

Two hundred and eighty-six patients (age, 15–75 years) who were diagnosed with irritable bowel syndrome at one of the participating institutions and gave oral or written consent to participate in the study. Exclusion criteria were as follows: lactose intolerance; complications that might influence the evaluation; serious complications of heart, liver, kidney, or blood; pregnancy (known or possible); lactation; ineligibility as determined by the investigators.

5. Intervention

Arm 1: treatment with Kanebo Keishikashakuyakuto (桂枝加芍薬湯) Extract Fine Granules 2.0 g t.i.d. (n=148).

Arm 2: treatment with placebo (granules containing a small amount of keishikashakuyakuto extract) (n=138).

6. Main outcome measures

Bowel movement abnormalities (abnormal stool properties, number of bowel movements, and feeling of incomplete evacuation), gastrointestinal symptoms (abdominal pain, abdominal bloating, flatulence, borborygmus, anorexia, nausea/vomiting, heartburn, and belching), laboratory findings (hematology, blood biochemistry, and urinalysis), and physical findings (blood pressure, body weight, and presence and degree of edema).

7. Main results

Outcomes were evaluated after 4 weeks, or 8 weeks of treatment if the response at 4 weeks was inadequate. Final global improvement ratings were not significantly different between arms 1 and 2. As for abdominal pain, rates of “moderate” or better improvement tended to be higher in arm 1 than in arm 2 (P=0.051). Stratified analysis of improvement of abdominal pain according to the subtypes of disease revealed that, in the diarrhea subtype, improvement rating tended to be higher (P=0.090) and rate of “moderate” or better improvement was significantly higher (P=0.037) in arm 1. There were no significant differences between arms 1 and 2 in bowel movement abnormalities or gastrointestinal symptoms. In all, 17 and 7 adverse drug reactions occurred in 13 keishikashakuyakuto-treated patients and 6 controls, respectively.

8. Conclusions

Keishikashakuyakuto is an effective and safe agent for treating abdominal pain associated with irritable bowel syndrome, especially in patients with the diarrhea subtype.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Keishikashakuyakuto was “safe” in 110 of 124 patients (88.7%) in the keishikashakuyakuto group, and 98 of 108 (90.7%) in the control group; there was no statistically significant between-group difference in safety.

11. Abstractor’s comments

This is a well-designed clinical study conducted as a multicenter randomized parallel-group trial. Since keishikashakuyakuto is an agent with a relatively early onset of action, it is clinically necessary to monitor the course of action of this agent, including the time of action onset. Also, from a Kampo medicine perspective, discussions on the relationships between the physique or diathesis and the efficacy, would make the study more valuable.

12. Abstractor and date

Arai M, 22 October 2008, 6 January 2010, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Mori H, Iwamoto M. Comparison study of keihito and trimebutine maleate for irritable bowel syndrome. *Therapeutic Research* 1999; 20: 2179-85 (in Japanese). Ichushi Web ID: 2000030973 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of keihito（啓脾湯）in patients with irritable bowel syndrome.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital (department of internal medicine) and one clinic (the author belongs to Yokohama Sotetsu-naika), Japan.

4. Participants

Patients aged ≥15 years who presented with a complaint of diarrhea between March 1, 1998 and February 28, 1999, in whom irritable bowel syndrome with diarrhea (IBS-D) was diagnosed after exclusion of organic intestinal diseases. Patients were excluded from the study if they were pregnant, possibly pregnant, had serious hepatic or renal disorder or other diseases, had abnormal bowel movements due to other causes than irritable bowel syndrome, were contraindicated for anticholinergics, or had used oral trimebutine maleate or anticholinergics before participation in the study. (n=13)

5. Intervention

Arm 1: TSUMURA Keihito（啓脾湯）Extract Granules 2.5 g three times daily orally after meals for 2–4 weeks (n=6).

Arm 2: Trimebutine maleate 100 mg three times daily orally after meals for 2–4 weeks (n=7).

6. Main outcome measures

The following parameters were evaluated before and at 2 weeks of treatment (if not possible, at 3 or 4 weeks of treatment): stool volume, stool characteristics, frequency of stools per day, subjective symptoms (i.e., feeling of residual stools, diarrhea, constipation, abdominal pain, bloating, abdominal discomfort, heavy stomach feeling, inappetence, nausea/vomiting, and borborygmus). In addition, global improvement was rated on a 5-level scale as "Very much improved", "Much improved","Minimally improved", "No change", or "worse", based on the frequency of stools, stool characteristics, and the symptoms over time.

7. Main results

Since 1 patient in Arm 1 and 3 patients in Arm 2 were lost to follow-up, the analysis was conducted on 5 patients in Arm 1 and 4 patients in Arm 2. The stool volume, stool characteristics, frequency of stools per day, subjective symptoms, and global improvement rating showed no significant inter-group differences between Arm 1 and Arm 2.

8. Conclusions

Keihito and trimebutine maleate did not differ in the effectiveness on irritable bowel syndrome with diarrhea, suggesting that keihito can be effective in treating the disease.

9. From Kampo medicine perspective

From the viewpoint of Kampo medicine, irritable bowel syndrome represents *Ura no Kyosho* (*裏の虚証*, interior deficiency pattern). This study thus evaluated the effectiveness of keihito used to treat interior deficiency.

10. Safety assessment in the article

According to the article, no adverse effects were reported in either group, but blood tests were performed only at the start of treatment.

11. Abstractor's comments

From the viewpoint of Kampo medicine, irritable bowel syndrome represents *Ura no Kyosho* (*裏の虚証*, interior deficiency pattern). This clinical study thus evaluated the effectiveness of keihito used to treat interior deficiency, compared with trimebutine maleate classified as a gastrointestinal motility regulator. Given that keihito is used relatively uncommonly, this clinical study is important in that it was conducted to determine keihito's clinical effectiveness. However, because of the small sample size of the study, it is unclear whether the absence of an inter-group difference was due to the similar effectiveness between keihito and trimebutine maleate or due to the small sample size. Furthermore, although the article states that keihito and trimebutine maleate had similar effectiveness because both groups showed improvement in the global improvement rating and other parameters, influence of placebo effect can be prominent in some conditions like irritable bowel syndrome, and thus warrants consideration. As the authors stated in the article, the sample size was small in this study. Searching for effective therapies is important for irritable bowel syndrome and other diseases that affect many people, and further continuation of the research is desired.

12. Abstractor and date

Goto H, 5 September 2019.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Acosta A, Camilleri M, Linker-Nord S, et al. A pilot study of the effect of daikenchuto on rectal sensation in patients with irritable bowel syndrome. *Journal of Neurogastroenterological Motility* 2016; 22: 69-77. Pubmed ID: 26486374

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on rectal sensation in patients with irritable bowel syndrome (IBS).

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

One hospital.

4. Participants

Forty female IBS patients who fulfilled the Rome III criteria.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (15g t.i.d for 14 days) (n=20)
Arm 2: Placebo granules (15g t.i.d for 14 days) (n=20)

6. Main outcome measures

Primary outcome measures:① Feeling of urgency in reaction to 32mmHg intrarectal expansion pressure (quantified on 100mm VAS); ② pain threshold in reaction to bowel expansion
Secondary outcome measures: ① Physiological measures (rectal sensation threshold, etc.); ② clinical measures (bowel movement frequency, etc.) ③ QOL score

7. Main results

No significant differences were observed between the 2 groups in any of the primary or secondary outcome measures.

8. Conclusions

Daikenchuto does not display any significant effect on rectal sensation in patients with IBS.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The authors mention in the abstract that they evaluated safety, but there is no mention in the results.

11. Abstractor's comments

This report is valuable for having evaluated the effects of daikenchuto in IBS patients using a method of measuring rectal sensation with an intrarectal balloon. The authors raised various reasons for the daikenchuto not demonstrating a significant effect: while the Kampo preparation they used was TSUMURA Daikenchuto (大建中湯) Extract Granules (TU-100), the participants were Americans, who have a different pharmacokinetics to Japanese people; the number of cases was small; the administration period was short; and the daikenchuto dosage was single-dose. It is certainly possible that these factors affected the results of this study. It is unclear whether there would be any significance in repeating a similar DB-RCT, but increasing the number of cases, extending the administration period, and changing the daikenchuto dosage.

12. Abstractor and date

Motoo Y, 18 May 2020.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Ishioka T. Comparison of the efficacy of junchoto and mashiningan for atonic constipation in the elderly stratified by physical strength*. *Kampo no Rinsho* (*Journal of Kampo Medicine*) 1996; 43: 1431-7 (in Japanese).

1. Objectives

To compare the efficacy of junchoto (潤腸湯) and mashiningan (麻子仁丸) for atonic constipation in the elderly.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

A special nursing home, Japan.

4. Participants

Thirty-two patients (8 males and 24 females) who usually had no bowel movements and were diagnosed with atonic constipation.

5. Intervention

Arm 1: treatment with TSUMURA Junchoto Extract Granules (潤腸湯) 2.5 g t.i.d., followed by TSUMURA Mashiningan Extract Granules (麻子仁丸) 2.5 g t.i.d. (n=14).

Arm 2: treatment with TSUMURA Mashiningan Extract Granules 2.5 g t.i.d., followed by TSUMURA Junchoto Extract Granules 2.5 g t.i.d. (n=17).

Thirty-one patients, after excluding one who withdrew, were included. After 2 weeks of the first treatment, patients were switched to the second drug without a wash-out period and followed up for 2 weeks.

6. Main outcome measures

Number of defecation supports (e.g., laxatives and enemas).

7. Main results

Disappearance of the need for defecation supports was rated as “marked response”, reduction of the number of defecation supports as “moderate response”, and no change in the number as “no response”. Response (marked + moderate) rate tended to be higher in the mashiningan-treated patients (74.2%) than in the junchoto-treated patients (61.3%) (P<0.1). Comparing arms 1 and 2, the efficacy was not influenced by the order of administration, and was superior in the mashiningan-treated patients in both arms (P<0.05). Response rate was not different between the two drugs in patients with moderate physical strength, whereas it was higher in mashiningan- than in junchoto-treated patients with low physical strength (P<0.01). While the rate of response to junchoto was independent of physical strength, the rate of response to mashiningan was higher in patients with low than in those with moderate physical strength (P<0.05).

8. Conclusions

For atonic constipation in the elderly, junchoto and mashiningan are effective drugs associated with very few adverse reactions. Mashiningan is especially effective for patients with low physical strength.

9. From Kampo medicine perspective

The response was evaluated separately in patients with moderate and low physical strength.

10. Safety assessment in the article

Compared with pretreatment levels, posttreatment levels of total cholesterol (T-Cho) (P<0.01) and Na (P<0.05) were increased and posttreatment level of uric acid (UA) was decreased (P<0.01). The one patient who withdrew complained of too many bowel movements during the junchoto treatment and was switched to other medications. Unusual subjective or objective symptoms were not observed.

11. Abstractor’s comments

Junchoto and mashiningan are clinically difficult to use differentially. This valuable paper assesses these two drugs using a cross-over design and from a Kampo medicine perspective. However, cross-over design with no wash-out period might be unsuitable for evaluation of the efficacy of individual drugs. Also, to improve the quality of this study, its methodology should be clarified, such as the criteria used for classifying physical strength based on Kampo medicine and the standardization of empirically selected defecation supports to enable objective assessment of the response. It is hoped that higher quality studies on this clinically very interesting theme will be conducted.

12. Abstractor and date

Arai M, 9 November 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-To Extract Granules for ethical use (TJ-84) on constipation using double blind design. *Shokakika* (*Gastroenterology*) 1994; 18: 299-312 (in Japanese with English abstract). Ichushi Web ID: 1994189708

Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-to Extract Granules for ethical use (TJ-84) against constipation based on the new standard. *Shokakika* (*Gastroenterology*) 1996; 22: 314-28 (in Japanese with English abstract). Ichushi Web ID: 1996228578

Harasawa S, Miyoshi A. Reevaluation of Kampo medicine in patients with constipation - efficacy of Daio-kanzo-to -. *Shokakigan* (*Japanese Journal of Cancer of the Digestive Organs*) 1996; 6: 271-7 (in Japanese with English abstract). Ichushi Web ID: 1997060417

1. Objectives

A preceding double-blinded controlled trial of daiokanzoto (大黄甘草湯), compared with placebo, in the treatment of constipation found it was effective against constipation, but not useful (no details available). The objective of this study was to reexamine the effects of daiokanzoto on constipation using a newly-defined assessment standard and the same results mentioned above.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Seven university medical schools (including Tokyo Women's Medical University [Second Department of Internal Medicine, Tokyo Women's Medical University Daini Hospital]; Tokai University School of Medicine [Sixth Department of Internal Medicine]; Kyoto University [First Department of Internal Medicine, Faculty of Medicine]) and 19 hospitals (26 institutions in total), Japan.

4. Participants

One hundred and fifty-six patients who had 3 or fewer bowel movements per week and complaints of constipation; sought therapy; and consented to participate in the study. Exclusion criteria were: age 15 or younger, constipation caused by organic disease; diagnosis of hypertension and severe edema; pregnancy, lactation, or signs of pregnancy, lactose intolerance, serious complications; patients otherwise considered ineligible by the treating physician.

5. Intervention

Arm 1: treatment with usual-dose TSUMURA Daiokanzoto (大黄甘草湯) Extract Granules 2.5 g t.i.d. (containing 1.5 g/day of extract powder) (n=53).
Arm 2: treatment with low-dose TSUMURA Daiokanzoto (大黄甘草湯) Extract Granules 2.5 g t.i.d. (containing 0.5 g/day of extract powder) (n=49).
Arm 3: treatment with placebo (excipient only) 2.5 g t.i.d (n=54).

6. Main outcome measures

Improvement in bowel movement rating, improvement in subjective and objective symptoms (global rating), efficacy, safety, and utility (global rating).

7. Main results

Outcomes were assessed after 2 weeks of treatment, using the new standard that takes "excessive response to test drugs into account. After excluding 10 withdrawals, 146 patients (47 in arm 1, 49 in arm 2, and 50 in arm 3) were included in the analysis. As for final global improvement, "marked improvement" was observed in 43.2%, 31.7%, and 27.7% of patients in arm 1, arm 2, and arm 3, respectively, and "moderate improvement" in 36.8%, 24.4%, and 14.9%, respectively; the differences among three arms (P<0.05) and between arms 1 and 3 (P<0.01) were significant. Final global improvement rate was high in arm 1. In addition, ratings of efficacy (P<0.001) and utility (P<0.01) were also high in arm 1.

8. Conclusions

Compared with placebo, Daiokanzoto had significantly higher final global improvement rating, efficacy, and utility (global rating) and was confirmed to be an effective and useful drug for treating constipation. The safety of this drug was apparent over the 2-week period of treatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Test drugs were characterized as "having no safety problem" in 91.5% of patients in arm 1, 93.9% in arm 2, and 96.0% in arm 3; as "having a mild safety problem" in 8.5%, 6.1%, and 0%, respectively; and as "having a moderate safety problem" in 0%, 0%, and 4%, respectively. There were no significant among-arm differences. No abnormal changes in laboratory data occurred.

11. Abstractor's comments

Using the new diagnostic standard, Miyoshi et al (1996) reevaluated the data of the preceding paper (Miyoshi et al [1994]). This is a highly valuable paper reporting a well-designed clinical study. Discussion from Kampo medicine perspective of cases with excessive response would make the content more meaningful. Studies that produce high-quality evidence, like this one, need to be developed for other Kampo preparations.

12. Abstractor and date

Arai M, 10 November 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Nishizawa Y, Nishizawa Y, Goto HG, et al. Prospective multicenter randomized group-parallelled study: effect of Chinese traditional herb medicine, jiu-wei-bing-lang-tang (Japanese name: kumi-binro-to) on constipation in elderly patients with renol dialysis. *Kampo Kenkyu* (*Kampo Research*) 2004; 388: 132-8 (in Japanese). Ichushi Web ID: 2004202082

1. Objectives

To evaluate the efficacy and safety of kumibinroto (九味檳榔湯) for chronic constipation in elderly dialysis patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Clinics and other services, Osaka, Japan.

4. Participants

Three-hundred and eighteen patients who were 75 years or older and on dialysis were enrolled during 15 years.

5. Intervention

Arm 1: treatment with Kotaro Kumibinroto (九味檳榔湯) Extract Fine Granules 2g, t.i.d., n=160.
Arm 2: treatment with magnesium laxative 2.0 g/day in three divided doses, n=158.
Duration of the study was 9 months.

6. Main outcome measures

Number of urges to have bowel movements and dosage of the laxatives (Western medicines) combined with the study drug.

7. Main results

Both the number of urges to have bowel movements and the dosage of the combined laxatives were significantly more improved in arm 1 than in arm 2. Symptoms associated with bowel movements were also significantly improved.

8. Conclusions

Kumibinroto is more effective than magnesium laxative for improving the number of bowel movements and the dosage of the combined laxatives in elderly dialysis patients with chronic constipation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Fewer adverse effects were reported in arm 1 than in arm 2 (data not shown). There were no abnormal examination findings.

11. Abstractor's comments

Although the word "multicenter" was mentioned in this article, none of the actual clinics, in contradistinction to research laboratories where this clinical trial was conducted, was specified. The authors conducted a 9-month, prospective, randomized study in 318 patients over a long period (15 years). Unfortunately, neither the number of withdrawals from the study nor the number of subjects included in the analysis was reported. Kumibinroto does not have a potent laxative effect. This study suggested that kumibinroto, combined with western laxatives, is more effective and safer than magnesium laxative for chronic constipation in elderly dialysis patients. Magnesium laxative, however, needs to be carefully administered and may cause hypermagnesemia in patients with renal impairment. Therefore, this type of laxative is usually avoided in patients undergoing hemodialysis. Regarding this point, the types and dosage of the western laxatives combined with the study drug are to be reported.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Horiuchi A, Nakayama Y, Tanaka N. Effect of traditional Japanese medicine, Daikenchuto (TJ-100) in patients with chronic constipation. *Gastroenterology Research* 2010; 3: 151–5.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) in combination for chronic constipation patients taking sennoside.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Twenty-two patients with chronic constipation presenting with abdominal pain and bloating and treated for more than 3 months by taking sennoside (24–60 mg/day). Participants' stool frequency was less than three times a week when not taking sennoside. Colonoscopy revealed no abnormality, and participants had no history of abdominal surgery.

5. Intervention

Arm 1: Sennoside 24 to 60 mg/day with TSUMURA Daikenchuto (大建中湯) Extract Granules 7.5 g/day for 6 weeks (n=14).

Arm 2: Sennoside 24 to 60 mg/day with TSUMURA Daikenchuto (大建中湯) Extract Granules 15 g/day for 6 weeks (n=8).

6. Main outcome measures

Abdominal bloating (visual analogue scale), abdominal pain (visual analogue scale), Gastrointestinal Symptoms Rating Scale (GSRS), Gas Volume Score (GVS).

7. Main results

Abdominal bloating scores decreased significantly in both arms from 55 before intervention to 20 after four weeks of intervention in arm 1 (P=0.006) and from 69 to 35 in arm 2 (P=0.007). Abdominal pain scores decreased significantly from 32 to 9 after four weeks in arm 2 (P=0.02). GSRS scores also decreased significantly in both arms after four weeks, from 2.6 to 2.2 in arm 1 (P=0.002), and from 2.8 to 2.3 in arm 2 (P=0.008). GVS scores decreased significantly in both arms after six weeks, from 0.049 to 0.040 in arm 1 (P=0.02), and from 0.042 to 0.036 (P=0.016) in arm 2.

8. Conclusions

Daikenchuto alleviates abdominal pain and bloating in chronic constipation patients taking a stimulant laxative.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor's comments

This study suggests that when taken in combination with sennoside, daikenchuto alleviates abdominal pain and bloating in chronic constipation patients. However, the study only makes before/after comparisons, not between-group comparisons. Daikenchuto is a prescription that warms the middle abdominal region and treats *kyosho* (虚証, deficiency patterns) (温中補虚), so it warms the gastrointestinal tract. On the other hand, the active constituent in senna leaf (番瀉葉) is sennoside, which resolves heat in the stomach and intestines and promotes intestinal peristalsis. In Kampo medical terms, these drugs are used for the opposing pattern. Hopefully, researchers will conduct a trial that compares sennoside + daikenchuto to control groups including placebo and daikenchuto alone. Lastly, if each participant's *sho* (証, pattern) had been identified in this comparative study, light might have been shed on the pathological conditions for which daikenchuto is indicated.

12. Abstractor and date

Okabe T, 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Iturrino J, Camilleri M, Wong BS, et al. Randomized clinical trial: the effects of daikenchuto, TU-100, on gastrointestinal and colonic transit and anorectal and bowel function in female patients with functional constipation. *Alimentary Pharmacology and Therapeutics* 2013; 37: 776-85. CENTRAL ID: CN-00853558, Pubmed ID: 23451764

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) in the treatment of functional constipation.

2. Design

Randomized controlled trial (RCT).

3. Setting

Mayo Clinic, U.S.A. (single institution).

4. Participants

Forty-five subjects with functional constipation recruited from October 2010 to November 2012.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules po 2.5 g t.i.d for 4 weeks (n=15).
Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules po 5 g t.i.d for 4 weeks (n=15).
Arm 3: Placebo (n=15).

6. Main outcome measures

Gastrointestinal transit, rectal compliance, rectal sensation thresholds, gastrointestinal motility in response to anal sphincter pressures and bowel movement status, changes in psychosensory symptoms associated with constipation, and quality of daily life.

7. Main results

Gastrointestinal motility was not significantly increased by arm 1 and arm 2 compared to arm 3. There was no difference in main outcome measures between arm 1 and arm 2. In arm 2, daikenchuto lowered the rectal sensation thresholds for the first bowel movement and gas sensation (P = 0.045 and 0.024, respectively).

8. Conclusions

In women with functional constipation, daikenchuto may increase the rectal sensation threshold for bowel movement but has no therapeutic effect on gastrointestinal motility, stool softness, frequency of stools, psychosensory symptoms, or quality of life. The mechanism of action of daikenchuto remains to be elucidated in clinical settings.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although daikenchuto produced adverse reactions such as headache and abdominal pain, no differences in adverse reactions were noted among the groups and daikenchuto was safe and well tolerated.

11. Abstractor's comments

This excellent study measured defecation sensation in the rectum associated with intestinal motility and defecation behavior in women with functional constipation by using various objective, physiological examination methods, in an attempt to elucidate the clinical efficacy of daikenchuto. The study revealed that 5 g/dose (15 g/day) of daikenchuto does not affect gastrointestinal motility or rectal sensation. However, it lowers the thresholds for bowel movement and gas sensation in the rectum, a finding which will contribute a great deal to the conduct of future clinical studies of daikenchuto. Daikenchuto is not widely used for the treatment of functional constipation, but has been shown to promote gastrointestinal motility in *in vitro* experiments. The present study may be the driving force for the elucidation of how daikenchuto-related sub-ileus can be prevented. I hope verification will be obtained from a different point of view or based on a study protocol that involves the *sho* (証, pattern) for daikenchuto.

12. Abstractor and date

Ushiroyama T, 6 June 2015

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Numata T, Takayama S, Tobita M, et al. Traditional Japanese medicine daikenchuto improves functional constipation in poststroke patients. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-8. doi: 10.1155/2014/231258

Numata T, Takayama S, Iwasaki K, et al. A prospective comparative trial using the Kampo medicine, daikenchuto (大建中湯) for constipation in poststroke patients. *Kampo & the Newest Therapy* 2015; 24:145-152

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) as treatment for functional constipation in poststroke patients.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Six hospitals.

4. Participants

Thirty-four patients (17 females / 17 males) who were diagnosed with functional constipation according to Roma III diagnostic criteria from September 2012 to December 2013 and who remained stable over 6 months or longer after having suffered cerebral hemorrhage, cerebral infarct, or subarachnoid hemorrhage.

5. Intervention

Arm 1: Common treatment for relief of constipation including laxative, enema, fecal disimpaction, etc. as well as oral administration of TSUMURA Daikenchuto (大建中湯) Extract Granules 5g divided in three doses per day before each meal or tube administration for 4 weeks (n=17).

Arm 2: Common treatment for relief of constipation including laxative, enema, fecal disimpaction, etc. for 4 weeks (n=17).

6. Main outcome measures

Constipation scoring system (CSS), gas volume score (GVS), calcitonin-gene related peptide (CGRP) concentration in blood.

7. Main results

Patients in arm 1 showed a statistically significant decrease in CSS ($P<0.01$), and also in GVS ($P=0.03$) compared to arm 2. The CGRP concentration in blood was similar between arm 1 and arm 2.

8. Conclusion

Daikenchuto is effective in improvement of constipation and retention of gas in the abdominal cavity in poststroke patients.

9. From Kampo medicine perspective

Daikenchuto is effective for constipation in yin pattern (陰証, insho) patients with loss of appetite and decreased gastrointestinal tract function.

10. Safety assessment in the article

Adverse reaction was not observed in the daikenchuto-administered arm.

11. Abstractor's comments

This paper reports the results of a clinical trial investigating the efficacy of daikenchuto for the treatment of constipation in poststroke patients. This RCT is significant for its demonstration of daikenchuto's efficacy in poststroke patients who often suffer from constipation and distension. Moreover, while hypothetically the effect of daikenchuto on constipation is mediated via CGRP, this RCT found no significant difference in blood levels of CGRP in spite of daikenchuto's clinical efficacy. This conflicting finding has warrants further basic studies of daikenchuto. As mentioned in this paper, some studies report that daikenchuto is not effective for constipation in other circumstances; therefore, further studies are anticipated to determine the efficacy of daikenchuto in a broader spectrum of constipation.

12. Abstractor and date

Koike H, 31 March 2017.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Ikemoto T. The role of Kampo in gastrointestinal surgery and the effectiveness of daikenchuto (大建中湯) for intestinal stress - From bacterial translocation to microbiome*. *Progress in Medicine* 2011; 31: 466-7 (in Japanese). MOL, MOL-Lib

1. Objectives

To verify the anti-inflammatory effects of daikenchuto (大建中湯) on intestinal distress in the aftermath of gastrointestinal surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Gastrointestinal and Transplant Department, Tokushima University Hospital, Japan.

4. Participants

Thirty-one patients who had either minimally invasive laparoscopic colon surgery or invasive hepatectomy.

5. Intervention

Arm 1: DKT group: oral administration of TSUMURA Daikenchuto (大建中湯) Extract Granules (2.5 g t.i.d.) before meals for 7 days beginning on the first day after surgery (n=15).

Arm 2: no daikenchuto (大建中湯) treatment (n=16).

6. Main outcome measures

Body temperature, number of days till flatus, and blood C-reative protein (CRP) concentration monitored beginning on the first postoperative day.

7. Main results

Body temperature was 36.2°C in arm 1 and 36.9°C in arm 2 on the third postoperative day. The number of days till flatus was significantly shorter in arm 1 (1.7 ± 0.4) than in arm 2 (2.9 ± 0.8) (P<0.05). Blood CRP concentration was significantly lower in arm 1 (5.1 ± 2.3 mg/dL vs 7.7 ± 4.7 mg/dL) (P<0.05).

8. Conclusions

Daikenchuto is clearly effective in controlling the increase in body temperature after surgery, in shortening the number of days till flatus, and in controlling inflammation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study investigated the clinical efficacy of daikenchuto for reducing inflammation. The results are valuable because they help elucidate the mechanisms underlying well-known problems that develop following intestinal surgery. The paper refers to experiments in fasted rats showing that oral administration of daikenchuto maintains diversity in the intestinal microbiome (which is the collective genome of all intestinal microorganisms) and suggesting that the microbiome is relevant to expression of daikenchuto's anti-inflammatory effects. However, further research is needed before it is known whether these animal data are relevant to the mechanism of action in humans.

The paper deserves praise for investigating daikenchuto's mechanism of action from the perspective of enteric bacterial diversity. Hopefully the researchers will conduct further study with a more adequate number of participants, and use clinically applicable protocols.

12. Abstractor and date

Ushiroyama T, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takahashi H, Maruyama K. Clinical aspects of Kampo treatment for alcoholic liver disease. *Igaku no Ayumi* (*Journal of Clinical and Experimental Medicine*) 1993; 167: 811-4 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) and shosaikoto + inchingoreisan (小柴胡湯合茵蔯五苓散) for alcoholic liver disease.

2. Design

Randomized controlled trial (RCT)

3. Setting

One general hospital, Japan.

4. Participants

Forty-nine alcoholics receiving inpatient treatment.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. (n=24).
Arm 2: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. and TSUMURA Inchingoreisan (茵チン五苓散) Extract Granules 2.5 g t.i.d. (n=25).
Each drug was administered for 3 months.

6. Main outcome measures

Subjective symptoms (anorexia, nausea, fatigue, etc.) and liver function test results.

7. Main results

Subjective symptoms were improved in both arms but without any between-arm difference in improvement. Liver functions were also improved in both arms. ALP decreased more in Arm 2 than in Arm 1.

8. Conclusions

Shosaikoto and shosaikoto + inchingoreisan improve subjective symptoms and liver dysfunction in patients with alcoholic liver disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The present paper is meaningful in that an RCT using multiple Kampo medicines was conducted. The clinical significance, however, might be limited by the absence of a non-treatment of placebo control group and the possible effects of abstinence during hospitalization (as pointed out by the authors).

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of sho-saiko-to in chronic active hepatitis. Gastroenterologia Japonica 1989; 24: 715–9. CENTRAL ID: CN-00064736, Pubmed ID: 2691317, Ichushi Web ID: 1991224424

Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis. *Kan-Tan-Sui* 1990; 20: 751–9 (in Japanese). Ichushi Web ID: 1991006763

Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis – Variation in serum enzyme activity*. *Kan-Tan-Sui* 1992; 25: 551–8 (in Japanese). Ichushi Web ID: 1993125235

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of chronic active hepatitis.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Seven university hospitals and 31 general hospitals, Japan.

4. Participants

Two hundred and twenty-two patients who were diagnosed with chronic active hepatitis based on liver biopsy within a year of the onset of symptoms.

5. Intervention

Arm 1: Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules (containing 0.9 g of shosaikoto extract/g) at a dose of 1 pack (2.0 g) t.i.d. for at least 12 weeks (n=116).

Arm 2: placebo fine granules (containing 0.09 g of shosaikoto extract/g) at a dose of 1 pack (2.0 g) t.i.d. for 12 weeks (n=106).

6. Main outcome measures

Hepatic function test (absolute value, %), presence of HBe antigen and anti-HBe antibody.

7. Main results

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly decreased in arm 1 at Week 12, but were almost comparable between arm 1 and arm 2 at Week 24. There was no significant difference between arms for γ-GT. By percentage decrease from the previous values, AST and ALT decreased significantly in the shosaikoto group after 12 weeks ($P<0.05$); however, there was no difference between groups for γ-GT. In arm 1 and arm 2, respectively, 4 of 27 patients and 5 of 32 patients became HBe antigen-negative, and 3 of 26 patients and 2 of 33 patients became anti-HBe antibody-positive. No significant between-arm difference was observed.

8. Conclusions

Shosaikoto significantly improves abnormal hepatic function compared with placebo.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Ten and 3 patients had adverse drug reactions to shosaikoto and placebo, respectively. Adverse drug reactions to shosaikoto requiring discontinuation of treatment were reported in 4 patients (general malaise [1 patient]; nausea [1 patient]; diarrhea [1 patient]; numbness of tongue [1 patient]). However, urinalysis results or blood pressure remained unchanged during the study.

11. Abstractor's comments

It is admirable that a multicenter DB-RCT was conducted. I consider that the efficacy of shosaikoto (24-month follow-up) was objectively evaluated. It is clinically significant that shosaikoto improved abnormal hepatic function more markedly in cases of hepatitis B, and was more effective in histologically mild disease.

12. Abstractor and date

Kogure T, 8 August 2008, 31 December 2013, 76June 2015.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Sasaki D, Sudoh T, Kunikane M, et al. Usefulness of Kanebo Saireito Extract Fine Granules for chronic hepatitis - a comparative study (with randomization carried out using the sealed-envelope method) -*. *Progress in Medicine* 1989; 9: 2923–37 (in Japanese). Ichushi Web ID: 1991131916

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) in the treatment of chronic hepatitis.

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

One university hospital and 20 general hospitals, Japan.

4. Participants

Hundred patients who were clinically diagnosed with chronic hepatitis.

5. Intervention

Arm 1: Kanebo Saireito (柴苓湯) Extract Fine Granules 2.7 g t.i.d. for 12 weeks (n=53).
Arm 2: Proheparum 2 tablets t.i.d. for 12 weeks (n=47).

6. Main outcome measures

Hepatic function test, HBsAg level, physical findings (hepatomegaly, etc.), subjective symptoms, hematology/biochemistry, and improvement in each measure rated on a 5-grade scale. Safety was considered a measure of overall usefulness.

7. Main results

Eighty-eight patients were included in the analyses. No significant between-group difference was observed in glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), γ-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), cholinesterase (ChE), zinc sulfate turbidity test (ZTT), total bilirubin, total cholesterol, triglyceride (TG), total protein (TP), albumin, or hepaplastin test (HPT). . Global improvement and usefulness were significantly greater in the saireito group (P<0.05).

8. Conclusions

It is suggested that saireito is useful in the treatment of chronic hepatitis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In the saireito group, 1 patient had dizziness and fatigability, 1 patient had anemia, and 3 patients had nausea.

11. Abstractor's comments

It is admirable that a multicenter RCT was conducted. However, caution should be used in the clinical interpretation of the usefulness and global improvement results, since these measures are not frequently evaluated. The authors stated that marked improvement was achieved in patients with high GOT and/or GPT in the saireito group.

12. Abstractor and date

Kogure T, 8 August, 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Kainuma M, Furusyo N, Murata M, et al. The effectiveness of traditional Japanese medicine (Kampo), in combination with pegylated interferon α plus ribavirin for patients with chronic hepatitis C: A pilot study. *Journal of Traditional Medicines* 2013; 30: 132-9. Ichushi Web ID: 2014095582 J-STAGE

1. Objectives

To evaluate whether use of Kampo medicines (Shimbuto [真武湯] and Ninjinto [人参湯]) in combination with pegylated interferon α plus ribavirin promotes therapeutic responses in patients with chronic hepatitis C.

2. Design

Randomized controlled trial (RCT).

3. Setting

General clinical department of a university hospital and 5 related hospitals.

4. Participants

Fifty-one patients (20 males and 31 females) diagnosed with chronic hepatitis C. All patients were hepatitis C virus (HCV) antibody-positive and HCV-RNA-positive for more than 6 months. The exclusion criteria were: (1) history of upper gastrointestinal (UGI) bleeding, ascites, hepatocellular carcinoma, hepatic failure, and cirrhosis with a risk of esophageal varices, (2) hemoglobin <11.5 g/dL, leukocyte count $<3 \times 10^3$/L, platelet count $<50 \times 10^9$/L; (3) hepatitis B surface antigen positive or human immunodeficiency virus (HIV) positive; (4) excessive alcohol use (>60 g/day), drug addiction; (5) severe mental disorder; (6) treatment with an antiviral drug and steroid therapy for 12 months before enrollment.

5. Intervention

Arm 1: Patient group treated with Kampo medicines (Group A) (n=26). Oral administration of pegylated interferon α 1.5μg/kg/week plus ribavirin 600–1000 mg/day (600mg for 60kg of body weight or below, 800mg for 60–80kg of body weight, 1000 mg for 80 kg of body weight or over) concurrently with Kampo medicines (mixed formulation of Shimbuto [真武湯] extract and Ninjinto [人参湯] extract, each 5g t.i.d. before each meal).

Arm 2: Control group (Group B)(n=25). Oral administration of pegylated interferon α 1.5μg/kg/week plus ribavirin 600–1000mg/day (600mg for 60kg of body weight or below, 800mg for 60–80kg of body weight, 1000 mg for 80kg of body weight or over) alone.

6. Main outcome measures

Early virological response (EVR), Sustained virological response (SVR).

7. Main results

EVR rate and SVR rate were significantly higher in Group A than in Group B (EVR, 22/26 patients [84.6%] vs 14/25 patients [56.0%], *P*=0.034; SVR, 20/26 patients [76.9%] vs 12/25 patients [48.0%], *P*=0.033). The minimum dose (80% or higher of pegylated interferon α and 60% or higher of ribavirin) was given to 22/26 patients (84.6%) in Group A and 18/25 patients (72.0%) in Group B. SVR rate showed no differences between arms. The dropout rate was significantly different between Group B (5/25 patients [20.0%]) and Group A (0/26 patients; *P*=0.0023).

8. Conclusions

Administration of a mixed formulation of Shimbuto and Ninjinto to patients with chronic hepatitis C who received concurrent administration of pegylated interferon α plus ribavirin decreases the dropout rate and promotes treatment efficacy.

9. From Kampo medicine perspective

The reason for the efficacy of Shimbuto and Ninjinto in patients with chronic hepatitis C has not been identified.

10. Safety assessment in the article

No adverse events were observed in the Kampo-administered group. Five patients dropped out in the control group. Adverse events, vomiting (week 4), interstitial pneumonia (week 10), hyperthyroidism (week 22), and hepatocellular carcinoma (week 19) were observed in 1 patient each. The remaining patient stopped treatment, as no clinical efficacy was observed at week 44.

11. Abstractor's comments

This RCT demonstrated the efficacy of concurrent use of Kampo medicines (mixed formulation of Shimbuto and Ninjinto) with pegylated interferon α plus ribavirin in patients with chronic hepatitis C. The study showed that the treatment decreased the onset rate of adverse events and increased the rate of early virological response and concluded that Kampo medicines were effective. In the original abstract, the line "Kampo medicines were given to Group B" was considered a misprint. This trial was carefully designed including the intent-to-treat (ITT) analysis; however blinding was not mentioned. If the trial had used measures such as blinding to reduce bias, it would have increased confidence in the results. We anticipate further developments.

12. Abstractor and date

Tsuruoka H, 31 March 2017.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Tajiri H, Kozaiwa K, Sawada A, et al. Efficacy of shosaikoto for chronic non-A, non-B hepatitis in children (non-A, non-B hepatitis in children and shosaikoto)*. *Nihon Shoni Toyo Igaku Kenkyukai Kaishi*（*Journal of the Japan Pediatric Society for Oriental Medicine*）1996; 12: 12-7 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for chronic non-A, non-B hepatitis in children.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital, Japan.

4. Participants

Patients were children with liver dysfunction persisting for at least 6 months and infected with viruses known to cause liver damage (hepatitis A virus [HAV], hepatitis B virus [HBV], cytomegalovirus [CMV], and Epstein-Barr virus [EBV]) were excluded. Six patients positive for hepatitis C virus (HCV) were included.

5. Intervention

Arm 1: treatment with TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day (dose adjusted for age) for at least 6 months (n=5).
Arm 2: natural course monitoring group (n=5).
One patient who took shosaikoto (小柴胡湯) for more than 6 months following natural course monitoring for 6 months was enrolled in both arms 1 and 2.

6. Main outcome measures

Levels of glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), serum neopterin, soluble interleukin-2 (IL-2) receptor, and HCV-RNA.

7. Main results

GPT and GOT levels were reduced significantly at 2, and 6 months in arm 1 ($P<0.05$). Serum neopterin was increased at 1 month in the 3 patients of arm 1 who had measurements. Soluble IL-2 receptor was also increased only at 1 month. One of the patients who showed reduction in GPT level remained positive for HCV-RNA.

8. Conclusions

Shosaikoto is effective for improving liver function in chronic non-A, non-B hepatitis, including chronic hepatitis C, in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The present paper is valuable in that it analyzed the clinical effects of Kampo medicine on chronic hepatitis in children—who are rarely the focus of clinical trials. Unfortunately, the between-arm comparison was insufficient because of the small number of patients enrolled.

12. Abstractor and date

Kogure T, 8 August 2008, 6 January 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Mizutani Y, Imai S, Watanabe H, et al. Saiko-keishi-to in patients with pulmonary tuberculosis: effect on liver dysfunction. *Donan Igakkaishi* (*Journal of the Medical Association of South Hokkaido*) 1994; 29: 247–9 (in Japanese).

1. Objectives

To evaluate the efficacy of saikokeishito (柴胡桂枝湯) for hepatic dysfunction associated with chemotherapy for pulmonary tuberculosis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Four hospitals, Japan.

4. Participants

Thirty-eight patients with pulmonary tuberculosis who received combination chemotherapy containing rifampicin for the first time.

5. Intervention

Arm 1: saikokeishito (柴胡桂枝湯) (unknown manufacturer) at a dose of 7.5 g t.i.d. for 8 weeks (n=21).
Arm 2: no treatment (n=17).

6. Main outcome measures

Serum glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) levels.

7. Main results

Thirty-three patients were included in the analysis. The incidence of abnormal GOT and GPT levels was 27.8% and 38.9% in arm 1, and 6.7% and 20.0% in arm 2, respectively. More patients had abnormal GOT and/or GPT in arm 1 than in arm 2, but the between-arm difference was not significant.

8. Conclusions

Saikokeishito is not effective for hepatic dysfunction associated with chemotherapy for pulmonary tuberculosis.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

While randomization by the envelope method is often difficult to attain, it is interesting that this clinical trial showed that saikokeishito was ineffective for prevention of hepatic dysfunction, an adverse reaction to chemotherapy for pulmonary tuberculosis. It is desirable to conduct a randomized controlled trial with more patients using an improved randomization scheme.

12. Abstractor and date

Okabe T, 21 August 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

21. Others

References

Kaido T, Shinoda M, Inomata Y, et al. Effect of herbal medicine daikenchuto on oral and enteral caloric intake after liver transplantation: A multicenter, randomized controlled trial. *Nutrition* 2018 54: 68-75. Pubmed ID: 29747091

1. Objectives

To evaluate the efficacy and safety of daikenchuto（大建中湯）to enhance oral and enteral caloric intake after liver transplantation

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

Fourteen institutions including university hospitals, Japan

4. Participants

A total of 112 patients with end-stage liver disease.

Inclusion criteria: Patients aged ≥20 years who met the indication criteria for liver transplantation at each study center.

Exclusion criteria: Uncontrollable acute infection other than in the liver, uncontrollable malignant disease other than hepatocellular carcinoma, severe postoperative adhesions, use of psychotropic, gastrointestinal prokinetic, or other Kampo medicines, current pregnancy or lactation.

5. Intervention

Arm 1: administration of TSUMURA Daikenchuto（大建中湯）Extract Granules 15.0 g/day (5 g three times daily orally immediately before meals or enterally via tube every 8 hours) (n=57)

Arm 2: administration of placebo 15.0 g/day (5 g three times daily orally immediately before meals or enterally via tube every 8 hours) (n=55)

In both Arms 1 and 2, the treatment was given from postoperative day (POD) 1 to POD 14.

6. Main outcome measures

Primary endpoints: total oral/enteral caloric intake at POD 7, abdominal distension, abdominal pain (numeric rating scale [NRS]).

Secondary endpoints: 1) chronological changes in total oral or enteral caloric intake, 2) chronological changes in abdominal distension and abdominal pain, 3) elapsed time from extubation to first postoperative defecation, 4) quality of life (QOL) assessment using the Gastrointestinal Symptom Rating Scale (GSRS) score, 5) liver regeneration rate between POD 14 and POD 21, 6) incidence of sepsis, 7) incidence of acute cellular rejection, 8) rate of discharge from the hospital within 2 months after liver transplantation, 9) portal vein flow volume and velocity.

7. Main results

Since 2 patients in Arm 1 and 6 patients in Arm 2 dropped out of the study, the analysis was conducted in 55 patients in Arm 1 and 49 patients in Arm 2. Arm 1 and Arm 2 did not significantly differ in total caloric intake (972.6±595.3 kcal in Arm 1 and 966.0±615.7 kcal in Arm 2; P=0.957), abdominal distension (3.5±2.9, 3.2±2.8; P=0.609), and abdominal pain (3.4±2.5, 3.0±2.3; P=0.530). As for chronological changes, the total caloric intake at PODs 3, 5, 7, 10, and 14 did not significantly differ between the two arms. However, between POD 3 and POD 10, the rate of increase in the caloric intake was significantly higher in Arm 1 (P=0.023). No significant intergroup differences were shown in the chronological changes in abdominal distension or abdominal pain, elapsed time from extubation to first postoperative defecation, QOL, liver regeneration rate, incidence of sepsis, incidence of acute cellular rejection, discharge rate within 2 months after liver transplantation. On the other hand, the portal vein flow volume was significantly higher in Arm 1 than in Arm 2 at POD 10 and POD 14 (P=0.047, P=0.025). The portal vein flow velocity at POD 14 was significantly higher in Arm 1 than in Arm 2 (P=0.014). In a subgroup analysis conducted on 70 patients (i.e., 37 in Arm 1 and 33 in Arm 2) in whom oral or enteral nutrition was started within 3 days postoperatively, the total caloric intake between POD 3 and POD 7 was significantly higher in Arm 1 than in Arm 2 (P=0.014). The portal vein flow volume was significantly higher in Arm 1 between POD 0 and POD 14 (P=0.010), and the portal vein flow velocity and volume were significantly higher in Arm 1 at POD 14 (P=0.032 and P=0.030, respectively).

8. Conclusion

Administration of daikenchuto after liver transplantation may enhance total oral and enteral caloric intake in the early postoperative period, in which involvement of increased portal vein flow volume and velocity is suggested.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

There was no significant difference in the frequency of grade ≥3 major complications between the daikenchuto group and the placebo group.

11. Abstractor's comments

This is a highly objective article describing an analysis from a DB-RCT (14 study centers) on the effect of daikenchuto in enhancing oral/enteral caloric intake in patients who underwent liver transplantation. As the authors described, unfortunately no significant intergroup difference was shown in total caloric intake as a primary endpoint. However, a subgroup analysis among the patients with early resumption of oral/enteral caloric intake showed significantly higher caloric intake in the daikenchuto group. Follow-up of this finding is awaited.

12. Abstractor and date

Kogure T, 1 June 2020.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Seki M, Fujioka M, Hatano T, et al. Differences between the effects of sho-saiko-to, gorei-san, and toki-shakuyaku-san on the sphincter of Oddi - An intraoperative cholangiomanometric study -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1993; 43: 395-402 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of shosaikoto (小柴胡湯), goreisan (五苓散), and tokishakuyakusan (当帰芍薬散) on the sphincter of Oddi.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Forty-nine patients who were admitted for gallstone disease and underwent cholecystectomy.

5. Intervention

Arm 1: treatment with TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 gt.i.d. for 6.6±4.2 days before surgery (n=8).
Arm 2: treatment with TSUMURA Goreisan (五苓散) Extract Granules 2.5 gt.i.d. for 7.8±6.0 days before surgery (n=12).
Arm 3: treatment with TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 gt.i.d. for 8.2±6.3 days before surgery (n=5).
Arm 4: bed rest only (n=24).

6. Main outcome measures

Biliary pressure (basal pressure, BP; perfusion pressure, PP; the time for biliary pressure to normalize, T)

7. Main results

At a perfusion rate of 0.1 mL/s, there were no among-arm differences in BP and PP. Regarding the biliary pressure curve, only shosaikoto resulted in significantly decreased $T_{1/2}$, $T_{1/4}$, and $T_{1/5}$ compared with the control (P<0.02–0.05). At a perfusion rate of 0.5 mL/s, PP was significantly higher in arms 1 and 2 than in arm 4. Regarding the biliary pressure curve, only shosaikoto resulted in significantly decreased $T_{1/4}$ and $T_{1/5}$ compared with the control (P<0.01).

8. Conclusions

Shosaikoto and goreisan both lower the threshold of biliary pressure, and shosaikoto results in a rapid relaxation of the sphincter of Oddi.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical trial evaluated biliary pressure as an endpoint in 4 groups. It provides valuable insights. The authors speculate that the treatment may prevent bile stasis.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takagi S. Increase of urinary 6-keto-prostaglandin F1α level by preoperative administration of gorei-san or toki-shakuyaku-san to the patients of gallbladder stones or polyps. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1992; 9: 32-9 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of goreisan (五苓散) and tokishakuyakusan (当帰芍薬散) on urinary 6-keto-prostaglandin F1α excretion in patients with gallbladder stones or polyps.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-nine female patients who underwent cholecystectomy for gallbladder stones or polyps.

5. Intervention

Arm 1: TSUMURA Goreisan (五苓散) Extract Granules (n=6).
Arm 2: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules (n=6).
Arm 3: TSUMURA Shosaikoto (小柴胡湯) Extract Granules (n=6).
Each preparation was administered at 2.5 g t.i.d. before meals for 5 or 6 days before surgery.
Arm 4: no continuous drug therapy (n=11).

6. Main outcome measures

Urinary excretions of prostaglandin E1 (PGE1) and 6-keto-prostaglandin F1α (6-keto-PGF1α).

7. Main results

There was no significant difference in urinary PGE1 excretion throughout the treatment course between each arm of treatment and the control arm (arm 4). Urinary 6-keto-PGF1α excretion was increased significantly on postoperative days 1 and 5–7 in arm 1 (P<0.05) and on postoperative days 1 and 3–7 in arm 2 (P<0.02–0.001). The urinary 6-keto-PGF1α excretions were not significantly different between arm 3 and arm 4, as well as between arm 1 and arm 2.

8. Conclusions

Preoperative administration of goreisan or tokishakuyakusan before cholecystectomy results in increased postoperative urinary excretion of 6-keto-PGF1α.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The author of the study deserves praise for conducting a 4-group RCT. The determination of relationship between urinary excretion and clinical outcome would make the study more clinically meaningful.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010, 12 October 2011, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Okabayashi T, Tanaka N, Orita K. The effect of a Kampo medicine, inchinko-to, on rate of bilirubin reduction after biliary drainage in patients with obstructive jaundice. *Nihon Rinsho Geka Gakkaishi* (*Journal of Japan Surgical Association*) 1998; 59: 2495-500 (in Japanese with English abstract). Ichushi Web ID: 1999080276, J-STAGE

1. Objectives

To evaluate the efficacy of inchinkoto (茵チン蒿湯) for improving the bilirubin reduction rate after biliary drainage in patients with obstructive jaundice.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

First Department of Surgery, Okayama University School of Medicine and 14 associated facilities, Japan.

4. Participants

Twenty-four patients with obstructive jaundice undergoing biliary drainage procedures such as percutaneous transhepatic cholangio-drainage (PTCD). The patients satisfying any of the following criteria were excluded: 1) age <15 years or ≥80 years; 2) oral intake not possible; 3) presence of serious cirrhosis or complications; and 4) ineligibility as judged by the patient's physician.

5. Intervention

Arm 1: drainage +oral administration of TSUMURA Inchinkoto (茵チン蒿湯) Extra Granules 2.5 g t.i.d., either for 4 weeks or before the surgery (n=11; of these, 10 were analyzed [the reason of study withdrawal not shown]).
Arm 2: drainage alone (n=13).

6. Main outcome measures

Total bilirubin, direct bilirubin, and daily volume of bile. Bilirubin reduction rate as determined by the formula of Shimizu et al. Changes in anorexia and general malaise rated on a 4-point scale.

7. Main results

Bilirubin reduction rate was significantly improved in arm 2 (P<0.05). AST, ALT, ALP, and γ-GTP were similarly improved in both arms, although more favorable results were obtained in arm 2. Anorexia was significantly improved in arm 2 early after the start of drainage (at Day 3, P<0.1; at Week 1, P<0.05). From week 2 onwards, however, subjective symptoms were also improved in arm 1, and there was no significant between-arm difference.

8. Conclusions

Inchinkoto improves the bilirubin reduction rate and subjective symptoms, suggesting its efficacy for obstructive jaundice after biliary drainage.

9. From Kampo medicine perspective

This paper mentions the choleretic action of 6, 7-demethyl-esculetin and capillarisin contained in inchinko (茵チン蒿), and geniposide contained in sanshishi (山梔子), in the discussion section from a pharmacognostic perspective.

10. Safety assessment in the article

No adverse events were observed.

11. Abstractor's comments

This paper discusses the effect of inchinkoto on bilirubin reduction. Combination of inchinkoto with drainage had only a slight additional effect on reduction of bilirubin level. Notably, however, no patients were rated grade 3 (i.e., as having relatively poor bilirubin reduction) after the inchinkoto treatment. Future reports on the mechanism of its action are awaited.

12. Abstractor and date

Nakata H, 1 January 2009, 6 January 2010, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Okuno S, Hirayama K, Inoue J, et al. Effects of rikkunshito on the postoperative nausea and vomiting (PONV) after laparoscopic gynecological surgery. *Masui* (*Japanese Journal of Anesthesiology*) 2008; 57: 1502-9 (in Japanese with English abstract). CENTRAL ID: CN-00668598, Pubmed ID: 19108494 MOL, MOL-Lib

1. Objectives

To evaluate the effect of rikkunshito (六君子湯) on postoperative nausea and vomiting.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

One hundred and forty-two patients undergoing gynecological laparoscopic surgery.

5. Intervention

Arm 1: oral administration of TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g on the morning of surgery + rectal administration of 2 TSUMURA Rikkunshito suppositories (containing rikkunshito 1.5 g per suppository) during surgery + oral administration of TSUMURA Rikkunshito Extract Granules (六君子湯) 7.5 g/day postoperatively for 2 days (n=91).

Arm 2: no treatment (n=51).

6. Main outcome measures

The incidence of postoperative nausea and vomiting, changes in nausea and vomiting score, postoperative dietary intake, etc.

7. Main results

There was no significant between-group difference in the incidence of postoperative nausea and vomiting and in nausea and vomiting scores at each time point. However, the vomiting score in arm 1 was significantly lower on postoperative day 2 than on arrival at the ward and on postoperative days 0 and 1, and significantly lower on postoperative day 1 than on arrival at the ward. In contrast, vomiting score in arm 2 was significantly lower only on postoperative day 2 than on postoperative day 1. The postoperative dietary intake in arm 1 had recovered by the morning of postoperative day 2, while in arm 2, it was significantly lower until lunchtime on postoperative day 2. There were no significant between-arm differences in nausea and vomiting scores or postoperative dietary intake at each time point.

8. Conclusions

Perioperative administration of rikkunshito did not decrease the incidence of postoperative nausea and vomiting. However, this study suggests that rikkunshito may relieve nausea and vomiting and facilitate earlier recovery of dietary intake.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In this study, the effect of Kampo medicine on perioperative symptoms was evaluated for the first time, and suppositories were used in patients unable to take medicines orally. Although there were no significant differences, the efficacy of rikkunshito was suggested. However, randomization itself and the method of randomization should be described in the article. The authors should have followed CONSORT guidelines for the conduct and reporting of RCTs. As the authors stated, more marked differences would have been observed if rikkunshito had been administered prophylactically at least 1 week before surgery. The dose of drug delivered by suppository inevitably tends to be low. Alternatively, rikkunshito could have been administered, for example, via gastric tube. However, as the induction of vomiting during extubation was a concern, suppositories were used on the day of surgery. Since rikkunshito suppositories are not usually used and alternative methods of administration have not been studied, there is no evidence to show that the suppository is the best method of drug delivery. Further evaluation by surgeons or anesthesiologists is expected.

12. Abstractor and date

Motoo Y, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Kori K, Oikawa T, Odaguchi H, et al. Go-rei-san, a Kampo medicine, reduces postoperative nausea and vomiting: A prospective, single-blind, randomized trial. *The Journal of Alternative and Complementary Medicine* 2013; 19: 946-50. CENTRAL ID: CN-00961902, Pubmed ID: 23837690

1. Objectives

To verify the inhibitory effect of goreisan (五苓散) on nausea and vomiting after surgery under general anesthesia.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Department of Anesthesiology, Osaka Medical College Hospital, Japan.

4. Participants

Ninety-nine gynecological patients who underwent laparoscopic surgery under general anesthetic.

5. Intervention

Arm 1: TSUMURA Goreisan (五苓散) Extract Granules (2.5 g t.i.d.) administered before meals on the day before surgery (GRS group) (n=49).
Arm 2: The above extract granules were not administered (control group) (n=50).

6. Main outcome measures

At 3 and 24 hours after surgery, an evaluator who did not know which patients belonged to which groups scored the intensity of nausea during 0 to 3 hours and 0 to 24 hours after surgery using a verbal rating scale (VRS) between 0 and 10, and recorded the frequency of vomiting over the respective periods.

7. Main results

Nausea intensity scores (VRS scores) up to 24 hours after surgery were significantly lower in arm 1 (2.16 ± 2.70) than arm 2 (4.08 ± 3.17), the percentage of patients who vomited up to 24 hours after surgery was significantly lower in arm 1 (15 patients, 30.6%) than arm 2 (26 patients, 52.0%), and the frequency of vomiting was also significantly lower in arm 1 (0.51 ± 0.89) than arm 2 (1.06 ± 1.16).

8. Conclusions

Administering goreisan on the day before gynecological laparoscopic surgery under general anesthesia is useful for reducing postoperative nausea and vomiting.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No goreisan-related adverse events occurred.

11. Abstractor's comments

This is a single blind randomized study into the clinical effects of goreisan aiming to verify its effectiveness for inhibiting nausea and vomiting after surgery under general anesthesia. It verified through a randomized controlled trial the previously known effectiveness of goreisan on nausea and vomiting. Being limited to gynecological laparoscopic surgery, the study did not elucidate the effects on males; however, the study does warrant certain appraisal. The results of future studies on whether or not it is effective for males, on administration for 5 to 7 days before surgery, and on the inhibitory effects on nausea and vomiting after non-gynecological surgery are therefore anticipated. The authors could not conduct a double blind trial using placebo because the extract manufacturer declined to provide a placebo, yet, hopefully in future it may be possible to use the extract in capsule form.

12. Abstractor and date

Ushiroyama T, 6 June 2015.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Kume K, Kasuya Y, Ozaki M. Effect of Goreisan, a traditional Japanese Kampo medicine, on postoperative nausea and vomiting in gynecological patients. *JA Clinical Reports* 2017; 3: 552: 1-6. doi: 10.1186/s40981-017-0122-5 Pubmed ID: 29457096

1. Objectives

To evaluate the efficacy and safety of goreisan（五苓散）on postoperative nausea and vomiting (PONV) after gynecological surgery under general anesthesia

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

One university hospital, Japan

4. Participants

Eighty-three patients aged 20 to 50 years who underwent gynecological surgery.

Exclusion criteria: American Society of Anesthesiologists Physical Status (ASA-PS) 3 or more, Body Mass Index (BMI) ≥35, pregnancy or lactation, use of other Kampo medicines, steroids, immunosuppressants, or chemotherapy agents, insufficient follow-up

5. Intervention

The following solution or water was administered through a nasogastric tube one hour before completion of the surgery:

Arm 1: Goreisan（五苓散）Extract Granules 7.5 g (manufacturer unknown) dissolved in 20 mL of water at 40°C (n=40)

Arm 2: placebo: 20 mL of water at 40°C (n=43)

6. Main outcome measures

The primary outcome measure was the incidence of PONV and the requirement of antiemetic use.

The secondary outcome measures were the incidence and severity of postoperative pain and the requirement of analgesic use.

7. Main results

The incidence of PONV during the first 2 hours after extubation was 45% in Arm 1 and 46.5% in Arm 2 (P = 0.89), showing no significant difference. The incidence and severity of PONV up to 24 hours after extubation showed no significant differences. Since the interim analysis showed no significant differences, the study was terminated with a sample size of 83 patients, although more patients were to be recruited.

8. Conclusion

Goreisan does not prevent PONV.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Postoperative pain, clinical course, etc. were assessed in the goreisan and placebo groups, and showed no significant differences. The study was conducted safely.

11. Abstractor's comments

There is evidence that drugs such as 5-HT_3 receptor antagonists reduce PONV. This clinical study investigated whether goreisan has such an effect, but unfortunately found none. However, this study appears to be meaningful in that it provided a foundation for other studies (to investigate other Kampo medicines, etc.).

12. Abstractor and date

Kato Y, 1 June 2020.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Kubo N, Uchida Y, Akiyoshi T, et al. Efficacy of daikenchuto for ileus - a multicenter study -*. *Progress in Medicine* 1995; 15: 1962-7 (in Japanese). Ichushi Web ID: 1996096062

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) for ileus in a multicenter study.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fourteen institutions, centered around Oita Medical University Hospital, Japan.

4. Participants

Thirty patients who developed simple adhesive ileus postoperatively and were judged by the investigator to need long tube placement. (Exclusion criteria were serious disorders of the heart, lungs, liver, or bone marrow; serious complications; determination of ineligibility by the treating physician.)

5. Intervention

Arm 1: treatment with TSUMURA Daikenchuto (大建中湯) Extract Granules dissolved in lukewarm water (5 g/20 mL) and infused through a gastric tube, three times daily for at least 5 days (n=18).
Arm 2: no treatment with daikenchuto (n=12).

6. Main outcome measures

Subjective symptoms (abdominal pain, nausea and vomiting, diarrhea, general malaise, anorexia, and abdominal bloating), radiograph, time to defecation and passage of flatus, number of days to removal of the ileus tube (long tube), number of days to resumption of oral intake, and rate of progression to surgery, as well as improvements in ileus, abdominal findings, and subjective symptoms, general improvement rating, and usefulness assessed by the attending physician.

7. Main results

There were no significant between-arm differences in the time to defecation, passage of flatus, and removal of the ileus tube, radiographic changes, and the proportion of patients who required surgery. Improvements in abdominal bloating and nausea and vomiting were significantly greater in arm 1 than arm 2. The rate of ileus resolution assessed by the attending physician was 94.4% in arm 1 and 66.7% in arm 2.

8. Conclusions

Daikenchuto is a safe and useful drug for treating postoperative adhesive ileus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred. The global safety rating was 94.4%.

11. Abstractor's comments

Similar to the preceding papers "Nagashima Y, Tanaka N, Furukawa K, et al. Effects of daikenchuto (TJ-100) on intestinal paralysis after surgery for colorectal cancer*. *Progress in Medicine* 1998; 18: 903-5 (in Japanese)" and "Ohyabu H, Matsuda S, Kurisu S, et al. Evaluation of daikenchuto in patients with adhesive ileus in a randomized trial*. *Progress in Medicine* 1995; 15: 1954-8 (in Japanese)", the present paper describes an evaluation of the clinical efficacy of daikenchuto in patients with adhesive ileus. Although the number of patients was small and between-group differences fell short of significance, the clinical utility of daikenchuto seems to be demonstrated. Some kind of control drug should have been administered in the non-daikenchuto-treatment arm, and daikenchuto should have been compared with the control. This would not have required much additional effort.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Itoh T, Yamakawa J, Mai M, et al. The effect of the herbal medicine dai-kenchu-to on post-operative ileus. *The Journal of International Medical Research* 2002; 30: 428-32. CENTRAL ID: CN-00410068, Pubmed ID: 12235926

1. Objectives

To evaluate the efficacy of daikenchuto (大建中湯) for the treatment of postoperative ileus and the improvement of postoperative conditions.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Cancer Research Institute of Kanazawa University), Japan.

4. Participants

Out of 154 abdominal surgery patients, 24 developed postoperative ileus were enrolled.

5. Intervention

Arm 1: treatment with daikenchuto (大建中湯) 15.0 g in 13 patients.
Arm 2: treatment with placebo (the same quantity and frequency of doses as arm 1) in 11 patients.
The study drugs were administered orally for 14 days.

6. Main outcome measures

Frequency of surgery for ileus and recurrence of ileus.

7. Main results

Surgery for postoperative ileus could be avoided significantly more frequently in the daikenchuto arm than in the placebo arm. In addition, daikenchuto tended to decrease, though not significantly, the recurrence rate of ileus.

8. Conclusions

Daikenchuto is a cost-effective and noninvasive therapeutic agent for postoperative ileus after abdominal surgery and has no adverse effects.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This RCT examined the efficacy of daikenchuto for postoperative ileus. This seems to be clinically relevant after abdominal surgery since the treatment for postoperative ileus is not established. Although mentioned in the conclusion, the safety and cost effectiveness of daikenchuto treatment were not described in the main text. It might have been better to mention those outcomes, and examine the dependence of these differences on subjects' underlying diseases or surgical procedures.

12. Abstractor and date

Arai M, 20 February 2007, 30 October 2007, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Okabayashi T, Mimura H, Orita K. Usefulness of Shosaikoto (TJ-9) in the treatment of postoperative liver dysfunction*. *Progress in Medicine* 1989; 9: 851-5 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of postoperative liver dysfunction.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and 14 general hospitals, Japan.

4. Participants

Forty-six patients who had no hepatic dysfunction preoperatively and underwent surgery under general anesthesia for non-hepato-biliary-pancreatic disease, but developed liver dysfunction 2–8 weeks after surgery.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. (n=20).
Arm 2: Glycyron, a glycyrrhizin preparation, 3 tablets t.i.d. (n=26).

6. Main outcome measures

Improvements in subjective symptoms and liver function, global utility rating, and safety rating.

7. Main results

Subjective symptoms, liver function, and global utility ratings were improved in both arms, but without any significant between-arm differences in these improvements. Glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactic dehydrogenase (LDH), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), and zinc sulfate turbidity test (ZTT) decreased in both arms but the between-arm differences were not significant. GOT, GPT, ALP, and γ-GTP tended to decrease slightly more rapidly in arm 1 than in arm 2. Abnormal total bilirubin (T-Bil) or blood urea nitrogen (BUN) was not noted postoperatively.

8. Conclusions

Shosaikoto is an effective and safe drug for the treatment of postoperative hepatic dysfunction and its efficacy is comparable to that of Glycyron.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions were not observed in the shosaikoto-treated group.

11. Abstractor's comments

This paper is clinically highly significant in that the efficacy of shosaikoto for treating postoperative liver dysfunction was demonstrated in an RCT using Glycyron as a control. Safety was evaluated in a small number of patients (n=20) in this study. Further safety studies including larger number of patients are required.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Usuba A, Gao L. S., Motoki R. Effect of sho-saiko-to (xao-chai-hu-tang) on liver dysfunction after surgery - the benefits of preoperative administration and the importance of diagnosis according to traditional Chinese logic -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1992; 43: 1–12 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for postoperative liver disorder.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Surgery 1, Fukushima Medical University, Japan.

4. Participants

Sixty-six patients who underwent respiratory or gastrointestinal surgery.

5. Intervention

Arm 1: shosaikoto (小柴胡湯) (manufacturer not specified) at a dose of 5.0 g for 7–33 days before surgery (n=16).
Arm 2: shosaikoto (小柴胡湯) (manufacturer not specified) at a dose of 5.0 g for 8–45 days before surgery and 11–45 days after surgery (n=17).
Arm 3: no treatment (n=33).

6. Main outcome measures

General malaise, anorexia, performance status (PS), and blood biochemistry.

7. Main results

Two weeks after surgery (Week 2), the level of glutamic-pyruvic transaminase (GPT—a measure of hepatic function) was significantly decreased in arms 1 (P<0.01) and 2 (P<0.01) compared with arm 3 (53.6±26.40, 35.9±16.95, and 91.3±61.84 IU/L in Arms 1, 2, and 3, respectively), and this significant decrease persisted at Weeks 4 and 6. Similar results were observed for glutamic-oxaloacetic transaminase (GOT) and γ-glutamyl transpeptidase (γ-GTP) levels. At Week 2, direct bilirubin was significantly increased to 0.80±0.84 mg/dL in Arm 3, but not in Arms 1 (0.36±0.24 mg/dL, P<0.01) or 2 (0.48±0.44 mg/dL, P<0.05). In addition, improvement in general malaise, anorexia, and PS was greater in arms 1 and 2 than in arm 3.

8. Conclusions

Shosaikoto is effective in reducing postoperative liver disorder.

9. From Kampo medicine perspective

The efficacy of shosaikoto was evaluated according to preoperative *sho* (証, pattern).

10. Safety assessment in the article

No adverse reactions were reported.

11. Abstractor's comments

In this article, shosaikoto (even prophylactic shosaikoto) was effective for postoperative liver disorder. It seems difficult to associate the efficacy of shosaikoto with *shoko* (証候, manifestation patterns) because of the variety of surgical stresses and diversity of diseases in this trial. The efficacy of shosaikoto (as indicated by change in GOT level) did not appear to be related to *shoko*. Nonetheless, it is desirable to use simpler designs in future controlled trials.

12. Abstractor and date

Okabe T, 22 August, 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Manabe N, Camilleri M, Rao A, et al. Effect of Daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2010; 298: G970–5.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal and colonic transit and bowel function in healthy humans.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Mayo Clinic, US.

4. Participants

Sixty healthy adults (18–65 years old) without gastrointestinal disorders recruited by advertisement. Those with a history of allergic reactions to egg, ginseng, ginger, and Sichuan pepper were excluded.

5. Intervention

Treatment was administered t.i.d. immediately before meals for 5 consecutive days. Participants and study personnel were blinded (double-blind) to treatment assignment.

Arm 1: daikenchuto (大建中湯) (manufacturer, not specified) 2.5 g t.i.d. (n=19).
Arm 2: daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. (n=20).
Arm 3: identical placebo (n=21).

6. Main outcome measures

Primary outcomes: gastric emptying half-time (GE $t_{1/2}$) measured by scintigraphy; colonic geometric center at 24 h (GC24); ascending colon emptying half-time (AC emptying $t_{1/2}$).
Secondary outcomes: colonic geometric center at 4 h and 48 h (GC4, GC48); colonic filling at 6 h; stool frequency and consistency (self-assessed using the Bristol Stool Form Scale).

7. Main results

There was a difference in colonic filling at 6 h between both daikenchuto groups and the placebo group (P=0.04). Pair-wise comparisons between Arm 1 and Arm 3 and between Arm 2 and Arm 3 showed no significant differences. Daikenchuto 7.5 g/day tended to accelerate ascending colon emptying half-time (P=0.07) and daikenchuto at both doses tended to raise GC24 (P=0.63). However, daikenchuto had no meaningful effects on gastric emptying half-time (P=0.45), stool frequency (P=0.80), or stool consistency (P=0.33).

8. Conclusions

Daikenchuto accelerated colonic filling at 6 h and ascending colon emptying half-time in healthy humans, suggesting that it promotes small bowel motility and hastens ascending colon transit.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One subject receiving daikenchuto 7.5 g/day had increased creatine phosphokinase (CPK) 1 month after receiving the study medication, which was discovered when the subject presented to the emergency department for muscle pain. With no evidence of myopathy, CPK level returned to normal at 4 months without intervention.

11. Abstractor's comments

This is a well-designed DB-RCT. Regrettably, no statistically significant difference was detected, which may be partly because the study population was healthy volunteers, considering the characteristics of Kampo medicine. The results of future RCTs being planned by the authors in patients with gastrointestinal disorders, including irritable bowel syndrome and constipation, are expected.

12. Abstractor and date

Tsuruoka K, 7 January 2011.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Hasebe K, Machida M, Yada M, et al. Clinical application of keishi-ka-syakuyaku-to for abdominal symptoms caused by the α-glucosidase inhibitor acarbose. *Kiso to Rinsho* (*The Clinical Report*) 1997; 31: 3179-86 (in Japanese with English abstract). Ichushi Web ID: 1998043002 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of keishikashakuyakuto (桂枝加芍薬湯) for the treatment of acarbose-induced symptoms.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Single institution (Showa General Hospital), Japan.

4. Participants

Twenty patients with non-insulin-dependent diabetes mellitus (NIDDM) and poor glycemic control in spite of diet and exercise.

5. Intervention

Arm 1: treatment with acarbose (50 mg t.i.d. right before meals) plus TSUMURA Keishikashakuyakuto (桂枝加芍薬湯) Extract Granules (2.5 g t.i.d. before meals) (n=10).

Arm 2: treatment with acarbose alone (n=10).

The treatment duration was 4 weeks.

6. Main outcome measures

Subjective symptoms (abdominal distension, flatus, flatulence, abdominal pain, borborygmus, diarrhea, loose stool, and constipation) were scored on a 4-point scale at baseline, and after 2 and 4 weeks of treatment.

Fasting blood glucose and glycosylated hemoglobin (HbA1c) levels were measured at baseline and after 4 weeks.

7. Main results

Subjective symptoms worsened in both arms at 2 weeks, but diarrhea and abdominal pain disappeared at 4 weeks only in arm 1. The total subjective symptom score decreased significantly both at 2 and 4 weeks in arm 2, while it decreased at 2 weeks but returned to baseline level at 4 weeks in arm 1. No significant change in fasting blood glucose occurred in either arm, whereas HbA1c level was significantly improved after 4 weeks of the combination therapy.

8. Conclusions

Keishikashakuyakuto is effective for relieving gastrointestinal symptoms (adverse drug reactions to acarbose, an α-glucosidase inhibitor [α-GI]). The combination can reduce HbA1c level.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no significant worsening of subjective symptoms in the combination group.

11. Abstractor's comments

Abdominal symptoms frequently occur as so-called adverse drug reactions to acarbose, an α-GI used for mild diabetes mellitus, and may lead to discontinuation of the drug. The reduction or elimination of these symptoms by keishikashakuyakuto helps patients continue acarbose treatment. For mild diabetes mellitus, however, other drugs have been developed and more treatment options are available now. Therefore, it is controversial to add an oral drug, even a Kampo medicine, just for the purpose of continuing acarbose treatment. Also, blood glucose or HbA1c level was not significantly reduced by acarbose in this study, indicating that there might have been an inhomogeneity of the study population. These results suggest that acarbose plus keishikashakuyakuto improves glucose tolerance and that oral administration of keishikashakuyakuto in selected patients may provide a way to continue the acarbose treatment. Further studies on this combination therapy are anticipated.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Oka T, Tamagawa Y, Hayashida S, et al. Rikkunshi-to attenuates adverse gastrointestinal symptoms induced by fluvoxamine. *Biopsychosoc Medicine* [Internet] 2007 [cited 2008 Dec 31]; 1: 21. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2204024 DOI: 10.1186/1751-0759-1-21. Ichushi Web ID: 2008214687

1. Objectives

To evaluate the clinical effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by fluvoxamine, an antidepressant.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Occupational and Environmental Health Hospital, Japan.

4. Participants

Fifty patients with depressive disorder (mean age, 40.2 years).

5. Intervention

Arm 1: treatment with fluvoxamine 150 mg/day (escalating from 50 mg/day) and TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 8 weeks, n=25.
Arm 2: treatment with fluvoxamine 150 mg/day (escalating from 50 mg/day) alone for 8 weeks, n=25.

6. Main outcome measures

Gastrointestinal symptoms (assessed by Gastrointestinal Symptom Rating Scale [GSRS] score) and depressive symptoms (by Self-rating Depression Scale [SDS] score).

7. Main results

Overall gastrointestinal symptoms due to fluvoxamine treatment were significantly relieved to a greater extent in arm 1 (GSRS total score, 1.97±0.81) than in arm 2 (2.52±0.99). No significant between-arm difference was observed in post-treatment SDS score.

8. Conclusions

Rikkunshito reduces fluvoxamine-induced gastrointestinal adverse reactions, especially nausea, without affecting the antidepressant effect of fluvoxamine.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the treatment, adverse reactions occurred significantly less frequently in arm 1 (6 patients) than in arm 2 (13 patients). In particular, the frequency of nausea was significantly lower in arm 1 (3 patients) than in arm 2 (9 patients).

11. Abstractor's comments

This paper reports that rikkunshito reduced nausea and other gastrointestinal adverse reactions induced by selective serotonin reuptake inhibitors (SSRI), such as fluvoxamine. Although sample size was relatively small, this trial was well-designed and valuable since it showed the usefulness of Kampo medicines from the perspective of reducing the adverse reactions to western medicines.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Oka T. Rikkunshito attenuates milnacipran–induced adverse gastrointestinal symptoms and potentiates its antidepressant effect. *Medical Tribune* 2008; 41: 82 (in Japanese).

1. Objectives

To evaluate the effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by milnacipran, an antidepressant.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Occupational and Environmental Health Hospital, Japan.

4. Participants

Forty-four patients with depressive disorder.

5. Intervention

Arm 1: milnacipran 100 mg/day (final dose) + TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 8 weeks (n=22).
Arm 2: milnacipran 100 mg/day (final dose) for 8 weeks (n=22).

6. Main outcome measures

Gastrointestinal symptoms (assessed by the Gastrointestinal Symptom Rating Scale [GSRS] score) and depressive symptoms (by the Self-rating Depression Scale [SDS] score).

7. Main results

Gastrointestinal symptoms induced by milnacipran, especially nausea, were significantly reduced in arm 1 compared to arm 2. Overall gastrointestinal symptoms, reflux symptoms, abdominal pain, and dyspepsia scores were significantly reduced in arm 1 compared to before treatment, but not in arm 2 (scores unchanged). The SDS score after 8-week but not 4-week treatment was significantly lower in arm 1 than arm 2.

8. Conclusions

Rikkunshito may suppress gastrointestinal symptoms induced by milnacipran and potentiate its antidepressive effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although the safety of rikkunshito was not addressed, rikkunshito significantly reduced adverse events of milnacipran, particularly nausea.

11. Abstractor's comments

This study reports that rikkunshito reduced gastrointestinal symptoms such as nausea, which is the most common adverse event of antidepressant treatment with the serotonin norepinephrine reuptake inhibitor (SNRI) milnacipran. The authors reported a similar study of fluvoxamine (SSRI) in 2007 "Oka T, Tamagawa Y, Hayashida S, et al. Rikkunshi-to attenuates adverse gastrointestinal symptoms induced by fluvoxamine. *Biopsychosoc Medicine* [Internet] 2007 [cited 2008 Dec 31]; 1: 21. [http://www.pubmedcentral. nih.gov/articlerender.fcgi?artid=2204024 DOI:10.1 186/1751-0759-1-21,]".
The combination of fluvoxamine and rikkunshito did not significantly reduce the SDS score in that study, while milnacipran with rikkunshito did significantly lower the score in this study. However, outcome measures based on subjective symptoms may have been affected by the absence of placebo administration in the control group. As SNRIs are used widely, this study provides evidence that Kampo medicines can be useful in modern medicine.

12. Abstractor and date

Motoo Y, 1 June 2010.

12. Skin Diseases

Reference

Shimoda S, Hashizume S, Morita M, et al. Efficacy of TSUMURA Shosaikoto for atopic dermatitis*. *Hifuka ni okeru Kampo Chiryo no Genkyo* (*The Current State of Kampo Medicine in Dermatology*) 1991; 2: 15–24 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) for treating atopic dermatitis and for withdrawing or tapering topical corticosteroids.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Sixty-five atopic dermatitis patients aged 12 years and older, excluding women who were pregnant, possibly pregnant, or lactating.

5. Intervention

Betamethasone valerate (0.12% Rinderon V ointment or cream) was used as a topical corticosteroid. During the 8-week observation period, corticosteroids were used as little as possible when improvement in symptoms was observed. Oral corticosteroids were not allowed.

Arm 1: topical corticosteroids + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for at least 8 weeks (n=41).

Arm 2: topical corticosteroids (n=24).

6. Main outcome measures

Subjective symptoms: pruritus.

Objective symptoms: papule, erythema, erosion, scales, infiltration, and hypertrophy.

Corticosteroids: could be withdrawn, reduced >50%, or reduced ≤50%.

7. Main results

Corticosteroids were withdrawn in two patients in arm 1 and reduced in 87.0% of patients in arm 2 and 62.5% in arm 1.

8. Conclusions

Shosaikoto is effective in tapering topical corticosteroid treatment of atopic dermatitis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two patients experienced nausea in arm 2.

11. Abstractor's comments

Although Kampo medicines have been said to be effective for atopic dermatitis, currently, only the remission of symptoms or withdrawal of topical corticosteroids have been quantitatively assessed. Statistical analyses can not be performed without quantification or scoring of variables such as the severity of skin lesions and objective improvement. Further effort to improve quantification is expected.

12. Abstractor and date

Fujisawa M, 13 October 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

References

Furue M, Tanaka Y, Kobayashi H, et al. Efficacy of Kanebo Hochuekkito in patients with atopic dermatitis with "*qikyo*" – a multicenter, double-blind trials*. *Arerugi* (*Japanese Journal of Allergology*). 2005; 54: 1020 (in Japanese). MOL, MOL-Lib

Kobayashi H, Ishii M, Takeuchi S, et al. Efficacy and safety of a traditional herbal medicine, *Hochu-ekki-to* in the long-term management of *Kikyo* (delicate constitution) in patients with atopic dermatitis: a 6-month, multicenter, double-blind, randomized, placebo-controlled study. *Evidence-based Complementary and Alternative Medicine* 2008 1-7 (2010; 7: 367-73). CENTRAL ID: CN-793369, Pubmed ID: 18955318

Kobayashi H, Ishii M, Furue M. Efficacy of hochuekkito for skin symptoms in patients with atopic dermatitis associated with *qikyo* – An investigation by rash element –*. *Nishinihon Hifuka* (*the Nishinihon Journal of Dermatology*) 2012; 74: 642-7 (in Japanese). Ichushi Web ID: 2013117615

1. Objectives

To evaluate the efficacy and safety of hochuekkito (補中益気湯) in patients with *qikyo* (気虚, *qi* deficiency) associated with atopic dermatitis (AD).

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Five university hospitals, 4 general hospitals, and 6 clinics, Japan.

4. Participants

Eighty-four patients with *qikyo* associated with atopic dermatitis.

5. Intervention

Arm 1: Kracie Hochuekkito Extract Granules 7.5 g/day in two divided doses for 24 weeks (n=40).
Arm 2: placebo granules for 24 weeks (n=44).
In both groups, treatment with topical preparations, etc., was continued according to the symptoms.

6. Main outcome measures

Skin lesion score (according to Japanese Dermatology Association criteria), dose of topical preparation (steroid/tacrolimus).

7. Main results

The analysis included 37 patients in the hochuekkito group and 40 patients in the placebo group. Seven patients (2 patients discontinued with worsening of skin symptoms and headache, and 5 patients with insufficient continuity of oral treatment) dropped out. There was a nonsignificant trend toward improvement in skin lesion score after 24 weeks, a significant decrease in the dose of topical preparation used after 24 weeks ($P<0.05$), a higher efficacy rate ($P=0.06$), and lower rate of worsening ($P<0.05$) in arm 1 than in arm 2. A reanalysis focusing on rash characteristics found that hochuekkito was successful for patients with rash that had low moisture/scabs and a high proportion of chronic stage papules, nodules, and lichenification.

8. Conclusions

Hochuekkito effectively improves skin symptoms and decreases the dose of topical preparation needed by patients with *qikyo* and atopic dermatitis.

9. From Kampo medicine perspective

The efficacy of hochuekkito for AD in patients with *qikyo* was evaluated. Changes in "*qikyo*" scores were not significantly different between the two arms.

10. Safety assessment in the article

Adverse events were reported in 32.5% and 27.3% of patients in the hochuekkito and placebo groups, respectively (no significant difference). Abnormal values were observed in glutamic-pyruvic transaminase (GPT), immunoglobulin (IgE), blood urea nitrogen (BUN), and potassium (K) in the hochuekkito group and in lactic dehydrogenase (LDH), glutamyl pyruvic transaminase (GOT), γ-glutamyl transpeptidase (GTP), and hemoglobin (Hb) in the placebo group. All symptoms including feeling queasy were mild in severity.

11. Abstractor's comments

This is an evidence-based appraisal of a 24-week multicenter, placebo-controlled RCT conducted using objective measures as endpoints. Since the efficacy of hochuekkito was more marked after 24 weeks than after 12 weeks, the authors state that it acts slowly. This finding may have clinical application. The results of the reanalysis of rash characteristics were suggestive of the features of rashes in the patients who ought to be given hochuekkito, which is clinically significant.

12. Abstractor and date

Kogure T, 1 June 2010, 31 December 2013, 6 June 2015.

12. Skin Diseases

Reference

Wadabayashi M. Kampo Clinical Report: Study on benefits of byakkokaninjinto in treating atopic dermatitis. *Phil Kampo* 2017; 73: 14-5 (in Japanese). Ichushi Web ID: 2019066152

1. Objectives

To evaluate the efficacy and safety of byakkokaninjinto（白虎加人参湯）used concomitantly in the treatment of atopic dermatitis.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One clinic, Japan.

4. Participants

Twenty-five patients with atopic dermatitis who provided consent to participate in this study and who were newly started on topically applied tacrolimus ointment.

5. Intervention

Arm 1: Tacrolimus ointment application once or twice daily as needed to the affected sites (face and neck) for 2 weeks (n=14).

Arm 2: Tacrolimus ointment application once or twice daily as needed plus KRACIE Byakkokaninjinto（白虎加人参湯） 4 tablets three times daily orally for 2 weeks (n=11).

6. Main outcome measures

Treatment response in the face and neck regions was assessed according to the severity grading criteria of the Japanese Clinical Practice Guideline for the Management of Atopic Dermatitis (simple method). Also, any symptoms of skin irritation associated with the tacrolimus ointment were evaluated at the same time.

7. Main results

Severity was assessed in 13 patients in Arm 1 and 9 patients in Arm 2, because of missing data in 1 patient in Arm 1 and 2 patients in Arm 2. After 2 weeks of treatment, the skin eruption significantly improved in Arm 2. Symptoms of skin irritation associated with the tacrolimus ointment were assessed in 13 patients in Arm 1 and 7 patients in Arm 2, because of missing data in 1 patient in Arm 1 and 4 patients in Arm 2. Within 1 week of treatment, complaints of hot sensation, tingling, or other symptoms of skin irritation were registered by 84.6% of the patients in Arm 1 and 57.1% in Arm 2, showing no statistically significant difference.

8. Conclusions

Although no significant difference was shown, byakkokaninjinto is expected to relieve tacrolimus ointment-related skin irritation symptoms including hot sensation.

9. From Kampo medicine perspective

Not stated.

10. Safety assessment in the article

No side effects were observed in either Arm 1 or Arm 2.

11. Abstractor's comments

This clinical study is interesting in that it demonstrated the potential of byakkokaninjinto for relieving symptoms of tacrolimus ointment-related skin irritation in patients with atopic dermatitis. Tacrolimus ointment-related skin irritation symptoms including hot sensation are troublesome to patients. Byakkokaninjinto was shown to potentially relieve skin irritation symptoms. In this study with a small sample size, the between-group difference was not statistically significant, but a tendency toward relief was observed. Further study results from more patients are awaited.

12. Abstractor and date

Kato Y, 1 September 2019

12. Skin Diseases

Reference

Choi I, Kim S, Kim Y, et al. The effect of TJ-15 plus TJ-17 on atopic dermatitis: a pilot study based on the principle of pattern identification. *The Journal of Alternative and Complementary Medicine* 2012; 18: 576-82. Pubmed ID: 22784344

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) and goreisan (五苓散) for dampness-heat pattern in atopic dermatitis (AD) patients.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Kyung Hee University Hospital, South Korea.

4. Participants

Twenty-four dampness-heat pattern patients with AD diagnosed using Hanifin and Rajka Diagnostic Criteria. (Patients were excluded who took antihistamines and steroids within the previous four weeks; had serious disease including infection; had seizure disorder; were pregnant and lactating; and had abnormal alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], or creatinine level.)

5. Intervention

Arm 1: orengedokuto + goreisan group: administration of a mixture of TSUMURA Orengedokuto (黄連解毒湯) Extract Granules (1.25 g) and TSUMURA Goreisan (五苓散) Extract Granules (1.25 g) t.i.d. after meals for four weeks (n=12).

Arm 2: orengedokuto group: administration of TSUMURA Orengedokuto (黄連解毒湯) (2.5 g) t.i.d. after meals for four weeks (n=12).

6. Main outcome measures

Primary endpoints: SCORing Atopic Dermatitis (SCORAD) index, and Eczema Area and Severity Index (EASI). Secondary endpoints: symptom scores for nine dampness-heat pattern symptoms and six other symptoms.

7. Main results

The SCORAD index (–27.2 ± 8.9 in arm 1 and –24.9 ± 13.7 in arm 2) and EASI (–16.9 ± 12.1 in arm 1 and –10.4 ± 7.9 in arm 2) were significantly improved by combined treatment. There was no significant difference in primary endopoints between the two arms. Reductions in symptom scores were similar in both groups (–2.4 ± 1.3 in arm 1 and –2.1 ± 1.6 in arm 2). There was no significant difference in secondary endopoints between the two arms.

8. Conclusions

Orengedokuto and orengedokuto + goreisan may be similarly effective for dampness-heat pattern AD.

9. From Kampo medicine perspective

Although administration did not deliberately target specific patterns within the two groups, yang pattern (i.e., rapid advance of symptoms, strong itchiness, wet phase rash, and tachycardia) was identified in all patients and was the precondition for inclusion in the study.

10. Safety assessment in the article

Liver and kidney function was normal in both groups. However, even though liver and kidney function was described as normal in the beginning, patients who showed elevated AST, ALT, and BUN levels were excluded from the analysis, which makes evaluation more difficult.

11. Abstractor's comments

This is a clinically significant study indicating that orengedokuto and orengedokuto + goreisan are effective for AD with dampness-heat (湿熱) in a randomized and controlled manner. While the authors assess specific clinical symptoms as secondary endpoints, it might be possible to elucidate further the effectiveness of Kampo medicines by presenting a differential analysis of those symptoms. Further research is anticipated.

12. Abstractor and date

Kogure T, 31 December 2013.

12. Skin Diseases

Reference

Kobayashi H, Yanagihara S, Tamiya H, et al. The combined effects of Kampo medicines on subjective/objective symptoms in atopic dermatitis patients - A comparative study of unseiin and shimotsuto -. *The Nishinihon Journal of Dermatology* 2016; 78: 171-6 (in Japanese). Ichushi Web ID: 2016282808

1. Objectives

To evaluate the effectiveness of unseiin (温清飲) and shimotsuto (四物湯) for moderate or more severe atopic dermatitis that does not improve with standard treatment.

2. Design

Randomized controlled trial (envelope method) (RCT-envelope)

3. Setting

Single-center (Osaka City University Hospital)

4. Participants

Sixteen participants who fulfilled the following conditions between February 2012 and December 2013: 1) diagnosed with atopic dermatitis (AD) according to the Japanese Dermatological Association's diagnostic criteria; 2) currently receiving the standard treatment in the Japanese Dermatological Association's AD treatment guidelines (no change in prescription in the first 2 weeks of the trial) and will continue that treatment during the trial; 3) itch is at least 5 on a visual analog scale (VAS: 0-10).

Patients with infectious disease or severe heart, kidney, or endocrine/metabolic disease, and patients currently taking Kampo or herbal medication were excluded.

5. Intervention

Arm 1: Standard treatment and Kracie Unseiin (温清飲) Extract Fine Granules 6.0g b.i.d. (n=8)
Arm 2: Standard treatment and Kracie Shimotsuto (四物湯) Extract Fine Granules 6.0g b.i.d. (n=8)
As a rule, administration for 4 weeks in both arms. No change of drug or dosage during period of administration.

6. Main outcome measures

Kampo medication compliance; subjective symptoms (itch, dryness, sleep disorder evaluated on a VAS); AD severity (measured with severity scoring of AD [SCORAD]); clinical blood tests (serum thymus and activation-regulated chemokine [TARC]; total serum IgE; peripheral eosinophil count, and LDH); specific skin disease QOL scale (Skindex-16: total and sub-scales [symptoms, emotions, functioning]).

7. Main results

One participant dropped out of arm 1 (after taking another Kampo medication). Trial drug compliance satisfactory in both arms 1 and 2. Significant improvements in 3 subjective symptoms were observed in arm 1, but no significant improvement was observed in arm 2. VAS score variation between the 2 groups before and after administration showed significant reduction only for dryness in arm 1 (P＝0.048). SCORAD decreased significantly only in arm 1 before and after administration (P<0.05), however, there was no significant difference in arm 2. There was no significant change in either group in clinical test values. Skindex-16 showed significant improvement in total, symptoms, and emotions in arm 1, and total, emotions, and functioning in arm 2. Variation before and after administration was lower in arm 1 than arm 2, but there was no significant difference between groups.

8. Conclusions

Unseiin alleviates itch and dryness, and improves QOL in AD, and its effects are superior to shimotsuto.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This is a clinically significant paper that evaluated in an RCT the effects of unseiin or shimotsuto for AD that had not improved with standard treatment. The 4-week follow-up found more marked improvements in clinical symptoms with unseiin. However, as the authors remark, there was no placebo group for comparison, which unfortunately meant that the study evaluated the effectiveness of the Kampo preparations by before and after comparison. The authors might have obtained greater significant differences in the effects of unseiin and shimotsu if they had increased the sample size, and they might have gleaned some insights into prescription management. The results of a repeated study with a placebo and larger sample size may be promising.

12. Abstractor and date

Kogure T, 18 May 2020.

12. Skin Diseases

Reference

Ohkawara A, Furuya K, Kurisu Y, et al. Experience with Orengedokuto (TJ-15) and Goshajinkigan (TJ-107) for the treatment of senile pruritus*. *Nishinihon Hifuka* (*The Nishinihon Journal of Dermatology*) 1991; 53: 1234–41 (in Japanese). Ichushi Web ID: 1992177261

1. Objectives

To compare the efficacy and safety of orengedokuto (黄連解毒湯) and goshajinkigan (牛車腎気丸) with antihistamine for the treatment of senile pruritus.

2. Design

Randomized controlled trial (RCT).

3. Setting

Fourteen institutions: five universities (Hokkaido University, Kansai Medical University, University of Tokushima, Kyushu University, and Kagoshima University) and other related medical institutions, Japan.

4. Participants

Ninety-six patients (55 or more years old) who were diagnosed with pruritus. Exclusion criteria were: 1) infection or purulent skin disease; 2) serious impairment of the liver, kidney, cardiovascular system, or gastrointestinal system; 3) oral or injectable steroids within 2 weeks before the study; 4) topical steroids including very strong ones given within a week before the study; 5) others considered ineligible by participating physicians.

5. Intervention

Based on the score table for deficiency or excess pattern identification, patients were grouped as follows according to their body type, complexion, muscle strength, and abdominal muscles strength: A group: *chukan-sho* (中間証, intermediate pattern) to *jitsu-sho* (実証, excess pattern) type (10 points or more); B group: *chukan-sho* to *kyo-sho* (虚証, deficiency pattern) type (9 points or less).

Group A

Arm 1: administration of TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. before meals for 6 weeks (11 males and 5 females). The *sho* (証, pattern) score was 12.25±1.98.

Arm 2: administration of antihistamine (Tavegyl tablet) 1 mg b.i.d. after meals for 6 weeks, (10 males and 6 females). The *sho* score was 13.05±2.20.

Group B

Arm 3: administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. before meals for 6 weeks (15 males and 10 females). The *sho* score was 6.12±1.50.

Arm 4: administration of antihistamine (Tavegyl tablet) 1 mg b.i.d. after meals for 6 weeks (19 males and 10 females). The *sho* score was 6.28±1.94.

6. Main outcome measures

One subjective symptom (itching assessed on a 3-point scale), objective symptoms (degree of scaling, dry skin, scratch marks, and ichthyosiform skin evaluated on a 4-point scale), and overall improvement (assessed on a 5-point scale: marked, moderate, and mild improvement, absent, and worse) at the start of the study and at 2, 4, and 6 weeks of treatment. Safety was evaluated on a 4-point scale based on side effects and laboratory findings.

7. Main results

At least moderate overall improvement was achieved in 68.8% (arm 1) *vs*. 50.0% (arm 2) in Group A, as well as 72.0% (arm 3) *vs.* 55.2% (arm 4) in Group B. When A and B groups are combined, 53.3% of patients given Tavegyl *vs*. 70.0% of patients given Kampo preparations achieved overall improvement, but the between-group difference was not significant. Likewise, the between-group difference in subjective or objective symptom-specific overall improvement and safety was not significant.

8. Conclusions

Orengedokuto and goshajinkigan are as effective as Tavegyl for senile pruritus.

9. From Kampo medicine perspective

Selection of the intervention was based on the *syo* score.

10. Safety assessment in the article

Two patients in arm 1 and one in arm 3 had gastrointestinal symptoms. One patient treated with Tavegyl had decreased urine volume.

11. Abstractor's comments

This was a well-designed RCT. Notably, the selection of the intervention with Kampo preparations was based on *sho* scores. The study could have been improved by introducing blinding methods.

12. Abstractor and date

Tsuruoka K, 10 April 2008, 1 June 2010.

12. Skin Diseases

Reference

Iida T, Nishiyama C, Suzuki H. The effects of toki-inshi and a bath preparation containing licorice extract on patients with senile pruritus. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1996; 47: 35-41 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the efficacy of tokiinshi (当帰飲子) combined with a bath preparation containing kanzo (甘草, licorice) extract in patients with senile xerosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One special elderly nursing home, Japan.

4. Participants

A total of 25 nursing home residents with xerosis senilis accompanied by senile pruritus, aged from 59 to 92 years, for whom the efficacy of tokiinshi is expected (12 men and 13 women). Of these, 19 were included for analysis.

5. Intervention

Arm 1: TSUMURA Tokiinshi (当帰飲子) Extract Granules (TJ-86) 2.5 g t.i.d. before meals for 4 weeks (n=4).

Arm 2: Bath preparation (kanzo extract, jojoba oil, and sodium bicarbonate) 30 g dissolved in 200 L of hot water (39-40°C), and used every other day for 4 weeks (n=5).

Arm 3: TSUMURA Tokiinshi (当帰飲子) Extract Granules (TJ-86) 2.5 g t.i.d. before meals used in combination with bath preparation containing kanzo extract (every other day) (n=4).

Arm 4: no treatment (n=6).

6. Main outcome measures

Degree of skin dryness (water content of the epidermal horny layer) measured using a surface hygrometer (Skicon-200, IBS Company, Hamamatsu, Japan) at baseline and at 7, 14, 21, 18, and 35 days after the start of treatment.

The average values of 3 measurements were compared. Alleviation of pruritus was evaluated by comparing the pruritus score (scale 1–5) at the beginning and the end of the treatment.

7. Main results

The ability of the skin to retain moisture after 21 days of treatment was improved in arm 1 (22.09±2.27), arm 2 (18.30±3.01), and arm 3 (17.07±3.80), but not in arm 4 (5.65±1.59). In other words, after 3–4 weeks of treatment, the ability to retain moisture increased significantly by 3–5 times in arms 1–3, compared to arm 4 (P<0.05 for each). At 35 days (7 days after the treatment was discontinued), the water content of the skin was maintained at high level in arm 1 (16.42±2.37) and arm 3 (15.97±3.06) but not in arm 2 (5.57±0.47), which was almost the same level as that in arm 4 (5.77±1.29). Alleviation of pruritus did not necessarily correspond to improvement in skin dryness.

8. Conclusions

In patients with xerosis senilis, an oral preparation of tokiinshi, a bath preparation containing kanzo extract, and the combination of both, all improve skin dryness. When used alone, the bath preparation soon loses its effect when the treatment is discontinued. Since improvement in skin dryness does not necessarily alleviate pruritus, involvement of factors other than skin dryness is suggested.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient in arm 4 (no treatment) died during this study (not drug related).

11. Abstractor's comments

A well-designed RCT. In the original article, the study participants were "men and women for whom the efficacy of tokiinshi is expected". However, a detailed explanation of how the enrolled patients were chosen should have been provided. Further studies with larger sample sizes using blind assessment methods are expected.

12. Abstractor and date

Tsuruoka K, 12 April 2008, 6 January 2010, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ishioka T, Aoi R. Comparative evaluation of hachimijiogan and ketotifen fumarate on senile pruritus*. *Shinyaku to Rinsho* (*Journal of New Remedies and Clinics*) 1992; 41: 2603–8 (in Japanese).

1. Objectives

To compare the efficacy of hachimijiogan (八味地黄丸) with that of antiallergic drugs for the treatment of senile pruritus.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One special nursing home for the elderly, Japan.

4. Participants

Thirty-two nursing home residents diagnosed with senile pruritus, who experienced itching almost every night (9 males and 23 females; mean age, 78.0±7.9).

5. Intervention

Arm 1: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks followed by ketotifen fumarate (Zaditen) 1 mg b.i.d. for two weeks (5 males and 11 females).

Arm 2: ketotifen fumarate 1 mg b.i.d. for two weeks followed by TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks (4 males and 12 females).

6. Main outcome measures

Changes in the severity of itching were assessed after 2 and 4 weeks. The severity was evaluated on a 4-point scale: intolerable itching causing sleep disturbance (+++), intolerable itching but not causing sleep disturbance (++), barely tolerable itching (+), and just annoying itching (±).

Global ratings of symptom severity whether before or after treatment were as follows: (1) completely disappeared: “marked response,” (2) clearly improved: “moderate response,” (3) at least slightly improved: “mild response,” (4) no improvement: “no response,” (5) symptoms worsened: “worse.”

7. Main results

Hachimijiogan resulted in a marked response in 11 patients (34%), moderate response in 14 (44%), mild response in 2 (6%), and no response in 5 (16%); 25 had at least a moderate response (78%). Ketotifen fumarate resulted in a marked response in 15 patients (47%), moderate response in 10 (31%), mild response in 4 (13%), and no response in 2 (6%), and symptoms worsened in 1 (3%); 25 had at least a moderate response (78%). There was no significant between-arm difference. The efficacy of the drug administered later seemed to be more effective. When comparing drug efficacy in 13 patients with more physical strength with that in 19 patients with less physical strength, significantly more patients in the latter group achieved at least moderate response to hachimijiogan ($P<0.05$). The efficacy of ketotifen fumarate did not correlate with physical strength.

8. Conclusions

The responses to both hachimijiogan and antiallergic drugs for the treatment of senile pruritus are similar (response rate, 78%). They are similarly effective. Hachimijiogan is effective especially in patients with less physical strength.

9. From Kampo medicine perspective

Although there is no in-depth description regarding “*sho* (証, pattern),” analyses comparing “patients with more physical strength” and “patients with less physical strength” are informative.

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor’s comments

This was an RCT with a cross-over design. Since the itching (depending on its severity) could interfere with sleep, sleepiness (an adverse reaction of ketotifen fumarate) was a concern. However, the authors stated that no drug-induced sleepiness was observed. Unfortunately, this study had no washout period, so a further more expanded study is expected.

12. Abstractor and date

Tsuruoka K, 12 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ishioka T. Comparative evaluation of rokumigan and hachimi-jiogan on senile pruritus. *Therapeutic Research* 1995; 16: 1497–504 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To compare the efficacy of rokumigan (六味丸) and hachimijiogan (八味地黄丸) for the treatment of senile pruritus.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One special nursing home for the elderly, Japan.

4. Participants

Nursing home residents with a diagnosis of senile pruritus and itching almost every night (9 males and 22 females; 62–95 years old; mean age, 77.5±9.4).

5. Intervention

Arm 1: TSUMURA Rokumigan (六味丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks followed by TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks (4 males and 11 females).

Arm 2: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks followed by TSUMURA Rokumigan (六味丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks (5 males and 10 females).

6. Main outcome measures

Changes in the severity of itching were assessed after 2 and 4 weeks. The severity was evaluated on a 4-point scale: sleep disturbance due to itching (+++), intolerable itching but no sleep disturbance (++), barely tolerable itching (+), and just annoying itching (±).

Global ratings of symptom severity whether before or after treatment were as follows: (1) completely disappeared: “marked response,” (2) clearly improved: “moderate response,” (3) at least slightly improved: “mild response,” (4) no improvement: “no response,” (5) symptoms worsened: “worse.” In addition, global assessments according to patients’ physical strength were also performed.

7. Main results

Rokumigan resulted in marked response in 17 patients (56.7%), moderate response in 6 (20.0%), mild response in 1 (3.3%), and no response in 4 (13.3%), and symptoms worsened in 2 (6.7%); 23 had at least a moderate response (76.7%). Hachimijiogan resulted in marked response in 18 patients (60.0%), moderate response in 6 (20.0%), mild response in 2 (6.7%), and no response in 4 (13.3%); 24 had at least a moderate response (80%). There was no significant between-arm difference. In the 12 patients with more physical strength, the response to rokumigan was marked in 8 (66.7%), moderate in 3 (25.0%), and mild in 1 (8.3%), while the response to hachimijiogan was marked in 4 (33.3%), moderate in 5 (41.7%), and absent in 3 (25.3%); significantly more patients achieved marked responses to rokumigan ($P<0.05$). In the 18 patients with less physical strength, response to rokumigan was marked in 9 (50.0%), moderate in 3 (16.7%), and absent in 4 (22.2%), and symptoms worsened in 2 (11.1%), while the response to hachimijiogan was marked in 14 (77.8%), moderate in 1 (5.6%), mild in 2 (11.1%), and absent in 1 (5.6%). Significantly more patients had marked response to hachimijiogan ($P<0.05$).

8. Conclusions

Rokumigan and hachimijiogan have similar efficacy for the treatment of senile pruritus. More patients with greater physical strength achieved a marked response to rokumigan while more patients with less physical strength achieved a marked response to hachimijiogan.

9. From Kampo medicine perspective

The degree of general physical strength does not necessarily correlate with *jitsu-sho* (実証, excess pattern) or *kyo-sho* (虚証, deficiency pattern) in Kampo medicine. However, the authors noted that less physical strength, assessed on the basis of ability to play balloon volleyball, almost corresponds to the minimum criterion defining weak constitution in the guidelines used to select Kampo extract formulations.

10. Safety assessment in the article

One patient (in arm 1) dropped out because of nausea and was not included in the analyses.

11. Abstractor’s comments

This study expanded the previous RCT of hachimijiogan reported by same authors (Ishioka T, Aoi R. Comparative evaluation of hachimijiogan and ketotifen fumarate on senile pruritus*. *Shinyaku to Rinsho* [*Journal of New Remedies and Clinics*] 1992; 41: 2603–8). There was no wash out period as in the prior study. Moreover, the analyses were not performed on an intent-to-treat basis and the sample size was small, so these limitations might affect the results. Further developments are expected.

12. Abstractor and date

Tsuruoka K, 12 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Kusumoto M, Fujimura Y, Yamada H, et al. Evaluation of the effectiveness of various drugs for relieving itching due to eczema carried out by personnel in inpatient pharmacy practice: assessment based on "itching" score -*. *Iyaku Journal* (*Medicine and Drug Journal*) 1993; 29: 973–6 (in Japanese).

1. Objectives

To compare the effect of unseiin (温清飲), antiallergic drugs, and antihistamines on itching due to eczema and other skin disorders.

2. Design

Randomized controlled trial (RCT).

3. Setting

One dermatology ward at a general hospital, Japan.

4. Participants

One hundred inpatients with eczema-induced itching and other skin disorders (60 males and 40 females): atopic dermatitis (n=42), asteatotic eczema (n=12), contact dermatitis (n=7), psoriasis (n=7), seborrheic dermatitis (n=6), and others (n=26). Age (in years) was 0–5 (n=2), 6–15 (n=23), and 16 or older (n=75).

5. Intervention

Arm 1: Kampo monotherapy: administration of TSUMURA Unseiin (温清飲) Extract Granules 7.5 g/day for 2 weeks (n=25).
Arm 2: antiallergic drug monotherapy: administration of Celtect (oxatomide) 2 tablets/day for 2 weeks (n=23).
Arm 3: Kampo medicine + antiallergic drug: administration of TSUMURA Unseiin (温清飲) Extract Granules 7.5 g/day + Celtect 2 tablets/day for 2 weeks (n=27).
Arm 4: antihistamine: administration of Tavegyl (clemastine) 2 tablets/day for 2 weeks (n=25).

6. Main outcome measures

The degree of itching was scored on a 5-point scale (0: no symptoms, 1: slight itching, 2: mild itching, 3: moderate itching, 4: intense itching). Patients themselves recorded the score every 1 hour. Daily total scores were calculated for days at the beginning, middle, and end of hospitalization.

7. Main results

The mean total scores for arms 1, 2, 3, and 4, respectively were 15.42, 15.69, 20.33, and 21.84 (first day), 14.70, 12.62, 14.88, and 17.12 (middle of hospitalization), 7.84, 8.06, 7.07, and 9.68 (last day). In all arms, significant differences were observed between the first and last days. The mean changes in scores from the first to last day were 7.58, 7.38, 13.59, and 12.16 in arms 1, 2, 3, and 4, respectively, and there were significant differences between arms 1 and 3, 1 and 4, 2 and 3, and 2 and 4 and no significant between-arm differences in sex, type of disease, and age.

8. Conclusions

All treatments significantly decrease itching. The effects in arms 1 and 2 as well as arms 3 and 4 are similar. The antipruritic effect is greater in arms 1 and 2 than in arms 3 and 4.

9. From Kampo medicine perspective

The authors noted that assessment of the efficacy of unseiin as well as other Kampo medicines for itching based on *sho* (証, pattern) is challenging.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In this RCT, degree of itching was considered an outcome measure. Since strong itching (scored 3 or 4) is associated with other symptoms such as insomnia, an assessment of the effect of antihistamine or antiallergic drugs on sleep would be informative. A more extensive study is expected.

12. Abstractor and date

Tsuruoka K, 13 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ohkuma M. Treatment of pruritus by Chinese drugs. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1993; 10: 126–30 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of tokiinshi (当帰飲子) and orengedokuto (黄連解毒湯) for the treatment of pruritus.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Dermatology, Kinki University School of Medicine, Japan.

4. Participants

One hundred sixty-two patients with pruritus associated with winter eczema, senile crural eczema, asteatotic eczema, and xeroderma. Nineteen patients had diabetes.

5. Intervention

Arm 1: oral administration of tokiinshi (当帰飲子) (manufacturer, not specified) + TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. after meals (n=68).
Arm 2: oral administration of tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=49).
Arm 3: TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. after meals (n=10).
Arm 4: oral administration of antihistamines (meguitazine 6 mg/day [n=13], terfenadine 120 mg/day [n=4], ketotifen fumarate 2 mg/day [n=14], or oxamide 60 mg/day [n=4]) after meals or at bedtime (n=35).
Treatment duration: at least 4 weeks.

6. Main outcome measures

Pruritus was assessed by history taking on a 3-point scale: marked response (disappeared or almost disappeared), moderate response (improved), and no response/worse (not changed or increased).
The observation period was at least 4 weeks. Patients who showed signs of improvement only after more than 4 weeks or stopped visiting within 4 weeks (except those with marked or moderate responses) were counted as dropouts.

7. Main results

In arm 1, the response was marked in 25 patients (66%), moderate in 9 (24%), absent or worse in 4 (11%), and there were 30 dropouts. The response in arm 1 was significantly better than that in arm 2 (marked in 39%, moderate in 29%, absent or worse in 32%) and arm 3 (marked in 13%, moderate in 50%, absent or worse in 38%) ($P<0.05$). The response in arm 4 (marked in 37%, moderate in 37%, absent or worse in 26%) did not differ significantly from that in arm 1; however, sleepiness occurred in 6 patients and malaise in 2 in arm 4, while these reactions were not observed in arms 1–3.

8. Conclusions

Tokiinshi combined with orengedokuto is as effective as antihistamines for pruritus.

9. From Kampo medicine perspective

Tokiinshi is used for *in-kyo* (陰虚, yin deficiency) and orengedokuto is used for *jitsu-you* (実陽, excess yang). These are not usually combined. However, the authors stated that this combination is not irrational, since unseiin (温清飲) is orengedokuto plus shimotsuto (四物湯) (used for *in-kyo*).

10. Safety assessment in the article

In arm 4, six patients had sleepiness and two had malaise. In arm 1, two patients experienced stomach fullness.

11. Abstractor's comments

This RCT demonstrated the efficacy of tokiinshi combined with orengedokuto for pruritus. In arm 1, 30 of 68 patients dropped out, but the analyses might not have been carried out on an intent-to-treat basis. Clarification of the analyses in this study is expected.

12. Abstractor and date

Tsuruoka K, 14 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ohkuma M. Treatment of pruritus by Chinese drugs with external application and oral antihistamine. *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1994; 11: 302–3 (in Japanese).

1. Objectives

To compare the efficacy of orengedokuto (黄連解毒湯), tokiinshi (当帰飲子), oral terfenadine (antihistamine), and heparinoid ointment containing peppermint oil monotherapy or combination therapy for the treatment of pruritus.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Dermatology, Kinki University School of Medicine, Japan.

4. Participants

Two hundred fifty-one patients with pruritus.

5. Intervention

Arm 1: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals + terfenadine 60 mg b.i.d. and topical administration of 0.3% heparinoid ointment + 1% peppermint oil (n=44).

Arm 2: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals + terfenadine 60 mg b.i.d. (n=72).

Arm 3: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=68).

Arm 4: topical administration of 0.3% heparinoid ointment + 1% peppermint oil (n=45).

Arm 5: terfenadine 60 mg b.i.d. (n=14).

Arm 6: 0.3% heparinoid ointment (n=3).

Arm 7: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals and topical administration of 0.3% heparinoid ointment + 1% peppermint oil (n=5).

Treatment duration: not mentioned in the article.

6. Main outcome measures

The response to treatment was evaluated on a 3-point scale (disappeared or almost disappeared ++, mitigated +, not changed or increased –).

7. Main results

The number of cases with responses of ++, +, –, and the number of dropouts were, respectively: 14, 9, 2, and 19 in arm 1; 23, 9, 5, and 35 in arm 2; 25, 9, 4, and 30 in arm 3; 7, 9, 9, and 20 in arm 4; 0, 3, 2, and 9 in arm 5; 0, 1, 1, and 1 in arm 6; 1, 1, 1, and 2 in arm 7. There were significant differences between arms 2 and 4 ($P<0.05$) and 3 and 5 ($P<0.01$) but not between arms 1 and 2, 1 and 3, and 2 and 3.

8. Conclusions

Oral administration of orengedokuto, tokiinshi, and terfenadine (antihistamine) and topical administration of heparinoid ointment + peppermint oil (arm 1) is effective for pruritus in the vast majority of cases. The effect of treatment in arm 1 and arm 7 (without antihistamine) is similar.

9. From Kampo medicine perspective

The authors stated that combining tokiinshi (used for *kyo-sho* [虚証, deficiency pattern]) with orengedokuto (for *yo-sho* [陽証, yang pattern]) is not irrational, given the fact that unseiin (温清飲) is a combination of orengedokuto (for *yo-sho*) and shimotsuto (四物湯) (for *kyo-sho*).

10. Safety assessment in the article

Five patients had difficulty in swallowing in arm 1; 6 had difficulty in swallowing and 1 had dermatitis in arm 2; 5 had difficulty in swallowing in arm 3; 1 had skin warmth in arm 4; none had adverse reactions in arms 5 and 6; 1 had difficulty in swallowing and 3 had bloating in arm 7.

11. Abstractor's comments

This RCT compared the efficacy of four agents including Kampo medicines alone or in combination. Basic information including background factors such as underlying disease, age, and sex of participants as well as follow-up period is not provided, making evaluation difficult. Further detailed study is expected.

12. Abstractor and date

Tsuruoka K, 17 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Kobayashi K, Ohkawara A. Therapeutic effect of jumihaidokuto on chronic eczema and atopic dermatitis*. *Hifuka ni okeru Kampo Chiryo no Genkyo* (*Current Situation of Kampo Therapy in Dermatology*) 1994; 5:25–34 (in Japanese).

1. Objectives

Efficacy and safety of jumihaidokuto (十味敗毒湯) for the treatment of chronic eczema and atopic dermatitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Dermatology, Hokkaido University Hospital and Asahikawa Medical College Hospital, and 8 hospital departments of dermatology.

4. Participants

Seventy-four patients (12 or more years old) with mild or moderate chronic eczema (except nummular eczema) and atopic dermatitis with little exudate and sporadic red rashes.

5. Intervention

Arm 1: oral administration of TSUMURA Jumihaidokuto (十味敗毒湯) Extract Granules 2.5 g t.i.d. for 8 weeks (n=35).

Arm 2: oral administration of clemastine fumarate 1 mg b.i.d. for 8 weeks (n=39).

Mild/moderate-strength topical steroids were allowed.

6. Main outcome measures

Itching and skin manifestations (erythema, papules, nodules, lichenification, desquamation, and scratch marks) were evaluated separately on a 4-point scale at baseline and at weeks 1, 2, 4, 6, and 8, and then their improvements were evaluated on a 5-point scale as compared with baseline.

7. Main results

The improvements in patients with chronic eczema were evaluated separately from those in patients with atopic dermatitis. Seventeen participants in arm 1 and 19 in arm 2 had chronic eczema, while 18 in arm 1 and 20 in arm 2 had atopic dermatitis. Similar proportions of patients with chronic eczema in arms 1 and 2 had at least moderate overall improvement (64.7% *vs*. 63.2%) or at least mild overall improvement (82.4% *vs*. 84.2%). Likewise, overall improvement in atopic dermatitis was similar in both arms (50% *vs*. 60% with at least moderate improvement, and 88.9% *vs*. 90% with at least mild improvement).

8. Conclusions

Jumihaidokuto is as effective for chronic eczema and atopic dermatitis as clemastine fumarate.

9. From Kampo medicine perspective

Since jumihaidokuto is used for patients with moderate or more physical strength, the degree of obesity and type of physique were considered. Including only patients whose degree of obesity was 0 or more and muscular patients with negative obesity scores, analysis found 68.8% had at least moderate improvement and 93.8% had at least mild improvement in arm 1, which was insignificantly lower than in arm 2.

10. Safety assessment in the article

One patient (2.9%) in arm 1 developed hypertension and stopped taking medication. Three patients (7.7%) had sleepiness, 1 (2.6%) had leucopenia, and 1 (2.6%) had constipation in arm 2.

11. Abstractor's comments

This meaningful clinical study compares the effect of jumihaidokuto with that of clemastine fumarate on chronic eczema and atopic dermatitis and examines the effect of Kampo medicines on skin diseases often seen in daily clinical practice. However, the authors do not describe the way they evaluated overall improvement using outcome measures. The results for each measure are also interesting, so further detailed description is expected. Moreover, although they noted "one patient stopped medication due to hypertension" in arm 1, the data of all 35 participants in arm 1 were included in the analysis of overall improvement. In Kampo medicine, muscularity is not clearly defined; more detailed description is expected. Despite these limitations, this may be a valuable study demonstrating similar efficacy for jumihaidokuto and antihistamines. Given the adverse effects of antihistamines such as sleepiness, jumihaidokuto is important alternative treatment for skin diseases.

12. Abstractor and date

Goto H, 12 September 2008, 1 June 2010.

12. Skin Diseases

Reference

Kukita A, Harada S, Fujisawa R, et al. The clinical efficacy of the herb medicine, TJ-114 (Sairei-to), on the topical steroid therapy of psoriasis vulgaris. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicines*) 1991; 7: 927–36 (in Japanese with English abstract). CENTRAL ID: CN-00716584, Ichushi Web ID: 1992091847 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) combined with topical steroid therapy for psoriasis.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

Six university hospitals (National Defense Medical College, Showa University, Jikei University School of Medicine, Tokyo Women's Medical University, Toho University, and Nihon University) and departments of dermatology of 8 hospitals, Japan.

4. Participants

One-hundred and four patients (15 or more years old) with psoriasis vulgaris. They had skin manifestations evaluable for drug efficacy, regardless of the severity, at the start of the study. Exclusion criteria were: 1) use of at least very strong topical steroids within 2 weeks before the study; 2) serious complications; 3) pregnant or nursing mother; 4) prior use of etretinate or methotrexate; 5) a determination of ineligibility by participating physicians.

5. Intervention

Arm 1: 0.12% betamethasone valerate ointment + oral administration of TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. before meals for 12 weeks (n=49).

Arm 2: application of 0.12% betamethasone valerate ointment (Rinderon V or Betnevate) 2 or 3 times daily. Rinderon VG lotion was used on the scalp for 12 weeks (n=45).

6. Main outcome measures

(1) Severity of symptoms including itching, erythema, scale, and infiltration/hypertrophy was assessed on a 5-point scale (4, severe; 3, moderate; 2, mild; 1, slight; 0, none). Patients were followed at the start and at 4, 8, and 12 weeks of treatment.

(2) Laboratory tests: blood count, blood biochemistry, and general urinalysis at the first visit (start) and last visit (end of the study).

(3) Overall improvement: assessed at each visit, compared to baseline values at the start of the study, on a 6-point scale (cured, markedly improved, moderately improved, mildly improved, not changed, and worsened).

(4) Safety: assessed on the basis of adverse effects and laboratory abnormalities found during the study on a 4-point scale (1: no safety problems, 2: some safety problems, 3: moderate safety problems, 4: marked safety problems).

(5) Efficacy: assessed on the basis of both overall improvement and safety (see “safety assessment” section below) on a 5-point scale (1: very effective, 2: effective, 3: slightly effective, 4: not effective, 5: unfavorable).

7. Main results

Of 104 patients, 4 in arm 2 and 7 in arm 1 were excluded because they were lost to follow-up or noncompliant with treatment. Symptom-specific severity did not differ between arms at the start of the study, but erythema and scaling improved significantly in arm 1 compared to arm 2 ($P<0.05$) and itching, infiltration, and hypertrophy tended to improve ($P<0.1$) after 12 weeks. There was a trend toward overall improvement in arm 1, compared to arm 2, after 4 weeks ($P<0.1$) and significant improvement after 12 weeks ($P<0.01$). More patients achieved at least moderate overall improvement in arm 1 (73.9%) than in arm 2 (52.5%) ($P<0.1$). The efficacy was greater in arm 1 (63.8%) than in arm 2 (44.2%) ($P<0.1$).

8. Conclusions

Combined therapy with saireito and topical steroids is suggested to be more effective than topical steroids, but only for psoriasis.

9. From Kampo medicine perspective

The authors stated that selection of Kampo medicines was not based on *sho* but disease name.

10. Safety assessment in the article

In arm 2, two patients had stomach discomfort and gastrointestinal symptoms, and one had laboratory data indicating transient hepatic dysfunction.

11. Abstractor’s comments

This study examined treatment for refractory psoriasis and was a well-designed, high-quality RCT. This was not a blinded study, so the comparison of topical monotherapy with combined therapy with oral medication may be biased. Further expanded study is expected.

12. Abstractor and date

Tsuruoka K, 20 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

References

Murota H, Azukizawa H, Katayama I. Impact of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) on treatment of chronic spontaneous urticaria: a randomized controlled study. *Chinese Journal of Integrative Medicine* 2017; 1-5. doi: 10.1007/s11655-017-2950-6 CENTRAL ID: CN- 01404751, Pubmed ID: 28819778

1. Objectives

To evaluate the efficacy of jumihaidokuto（十味敗毒湯）on urticaria

2. Design

Randomized controlled trial (RCT)

3. Setting

One university hospital, Japan

4. Participants

Twenty-one patients who met the diagnostic criteria for urticaria in the guideline set by the Japanese Dermatological Association

5. Intervention

Arm 1: administration of Kracie Jumihaidokuto（十味敗毒湯） 6.0 g/day (3.0 g b.i.d.) plus an antihistamine for 8 weeks (n=11)

Arm 2: administration of an antihistamine alone for 8 weeks (n=10)

6. Main outcome measures

Primary endpoint: Urticaria severity score proposed by the Japanese Dermatological Association

Secondary endpoints: Comparison of itch VAS score, scores from a brief questionnaire about itch and skin condition, and QOL (Skindex-16 score)

7. Main results

The urticaria severity score at 8 weeks of the treatment was significantly lower in Arm 1 than in Arm 2 (P<0.01). The itch VAS score did not significantly differ between the two arms. The brief questionnaire results showed significant improvement of itch and skin condition in Arm 2 (P<0.05). The Skindex-16 results showed no significant differences between the two arms for all symptoms.

8. Conclusion

In patients with refractory chronic urticaria, jumihaidokuto may be effective treatment.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

No adverse events were noted.

11. Abstractor’s comments

Refractory chronic urticaria impairs the quality of life of the patients. For urticaria that does not improve with antihistamines, concomitant use of jumihaidokuto is considered to be an effective approach. The itch VAS score analysis in this study did not show a significant difference, but graphically, tended to favor jumihaidokuto use. Thus, further studies with larger sample sizes are desired.

From the viewpoint of Oriental medicine, spleen deficiency may play a role in the background of chronic urticaria. Thus, dietary advice and prescription of medicine that can promote gastrointestinal function may warrant investigations.

12. Abstractor and date

Nakata H, 1 June 2020.

12. Skin Diseases

Reference

Tanaka M. Effects of oxatomide on urticaria. *Yakuri to Chiryo* (*Japanese Pharmacology and Therapeutics*) 1991; 19:5029–31 (in Japanese).

1. Objectives

Efficacy of kakkonto (葛根湯) as an adjuvant for reducing adverse reactions to oxatomide.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital department of dermatology, Japan.

4. Participants

Fifty-three patients with urticaria.

5. Intervention

Arm 1: oral administration of TSUMURA Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals for 7 days (n=10).
Arm 2: oral administration of TSUMURA Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals + oxatomide 30 mg once daily at bedtime for 7 days (n=22).
Arm 3: oral administration of oxatomide 30 mg twice daily, after breakfast and dinner, for 7 days (n=21).

6. Main outcome measures

Itching and wheals were scored separately on a 3-point scale (marked, 2; mild, 1; none, 0). The rates of improvement compared with pre-treatment values were then calculated and classified as marked, moderate, or no response. These classifications were used as scores for the global assessment. The presence of sleepiness was also evaluated.

7. Main results

The rate of improvement was 31.6%, 68.2%, and 68.8% in arms 1, 2, and 3, respectively. For global assessment, the proportion of patients who had at least moderate response was significantly smaller in arm 1 (40%) than in arms 2 and 3 (82% and 76%, respectively, $P<0.05$). No patient in arms 1 and 2 and 10% of patients in arm 3 experienced sleepiness.

8. Conclusions

When oxatomide is used with kakkonto, the dose of oxatomide can be halved to prevent sleepiness.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This was a resourceful clinical trial that evaluated the efficacy of kakkonto as an adjuvant and as a reductant of adverse effects when used with oxatomide for urticaria. However, although the authors stated that the trial was randomized, there was a big between-group difference in the number of patients. In addition, the details of dropouts should be described. Regarding sleepiness, oxatomide was administered at the bedside in arm 2 but not at the bedside (after breakfast and dinner) in arm 3. Of course more marked sleepiness is noticed on awakening in patients in arm 3. For comparison, the drug should have been administered at the bedside in arm 3, too. Daily costs of medication were also compared among the groups and the kakkonto combined therapy was less expensive than oxatomide monotherapy. This clinical study is of interest to general physicians.

12. Abstractor and date

Goto H, 12 September 2008, 1 June 2010.

12. Skin Diseases

References

Ohkuma M. Treatment of acne by Chinese drugs and external application. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1993; 10: 131–4 (in Japanese with English abstract).

Ohkuma M. Treatment of acne by Chinese drugs and external application - comparison with oral antibiotics -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1993;44:173–7 (in Japanese)

1. Objectives

Efficacy of jumihaidokuto (十味敗毒湯) and orengedokuto (黄連解毒湯) for the treatment of acne vulgaris.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (author belongs to the Department of Dermatology, Kinki University School of Medicine), Japan.

4. Participants

Two hundred sixty-eight patients with acne vulgaris.

5. Intervention

Arm 1: oral administration of jumihaidokuto (十味敗毒湯) (manufacturer, not specified) 2.5 g t.i.d. and orengedokuto (黄連解毒湯) 2.5 g t.i.d. after meals + topical application of clindamycin lotion in the morning + 1% gentamicin sulfate-containing 0.12% betamethasone valerate lotion in the afternoon or evening + topical application of sulfur-camphor lotion before sleep for eruptions (n=90).

Arm 2: oral administration of jumihaidokuto (十味敗毒湯) (manufacturer, not specified) 2.5 g t.i.d. and orengedokuto (黄連解毒湯) 2.5 g t.i.d. after meals (n=91).

Arm 3: oral administration of jumihaidokuto (十味敗毒湯) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=55).

Arm 4: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=20).

Arm 5: topical application of clindamycin lotion in the morning + 1% gentamicin sulfate-containing 0.12% betamethasone valerate lotion in the afternoon or evening + topical application of sulfur-camphor lotion before sleep for eruptions (n=12).

Observation period was 4 weeks or more.

6. Main outcome measures

Improvement in skin condition,

rated on the basis of disappearance of skin eruptions (comedones, small papules, pustules, etc.), was defined as marked (if 90% disappeared), moderate (if 50–90% disappeared), mild (if 10–50% disappeared), and absent (if less than 10% disappeared).

7. Main results

The percentage of patients who had marked response was 47, 52, 51, 20, and 8 in arms 1, 2, 3, 4, and 5, respectively. There was no significant difference in efficacy between arms 1 and 2, arms 1 and 3, and arms 2 and 3. The time to cure was significantly shorter in arm 1 than in arm 2 ($P<0.001$).

8. Conclusions

Combined therapy with oral jumihaidokuto and orengedokuto plus clindamycin lotion, steroid lotion, and sulfur-camphor lotion is effective in reducing comedones, small papules, and pustules in acne vulgaris.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical trial compared the effect of jumihaidokuto and orengedokuto on acne vulgaris with or without topical drugs. This interesting clinical study showed that although oral administration of jumihaidokuto or orengedokuto is itself effective for the treatment of acne, combination with topical agents can further shorten the duration of treatment. This paper notes that the patients were randomly assigned to each group, but the number of patients differs between groups. The reasons for dropping out should therefore be described. Although he also notes that "patients who improved only after 4 weeks or more and who had no response within the 4-week observation period were excluded from the analysis [sic]," it is questionable because the numbers of patients who participated in the study and whose outcomes are shown in the results are same. However, this study suggests the effect of combined therapy. Further clinical study that examines the placebo effect of combined topical agents is expected. The author has reported another study published in the *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1993, in which a non-randomized group treated with minocycline was compared to the groups included in this study.

12. Abstractor and date

Goto H, 12 September 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ito K, Masaki S, Hamada M, et al. Efficacy and safety of the traditional Japanese medicine keigairengyoto in the treatment of acne vulgaris. *Dermatology Research and Practice* 2018: 1-7. CENTRAL ID: CN-01618253, Pubmed ID: 30057596, UMIN ID: UMIN000014831

1. Objectives

To examine the effectiveness and safety of keigairengyoto（荊芥連翹湯）in treating acne vulgaris.

2. Design

Randomized controlled trial (RCT).

3. Setting

Eight hospitals (departments of dermatology), Japan.

4. Participants

Patients aged 15–64 years with acne vulgaris (inflammatory acne) on the face who visited one of the eight facilities between August 2014 and January 2016 and provided consent to participate in this study. For patients under 18 years of age, consent was obtained from their parent or guardian. Exclusion criteria were as follows: (1) severe complications such as liver disease, renal disease, heart disease, blood disease, or metabolic disease; (2) being pregnant, lactating, or planning to become pregnant during the study observation period; (3) taking concomitant medications and research medicines within 1 week before the start of the study; (4) participation in another trial within one month before the initiation of this study; (5) scheduling to undergo a chemical peel or laser therapy during the study observation period; (6) a history of allergies to traditional Japanese medicine; and/or (7) patients for whom, in the opinion of the study scientist or collaborating research doctor, it is not in their best interest to be enrolled in the study. (n=64)

5. Intervention

Arm 1: Conventional topical treatment (adapalene and nadifloxacin or clindamycin) for 12 weeks (n=33).
Arm 2: Conventional topical treatment (adapalene and nadifloxacin or clindamycin) plus TSUMURA Keigairengyoto（荊芥連翹湯） Extract Granules 2.5 g three times daily for 12 weeks (n=31).

6. Main outcome measures

The amount of inflammatory and noninflammatory acne lesions on the face was counted at baseline (study entry) and at weeks 2, 4, 8, and 12. The reduction in this number was calculated for inflammatory, noninflammatory, and all acne lesions.

7. Main results

The efficacy analysis was conducted on 52 patients (28 patients in Arm 1 and 24 patients in Arm 2), after exclusion of 4 patients in Arm 1 and 2 patients in Arm 2. At Weeks 4 and 8, the amount of inflammatory acne lesions significantly decreased in the keigairengyoto combined group ($P<0.05$).

8. Conclusions

Keigairengyoto in combination with conventional treatments may be a useful agent in patients with inflammatory acne.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no serious adverse events in both groups.

11. Abstractor's comments

This clinical study is interesting in that it was designed to determine the effectiveness of keigairengyoto used in the treatment of acne vulgaris. This study suggested that keigairengyoto may be a useful agent in patients with inflammatory acne, and this report may lead to clinical application in the future. Inflammatory acne in the keigairengyoto combined group, compared with the control group, was reported to be significantly improved at Weeks 4 and 8, but not at Week 12. Further study results from more patients are awaited. In addition, studies investigating the effects on inflammatory diseases other than acne vulgaris are desired.

12. Abstractor and date

Kato Y, 1 September 2019.

12. Skin Diseases

Reference

Nagai Y, Hasegawa M, Tago O, et al. Assessment of the therapeutic effect of juzentaihoto on pressure ulcer. *Kampo to Saishin-chiryo* (*Kampo & The Newest Therapy*) 2009;18:143-9. Ichushi Web ID: 2009244595

1. Objectives

To evaluate the effects of juzentaihoto (十全大補湯) on pressure ulcers.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Dermatology, Gunma University Hospital and eight affiliated hospitals, Japan.

4. Participants

Twenty-eight chronic-phase patients whose pressure ulcers showed no change or worsening during a 2-week observation period (age and sex, not specified).

5. Intervention

Arm 1: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. orally before or after meals for 12 weeks. For patients with a body weight below 35 kg, the drug was administered b.i.d (n=16, including 12 infected with methicillin-resistant *Staphylococcus aureus* [MRSA]).

Arm 2: continuation of conventional treatment (n=12, including 5 infected with MRSA).

6. Main outcome measures

Long × short axes, size, and depth of pressure ulcers; prealbumin level, serum albumin level, lymphocyte count, prognostic nutritional index, serum hemoglobin level, and bacterial culture from the site of pressure ulcer (scoring from – to 3+) were measured at baseline, 4, 8, and 12 weeks.

7. Main results

There were no between-arm differences in the size of pressure ulcers, prealbumin level, and prognostic nutritional index. Detection of methicillin-resistant *Staphylococcus aureus* (MRSA) declined significantly during the course of treatment in arm 1 compared with arm 2 ($P<0.05$).

8. Conclusions

Oral administration of juzentaihoto lowers the detection rate of MRSA but has no effect on the healing rate of pressure ulcers or nutritional status.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an interesting clinical study that evaluated the effects of juzentaihoto on various aspects of outcome, including improvement rate, nutritional status, and local antibacterial activity, in chronic-phase patients. The data of 28 patients were analyzable in this study, but the number of patients initially enrolled, including withdrawals, is not reported. Moreover, data on age, sex, underlying disease, and presence of complications are not available. Although prealbumin level, prognostic nutritional index, serum albumin level, lymphocyte count, and serum hemoglobin level were measured, only prealbumin level and prognostic nutritional index are reported. Thus, a more detailed report is desired. As for prealbumin level and prognostic nutritional index, the authors reported "no differences" in the results section based on the lack of significant between-arm differences, whereas they reported "better in arm 1" in the summary section based on the higher mean values in arm 1; the lack of significant differences should have been mentioned. Yet, as the authors noted, the disease course may be better (albeit not significantly) in patients who take juzentaihoto than in those who do not. Future studies including a larger number of patients and a longer follow-up might demonstrate the efficacy of juzentaihoto in patients with chronic pressure ulcers.

12. Abstractor and date

Goto H, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Matsuura M. Efficacy of saireito in the management of chronic rheumatoid arthritis (RA)*. *Modern Physician* 1994; 14: 403–8 (in Japanese). Ichushi Web ID: 1994187959

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) in the management of chronic rheumatoid arthritis in a controlled trial using lobenzarit, a western medicine with the established efficacy, as control.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Six facilities including the Department for Rheumatic Diseases, Tokyo Metropolitan Fuchu General Hospital, Japan.

4. Participants

Forty-nine patients (12 males and 37 females) seen at the above facilities and diagnosed with chronic rheumatoid arthritis.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. before meals for 16 weeks (n=24).
Arm 2: lobenzarit 80 mg t.i.d. after meals for 16 weeks (n=25).

6. Main outcome measures

Clinical usefulness taking into account improvement in clinical symptoms and incidence of adverse drug reactions after 16 weeks of treatment.

7. Main results

Symptoms were improved in 7 of 18 patients (38.9%) and 3 of 20 patients (15.0%) receiving saireito and lobenzarit, respectively, although there was no significant difference between treatments. Clinical usefulness was noted in 7 of 18 patients (38.9%) and 4 of 21 patients (19.1%) receiving saireito and lobenzarit, respectively, showing that saireito was clinically useful in a significantly larger proportion of patients ($P<0.05$).

8. Conclusions

Saireito seems to be useful for the management of systemic symptoms of chronic rheumatoid arthritis, and is associated with comparable or higher global improvement and significantly fewer adverse drugs reactions compared with lobenzarit, a western medicine with established efficacy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions including laboratory abnormalities occurred in 13.0% and 36.0% of patients receiving saireito and lobenzarit, respectively. Adverse reactions to saireito included renal impairment (in 2 of 3 cases), and those to lobenzarit included gastrointestinal disorders (in 4 of 9 cases).

11. Abstractor's comments

The use of a positive control in this trial helped establish the clinical usefulness of saireito for chronic rheumatoid arthritis. However, no objective measures were used. Efficacy was based on global symptom improvement (measured by interview) and on development of adverse reactions. A prospective confirmatory study incorporating changes in biomarkers, imaging findings, and laboratory data is desired.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

References

Matsuta K, Gu XP, Ito K, et al. Evaluation of jiinkokato and steroid combination therapy for chronic rheumatoid arthritis*. *Kampo Igaku* (*Kampo Medicine*) 1995;19:50–2 (in Japanese).

1. Objectives

To evaluate the efficacy of jiinkokato (滋陰降火湯) for reducing adverse effects of steroids in patients with chronic rheumatoid arthritis mainly by blood cell examination.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two facilities (Department of Medicine and Physical Therapy, the University of Tokyo Hospital, and Matsuta Internal Medicine Clinic), Japan.

4. Participants

Fourteen female patients with chronic rheumatoid arthritis visiting the above facilities between 1992 and 1993 and continuously receiving prednisolone (5–7.5 mg/day) for at least 1 year (mean age, 61 years; range, 38–76 years).

5. Intervention

Arm 1: prednisolone 5–7.5 mg/day + TSUMURA Jiinkokato (滋陰降火湯) Extract Granules 2.5 g t.i.d. before meals (n=6).
Arm 2: prednisolone 5–7.5 mg/day (n=8).

6. Main outcome measures

Hemoglobin; peripheral hematological parameters, including leukocyte and lymphocyte counts; and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and albumin/globulin (A/G) ratio as indices of the activity of chronic rheumatoid arthritis, evaluated before and after treatment (treatment period varying from 6 to 28 weeks).

7. Main results

There were no changes in any measures in the control group. In contrast, the percentage of neutrophils was significantly reduced to 64.1±8.2 from 75.9±9.0 and the percentage of lymphocytes was significantly increased to 24.3±6.8 from 17.3±9.0 after treatment ($p<0.05$) with jiinkokato. In two patients, lymphocyte count more than doubled after jiinkokato treatment from less than 1000/μL at baseline. The indices of the activity of chronic rheumatoid arthritis remained unchanged in both arms.

8. Conclusions

Jiinkokato is effective for reducing the adverse effects of steroids including increased neutrophils (%) and decreased lymphocytes (%).

9. From Kampo medicine perspective

The adverse effects of steroids are considered to represent the state of *yinkyonainetsu* (陰虚内熱, *yin* deficiency with internal heat) according to Kampo (traditional Chinese) medicine, and are an indication for jiinkokato. The hematologic abnormalities noted in steroid-treated patients were improved by jiinkakoto, suggesting an immunoregulatory effect.

10. Safety assessment in the article

Jiinkokato did not increase the incidences of the following adverse effects of steroids: hypertension, obesity, peptic ulcer, purpura, osteoporosis, diabetes mellitus, and edema.

11. Abstractor's comments

Collagen disorders including chronic rheumatoid arthritis are often treated with long-term steroid therapy, which is associated with a reduction in lymphocyte count in some cases, even to 1000/μL, posing a problem for outpatient management. This study showed that the jiinkokato combination decreased neutrophil count and increased lymphocyte count, suggesting that it has efficacy for reducing the adverse effects of steroids. However, possibly because of the small sample size, the measures of chronic rheumatoid arthritis activity were unchanged, and the various adverse effects of steroids were clinically unimproved. A future case series investigation of the efficacy of long-term combination therapy is awaited.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nishizawa Y, Nishizawa Y, Amenomori Y, et al. A comparison of the analgesic effect of non-steroid anti-inflammatory drugs (NSAIDs alminoprofen) and those of a Chinese traditional herbal medicine, boi-ogi-to and shuchi-bushi-powder on osteoarthropathy of the knee joint in middle-aged and elderly patients with knee-joint osteoarthropathy. *Itami to Kampo* (*Pain and Kampo Medicine*) 1998; 8: 17-32 (in Japanese with English abstract). Ichushi Web ID: 1999041737

1. Objectives

To compare the efficacy of Kampo medicines (boiogito [防己黄耆湯] and shuchibushimatsu [修治附子末]) with NSAIDs for improving analgesia, quality of life (QOL), and exercise capacity in patients with knee osteoarthritis.

2. Design

Randomized controlled trial (RCT).

3. Setting

Three clinics, one hospital, and the Department of Anesthesiology, Shiga University of Medical Science, Japan.

4. Participants

One hundred and fifty patients with knee osteoarthritis associated with knee pain and swelling who were candidates for surgery or required steroid treatment were included after 9 detailed exclusion criteria were applied.

5. Intervention

Arm 1: Kampo formulations only. Oral administration of Boiogito (防己黄耆湯) (manufacturer, not specified) 0.125 mg/kg/day + shuchibushimatsu (修治附子末) (manufacturer, not specified) 15 mg/kg/day on an empty stomach with 350 mL of water at 6:00, 14:00, and 22:00 for 1 year (2 males and 48 females: n=50; mean age, 65.7±7.3).

Arm 2: NSAIDs and Kampo formulations. Oral administration of NSAIDs (alminoprofen 600 mg/day) + boiogito (防己黄耆湯) (manufacturer, not specified) 0.125 mg/kg/day + shuchibushimatsu (修治附子末) (manufacturer, not specified) 15 mg/kg/day for 1 year (4 males and 46 females: n=50; mean age, 65.3±7.8).

Arm 3: NSAIDs only. Oral administration of alminoprofen 600 mg/day for 1 year (3 males and 47 females: n=50; mean age, 64.5±8.1).

6. Main outcome measures

Pain assessment using a visual analog scale for pain (VAS-P) every month and face rating score (FRS) at the start and end of the study. The physical, mental, economic, social, and pharmacological aspects of quality of life (QOL) assessed using VASs at the start and end of the study. Motor function assessed by the Japanese Orthopaedic Association (JOA) score and others.

7. Main results

Before the study began, there were no between-group differences in VAS-P and FRS. After 1 year of treatment, both measures improved in arms 1 > 2 > 3 and for each month differed significantly between arms 1 and 3 (P<0.01), as well as arms 2 and 3 (P<0.05). Total QOL improved in arm 1 (202.9±28.5%) > 2 (180.6±28.3%) > 3 (125.0±11.4%), showing significant differences between arms 1 and 3 (P<0.01), as well as arms 1 and 2 (P<0.01). Exercise capacity showed similar results. For arm 1, the response was marked in 33 patients (67.3%), moderate in 15 (20.4%), mild in 2 (4.1%), absent 2 (4.1%), worse in 2 (4.1%) with 1 dropout (due to relocation); for arm 2, the response was marked in 15 patients (31.3%), moderate in 8 (16.7%), mild in 5 (10.4%), absent in 3 (6.3%), worse in 17 (35.4%), with 2 dropouts (due to relocation); for arm 3, the response was marked in 4 patients (8.3%), moderate in 5 (10.4%), mild in 7 (14.6%), absent in 5 (10.4%), worse in 27 (56.8%), with two dropouts (due to relocation). The response rates were higher in arms 1 > 2 > 3, and differed significantly between arms 1 and 3 and between arms 2 and 3 (P<0.01 for both comparisons).

8. Conclusions

Kampo medicine is useful for the treatment of elderly patients with knee osteoarthritis.

9. From Kampo medicine perspective

The authors stated that arthralgia and neuralgia correspond to “wind-dampness（風湿）” and edema corresponds to “heavy body （身重）”.

10. Safety assessment in the article

The proportion of patients with adverse effects or abnormal laboratory test results were greater in arms 3 > 2 > 1; the number of cases were reported without giving details.

11. Abstractor’s comments

This study was considered an RCT because the allocation was made using a random number table. Unfortunately, it was not conducted in a blind manner, but was well designed as a whole. As knee osteoarthritis is common in the elderly and NSAIDs have adverse effects, there are great expectations for Kampo medicines.

12. Abstractor and date

Tsuruoka K, 24 April 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Therapeutic effect of boiogitokashuchibushimatsu on gonarthrosis: a 10-year prospective randomized controlled trial with loxoprofen sodium*. *Pharma Medica* 2007; 25: 15-21 (in Japanese). Ichushi Web ID: 2008070613 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of boiogitokashuchibushimatsu (防已黄耆湯加修治附子末) for gonarthrosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

University hospital (Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine; Pain Clinic, Department of Anesthesiology, Shiga University of Medical Science; and Graduate School of Pharmaceutical Sciences, Osaka University) and 4 other hospitals, Japan.

4. Participants

Two hundred eleven patients with gonarthrosis.

5. Intervention

Arm 1: administration of boiogitokashuchibushimatsu (防已黄耆湯加修治附子末) (manufacturer unknown) (n=110); age at completion, 81.5±3.4 years; male/female ratio, 8:102.
Arm 2: administration of loxoprofen (n=101); age at completion, 82.0±3.1 years; male/female ratio, 9:92.
Ten-year trial. Capsules were taken with 350 mL of water 30 min before meals.
No more details (e.g. dose, dose frequencies) were indicated in the original paper.

6. Main outcome measures

Exercise capacity (EC), range of motion of knee, various chronic pains (CP), health-related quality of life (Hr-QOL), adiponectin, leptin, and orexin levels, knee circumference, synovial fluid retention as assessed by ultrasound, degree of joint space narrowing as assessed by CT scan, (direct, indirect, total) medical expenses monitored over a 10-year period.

7. Main results

All EC parameters (continuous walking distance, continuous upslope walking distance, number of steps in continuous downslope walking) were larger in arm 1 than in arm 2 (P<0.001). All parameters used to evaluate activities of daily living (ADL) (pain in passive exercise, spontaneous pain, pain on pressure, patella ballottement/soft tissue swelling, local heat, etc.), various CP, and Hr-QOL were significantly improved in arm 1 compared with arm 2 (P<0.001).

8. Conclusions

The treatment significantly improves EC, ADL, CP, and Hr-QOL and lowers total medical expenses.

9. From Kampo medicine perspective

The *sho* (pattern) concept was a criterion for inclusion. Although “gonarthrosis complying with the *sho* for boiogitokabushi” was used as a criterion, the *sho* concept was not defined. The authors appear to consider that all patients with gonarthrosis in the study satisfy the sho for boiogitokabushi. There was no *sho* concept as an exclusion criterion and no subgroup analyses according to *sho*.

10. Safety assessment in the article

A significantly larger number of adverse events occurred in arm 2 (P<0.001 for all items): gastric ulcer (0 event in arm 1 *vs.* 24 events in arm 2), eruption/sleepiness/stomach discomfort/oedema (11 events *vs.* 348 events), and laboratory abnormality (3 events *vs.* 417 events).

11. Abstractor’s comments

The filling of capsules to make the investigational products indistinguishable from each other is necessary for double-blind study of Kampo medicine. However, the dose of loxoprofen is missing from this paper (misprint?). This study assumed that “patients with gonarthrosis satisfy the *sho* for boiogitokashuchibushi.” This assumption should have been verified in a pilot study. However, it is extremely rare that a particular disease corresponds one-on-one to an effective Kampo treatment; the treatment of most diseases needs several Kampo medicines selected according to patient conditions. Furthermore, prolonged administration of drugs (including loxoprofen used as the control drug in this study) causing potentially fatal adverse reactions in the elderly such as gastric mucosal disorder is problematic. Also problematic is the therapeutic use of fixed doses for painful disease. Moreover, duration of the study was too long, given the nature of this disease and the old age of most subjects. Conclusion should be drawn in a shorter term.

12. Abstractor and date

Hoshino E, 15 March 2009, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Majima T, Inoue M, Kasahara Y, et al. Effect of the Japanese herbal medicine, boiogito, on the osteoarthritis of the knee with joint effusion. *Sports Medicine Arthroscopy Rehabilitation Therapy & Technology* 2012; 4: 1-6. Pubmed ID: 22230247

1. Objectives

To evaluate the efficacy and safety of boiogito (防已黄耆湯), a Kampo medicine for gonarthrosis with joint effusion.

2. Design

Randomized controlled trial (RCT).

3. Setting

Hokkaido University Hospital, Japan.

4. Participants

Forty-seven gonarthrosis patients with clinically confirmed joint effusion.

5. Intervention

Arm 1: Combined group: TSUMURA Boiogito (防已黄耆湯) Extract Granules (2.5 g t.i.d.) before meals and loxoprofen (60 mg t.i.d.) after meals for 12 weeks (n=24).

Arm 2: Loxoprofen group: Loxoprofen (60 mg t.i.d.) after meals for 12 weeks (n=23).

6. Main outcome measures

Knee score (Knee Society Rating System), function score (Knee Society Rating System), joint effusion volume, and evaluation of health status and joint symptoms using the 36-item short form health survey (SF-36).

7. Main results

Knee scores (Knee Society Rating System) improved significantly in both arms, while the function score (Knee Society Rating System) improved significantly in arm 1 but not in arm 2. SF-36 Physical Function scores improved significantly in both groups, but scores for the other seven domains showed no significant improvement. Joint effusion volume decreased significantly in arm 1 after four weeks, but not in arm 2.

8. Conclusions

Boiogito may be an effective conservative therapy for gonarthrosis with joint effusion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One participant in the combined group showed signs of oral dryness, but it was slight and improved after discontinuation of the drugs.

11. Abstractor's comments

This is the first clinically significant paper on an RCT demonstrating the add-on effect of boiogito with loxoprofen for gonarthrosis with joint effusion. The paper looked for significant between-group differences in before-after comparisons; however, it might also have been able to objectively demonstrate the efficacy of boiogito if it had included an examination of the stochastic differences between the two groups. Further research is anticipated.

12. Abstractor and date

Kogure T, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effects of traditional Chinese herbal medicine, mai-men-dong-tang (Japanese name: bakumondo-to) compared with bromhexine, hydrochloride on sicca syndrome, especially, salivary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group parallel comparative trial study with bromhexine. *Nihon Daekisen Gakkaishi* (*Journal of the Japan Salivary Gland Society*) 2002; 43: 62-6. Ichushi Web ID: 2005101735

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for dryness associated with primary Sjögren's syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned, Japan.

4. Participants

One-hundred and six patients with primary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. for 1 year. (n=51)
Arm 2: bromhexine hydrochloride 4 g t.i.d. for 1 year. (n=54)

6. Main outcome measures

Dryness, amount of salivation/lacrimation, and inflammatory reaction.

7. Main results

Salivation was increased in both groups but was significantly increased in the bakumondoto group. Lacrimation was significantly increased only in the bakumondoto group. Dryness was also improved only in the bakumondoto group. The inflammatory reaction remained unchanged in both groups.

8. Conclusions

Bakumondoto is more effective than bromhexine hydrochloride and safe in the treatment of dryness associated with primary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not specified).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto for relieving dryness associated with primary Sjögren's syndrome.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 12 October 2011.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effect of traditional Chinese herbal medicine, mai-men-don-tang on sicca syndrome, especially, salicary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group-pararell double-blined study. *Nihon Daekisen Gakkaishi* (*Journal of the Japan Salivary Gland Society*) 2004; 45: 66-74.

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for salivary hyposecretion associated with primary Sjögren's syndrome.

2. Design

Double-blind, randomized controlled trial (RCT).

3. Setting

Two clinics, three university hospitals, and one general hospital, Japan.

4. Participants

Two-hundred and twenty-nine patients with primary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. before meals for 6 months (n=115).
Arm 2: placebo 3 g t.i.d. before meals for 6 months (n=114).

6. Main outcome measures

Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud's symptom, limb skin temperature, and inflammatory reaction.

7. Main results

Salivation was increased in the bakumondoto group but decreased in the placebo group. Subjective symptoms were improved in the bakumondoto group but remained unchanged or were aggravated in the placebo group. Inflammatory reaction improved significantly only in the bakumondoto group.

8. Conclusions

Bakumondoto is effective and safe for the relief of subjective symptoms and salivary hyposecretion associated with primary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities or fewer patients with ADRs or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group. There were no serious ADRs or laboratory abnormalities leading to treatment discontinuation in either group (the number of events not specified).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto in the treatment of dryness associated with primary Sjögren's syndrome.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nishizawa Y, Nishizawa Y, Goto GH, et al. The multicenter randomized comparative study of Kampo herbal medicine, mai-men-dong-tang (Japanese name bakumondo-to) compared with bromhexine on salivary secretion in secondary Sjögren's syndrome. *Itami to Kampo* (*Pain and Kampo Medicine*) 2004; 14: 10-7 (in Japanese with English abstract). Ichushi Web ID: 2006260917

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for treatment of secondary Sjögren's syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Three clinics and 3 university hospitals, Japan.

4. Participants

Eight-hundred and forty-seven patients with secondary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. before meals for 1 year (n=424).
Arm 2: bromhexine hydrochloride 4 g t.i.d. before meals for 1 year (n=423).

6. Main outcome measures

Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud's symptom, limb skin temperature.

7. Main results

The amount of salivation was increased in both arms but was significantly higher in the bakumondoto group. Among bakumondoto-treated patients, those with mild disease showed significantly larger increases, whereas those with severe disease showed larger percent increases. The amount of lacrimation was significantly increased only in the bakumondoto group. Only in the bakumondoto group, the following variables were also improved: dryness, Raynaud's symptom, joint pain, cough/amount of sputum, and lowered temperature of the limb skin.

8. Conclusions

Bakumondoto is more effective and safer than bromhexine hydrochloride and therefore beneficial for treatment of mouth dryness associated with secondary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not indicated).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto for the treatment of dryness associated with secondary Sjögren's syndrome. In the text, the dose of bromhexine hydrochloride was indicated as 120 mg, instead of the correct dose of 12 mg.
This paper seems to include data from the preliminary clinical trial published in *Nihon Daekisen Gakkaishi* (*Journal of the Japan Salivary Gland Society*) 2003; 44: 65-70.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Improving effect of Chinese herb medicine mai-men-dong-tang (Japanese name: bakumondo-to) comparative with sicca syndrome in especial salivary patients with secondary Sjögren's syndrome in multicenter, well controlled, long-term comparative study. *Nihon Daekisen Gakkaishi* (*Journal of the Japan Salivary Gland Society*) 2003; 44: 65-70.

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for treatment of dryness associated with secondary Sjögren's syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned, Japan.

4. Participants

Seven-hundred and fifty-six patients with secondary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. for 1 year (n=380).
Arm 2: bromhexine hydrochloride 4 g t.i.d. for 1 year (n=374).

6. Main outcome measures

Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud's symptom.

7. Main results

The amount of salivation was increased in both arms, but it was significantly higher in the bakumondoto group. The amount of lacrimation was significantly increased only in the bakumondoto group. The following outcome measures were also improved only in the bakumondoto group: dryness, Raynaud's symptom, joint pain, and cough/amount of sputum. The inflammatory reaction remained unchanged in both groups.

8. Conclusions

Bakumondoto is more effective and safer than bromhexine hydrochloride and therefore useful for treating dryness associated with secondary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not indicated).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto for treating dryness associated with secondary Sjogren's syndrome. The duration and dosage of bakumondoto treatment was correlated with the amount of salivation, suggesting a dose-dependent effect.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Ohno S. The effect of Kampo medicine on salivary secretion in Sjögren's syndrome. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2006; 15: 134-40 (in Japanese). Ichushi Web ID: 2006203175

1. Objectives

To evaluate the efficacy for Sjögren's syndrome.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Outpatient Department of Rheumatology, Samitama Medical University Hospital, Japan.

4. Participants

Sixty-four patients with Sjögren's syndrome.

5. Intervention

Arm 1: 4-week administration of Kampo medicine extracts that affect salivary secretion (3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules alone [n=23]; 3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules + 2.5 g t.i.d. of TSUMURA Rokumigan (六味丸) Extract Granules [n=3]; 3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules + 2.5 g t.i.d. of TSUMURA Hachimijiogan (八味地黄丸) Extract Granules [n=4]) according to *sho* (証, pattern) (n=32; after 2 dropped out, 30 included for analysis).

Arm 2: 4-week administration of 2.5 g t.i.d. of TSUMURA Hochuekkito (補中益気湯) Extract Granules (n=32; after 4 dropped out, 28 included for analysis).

6. Main outcome measures

Change in salivary secretion from pre- to post-administration, measured using a chewing gum test.

7. Main results

Twenty-seven out of 30 patients in arm 1 demonstrated increase in salivary secretion, with a significant increase in mean pre-treatment secretion of 8.2+1.2 mL to post-treatment average of 12.0+1.4 mL (P<0.005). There was no statistical significance between pre- and post-treatment secretions in arm 2. The amount of increase in salivary secretions before and after the treatment in arm 1 was significantly greater than arm 2 (P<0.005).

8. Conclusions

A Kampo medicine with moisturizing effect (but not a medicine without this effect) increases the amount of salivary secretion.

9. From Kampo medicine perspective

Arm 1 used "bensho (弁証)" (Kampo diagnosis) to allocate patients, specifically "jinkyo" (腎虚, kidney deficiency) which included 3 or more of the following 6 symptoms: 1) heaviness of the back; 2) heaviness in the lower legs with pain in heels and lateral surface of the lower legs; 3) tinnitus/hearing loss; 4) loss of hair and hair luster; 5) looseness or loss of teeth; and 6) sexual dysfunction (impotence, nocturnal emission). Kampo formulations for Arm 1 were selected based on the status of jinkyo: 1) bakumondoto alone for negative jinkyo; 2) bakumondoto plus rokumigan for jinkyo without chills; and 3) bakumondoto plus hachimijiogan for jinkyo with chills.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an interesting quasi-randomized controlled trial that is plausible for its attempt in incorporating "sho" (証) diagnosis for selection of treatment. Results from the trial demonstrated that bakumondoto, moisturizing formuala, with other Kampo forumalations comibination effectively enhanced salivary secretion in patients with Sjögren's syndrome than hochuekkito which was used as a control. A total of three pattern of combinations of Kampo formulation(s) were established for arm 1 based on various manifestations of jinkyo. 23 out of 30 patients (77%) in arm 1 received bakumondoto only. Future studies with improved RCT design and comparison with placebo or Western drug as a control appear warranted.

12. Abstractor and date

Namiki T, 17 March 2009, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. *Kampo to Saishin-Chiryo* (*Kampo & the Newest Therapy*) 2004; 13: 232-6 (in Japanese). Ichushi Web ID: 2004301321

1. Objectives

To evaluate the efficacy of hachimijiogan (八味地黄丸), goshajinkigan (牛車腎気丸), and shuchibushi (修治附子) powder for relief of residual symptoms after surgical treatment of cervical spinal stenosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-four patients with residual symptoms following surgical treatment of cervical spinal stenosis.

5. Intervention

Arm 1: 2-month administration of hachimijiogan (八味地黄丸).
Arm 2: 2-month administration of goshajinkigan (牛車腎気丸).
Arm 3: 2-month administration of goshajinkigan (牛車腎気丸) + 1.0 g of shuchibushi powder (修治附子末).

No between-arm difference was noted in operative effect. Administration started at postoperative 2 months in all arms.
No details in original paper.

6. Main outcome measures

Subjective symptoms (pain and paresthesia) evaluated on a visual analogue scale (VAS).

7. Main results

Pain was improved in 24.8%, 37.1%, and 45.5% of patients receiving hachimijiogan, goshajinkigan, and goshajinkigan + shuchibushi powder, respectively. The efficacy of goshajinkigan + shuchibushi powder was significantly higher than that of hachimijiogan. Paresthesia was improved in 21.4%, 24.2%, and 28.5%, respectively, showing no difference between arms.

8. Conclusions

Hachimijiogan, goshajinkigan, and goshajinkigan + shuchibushi powder are all effective for residual symptoms of surgically treated cervical spinal disease, with the highest efficacy achieved by goshajinkigan + shuchibushi powder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions (ADRs) or withdrawals occurred (the number of ADRs not indicated).

11. Abstractor's comments

This study provides evidence that Kampo formulations can be a therapeutic option for residual symptoms of surgically treated cervical spinal diseases. Given the higher efficacy at higher doses of shuchibushi, the authors infer that shuchibushi acts on opioid receptors.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Hayashi Y, Saito E, Takahashi O. Usefulness of hachimijiogan for lumbar spinal stenosis*. *Geriatric Medicine* 1994; 32: 585–91 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of hachimijiogan (八味地黄丸) for lumbar spinal stenosis.

2. Design

Quasi-Rrandomized controlled trial (quasi-RCT).

3. Setting

Not mentioned (the authors belong to the faculty of Tokyo Metropolitan Rehabilitation Hospital), Japan.

4. Participants

Twenty-seven patients with radiographically demonstrable spinal column stenosis and symptoms arising from compression of the sciatic nerve or its branches.

5. Intervention

Arm 1: oral administration of TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 7.5 g/day for 8 weeks (n=19).
Arm 2: oral administration of propionic acid (details unknown) for 8 weeks (n=8).

6. Main outcome measures

Subjective symptoms including lumbar pain on motion, lower limb tightness, and coldness; objective parameters including lower back tension, time from the start of walking to the occurrence of intermittent claudication, and fingertips-to-floor distance in patients bending forward; Kampo medicine findings including physical strength, complexion and hot flashes; hematology/urinalysis; measurements of bilateral tibial nerve F-wave latency, blood substance P concentration, and blood β-endorphin concentration.

7. Main results

All subjective symptoms were significantly improved in arm 1 compared with arm 2. Among objective variables, duration of intermittent claudication was significantly improved in arm 1 (P=0.03), but bilateral tibial nerve F-wave latency, blood substance P concentration, and blood β endorphin concentration were not changed significantly in either arm.

8. Conclusions

Hachimijiogan improves subjective symptoms, but not objective measures of spinal column stenosis.

9. From Kampo medicine perspective

Within arm 1, significantly more patients without "*hie*" (冷え, a feeling of coldness in the body) than those with moderate or severe "*hie*" responded (P=0.001).

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor's comments

This is an epoch-making clinical study that investigated the efficacy of hachimijiogan for spinal column stenosis using not only subjective symptoms but also objective measures. However, the introduction states that patients were randomly allocated but the method section states that patients were allocated to arm 1 and arm 2 in the order of hospital arrival time. In addition, since the analysis population consisted of 19 patients in arm 1 and 8 patients in arm 2, the method of randomization should be specified. Similarly, the dosage and method of administration of propionic acid used as control were not mentioned and should be specified since the paper says that proprionic acid was not effective for subjective symptoms. Nevertheless, this is an excellent attempt because not only subjective symptoms but also objective measures are used to evaluate efficacy. Increasing its sample size would improve this excellent clinical study.

12. Abstractor and date

Goto H, 13 September 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. *Kampo to Saishin-Chiryo* (*Kampo & the Newest Therapy*) 2004; 13: 232-6. Ichushi Web ID: 2004301321

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) and shuchibushi powder (修治附子末) for relief of chronic low back pain associated with lumbar spinal stenosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Eighty-nine patients with chronic low back pain associated with lumbar spinal stenosis for which surgery is not indicated.

5. Intervention

Arm 1: 3-month administration of western medicines including non-steroidal anti-inflammatory drugs (NSAIDs), prostaglandin E2, vitamin B12, and/or H2 blockers (n=29).
Arm 2: 3-month administration of goshajinkigan (牛車腎気丸) alone (n=30).
Arm 3: 3-month administration of goshajinkigan (牛車腎気丸) + 2.0 g of shuchibushi powder (修治附子末) (n=30).
No details indicated in the original paper.

6. Main outcome measures

Low back pain and lower limb paresthesia evaluated on a visual analogue scale (VAS).

7. Main results

Lower back pain score was decreased from 6.7, 6.5, and 6.8 to 3.5, 4.5, and 3.2 in arms 1, 2, and 3, respectively. Lower limb paresthesia score was decreased from 5.6, 5.7, and 5.9 to 4.2, 3.9, and 3.2, respectively. Thus, there were no significant between-arm differences in therapeutic effects.

8. Conclusions

Both oshajinkigan and shuchibushi powder are as effective as western medicines for the relief of chronic low back pain and lower limb paresthesia associated with lumbar spinal stenosis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions (ADRs) or withdrawals occurred in either arm (the number of ADRs not indicated).

11. Abstractor's comments

This study is of clinical significance since it provides evidence that Kampo medicines can be a therapeutic option for lumbar spinal stenosis, expanding the range of therapeutic options.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Tamakawa S, Ogawa H. The effect of shakuyaku-kanzo-to and goshakusan on lumbago. *Itami to Kampo* (*Pain and Kampo Medicine*) 1997; 7: 83-5 (in Japanese with English abstract).

1. Objectives

To evaluate the clinical effect of shakuyakukanzoto (芍薬甘草湯) on acute lumbago (so-called strained back).

2. Design

Randomized controlled trial (RCT).

3. Setting

Asahikawa Medical College and Pain Clinic of Wakkanai City Hospital (two institutions), Japan.

4. Participants

Seventy patients who visited the above institutions and were diagnosed with acute lumbago within 1 week after onset (44 males and 26 females).

5. Intervention

Arm 1: epidural block with 0.125% bupivacaine, acupuncture, and poultices + TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 g t.i.d. before meals for 2 weeks (n=35).

Arm 2: epidural block with 0.125% bupivacaine, acupuncture, and poultices for 2 weeks (n=35).

6. Main outcome measures

Improvement in subjective symptoms of lumbago assessed on a 3-point scale: marked remission of lumbago (marked response), improvement in daily living but with persistent pain (moderate response), and limitations in daily living despite remission of lumbago (no response).

7. Main results

In the shakuyakukanzoto arm, 10 patients had marked response and 18 had moderate response, while in the control arm, 8 had marked response and 12 had moderate response; there was no significant between-arm difference. However, only 7 patients in the shakuyakukanzoto arm and 15 in the control arm had no response. In this study, 5 patients with chronic lumbago who complained of *jokan-genetsu* (上寒下熱, upper body heat and lower body cold) (in terms of Kampo medicine) received goshakusan, which resulted in a marked response in 3 patients and a moderate response in 2 patients.

8. Conclusions

Shakuyakukanzoto was administered for strained back to relieve myotonia without *sho* (証, pattern) diagnosis（証診断）. Since shakuyakukanzoto seems to be effective, it can be used as a symptomatic treatment in clinical practice.

9. From Kampo medicine perspective

Shakuyakukanzoto, which has two flavors known as shiroshakuyaku (白芍薬) and kanzo (甘草), strongly relaxes smooth muscles.

10. Safety assessment in the article

No corticoid-like effects due to kanzo were experienced.

11. Abstractor's comments

This study took a Kampo medical approach to the treatment of strained back. Although epidural block with local anesthetics has been used for the treatment of strained back, its efficacy is inadequate in about half of patients whose symptoms are refractory. To improve efficacy, it can be combined with oral non-steroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs have GI adverse effects that may inevitably result in the drug withdrawal. To resolve these problems, authors applied the strong muscle-relaxing effects of shakuyakukanzoto. Fewer patients seemed to have no response in the shakuyakukanzoto group. This result is encouraging to clinicians because it indicates that shakuyakukanzoto (without being a treatment based on *sho*) provides some symptomatic relief. Unfortunately, patients treated with only epidural block, acupuncture, and poultices in the control group also had a marked response, and there was no between-group difference in the response rate. Consequently, this was a controlled study in which the control treatment might also be highly effective. A study of simpler design (e.g., a controlled trial with poultices) to confirm the clinical efficacy of shakuyakukanzoto is expected. In this paper, favorable treatment outcomes with goshakusan (五積散) given according to *sho* for patients with chronic lumbago were also described, so further studies on practical treatment with Kampo medicine for lumbago are expected.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 6 January 2010, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Ohta H, Makita K. Lumbago - with emphasis on nonspecific lumbago, which obstetricians and gynecologists think is the most common form in women -*. *Chiryo* (*The Journal of Therapy*) 1995; 77: 1646–57 (in Japanese). MOL, MOL-Lib

1. Objectives

To clinically evaluate the effects of keishibukuryogan (桂枝茯苓丸) and its combination with bushi (附子) on nonspecific lumbago in women during menopause.

2. Design

Randomized controlled trial (RCT).

3. Setting

One facility (currently the first author is affiliated with Outpatient Department for Climacteric Disorders, Tokyo Women's Medical University Hospital), Japan.

4. Participants

Thirty-seven female patients with lumbago.

5. Intervention

Arm 1: keishibukuryogan (桂枝茯苓丸) (manufacturer unknown) 2.5 g t.i.d. before meals for 3 months (n=14).

Arm 2: keishibukuryogan (桂枝茯苓丸) (manufacturer unknown) 2.5 g t.i.d. + crude drug shujibushimatsu (manufacturer unknown) 0.17 g t.i.d. before meals for 3 months (n=23).

6. Main outcome measures

Lumbago symptoms (4-point scale) evaluated after 12 weeks of treatment: complete response (increase of 2 or more points) and partial response (increase of 1 point).

7. Main results

Complete response and partial response were respectively achieved in 21.4% and 14.3% of patients receiving keishibukuryogan alone and 26.1% and 34.8% of patients receiving keishibukuryogan + shujibushimatsu.

8. Conclusions

Combining keishibukuryogan with shujibushimatsu improves nonspecific lumbago in women during menopause, indicating that a *kuoketsu* (駆オ血, blood stasis-expelling) Kampo medicine is clinically useful when combined with bushi, a crude drug with an analgesic/anti-inflammatory effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Nonspecific lumbago in women during menopause has various etiologies and is not unambiguously related to the presence of inflammation and impaired blood flow. To treat it, therefore, various measures should be tried. This study produced favorable results using a therapy combining bushi (a pain reliever and blood flow enhancer) with keishibukuryogan, which is used to treat *oketsu* (オ血, blood stasis), the most frequent pathology in women with climacteric unidentified complaints and a useful reference for many clinicians. It would be interesting to incorporate into the study protocol the theory of Kampo medicine, including choice of *kuoketsuzai* (駆オ血剤, blood stasis-expelling formula) according to the diagnosis of *oketsu* (オ血, blood stasis), and combination with bushimatsu taking the presentation of a feeling of coldness into consideration. A case series investigation incorporating the measurement of biomarkers is expected.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nakamura T, Souza ACA, Ouchi Y, et al. Effects of goshajinkigan on lumbago*. *Dai 4 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu* (*Proceedings of the 4th Meeting of the Tokyo Society for Internal Kampo Medicine*) 1989; 4: 24–9 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in comparison with that of tiaramide hydrochloride for lumbago in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One facility (Department of Geriatric Medicine, University of Tokyo Hospital), Japan.

4. Participants

Twenty-five elderly patients with lumbago visiting the above facility (3 males and 22 females; 60–87 years old).

5. Intervention

Arm 1: goshajinkigan (牛車腎気丸) (manufacturer, not specified) 2.5 g t.i.d. before meals (n=11).
Arm 2: tiaramide hydrochloride 100 mg t.i.d. after meals (n=7).
Arm 3: goshajinkigan (牛車腎気丸) (manufacturer, not specified) 2.5 g t.i.d. before meals + tiaramide hydrochloride 100 mg t.i.d. after meals (n=7).
Treatment duration: 4 weeks.

6. Main outcome measures

Improvement rating of subjective symptoms including lumbago evaluated on a 4-point scale.

7. Main results

Goshajinkigan was effective for lumbar numbness and stiffness, while tiaramide hydrochloride was effective for lumbago and irradiating pain at rest (no test for significance of the difference). Goshajinkigan had an equivalent or greater effect than tiaramide hydrochloride on reducing pain while rising to a standing position from sitting, anteflexion, retroflexion, and rolling over (no test for significance of the difference). Severity of lumbago was improved in all groups, although there was no significant among-arm difference in this improvement.

8. Conclusions

In the elderly with lumbago, goshajinkigan is equally or more effective than tiaramide hydrochloride for pain during movement but not effective for pain at rest.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions occurred in 2 patients receiving goshajinkigan (discomfort [n=1]; administration discontinued] and anorexia [n=1]) and 1 patient receving tiaramide hydrochloride (anorexia). However, anorexia disappeared during continued administration.

11. Abstractor's comments

Goshajinkigan has traditionally been reported to be effective in the elderly for lumbago, which has a pathology of *jinyokyo* (腎陽虚, kidney *yang* deficiency). This study demonstrated that goshajinkigan and a Western medicine with established efficacy have comparable efficacy. The small sample size regrettably prevented sufficient group comparison in this study. Future case series are expected to include investigation of the influence of *sho* (証, pattern).

12. Abstractor and date

Ushiroyama T, 16 August 2008, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Wang XD, Yoshida K, Honda K, et al. Study of the immunoregulatory activity of the combination therapy with juzentaihoto and hachimijiogan in patients with disuse syndrome*. *Kampo Igaku* (*Kampo Medicine*) 2006; 30: 65-7 (in Japanese). Ichushi Web ID: 2006283912

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯) combined with hachimijiogan (八味地黄丸) in patients with disuse syndrome.

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

One community hospital, Japan.

4. Participants

Patients after a prolonged period of bed rest and tube feeding.

5. Intervention

Arm 1: Tsumura Juzentaihoto (十全大補湯) Extract Granules and Tsumura Hachimijiogan (八味地黄丸) Extract Granules 2.5 g b.i.d. each for 24 weeks, n=13.
Arm 2: No administration of Kampo drugs, n=15.

6. Main outcome measures

Laboratory tests: hemograms and urine tests performed at 0, 4, 8, 12, 16, 20, and 24 weeks.
CD4 count, CD8 count, CD4/CD8 ratio, neutrophil phagocytotic activity, levels of immunoglobulins (IgM, IgG, and IgA) examined at 0, 12, and 24 weeks.

7. Main results

CD4/CD8 ratio and CD4 count were significantly increased in arm 1 compared to arm 2 at 12 weeks; however, no significant difference was observed at 24 weeks. There were no significant between-arm differences in the results of other tests.

8. Conclusions

In many cases, CD4/CD8 ratio and CD4 count are elevated at 12 weeks of administration.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Immunoregulatory effect of the combination two Kampo drugs was assessed using lymphocyte surface markers CD4 and CD8. The finding of significant increases in CD4/CD8 ratio and CD4 count at 12 weeks, but not at 24 weeks, demands the conduct of further studies designed to reveal whether immune status was restored or regulated.

12. Abstractor and date

Namiki T, 12 March 2009, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Nakajima K, Sato H, Ooyama K, Is maobushisaishinto effective for neuropathic pain? Effect of maobushisaishinto on occipital neuralgia* *Itami to Kampo* (*Pain and Kampo Medicine*) 2014: 24: 31-7 (in Japanese with English abstract). Ichushi Web ID: 2015016097

1. Objectives

To evaluate the efficacy of maobushisaishinto (麻黄附子細辛湯) for treatment of occipital neuralgia.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

Three clinics, Japan.

4. Participants

Twenty-two patients with occipital neuralgia who visited three clinics between November 2011 and April 2012, a total of 6 months.

5. Intervention

Arm 1: TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules administered at 2.5 g t.i.d. before or between meals (n=12).

Arm 2: A loxoprofen tablet administered orally at a dose of 60 mg up to three times daily (n=10).

The longest treatment period was 21 days in both Arms 1 and 2. Treatment was discontinued if the patient's pain disappeared or if an adverse drug reaction occurred.

6. Main outcome measures

Treatment period. Pain assessed on a visual analogue Scale (VAS). A subject who reported a change in VAS value of 50 mm or more within 1 week of the last dose was regarded as "very responsive"; 50 mm or more 8 or more days after the last dose or of 20–49 mm, as "responsive"; and of 20 mm or less, as "nonresponsive."

7. Main results

No significant inter-arm difference was found for treatment period. The VAS value was 51.8±16.1 mm (standard deviation: SD) before treatment and 7.8±14.3 mm (SD) after treatment in the maobushisaishinto arm, showing a significant decrease (P=0.0001 in the U-test), and 56.0±19.6 mm (SD) before treatment and 10.1±17.5 mm (SD) after treatment in the loxoprofen arm, showing a significant decrease (P=0.0001 in the U-test). The number of subjects assessed as very responsive, responsive, and nonresponsive was 4, 7, and 1 to maobushisaishinto, and 5, 4, and 1 to loxoprofen, respectively.

8. Conclusions

Maobushisaishinto is effective for the treatment of occipital neuralgia.

9. From Kampo medicine perspective

The relationship between the efficacy of maobushisaishinto and *kan-sho* (寒証, cold pattern) was not found.

10. Safety assessment in the article

No description of adverse drug reactions were provided. Since discontinuation due to adverse drug reactions was not mentioned, there seemed to be no adverse responses.

11. Abstractor's comments

This study is very meaningful from the standpoint of clinical practice because it was a randomized controlled clinical trial using envelopes for allocation and evaluated the efficacy of maobushisaishinto for treatment of occipital neuralgia, as compared with loxoprofen. An evaluation of the outcomes suggests that maobushisaishinto has a similar or higher efficacy than loxoprofen. Considering the randomized controlled design of the trial, it is regrettable that the statistical procedures used to analyze between-arm differences were insufficient. In the Kampo medicine perspective section, the authors suggested that the diagnosis of *hyo-sho* (表証, exterior pattern) was appropriate in study subjects because the disease period was short (around 10 days).However, most occipital neuralgia lesions generally are considered to be appeared on the exterior surface of the body. Given these, further evaluation in a larger number of subjects is anticipated.

12. Abstractor and date

Kogure T, 31 March 2017.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Ohta H, Nemoto K. Combined effect of vitamin D_3 and TSUMURA Keishibukuryogan on osteopenia following oophorectomy*. *Kampo Igaku* (*Science of Kampo Medicine*) 1989; 13: 173–9 (in Japanese).

1. Objectives

To evaluate the combined effect of keishibukuryogan (桂枝茯苓丸) and vitamin D3 on osteopenia in women during menopause.

2. Design

Randomized controlled trial (RCT).

3. Setting

One facility (Department of Obstetrics and Gynecology, Tokyo Electric Power Hospital), Japan.

4. Participants

Thirty patients diagnosed with osteopenia following oophorectomy at the above facility, with a total bone mineral density (MD) score of 4 or more points.

5. Intervention

Arm 1: oral TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals + α-calcidol 0.5 μg b.i.d. after meals (n=6).

Arm 2: oral α-calcidol 0.5 μg b.i.d. after meals (n=6).

Arm 3: oral α-calcidol 0.5 μg b.i.d. after meals + Premarin 0.625 mg q.d. after meals or Metharmon F tablet t.i.d. after meals (n=7).

Arm 4: follow-up without drug administration (n=11).

6. Main outcome measures

Change in MD (mean percentage change in actual values of 5 variables: bone cortex width index, bone marrow width, bone cortex and marrow integrated density index, bone cortex density index, and bone density per unit length) compared between baseline and after 10 months of treatment.

Serum concentration of bone metabolic markers (alkaline phosphatase [AL-P], calcium [Ca], and phosphate [P] compared between baseline and after 10 months of treatment).

7. Main results

Combination of keishibukuryogan and vitamin D3 significantly increased bone mineral content compared with baseline ($P<0.05$), vitamin D3 alone, and no drug administration ($P<0.05$) and significantly increased serum AL-P and Ca concentrations ($P<0.05$). The hormones increased serum Ca concentration ($P<0.05$).

8. Conclusions

Combination of keishibukuryogan and vitamin D3 decreased osteopenia in women without ovaries.

9. From Kampo medicine perspective

Keishibukuryogan controlled mental and physical disorders associated with ovarian deficiency syndrome consisting of *qi-no-josho* (気の上衝, *qi* counterflow pattern syndrome), *oketsu* (オ血, blood stasis), and *suidoku* (水毒, water toxin), resulting in increases in appetite, and consequently Ca intake, intestinal absorption and motility, which may have indirectly increased bone mineral content.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

A representative *kuoketsuzai* (駆オ血剤, blood stasis-expelling formula), keishibukuryogan improves *suidoku* and *qitai* (気滞, *qi* stagnation) and is therefore frequently used for treatment of unidentified complaints in postmenopausal women. This study demonstrated that use of vitamin D3 as an adjuvant increases bone mineral content in patients following ovariectomy. Given that long-term intervention is needed to prevent and treat osteoporosis, a Kampo therapy such as keishibukuryogan can be optimal. However, the need for keishibukuryogan in therapy according to *sho* (証, pattern) of postmenopausal women with unidentified complaints, most whom have *kyosho* (虚証, deficiency pattern), should be investigated.

12. Abstractor and date

Ushiroyama T, 16 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Ohta H, Nemoto K. Preventive effect of 1α-hydroxyvitamin D_3 plus Kampo medicine combination therapy on osteopenia following oophorectomy - comparison between keishibukuryogan and tokishakuyakusan -*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 1990; 7: 65–70 (in Japanese).

1. Objectives

To evaluate the combined effect of keishibukuryogan (桂枝茯苓丸) or tokishakuyakusan (当帰芍薬散) and vitamin D3 on osteopenia in women during menopause.

2. Design

Randomized controlled trial (RCT).

3. Setting

One facility (Department of Obstetrics and Gynecology, Tokyo Electric Power Hospital), Japan.

4. Participants

Thirty patients diagnosed with osteopenia following oophorectomy at the above facility, with a total bone mineral density (MD) score of 4 or more points.

5. Intervention

Arm 1: oral α-calcidol 0.5 μg b.i.d. after meals (n=6).
Arm 2: oral α-calcidol 0.5 μg b.i.d. after meals + TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals (n=6).
Arm 3: oral α-calcidol 0.5 μg b.i.d. after meals + TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals (n=6).
Arm 4: follow-up without drug administration (n=12).

6. Main outcome measures

Change in MD (mean percentage change in actual values of 5 variables: bone cortex width index, bone marrow width, bone cortex and marrow integrated density index, bone cortex density index, and bone density per unit length) compared between baseline and after 10 months of treatment.

7. Main results

Bone mineral content was significantly higher in arm 2 than in arm 1 and arm 4 ($p<0.05$), but similar to that in arm 3. Bone cortical width index was higher, although not significantly, in arm 3 than in arms 1 and 4.

8. Conclusions

Combination of keishibukuryogan and vitamin D3 decreases osteopenia in women without ovaries and seems to improve osteopenia.

9. From Kampo medicine perspective

These Kampo medicines controlled mental and physical disorders associated with ovarian deficiency syndrome consisting of *qi-no-josho* (気の上衝, *qi* counterflow pattern syndrome), *oketsu* (オ血, blood stasis), and *suidoku* (水毒, water toxin), resulting in increases in appetite, and consequently Ca intake, intestinal absorption and motility, which may have indirectly increased bone mineral content. The higher efficacy of keishibukuryogan is attributable to its keishi and botanbi components, which may improve bone metabolism via PGE2- and cytokine-mediated immunostimulation.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study demonstrated that use of vitamin D3 as an adjuvant increases bone mineral content in patients following ovariectomy. The study results suggested that keishibukuryosan administered to those with *jitsusho* (実証, excess pattern), and tokishakuyakusan administered to those with *kyosho* (虚証, deficiency pattern), can be used for prevention and treatment of osteoporosis, greatly contributing to climacteric and geriatric medicine. Although the slightly higher efficacy of keishibukuryogan is pharmacologically discussed from the perspective of Kampo components in this study, it is desirable that future studies use a protocol that reflects the mechanism of bone metabolism and bone substance improvement from the perspective of Kampo theory.

12. Abstractor and date

Ushiroyama T, 16 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue

Reference

Kanai S. The effect of kami-kihi-to on the maintenance of bone mass in patients with osteoporosis. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1998; 49: 59-66 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the effects of kamikihito (加味帰脾湯) on menopause index, bone mass, and anemia in postmenopausal women with osteoporosis.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Research Institute of Oriental Medicine, Kinki University, Japan.

4. Participants

Eighty-three women (aged 59–84 years) who visited the above institution, were diagnosed with osteoporosis according to the criteria for osteoporosis by the Ministry of Health and Welfare (currently the Ministry of Health, Labour, and Welfare), and had been followed for two years since 1993.

5. Intervention

Arm 1: oral administration of alfacalcidol (1 μg) once daily after breakfast and zaltoprofen 80 mg t.i.d. after meals.

Arm 2: oral administration of kamikihito (加味帰脾湯) (manufacturer, not specified) 2.5 g t.i.d. after meals and zaltoprofen 80 mg t.i.d. after meals.

Arm 3: oral administration of zaltoprofen 80 mg t.i.d. after meals.

All treatments were administered for 2 years.

6. Main outcome measures

Bone density measured by Computed X-ray Densitometry (CXD), cytometry, and efficacy based on Simplified Menopausal Index (SMI) score before treatment and at 1 and 2 years after the start of treatment.

7. Main results

As compared with bone mass in arm 1, bone mass in arm 2 and arm 3 increased significantly after 1 year of treatment ($P<0.05$). However, after 2 years, bone mass was further increased in arm 1, but remained stable in arm 2. Red blood cell and reticulocyte counts increased significantly after 1 year in arm 2 compared with arm 3 ($P<0.05$), but their increases were stabilized after 2 years. SMI decreased significantly after 1 year in arm 2, as compared with arms 1 and 3 ($P<0.05$). A weak but significant positive correlation between changes in bone mass and SMI was observed ($P<0.05$). In patients with increased bone mass and treated with kamikihito, compared with patients with decreased bone mass, SMI decreased and anemia improved.

8. Conclusions

Treatment of osteoporosis with kamikihito in women is clinically effective in increasing bone mass, as well as in improving anemia and decreasing SMI.

9. From Kampo medicine perspective

Kampo prescription was not based on *sho* (証, pattern). Kamikihito seemed to exert its effects by improving general physical status which resulted in increased energy in individual patients, and subsequent increase in bone density.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Kamikihito has been conventionally prescribed for nonspecific climacteric symptoms or for improving anemia and its effects are also apparent in the present study. Its bone density-increasing effect appears to be about half of that of vitamin D. However, clinical application of kamikihito for osteoporosis in postmenopausal women is strongly expected. According to a number of osteoporosis-related studies, the effect of vitamin D varies greatly among individuals. It is currently understood that vitamin D preserves but does not increase bone mass. Therefore a multidrug approach with kamikihito would be more desirable for the therapy of osteoporosis. A case series study examining the combined therapy with western medicines is expected.

12. Abstractor and date

Ushiroyama T, 20 August 2008, 6 January 2010, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Yoshikawa N, Ito H, Sakai T, et al. A prospective controlled study of sairei-to in childhood IgA nephropathy with focal/minimal mesangial proliferation. *Nihon Jinzo Gakkaishi* (*The Japanese Journal of Nephrology*) 1997; 39: 503-6 (in Japanese with English abstract). CENTRAL ID: CN-00143175, Pubmed ID: 9283216

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) in childhood IgA nephropathy with focal/minimal mesangial proliferation.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Departments of Health Science of Kobe University School of Medicine, Kidney Center of Kitasato University Hospital, Department of Pediatrics of Hokkaido University, etc. (a total of 29 institutions including 16 university hospitals and 9 departments of pediatrics), Japan.

4. Participants

One hundred and one patients aged 15 or under with newly diagnosed IgA nephropathy with focal/minimal mesangial proliferation.

5. Intervention

Arm 1: administration of TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. (body weight ≥40 kg), 3.0 g b.i.d. (body weight 20–40 kg), or 1.5 g b.i.d. (body weight ≤20 kg) for two years (n=50).
Arm 2: no treatment (n=51).

6. Main outcome measures

Daily urinary protein excretion, hematuria in morning urine, and renal function (blood urea nitrogen, serum creatinine, creatinine clearance, etc) at the start and end of treatment.

7. Main results

At the end of the trial, mean daily urinary protein excretion was significantly decreased from the initial 0.39±0.31 g/day to 0.25±0.21 g/day in the 46 patients included for analysis in arm 1(P=0.005), while it remained unchanged in the 48 patients included for analysis in arm 2 (0.41±0.48 g/day *vs.* 0.43±0.56 g/day). Hematuria in the morning urine was also significantly attenuated after two years of the trial in arm 1 (from 2.3±1.0 to 1.0±1.1) (P<0.0001), but was not decreased in arm 2 (from 2.1±1.1 to 1.8±1.2). Urinary findings became normal in 46% of arm 1 and 10% of arm 2, showing significant difference between arms (P<0.001).

8. Conclusions

Saireito is effective for childhood IgA nephropathy with focal/minimal mesangial proliferation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor's comments

Although in Japan randomization by the RCT-envelope method tends not to be maintained, the present study suggests the efficacy of saireito for early treatment of childhood IgA nephropathy with focal/minimal mesangial proliferation. It is interesting that urinary findings were normalized in 46% of patients.

12. Abstractor and date

Okabe T, 22 August 2008, 6 January 2010, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Saruta T, Konishi K. Efficacy of Kampo medicines for renal diseases - with emphasis on saireito -*. *21 Seiki no Iryo to Kampo* (*The 21st Century Medicine and Kampo*) 1994: 157–65 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) for IgA nephropathy in adults.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Internal Medicine, Keio University School of Medicine and related facilities, Japan.

4. Participants

Forty-four patients with IgA nephropathy, aged ≥ 16 years.

5. Intervention

Arm 1: saireito (柴苓湯) (manufacturer not specified) 3 g t.i.d. for 24 weeks (n=22).
Arm 2: dilazep hydrochloride 100 mg t.i.d. for 24 weeks (n=22).

6. Main outcome measures

Urinary protein excretion, RBC count in urinary sediment, and creatinine clearance.

7. Main results

The mean urinary protein excretion for the analysis population of arm 1 (13 patients) was significantly decreased from 2.1±0.4 g/day at baseline to 1.5±0.3 g/day at 24 weeks after administration (P<0.01) but not for the analysis population of arm 2 (12 patients; 2.2±0.7 g/day at baseline and 1.9±0.4 g/day at 24 weeks). There were no significant changes in serum albumin concentration, cholesterol level, or creatinine clearance.

8. Conclusions

Saireito decreases urinary protein excretion in adult patients with IgA nephropathy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions in either arm.

11. Abstractor's comments

Although using sealed envelopes for allocation is likely to have compromised randomization, this study suggested that saireito decreases urinary protein excretion in adult patients with IgA nephropathy. A future randomized controlled trial should be performed with larger sample size and improved allocation.

12. Abstractor and date

Okabe T, 25 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Yoshikawa N, Ito H, Takekoshi Y, et al. Standard versus long-term prednisolone with sairei-to for initial therapy in childhood steroid-responsive nephrotic syndrome: A prospective controlled study. *Nihon Jinzo Gakkaishi* (*The Japanese Journal of Nephrology*) 1998; 40: 587-90 (in Japanese with English abstract). CENTRAL ID: CN-00158912, Pubmed ID: 9893457, Ichushi Web ID: 1999105890

1. Objectives

To evaluate the efficacy of initial steroid therapy with saireito (柴苓湯) for preventing relapse in childhood steroid-responsive nephrotic syndrome.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Departments of Health Science of Kobe University School of Medicine, Department of Pediatrics of Hokkaido University, Department of Pediatrics of Keio University School of Medicine, and others (a total of 35 institutions), Japan.

4. Participants

Two hundred and twenty-one patients diagnosed with childhood-onset minimal change nephrotic syndrome based on clinical features, and not manifesting persistent hematuria, renal dysfunction, and hypertension at onset.

5. Intervention

Arm 1: prednisolone 2 mg/kg/day in three divided doses for 4 weeks followed by prednisolone 1.3 mg/kg every other day for 4 weeks (n=109).

Arm 2: prednisolone 2 mg/kg/day in three divided doses for 4 weeks followed by prednisolone 2 mg/kg every other day for 8 weeks, 1.5 mg/kg every other day for 2 weeks, 1 mg/kg every other day for 2 weeks, and 0.5 mg/kg every other day for 2 weeks (n=112).

Kanebo Saireito (柴苓湯) Extract Fine Granules were administered in doses of 2.7 g t.i.d. (in all patients weighing ≥40 kg), 2.7 g b.i.d. (in all patients weighing 20–40 kg), or 1.35 g b.i.d. (in all patients weighing ≤20 kg).

6. Main outcome measures

The rates of relapse and frequent relapse.

7. Main results

Eighty-eight of 109 patients in arm 1 and 83 of 112 in arm 2 with steroid-responsive nephrosis were followed for 2 years. There were no between-arm differences in the rate of relapse and rate of frequent relapse (70% *vs.* 65% and 21% *vs.* 24%, respectively).

8. Conclusions

The duration of the initial steroid therapy with saireito for childhood steroid-responsive nephrotic syndrome has no effect on relapse rate.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects included mild liver dysfunction in 1 patient treated with steroid for 8 weeks, and allergic cystitis in 1 patient treated with steroid for 18 weeks. Both effects were reversed with drug withdrawal.

11. Abstractor's comments

Although in Japan randomization by the RCT-envelope method tends not to be maintained, in the present study, the relapse rates did not differ between 8-week and 18-week treatments with steroid and saireito. As the authors mentioned, the rate of frequent relapse is lower in their study (21% in arm 1) than in other reports examining a short-term steroid treatment similar to that used in arm 1 (35–40%). Comparison with a treatment without saireito may be needed to confirm this observation. A randomized controlled trial using other methods of random allocation is also expected.

12. Abstractor and date

Okabe T, 25 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Kinoshita H, Kanaya H, Yamamoto S, et al. Effects of Chinese herbal medicine in promoting the spontaneous discharge of upper urinary tract stones after ESWL. *Nishinihon Hinyokika* (*The Nishinihon Journal of Urology*) 1993; 55: 61–6 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of choreitogoshimotsuto (猪苓湯合四物湯) + shakuyakukanzoto (芍薬甘草湯) for promoting the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Sixty-one postoperative patients undergoing extracorporeal shock wave lithotripsy for upper urinary tract stones (72 stones).

5. Intervention

Arm 1: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 5 g/day + TSUMURA Choreitogoshimotsuto (猪苓湯合四物湯) Extract Granules 7.5 g/day for at least 3 months, 35 stones.

Arm 2: no administration, 37 stones.

6. Main outcome measures

Cumulative stone clearance rate.

7. Main results

The cumulative stone clearance rate at 30 and 90 postoperative days was significantly higher in arm 1 (65.7% and 82.9%, respectively) than in arm 2 (47.2% and 61.1%, respectively; $P<0.05$) and higher in the renal pelvis/calyx and uteropelvic junction of arm 1 than in the renal pelvis/calyx and uteropelvic junction of arm 2.

8. Conclusions

The choreitogoshimotsuto + shakuyakukanzoto combination promotes the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor's comments

This study suggests the efficacy of choreitogoshimotsuto + shakuyakukanzoto for promoting the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy. RCT using the *zuisho* (随証, based on pattern) approach to Kampo medicine may verify even higher efficacy. Future studies are expected.

12. Abstractor and date

Okabe T, 26 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Kobayashi M, Naya Y, Kino M, et al. Low dose tamsulosin for stone expulsion after extracorporeal shock wave lithotripsy: Efficacy in Japanese male patients with ureteral stone. *International Journal of Urology* 2008; 15: 495-8. Ichushi Web ID: 2008254384

1. Objectives

To evaluate the efficacy of low-dose tamsulosin and choreito (猪苓湯) for stone expulsion after extracorporeal shock wave lithotripsy (ESWL) in patients with ureteral stones.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two departments of urology: one in Chiba University Hospital and one in another hospital, Japan.

4. Participants

One hundred and two patients with ureteral stones measuring at least 4 mm in diameter who underwent ESWL.

5. Intervention

Arm 1: tamsulosin 0.2 mg/day from post-ESWL day 1 to stone expulsion (n=38).
Arm 2: TSUMURA Choreito (猪苓湯) 7.5 g/day from post-ESWL day 1 to stone expulsion (n=30).
Arm 3: no treatment (n=34).

6. Main outcome measures

Stone clearance was evaluated using abdominal plain radiography and ultrasonography.

7. Main results

The stone-free rate was 84.21%, 90%, and 88.24% for arms 1, 2, and 3, respectively; there were no significant differences. The time to stone expulsion was 15.55±6.14 days, 27.74±25.36 days, 35.47±53.70 days, for arms 1, 2, and 3, respectively. The time to expulsion was significantly shorter in arm 1 than in arm 2 (P=0.0116) or arm 3 (P=0.0424), while there was no significant difference between arms 2 and 3 (P=0.4982).

8. Conclusions

Tamsulosin treatment after ESWL appears to reduce the time to expulsion of ureteral stones.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study demonstrated the efficacy of tamsulosin, an α1-receptor blocker, for reducing time to expulsion of ureteral stones after ESWL. Choreito, which is thought to enhance clearance of ureteral stones by increasing urine output, on the other hand, had no effect. Previous similar studies have reported a significant reduction in time to expulsion by choreito treatment. Further studies including a larger number of patients are needed to evaluate the effects of choreito.

12. Abstractor and date

Okabe T, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Nishizawa Y, Nishizawa Y, Yoshioka H, et al. Efficacy and safety of Chinese traditional medicine, niu-che-shwn-qi-wan (Japanese name: goshajinki-gan) versus propiverine hydrochloride on health-related quality of life in patients with overactive bladder in prospective randomized comparative study. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2007; 16: 131-42 (in Japanese). Ichushi Web ID: 2007260946

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) and propiverine hydrochloride for overactive bladder.

2. Design

A randomized controlled trial (RCT).

3. Setting

Not mentioned (authors belong to Nishizawa Clinic, Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine and Department of Anesthesiology, Shiga University of Medical Science), Japan.

4. Participants

Seven hundred and four patients with overactive bladder, aged 45 years or older, prospectively enrolled over a 10-year period (1997–2006).

5. Intervention

Arm 1: administration of goshajinkigan (牛車腎気丸) (manufacturer not specified), 4.5 g/day, for 1 year (n=352).
Arm 2: administration of propiverine hydrochloride, 60 mg/day, for 1 year (n=352).

6. Main outcome measures

Symptoms of overactive bladder (urge to urinate, daytime urinary frequency, nocturia, and urine leak).
Quality of life (pain, erection dysfunction, cold sensation, etc.).

7. Main results

Symptoms of overactive bladder were significantly more improved in arm 2 than in arm 1 during the first month after treatment initiation, but significantly more improved in arm 1 than arm 2 during the second and subsequent months. At the completion of the study, the other concomitant symptoms and quality of life (QOL) were also significantly more improved in arm 1 than in arm 2.

8. Conclusions

It is suggested that goshajinkigan is effective for overactive bladder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Four and 375 events of adverse drug reactions occurred in arm 1 and arm 2, respectively.

11. Abstractor's comments

This 1-year prospective randomized controlled trial in 704 patients suggests the efficacy of goshajinkigan for overactive bladder. Its efficacy for concomitant symptoms and QOL was also suggested. However, there is no mention of the number patients who withdrew, the facility or facilities where this trial was actually conducted, and the method of randomization. Future studies considering these points are awaited.

12. Abstractor and date

Okabe T, 28 November 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Oh-oka H. Effect of Saireito for Prevention and Improvement of Urethral Stricture after Transurethral Resection of the Prostate. *Kampo Medicine* 2016; 67: 244-50 (in Japanese with English abstract). Ichushi Web ID: 2017003685, J-STAGE

1. Objectives

To evaluate the preventive effect of saireito (柴苓湯) on postoperative urethral stricture.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital.

4. Participants

Prostatic hyperplasia patients (142) without overactive bladder, who underwent TUR-P between April 2011 and March 204; received lifestyle guidance at initial consultation, including instruction on fluid intake and sleep hygiene; and were administered an α-blocker as drug therapy. Times since diagnosis ranged from 3.5 to 5.5 (mean 4.3) years, and ages were 68 to 85 (mean 75.5) years.

5. Intervention

Arm 1: Saireito (柴苓湯) administration group (n=70)
Saireito (1g t.i.d before meals for 3 months) from first intake after TUR-P surgery
Arm 2: No administration group (n=72)

6. Main outcome measures

Primary outcome measures examined include preventive effect on urethral stricture after TUR-P surgery; the clinically verified effect of saireito on postoperative urethral stricture; and clinical utility when administering and when not administering saireito in patients who meet and who don't fit the "pattern" indicated for saireito, defined as depressed liver qi transforming into fire, spleen qi deficiency, and water retention.

7. Main results

1) Saireito administration significantly reduced the occurrence of postoperative urethral stricture (P=0.043).
2) Improvement was observed after saireito administration for urethral stricture in 5 out of 8 participants in the no administration group.
3) Comparison of the group without the non-saireito pattern and without medication, with the group with the saireito pattern and with medication showed significantly lower frequency of urethral stricture in the latter (P=0.042).

8. Conclusions

Saireito administration after TUR-P surgery prevents postoperative urethral stricture and its improvement of stricture in clinically ascertained postoperative urethral stricture is acknowledged. It is acknowledged as having most effectiveness for saireito pattern patients.

9. From Kampo medicine perspective

During and after TUR-P, patients are considered to exhibit a half-exterior half-interior pattern; the heat-clearing action of saiko with ogon and the anti-inflammatory action of ogon with bukuryo, also medical insults such as the water dampness caused by perfusate arising from endoscopic surgery, and the urethral ischemia, etc. attributable to resectoscope are considered factors causing postoperative urethral stricture; so saireito, which combines the properties of goreisan, which has a diuretic effect, with shosaikoto, promises effects for postoperative urethral stricture.

10. Safety assessment in the article

The compliance rate across all patients was 88-100% (mean 95%), and there was no dropout due to adverse effect.

11. Abstractor's comments

This is an interesting clinical study designed to clarify the effects of saireito on postoperative urethral stricture. There was 1 clinically verified case of postoperative urethral stricture in the saireito group, and 8 in the no administration group, and the number of confirmed postoperative strictures was significantly smaller in the postoperative saireito administration group, which suggests that saireito administration is a very useful therapy. Hopefully future research will accumulate additional cases and further yield results that take "patterns" into account, and the results from treatment period, etc.

12. Abstractor and date

Kato Y, 18 May 2020.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Toba K. Role in host defense mechanisms and effect on prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation. *Taisha* (*Metabolism and Disease*) 1992; 29 suppl: 350–4 (in Japanese).

Toba K. Role in host defense mechanisms and effect on the prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation*. *Dai 8 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu* (*Proceedings of the 8th Meeting of the Tokyo Society for Internal Kampo Medicine*) 1993; 8: 31–42 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for improving immunity in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (Department of Geriatric Medicine, Faculty of Medicine, University of Tokyo), Japan.

4. Participants

Seventeen outpatients without urinary tract infection and 14 inpatients with urinary tract infection.

5. Intervention

Arm 1: shosaikoto (小柴胡湯) (manufacturer not specified) for at least 3 months, outpatients without urinary tract infection (n=9).
Arm 2: no administration, outpatients without urinary tract infection (n=8).
Arm 3: shosaikoto (小柴胡湯) (manufacturer not specified) for at least 3 months, inpatients with urinary tract infection (n=10).
Arm 4: no administration, inpatients with urinary tract infection (n=4).

6. Main outcome measures

Neutrophil function, lymphocyte function, nutritional index, and infection index.

7. Main results

In arm 1, significant increases from baseline were noted in neutrophil superoxide generation at 1 month post-dose ($P<0.05$), complement at 3 months post-dose ($P<0.01$), [3H]-thymidine incorporation of phytohemagglutin (PHA)-induced lymphocytes at 3 months post-dose ($P<0.01$), interleukin-2 production ($P<0.05$), serum γ-globulin, IgA ($P<0.01$), and IgG ($P<0.05$). In arm 3, none of the following variables were increased from baseline after shosaikoto administration: neutrophil superoxide generation, complement, [3H]-thymidine incorporation of PHA-induced lymphocytes, interleukin-2 production, and γ-globulin, and the urinary bacterial culture findings were similar before and after shosaikoto administration. In arm 1 and arm 2, none of the nutritional indices (serum total protein, albumin, cholinesterase, total cholesterol) were significantly increased.

8. Conclusions

Shosaikoto partially improves immunity in elderly individuals without urinary tract infection.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor's comments

Although using sealed envelopes for allocation is likely to have compromised randomization, this study concluded that shosaikoto partially improves immunity in elderly subjects without urinary tract infection but not in those with urinary tract infection. It was also suggested that shosaikoto does not improve nutritional status. As pointed out by the author, inpatients with urinary tract infection have poor nutritional status (i.e., decreased serum albumin), which is unresponsive to shosaikoto treatment. This may be an indication for *hozai* (補剤, formulations with tonic effects) using the *zuisho* (随証, based on pattern) approach.

12. Abstractor and date

Okabe T, 26 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Ohkawa T, Ebisuno S, Watanabe T. Urological diseases and Kampo medicine*. *Dai 23 Kai Nihon Igakkai Sokai Sateraito Shinpojiumu Nihon Toyo Igakkai Rinsho Kampo Kenkyukai Koen Naiyo Shu* (*Proceedings of the Meeting for Clinical Kampo Medicine of the Japan Society for Oriental Medicine, the Satellite Symposium of the 23rd General Assembly of the Japan Medical Congress*) 1992: 22–39 (in Japanese).

1. Objectives

To evaluate the efficacy of choreito (猪苓湯) and choreitogoshimotsuto (猪苓湯合四物湯) for relieving nonspecific lower urinary tract complaints.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (Department of Urology, Wakayama Medical University), Japan.

4. Participants

Three-hundred and sixty-four patients with nonspecific lower urinary tract complaints.

5. Intervention

Arm 1: choreito (猪苓湯) (manufacturer not specified) for 4 weeks (n=150).
Arm 2: choreitogoshimotsuto (猪苓湯合四物湯) (manufacturer unknown) for 4 weeks (n=152).
Arm 3: placebo for 4 weeks (n=61).

6. Main outcome measures

Incomplete emptying, voiding discomfort, nocturnal urinary frequency, and voiding pain.

7. Main results

The analysis population consisted of 137, 134, and 50 patients in arm 1, arm 2, and arm 3, respectively. Nonspecific complaints were quantified by scoring incomplete emptying and other symptoms. Relief of nonspecific lower urinary tract complaints was significantly greater in arm 1 than in arm 3 (P<0.02), significantly greater in arm 2 than in arm 3 (P<0.05), but not significantly different between arm 1 and arm 2.

8. Conclusions

Choreito and choreitogoshimotsuto appears to have efficacy for relieving nonspecific lower urinary tract complaints.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Although using sealed envelopes for allocation is likely to have compromised randomization, this clinical trial demonstrated the efficacy of choreito and choreitogoshimotsuto for relieving nonspecific lower urinary tract complaints. Future RCT is expected to apply improved methods of randomized allocation, and statistical processing using more objective variables and a larger control group.

12. Abstractor and date

Okabe T, 28 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Fuse H, Sakamoto M, Iwasaki M, et al. Effect of chorei-to and hachimi-jio-gan on unidentified complaints on urinary tract. *Hinyoki Geka* (*Japanese Journal of Urological Surgery*) 1995; 8: 603–9 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the efficacy of choreito (猪苓湯) and hachimijiogan (八味地黄丸) for relieving urinary frequency, voiding pain, and incomplete emptying in patients without organic urinary tract disease.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and three other hospitals, Japan.

4. Participants

Twenty-three patients with unidentified urinary tract complaints other than organic urinary tract disease (chronic prostatitis included). The analysis population consisted of 20 patients including 9 with nervous urinary frequency (all in the choreito arm) and 11 (2 with chronic prostatitis and 9 with nervous urinary frequency) in the hachimijiogan arm.

5. Intervention

Efficacy evaluated 4 weeks later by patient's physician based on subjective symptoms.
Arm 1: TSUMURA Choreito (猪苓湯) Extract Granules 2.5 g t.i.d. (n=9).
Arm 2: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. (n=11).

6. Main outcome measures

Subjective symptoms: daytime urinary frequency, nocturnal urinary frequency, voiding pain, incomplete emptying, and voiding discomfort.

7. Main results

Daytime and nocturnal urinary frequency was significantly decreased from baseline in both arms, but the effect occurred earlier in arm 2 than in arm 1. Also, both treatments tended to improve voiding pain, incomplete emptying, and voiding discomfort. Usefulness was achieved in 88.9% in arm 1 and 100% in arm 2, as judged by the treating physicians.

8. Conclusions

Choreito and hachimijiogan are useful for unidentified urinary tract complaints.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study compared efficacy of two Kampo medicines. Eviprostat (herbal extract product), Cernilton (cernitin pollen extract), Bladderon, Prostal, and Harnal were released in 1967, 1969, 1979, 1981, and 2005, respectively; control drugs seem to have been available as of 1995. In addition, the distribution of underlying diseases is not uniform (i.e., there are 2 cases of chronic prostatitis *v.s.* 18 cases of nervous urinary frequency).

12. Abstractor and date

Fujisawa M, 14 October 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Aoki Y, Ueda K, Tsutani K, et al. The influence of formula ma-huang-fu-zi-xi-xin-tang (mao-bushi-saishin-to; Mbst) on the results of urodynamic studies. *Journal of Traditional Medicine* 2001;18:203-9. Ichushi Web ID: 2002139756 CiNii

1. Objectives

To evaluate the effect of single-dose administration of maobushisaishinto (麻黄附子細辛湯) on urine flow.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Department of Urology, Nagoya City University Medical School and associated facilities, Japan.

4. Participants

Thirteen young male volunteers (mean age: 38.0 years) and six elderly male volunteers (mean age: 64.5 years).

5. Intervention

Arm 1: administration of 2 capsules of Kotaro Maobushisaishinto (麻黄附子細辛湯) in the 1st course followed by 2 capsules of placebo in the 2nd course, with 4-week withdrawal between courses.
Arm 2: administration conducted in the reverse order of arm 1.

6. Main outcome measures

Maximum urine flow rate at 3 hr after administration, mean urine flow rate, and voiding efficiency.

7. Main results

Regardless of the order of administration, no significant differences were observed in the maximum urine flow rate at 3 hr after administration, mean urine flow rate, or voiding efficiency between maobushisaishinto - and placebo-groups. There was no significant difference in the maximum urine flow rate, mean urine flow rate, or voiding efficiency between pre- and post-dose levels when treated with maobushisaishinto in the elderly.

8. Conclusions

It is suggested that single-dose administration of maobushisaishinto has no effect on urine flow in both young and old men.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In elderly males with impaired urination due frequently to prostatic hyperplasia, ephedrine-containing formulations such as mao have been shown to aggravate the problem. This study concludes that single-dose administration of maobushisaishinto does not adversely affect urine flow in the elderly. However, since treatment with a Kampo formulation usually requires repeated administration for a certain period, the results of a clinical study with repeated administration will also need to be considered.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Sakamoto Y, Iwasaki M, Kazama T, et al. Study of effects hachimi-jio-gan and chorei-to on prostatic hypertrophy. *Dai 13 Kai Hinyokika Kampo Kenkyukai Koen Shu* (*Proceedings of the 13th Meeting of the Urological Society for Kampo Medicine*) 1996: 7-14 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of hachimijiogan (八味地黄丸) and choreito (猪苓湯) in patients with prostatic hyperplasia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and three hospitals, Japan.

4. Participants

Fifty-three patients with prostatic hyperplasia who were enrolled from May 1992 to April 1994.

5. Intervention

Arm 1: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules for Prescription 2.5 g t.i.d., for 8 weeks (n= 27 patients,15 patients analyzed; 12 patients excluded from the analysis, including 2 patients with worsening symptoms).

Arm 2: TSUMURA Choreito (猪苓湯) Extract Granules for Prescription 2.5 g t.i.d., for 8 weeks (n=26 patients, 14 patients analyzed; 12 patients, most of whom failed to return to the hospital, were excluded).

No concomitant use of drugs for urinary disturbance was allowed.

6. Main outcome measures

Subjective symptoms and objective findings before and after treatment.

7. Main results

Significant subjective improvement was observed in six symptoms (delayed urination, prolonged urination, weak urinary stream, feeling of residual urine, and urination within 2 hours) after treatment with hachimijiogan and in two symptoms (prolonged urination and feeling of residual urine) after treatment with choreito. Significant objective improvement was observed in the maximum and mean urinary flow rates after treatment with hachimijiogan ($P<0.01$) and choreito ($P<0.05$).

8. Conclusions

According to the investigators, both drugs are useful in 80% of patients. Even if all of the patients excluded from the analysis were included in the analysis and were unresponsive, the utility rate would be 40%, indicating that both drugs are moderately useful in improving subjective symptoms associated with prostatic hyperplasia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Appetite loss was observed in 1 patient treated with hachimijiogan, and sleepiness and stomach discomfort were observed in 2 patients treated with choreito.

11. Abstractor's comments

According to the "Abstract" and "Discussion", this study evaluated the efficacy of individual Kampo medicines for urinary disturbance in order to determine whether combinations of these drugs with western medications for urinary disturbance (antiandrogenic agents, α-blockers, plant extracts, amino acid preparations, etc.) were useful. Good results were obtained, showing that hachimijiogan and choreito are meaningful concomitant drugs. According to the "Methodology" and "Analytical Methods" sections, patients were randomly assigned to one of two groups. The absence of significant between-group differences was not mentioned in the Abstract or Discussion. Since this was an RCT, a group of patients treated with both drugs should have been included.

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Horiba M, Kato S, Tanaka T, et al. Clinical validity of gosha-jinki-gan in the treatment of chronic prostatitis - open comparative study with gosha-jinki-gan vs ciprofloxacin -. *Gendai Toyo Igaku* (*The Journal of Traditional Sino-Japanese Medicine*) 1994; 15: 37–44 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in the treatment of chronic prostatitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital, Japan.

4. Participants

Fifty-eight patients with chronic prostatitis.

5. Intervention

Arm 1: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. for 4 weeks (n=15).
Arm 2: ciprofloxacin 200 mg b.i.d. for 4 weeks (n=15).
Arm 3: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. + ciprofloxacin 200 mg b.i.d. for 4 weeks (n=14).
Arm 4: serratiopeptidase 10 mg t.i.d. for 4 weeks (n=14).

6. Main outcome measures

Subjective symptoms, prostate palpation findings, and white blood cell (WBC) in expressed prostatic secretion.

7. Main results

The analysis population consisted of a total of 48 patients: 14, 13, 9, and 12 patients in arm 1, arm 2, arm 3, and arm 4, respectively. Subjective symptoms were improved in 60.0%, 54.5%, 68.1%, and 33.3% of patients in arms 1 to 4, respectively, at 2 weeks; and in 80.0%, 66.7%, and 71.4% of patients in arms 1 to 3, respectively, at 4 weeks. Prostate palpation findings were improved in 21.5%, 10.0%, 14.3%, and 20.0% of patients in arms 1 to 4, respectively, at 2 weeks; and in 28.6%, 11.1%, and 44% of patients in arms 1 to 3, respectively, at 4 weeks. Normalization of WBC count in expressed prostatic secretion was noted in 12.5%, 11.1%, 28.6%, and 12.5% of patients in arms 1 to 4, respectively, at 2 weeks; and 30%, 12.5%, and 16.7% in arms 1 to 3, respectively, at 4 weeks. The efficacy rate judged by investigators was 85.7%, 63.6%, 88.8%, and 25% in arms 1 to 4, respectively, showing significantly higher efficacy in arm 1 than in arm 4 ($P<0.05$). As well, higher efficacy was obtained in arm 3 than in arm 4 ($P<0.05$).

8. Conclusions

It was suggested that Goshajinkigan is effective for chronic prostatitis.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

Mild adverse drug reactions were observed in 6 and 1 patient receiving ciprofloxacin and goshajinkigan, respectively, for a total of 7. The reactions were gastrointestinal symptoms, central nervous system symptoms, and allergic symptoms occurring in 3, 3, and 1 patient, respectively. The adverse reaction to goshajinkigan was intraoral inflammation in 1 patient.

11. Abstractor's comments

Although using seal envelopes for allocation is likely to have compromised randomization, this clinical trial demonstrated the efficacy of goshajinkigan for chronic prostatitis. A future randomized controlled trial is expected to be performed and to use an improved method of randomized allocation, statistical analysis of results, more objective variables, and larger sample size.

12. Abstractor and date

Okabe T, 28 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Ishizuka O, Yamanishi T, Gotoh M, et al. LUTS: new evidence – clinical efficacy of Kampo formulations focusing on goshajinkigan -*. *Urology View* 2009; 7: 81-41. Ichushi Web ID: 2009114396

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for relieving lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH) and concomitant overactive bladder (OAB).

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

Multiple institutions (urology departments in 5 university hospitals including Shinshu University), Japan.

4. Participants

Eighteen male patients aged under 80 years with BPH, concomitant OAB, and urinary frequency and urgency even after receiving 8-week treatment with tamsulosin hydrochloride.

5. Intervention

Arm 1: tamsulosin hydrochloride 0.2 mg/day + TSUMURA goshajinkigan (牛車腎気丸) Extract Granuiles 7.5 g/day for 4 weeks, followed by monotherapy with tamsulosin hydrochloride 0.2 mg/day for 4 weeks (n=9).

Arm 2: tamsulosin hydrochloride 0.2 mg/day for 4 weeks, followed by tamsulosin hydrochloride 0.2 mg/day + TSUMURA goshajinkigan (牛車腎気丸) Extract Granuiles 7.5 g/day for 4 weeks (n=9).

6. Main outcome measures

OAB symptoms (frequencies of daytime urination, nighttime urination, urgency, and incontinence), BPH symptoms (International Prostate Symptom Score [IPSS], postvoid residual urine volume), King's Health Questionnaire (KHQ), and quality of life (QOL) index.

7. Main results

Comparing the combination therapy period and the monotherapy period, there were no significant differences in frequencies of daytime urination, nighttime urination, and urgency (P=0.225, P=0.882, and P=0.348, respectively). The QOL index improved significantly (P=0.008) and the frequency of incontinence tended to improve, though not significantly, during the combination therapy period (P=0.090). No significant differences were found in IPSS (P=0.563), postvoid residual urine volume (P=0.846), and KHQ score.

8. Conclusions

The concomitant use of goshajinkigan improves QOL but not urinary urgency in patients who have OAB symptoms after treatment with tamsulosin hydrochloride for BPH.

9. From Kampo medicine perspective

It was mentioned in the "discussion" section.

10. Safety assessment in the article

Gastric distress and diarrhea occurred in one goshajinkigan-treated patient each.

11. Abstractor's comments

This study reports that the concomitant use of goshajinkigan did not improve frequency of urination or urinary urgency, but did improve QOL in patients with BPH who had OAB symptoms after the treatment with tamsulosin hydrochloride, an α1-receptor blocker. In the practice of Kampo medicine, goshajinkigan is effective for nocturia. Demonstration of the efficacy of this agent requires selection of patients based on differential diagnosis using Kampo medicine-based criteria (*sho* [証, pattern]), such as *kan-netsu* (寒熱, cold and heat) and *kyo-jitsu* (虚実, excess or deficiency), as the authors mentioned in the discussion. Clinical trials with a new design are needed.

12. Abstractor and date

Okabe T, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Koga N, Moriya F, Waki K, et al. Immunological efficacy of herbal medicines in prostate cancer patients treated by personalized peptide vaccine. *Cancer Science* 2017; 108: 2326-32. Pubmed ID: 28898532

1. Objectives

To evaluate the immune-enhancing efficacy and safety of Kampo medicines using hochuekkito （補中益気湯） and keishibukuryogan（桂枝茯苓丸)in combination with personalized cancer peptide vaccination (PPV) in patients with castration-resistant prostate cancer (CRPC)

2. Design

Randomized controlled trial (RCT)

3. Setting

One university hospital, Japan

4. Participants

Seventy patients with CRPC aged 20 years or older with a Performance Status score of 0 or 1 (ECOG).
Inclusion criteria: life expectancy of 12 weeks or more, HLA haplotype of A2, A24, A26, A3, A11, A31, or A33, and normal hepatorenal functions.
Exclusion criteria: acute infection, history of severe allergic reactions, cardiac or pulmonary insufficiency

5. Intervention

Arm 1: PPV (weekly 8 times) plus TSUMURA Hochuekkito（補中益気湯）Extract Granules 7.5 g/day and TSUMURA Keishibukuryogan（桂枝茯苓丸）Extract Granules 7.5 g/day (2.5 g t.i.d. administered orally before meals for 50 days) (n=31)
Arm 2: PPV alone (weekly 8 times) (n=35)

6. Main outcome measures

Primary endpoint: immune response to PPV.
Secondary endpoints: overall survival (OS), progression-free survival (PFS), and safety.

7. Main results

Four patients withdrew consent prior to treatment in Arm 1. Treatment was discontinued because of disease progression or death in 3 patients in Arm 1 and 4 patients in Arm 2. At the end of follow-up, 19 patients in Arm 1 (63%; median duration of follow-up 14.9 months) and 26 patients in Arm 2 (74%; 13.6 months) had disease progression or died. The OS and PFS did not differ significantly between the arms. The baseline and Week 8 cancer peptide-specific IgG, CTL, and regulatory T cells (Treg) did not significantly differ between the arms. Comparing before to after the treatment, the frequency of monocytic myeloid-derived suppressor cells (Mo-MDSC) (before-after: 1.91%–1.92%) and the IL-6 level (19.2 pg/mL–16.1 pg/mL) were stable in Arm 1 but significantly increased in Arm 2 (0.91%–1.49% for Mo-MDSC [*P*=0.012] and 9.2 pg/mL–19.4 pg/mL for IL-6[*P*=0.043]).

8. Conclusion

In CRPC patients, the use of herbal medicines of hochuekkito and keishibukuryogan during PPV treatment had no impact on clinical outcome but has the potential to modify the immune response to PPV.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

No treatment-related deaths occurred in either arm. Adverse events such as injection site reactions did not differ between the two treatment arms. Appetite loss was less frequent in the PPV + herbal medicines arm than in the PPV alone arm.

11. Abstractor's comments

While cancer immunotherapies are entering a new phase, this pioneering study applied a novel immunotherapy with personalized cancer peptide vaccination (PPV) to patients with CRPC, and analyzed whether herbal medicines could modify the immune response to PPV. Since the RCT design was employed, the study yielded objective results, and was meaningful both basically and clinically. In Arm 1, the frequency of Mo-MDSC (%) and the IL-6 level were stable, suggesting the possibility that these herbal medications may prevent a decrease in the immune response to PPV, although clinical endpoints unfortunately failed to show significant differences. The results of this study are clinically interesting, considering that the authors previously reported significantly lower IL-6 levels in long-term survivors of prostate cancer. As the authors state that more research is needed, new results are awaited in the future.

12. Abstractor and date

Kogure T, 1 June 2020.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Hiramatsu M, Maehara I, Takahashi M, et al. Treatment experience with saikokaryukotsuboreito and hochuekkito in male infertility patients*. *Kampo Igaku* (*Kampo Medicine*) 1993;17: 246–8 (in Japanese).

1. Objectives

To objectively evaluate the positive effect of saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) or hochuekkito (補中益気湯) monotherapy on sperm profiles of male infertility patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Four facilities including the Department of Urology, Tohoku University Hospital, Japan.

4. Participants

Twenty-eight patients diagnosed with oligozoospermia (sperm concentration of $<20\times10^6$/mL) or asthenospermia (motility of <50%) at the above facilities between February 1990 and March 1992.

5. Intervention

Arm 1: TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) Extract Granules 2.5 g t..i.d., before meals for 12 weeks (n=12).
Arm 2: TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5 g t..i.d., before meals for 12 weeks (n=16).

6. Main outcome measures

Sperm parameters including sperm concentration, motility, and sperm motile efficiency index (SMEI); and lutenaizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and prolactin levels. Global improvement evaluated at baseline and at weeks 4, 8, and 12 of treatment.

7. Main results

Both saikokaryukotsuboreito and hochuekkito significantly increased sperm motility and SMEI at 8 weeks of treatment but had no effect on sperm concentration or hormone levels. However, SMEI returned to baseline level at 12 weeks of treatment with hochuekkito. Saikokaryukotsuboreito and hochuekkito markedly improved sperm concentration (in 41.7% and 18.8% of patients, respectively) and sperm motility (in 41.7% and 50.0% of patients, respectively). Furthermore, 75.0% and 37.5% of patients showed moderate or marked global improvement, respectively.

8. Conclusions

Saikokaryukotsuboreito or hochuekkito monotherapy improves sperm parameters and is effective for male infertility.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

While an effective therapy for male infertility has not yet been established, this study demonstrated the effectiveness (overall efficacy and improved sperm parameters) of Kampo medicines in clinical practice. Particularly, saikokaryukotsuboreito increased sperm concentration to 20×10^6/mL or higher and sperm motility ≥30% in more than 40% of patients, increasing the number of candidates for artificial insemination and expectations for spontaneous pregnancy in clinical practice. However, since therapy was not prescribed according to *sho* (証, pattern) and random assignment to an experimental or control drug was not performed, the results of this study do not necessarily reflect true drug efficacy. The mechanism of action of Kampo medicines was not considered, and therefore in a future study protocol, the drug should be prescribed on the basis of *sho* (証, pattern) (*jitsu* [実, excess] or *kyo* [虚, deficiency]), *saiko-sho* (柴胡証), and presence or absence of *jinkyo* (腎虚, kidney deficiency).

12. Abstractor and date

Ushiroyama T, 20 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Kazama T. Male infertility*. *Current Therapy* 1988; 6: 1683–6 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of hochuekkito (補中益気湯) in the treatment of male infertility in comparison with Kallikrein (kallidinogenase).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Urology, Toyama Medical and Pharmaceutical University Hospital, Japan.

4. Participants

Forty-two patients (including ten withdrawals) diagnosed with male infertility (sperm count, 10–40 × 10^6/mL) at the above facility between January 1987 and January 1988.

5. Intervention

Arm 1: hochuekkito (補中益気湯) (manufacturer, not specified) 2.5 g t.i.d., before meals (n=16).
Arm 2: Carnaculin Capsule (kallinogenase 150 IU) t.i.d., after meals (n=16).
Treatment duration: 12 weeks (up to 36 weeks).

6. Main outcome measures

Sperm profiles including sperm concentration, motile sperm count, and percentage of motile sperm evaluated at baseline and week 12 of treatment. Treatment was considered effective if sperm concentration increased by ≥ 20 × 10^6/mL and motility increased ≥ 20%.

7. Main results

Sperm concentration increased in 56.3% of the patients in arm 1 and 25.0% of the patients in arm 2, and motility increased in 25.0% of the patients in arm 1 and 18.8% of the patients in arm 2. In addition, the total count of motile sperm was higher in the hochuekkito group than in the kallidinogenase group, although the between-group difference was not significant.

8. Conclusions

Treatment with hochuekkito confers a favorable outcome without adverse reactions and is therefore useful and indicated for male infertility.

9. From Kampo medicine perspective

Although drug prescription was not based on *sho* (証, pattern) in this study, activities including peripheral vasodilation, lipid metabolism improvement, protein synthesis promotion, and immunostimulation are suggested.

10. Safety assessment in the article

No adverse reactions occurred in both arms.

11. Abstractor's comments

No therapeutic approach to male infertility is currently established. This controlled study comparing hochuekkito with kallidinogenase (a conventional western medicine with reported efficacy for treatment of male infertility) demonstrated that hochuekkito confers a favorable clinical outcome with no adverse reactions. This study suggests that hochuekkito is a viable pharmacotherapeutic option for treating male infertility. However, sperm motility was not necessarily improved in all patients of this study but varied between individuals, indicating the importance of *sho*. Additionally, probably because the study period (12 weeks) was too short, successful pregnancy, a general endpoint of fertility treatment, was not reported, making it impossible to know whether sperm quality was improved enough to ensure pregnancy. It would be interesting to find out the diagnosis (based on the concept of oriental medicine *sho*) of patients responding favorably to hochuekkito and the characteristics of those responding poorly to it. Future studies using a protocol focusing on *sho* are expected to investigate the relationship between improved sperm profile and pregnancy rate in hochuekkito-treated patients, as well as ascertain the true therapeutic effect of hochuekkito on male infertility.

12. Abstractor and date

Ushiroyama T, 20 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Sugimoto K, Shigehara K, Izumi K, et al. Effect of combination of saiko-ka-ryukotsu-borei-to with androgen replacement therapy for LOH syndrome. *Nihon Sei Kino Gakkai Zasshi* (*Japanese Journal of Sexual Medicine*) 2009; 24: 349–53 (in Japanese). Ichushi Web ID: 2010196632

1. Objectives

To evaluate the efficacy of androgen replacement therapy (ART) combined with saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) for late-onset hypogonadism (LOH) syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two facilities (Kanazawa University Hospital and Ishikawa Prefectural Central Hospital), Japan.

4. Participants

Thirteen subjects who were diagnosed with LOH syndrome at the above facilities and desired to receive treatment.

5. Intervention

Arm 1: intramuscular testosterone enanthate 250 mg/3–4 weeks + administration of saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) (manufacturer, not specified) 2.5 g t.i.d. immediately before meals for 12 weeks (n=6).

Arm 2: intramuscular testosterone enanthate 250 mg/3–4 weeks for 12 weeks (n=7).

6. Main outcome measures

1) Aging Males Symptoms (AMS) rating scale, 2) Self-rating Depression Scale (SDS), 3) self-rating Internal Index of Erectile Function-5 (IIEF-5), and 4) blood testosterone concentration, evaluated at the start of treatment and after 12 weeks of treatment.

7. Main results

Combination treatment tended to improve AMS, SDS, and IIEF-5 scores compared with ART alone. Decreases in blood total testosterone and free testosterone concentrations were greater after ART alone than after combination treatment.

8. Conclusions

Saikokaryukotsuboreito plus ART for late-onset hypogonadism (LOH) syndrome improves psychiatric and physical symptoms and alleviates ART-induced gonadal function depression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Blood biochemistry identified no serious adverse events.

11. Abstractor's comments

This study focused on the central nervous system depressant activity of saikokaryukotsuboreito as a *saiko-zai* (柴胡剤, saiko formulation) or ryukotsu (竜骨)- and borei (牡蛎)-containing Kampo medicine, and compared the effect of its combination with androgen replacement therapy to that of androgen replacement therapy alone, using major rating scales clinically used to evaluate late-onset hypogonadism (LOH) syndrome. Its attempt to find out the favorable effects of Kampo medicine (when in combination) is worthy of appreciation. This study, however, fails to determine *sho* (証, pattern) of cases with appreciable depression and unidentified complaints, which are common in middle-aged and elderly men, and its finding that saikokaryukotsuboreito is more effective than ART alone for anxiety and depressive symptoms in cases of *ki-tai* (気滞, qi stagnation) and *hi-ki-kyo* (脾気虚, spleen qi deficiency) is consistent with conventional clinical wisdom and practice, and is not new. Furthermore, the sample size of 6–7 subjects per group was extremely small. It is hoped that similar studies will be performed with many more "saiko-*sho* (証, pattern)" and "ryukotsuborei- *sho* (証, pattern)" cases, which can be diagnosed by clinicians relatively early and without uncertainty to establish the guidelines for not only combination therapy with ART but also for selecting usage according to *sho* (証, pattern). Evaluation of whether a high percentage of patients with LOH syndrome is indicated for saikokaryukotsuboreito is also expected.

12. Abstractor and date

Ushiroyama T, 15 January 2011, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Inoue M. Kampo treatment for mastitis - kamishoyosan -*. *Kampo Igaku* (*Kampo Medicine*) 1994; 18: 238–41 (in Japanese).

1. Objectives

To evaluate the efficacy of kamishoyosan (加味逍遙散) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast, Japanese Red Cross Medical Center, Japan.

4. Participants

Two-hundred and eighty-one patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography.

5. Intervention

Arm 1: TSUMURA Kamishoyosan (加味逍遙散) Extract Granules 2.5 g t.i.d. for 4 weeks (n=169).
Arm 2: TSUMURA Keishibukuryogan (桂枝茯苓丸群) Extract Granules 2.5 g t.i.d. for 4 weeks (n=39).

6. Main outcome measures

Patients were classified into *jitsusho* (実証, excess pattern), *chukansho* (中間証, intermediate pattern), or *kyosho* (虚証, deficiency pattern) based on appetite, bowel movements, sensitivity to heat or cold, presence or absence of feeling cold, menstruation, use of hormones, tongue diagnosis, abdominal examination, etc. In patients with each *sho* (証, pattern), efficacy for breast pain, mammary gland swelling, symptoms of mastopathy, was judged from patient complaints.

7. Main results

Kamishoyosan and keishibukuryogan had similar efficacies.

8. Conclusions

Since *kuoketsuzai* (駆オ血剤, blood stasis-expelling formulae) such as keishibukuryogan and tokakujokito are indicated for *jitsusho* (実証, excess pattern), kamishoyosan will provide another therapeutic option.

9. From Kampo medicine perspective

Mastopathy is frequently treated with *kuoketsuzai* (駆オ血剤, blood stasis-expelling formulae); however, since its symptoms overlap with those of *kanqiukketsu* (肝気鬱結, liver *qi* depression) including breast pain, kamishoyosan, a saiko-agent (柴胡剤), would also be important.

10. Safety assessment in the article

There were no adverse events.

11. Abstractor's comments

This paper argues that while keishibukuryogan is used for *jitsusho* (実証, excess pattern), formulae for *chukansho* (中間証, intermediate pattern) or *kyosho* (虚証, deficiency pattern) such as kamishoyosan are necessary. This trial is meaningful because it was designed from such a viewpoint. This argument is verifiable, only if patients with *kyosho* (虚証, deficiency pattern) are allocated to and do not respond to treatment with keishibukuryogan (used as control). Regrettably, however, the allocation of patients at a ratio of 3:1 to kamishoyosan and keishibukuryogan in this trial resulted in a keishibukuryogan group without patients with *kyosho* (虚証, deficiency pattern), making it impossible to justify the author's argument. A similar trial demonstrating the usefulness of kamishoyosan in patients with *kyosho* (虚証, deficiency pattern) is awaited.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Inoue M. Kampo therapy for mastitis - shigyakusan -*. *Kampo Igaku* (*Kampo Medicine*) 1990; 14: 132–6.

1. Objectives

To evaluate the efficacy of shigyakusan (四逆散) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast, Japanese Red Cross Medical Center, Japan.

4. Participants

Two-hundred and twenty patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography between July 1988 and June 1989.

5. Intervention

Arm 1: shigyakusan (四逆散) group, TSUMURA Shigyakusan (四逆散) Extract Granules 2.5 g t.i.d. (n=111).
Arm 2: keishibukuryogan (桂枝茯苓丸) group, TSUMURA Keishibukuryogan (桂枝茯苓丸群) Extract Granules 2.5 g t.i.d. (n=41).
Patients were allocated to arm 1 and arm 2 at a ratio of 3:1.
Patients with symptoms completely resolved when primary efficacy was evaluated at 4 weeks completed treatment. Patients showing a tendency for improvement were given the same prescription for additional 4 weeks. Patients showing no tendency for improvement underwent fine-needle aspiration biopsy to eliminate the possibility of malignancy, received keishibukuryogan (桂枝茯苓丸) when they were in arm 1 and shigyakusan (四逆散) when they were in arm 2, and underwent a final efficacy evaluation at 8 weeks.

6. Main outcome measures

Patients were classified into *jitsusho* (実証, excess pattern), *chukansho* (中間証, intermediate pattern), or *kyosho* (虚証, deficiency pattern) based on appetite, bowel movements, sensitivity to heat or cold, presence or absence of feeling of cold, menstruation, use of hormones, tongue diagnosis, abdominal examination, etc. In patients with each *sho* (証, pattern), efficacy for breast pain and mammary gland swelling, and symptoms of mastopathy was judged from patient complaints.

7. Main results

There were 68 dropouts. Shigyakusan and keishibukuryogan had similar efficacy.

8. Conclusions

No definite conclusions were reached.

9. From Kampo medicine perspective

Mastopathy is frequently treated with *kuoketsuzai* (駆オ血剤, blood stasis-expelling formula); however, since its symptoms overlap with those of *kanqiukketsu* (肝気鬱結, liver *qi* depression) including breast pain, shigyakusan, a saiko-agent, is important.

10. Safety assessment in the article

There were no adverse events.

11. Abstractor's comments

This study investigated the efficacy of shigyakusan, a different series of Kampo medicines from those of *oketsu* (オ血) (blood stasis) treatment including keishibukuryogan, tokakujokito, and tokishakuyakusan. In this trial, keishibukuryogan was used as the control; however, since its efficacy has not been established, the results are quite obscure. If the efficacy of shigyakusan is to be considered a new therapeutic option, as intended by the author, more in-depth discussion of the indications for shigyakusan and keishibukuryogan will be needed. A follow-up report is awaited.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Inoue M. Clinical study of effects of tsu-do-san on mastitis. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1993; 43: 517–21 (in Japanese).

1. Objectives

To evaluate the efficacy of tsudosan (通導散) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast Medicine, Japanese Red Cross Medical Center, Japan.

4. Participants

Two-hundred and forty-eight patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography between July 1990 and June 1991, and classified into *chukansho* (中間証, intermediate pattern) or *jitsusho* (実証, excess pattern).

5. Intervention

Arm 1: TSUMURA Tsudosan (通導散) Extract Granules 2.5 g t.i.d. for 4 weeks (n=150).
Arm 2: TSUMURA Keishibukuryogan (桂枝茯苓丸群) Extract Granules 2.5 g t.i.d. for 4 weeks (n=33).
Patients were allocated to arm 1 and arm 2 at a ratio of 4:1.

6. Main outcome measures

The measures (disappearance of subjective breast pain and percent disappearance of mammary gland swelling) are not clear, since only exceptionally large reduction in mammary gland swelling was defined as a response.

7. Main results

Sixty-five patients dropped out. There was no difference in the efficacy of tsudosan between the *chukansho* (中間証, intermediate pattern) and *jitsusho* (実証, excess pattern) groups. The statistical significance of the difference in efficacy between tsudosan and keishibukuryogan was not mentioned.

8. Conclusions

No definite conclusions were reached.

9. From Kampo medicine perspective

The historical background of *oketsu* (才血, blood stasis) as an indication was discussed.

10. Safety assessment in the article

Twenty patients (14%) were withdrawn because of diarrhea/abdominal pain.

11. Abstractor's comments

The intention of this study was to investigate the efficacy of tsudosan for mastitis and thereby to provide another therapeutic option, while keishibukuryogan is used for treatment of patients with *jitsusho* (実証, excess pattern). Patients were classified into groups based on criteria (not mentioned) defining *chukansho* (中間証, intermediate pattern: medium build, well-developed breast, slightly weak or strong tone of the abdominal wall, good appetite, normal bowel movements or slight *hiketsu* [秘結, constipation], and normal menstruation), and *jitsusho* (実証, excess pattern: details not mentioned) by one physician. However, with a wide range of diagnostic criteria, the classification remains obscure. It is unclear whether the absence of difference between *chukansho* (中間証, intermediate pattern) and *jitsusho* (実証, excess pattern) groups reflects misclassification or the meaninglessness of the classification system itself. Although this paper demonstrated a response to tsudosan in some patients, it is desirable that the above problems be solved in a future report.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Inoue M. Clinical studies on effects of tokakujoki-to for fibro-cystic disease of the breast. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1992; 42: 415–8 (in Japanese).

1. Objectives

To evaluate the efficacy of tokakujokito (桃核承気湯) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast, Japanese Red Cross Medical Center, Japan.

4. Participants

One-hundred and ninety-six patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography between July 1989 and June 1990.

5. Intervention

Arm 1: tokakujokito (桃核承気湯) group, tokakujokito (桃核承気湯) (manufacturer unknown) 2.5 g t.i.d. (n=103).

Arm 2: keishibukuryogan (桂枝茯苓丸群) group, keishibukuryogan (桂枝茯苓丸群) (manufacturer unknown) 2.5 g t.i.d. (n=22)

Patients were allocated to arm 1 and arm 2 at a ratio of 4:1.

Patients whose symptoms were resolved when efficacy was evaluated at 4 weeks were considered to be responders and treatment was ended. Patients showing a tendency for improvement were given the same prescription for an additional 4 weeks and final efficacy was evaluated at 8 weeks. Patients with no therapeutic effect at the time of the primary efficacy evaluation were considered to be non-responders and treatment was stopped.

6. Main outcome measures

The presence or absence of subjective breast pain and mammary gland swelling was used to evaluate efficacy, and therefore the criteria for efficacy are not clear.

7. Main results

There were 71 dropouts. The significance of the difference in efficacy between tokakujokito and keishibukuryogan was not indicated.

8. Conclusions

No definite conclusions were reached.

9. From Kampo medicine perspective

Aspects of the topic “crude drug” are discussed in the discussion section of the reference.

10. Safety assessment in the article

Treatment was stopped in 13 patients (11%) because of diarrhea and abdominal pain.

11. Abstractor’s comments

This paper reported the efficacy of tokakujokito for patients with mastopathy. Tokakujokito and keishibukuryogan had similar efficacy, but the former was associated with a higher incidence of diarrhea, which occurred in nearly half the patients treated. Without knowing the criteria used to select treatment with tokakujokito rather than keishibukuryogan, the intent of the article is obscure. A follow-up report with in-depth discussion on the indications for tokakujokito is awaited.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Oribe K, Nishida Y. Efficacy of hachimijiogan for discomfort after surgery for uterine prolapse. *Gekkan Kampo Ryoho* (*Monthly Journal of Kampo Medicine and Herbs*) 2006; 10: 282-8 (in Japanese).

1. Objectives

To evaluate the hachimijiogan (八味地黄丸)-induced improvement in postoperative discomfort associated with surgery for uterine prolapse and quality of life (QOL).

2. Design

A randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, National Hospital Organization Oita Medical Center, Japan.

4. Participants

Nineteen patients with uterine prolapse who did not respond to hochuekkito and underwent vaginal radical operation for uterine prolapse at the above facility between December 2005 and March 2006.

5. Intervention

Arm 1: oral administration of TSUMURA Hachimijiogan (八味地黄丸)Extract Granules 2.5 g t.i.d. before meals, n=12.
Arm 2: no treatment, n=7.

6. Main outcome measures

Frequency of urination per day and mean residual urine volume at the start and 1 and 2 weeks after the start of hachimijiogan.

7. Main results

There was no significant difference in urination frequency. Residual urine volume was significantly decreased after hachimijiogan treatment for 1 week (21±2.3 mL *vs*. 13±4.2 mL, $P<0.05$) and 2 weeks (12±1.7 mL *vs*. 8.3±1.5 mL, $P<0.05$). In addition, 2 weeks of treatment with hachimijiogan decreased residual urine volume more significantly in patients with *shofukufujin* (小腹不仁, soft, weak lower abdomen) than in those without *fukusho* (腹証, abdominal pattern) (8.3±1.5 mL *vs*. 5.3±2.5 mL, $P<0.05$).

8. Conclusions

Hachimijiogan administered after surgery for uterine prolapse may accelerate tissue repair postoperatively, thereby improving patient QOL, particularly in patients with *shofukufujin.*

9. From Kampo medicine perspective

Traditionally, hochuekkito has been considered to be the effective treatment for uterine prolapse. However, because of a change in nutritional status, many women do not present conventional "*sho*", leaving room for reconsideration of the appropriate agent. Hachimijiogan is highly effective for decreasing residual urine volume after surgery for uterine prolapse and aiding recovery of the bladder and surrounding tissues.

10. Safety assessment in the article

No adverse drug reactions occurred after hachimijiogan treatment.

11. Abstractor's comments

This research raises questions about what Kampo medicine should be or how it should be utilized in an aging society. None of the existing treatments for genitourinary prolapse (including surgery, pessary insertion, and pharmacotherapy) are totally effective, raising concerns among clinicians. This research demonstrated that hachimijiogan is highly effective in decreasing postoperative residual urine volume particularly in patients with *shofukufujin*. Future research is desired to determine whether this clinical approach fusing western and oriental medicines can prevent recurrent uterine prolapse and how Kampo medicine can be used to treat uterine prolapse for *sho* of unclear *jinkyo* (腎虚, kidney deficiency).

12. Abstractor and date

Ushiroyama T. 12 December 2008, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Iwabuchi S. Effect of kyuki-kyogai-to on stopping dysfunctional uterine bleeding – comparison with occidental hemostatic drugs -. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 2000; 50: 883-903 (in Japanese with English abstract). Ichushi Web ID: 2000172969 CiNii

1. Objectives

To evaluate the efficacy and safety of kyukikyogaito (キュウ帰膠艾湯) for menometrorrhagia.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Obstetric and gynecologic practitioner, Yamagata, Japan.

4. Participants

The analysis population included 183 out of 200 randomized patients with menometrorrhagia.

5. Intervention

Arm 1: administration of 9.0 g of TSUMURA Kyukikyogaito (キュウ帰膠艾湯) Extract Granules for 7 days (n=100). Ninety-three patients were included for analysis.

Arm 2: administration of tranexamic acid (3 tablets of Transamin) and carbazochrome/VK mixture (3 tablets of Ophtharum K) for 7 days (n=100). Ninety patients were included for analysis.

6. Main outcome measures

Number of days from exploratory endometrial curettage to hemostasis.

7. Main results

The time to hemostasis was significantly shorter in arm 1 (4.29±1.54 days) than in arm 2 (5.45 ± 2.13 days). When response was determined by the criterion of 'hemostasis by day 7', the response rate was significantly higher (94.6%) in arm 1, compared with 72.2% in arm 2. By *sho* (証, pattern), cases of hypofunction or intermediate function required significantly fewer days to hemostasis when receiving kyukikyogaito, whereas cases of hyperfunction showed no difference in the days to hemostasis between arms. By the appearance of the endometrium on imaging, cases of the proliferative phase or simple hyperplasia required significantly fewer days to hemostasis when receiving kyukikyogaito, whereas cases of stationary phase, atrophic phase and mixed proliferative/secretory phase or secretory phase showed no difference in the days to hemostasis between arms.

8. Conclusions

Kyukikyogaito is more effective for hemostasis in menometrorrhagia, compared with hemostatic drugs tranexamic acid and carbazochrome/VK mixture.

9. From Kampo medicine perspective

After, but not before, dosing, differential diagnosis of *sho* was made visually and by abdominal palpation, and it was concluded that kyukikyogaito is effective regardless of *sho*.

10. Safety assessment in the article

A 32-year-old patient complained of feeling bad after receiving 1 sachet of kyukikyogaito, and of stomach discomfort and nausea after receiving 2 sachets, and then discontinued the medicine after receiving 4 sachets and was switched to another drug.

11. Abstractor's comments

Various pathogenic mechanisms can cause menometrorrhagia in Kampo medicine, as in western medicine. Kyukikyogaito is a combination of a single medicine that acts on one of these mechanisms, called *shoninkyoson* (衝任虚損), and a hemostatic drug (In: *Jinguiyaolue* [金匱要略, *Synopsis of Prescriptions of the Golden Chamber*]). Presence of both responders and non-responders to this combination suggests that the disease has a more than one pathogenesis. Although this study is a quasi-randomized controlled trial, in which patients were alternately randomized and placed in the order of visitation, a certain efficacy of kyukikyogaito for menometrorrhagia is suggested.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Kotani N, Oyama T, Sakai I, et al. Analgesic effect of an herbal medicine for treatment of primary dysmenorrhea - a double-blind study. *The American Journal of Chinese Medicine* 1997; 25: 205-12. CENTRAL ID: CN-00143317, Pubmed ID: 9288368

1. Objectives

To evaluate the efficacy of tokishakuyakusan (当帰芍薬散) on dysmenorrhea.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Not indicated (the authors were affiliated with the Department of Anesthesiology, Hirosaki University School of Medicine), Japan.

4. Participants

Forty females suffering from dysmenorrhea for at least 1 year, with all *kikyo* (気虚, *qi deficiency*), *in* (陰, *yin*), and *oketsu* (瘀血, static blood) scores of 30 or more, without orthopedic disorders, and not receiving oral low-dose medications or prescribed anxiolytics.

5. Intervention

The study covered a total of 6 menstrual cycles (half a year): 2 cycles for baseline observation, followed by two cycles for treatment and then two cycles for follow-up observation.

Arm 1: oral administration of tokishakuyakusan (当帰芍薬散) (manufacturer unknown) 2.5 g t..i.d. (during the third to fourth menstrual cycles in the treatment period) (n=20).

Arm 2: oral administration of placebo (during the third to fourth menstrual cycles in the treatment period) (n=20).

6. Main outcome measures

Pain assessed on a visual analogue scale (VAS) and use of diclofenac sodium (Voltaren).

7. Main results

Dysmenorrhea was significantly improved in patients receiving tokishakuyakusan (P<0.001).

8. Conclusions

Adding Kampo indices *kikyo*, *in*, and *oketsu* to the diagnostic criteria enables selection of patients indicated for tokishakuyakusan, who can benefit from its analgesic effect.

9. From Kampo medicine perspective

Although the usefulness of each score is mentioned, it is not discussed from a Kampo medicine perspective.

10. Safety assessment in the article

No adverse events occurred.

11. Abstractor's comments

This study can be recognized as an attempt to define the indications for tokishakuyakusan using the Kampo diagnostic system (i.e., rating *kikyo*, *in*, and *oketsu* in patients with dysmenorrhea. While it is important to reduce the use of analgesics through pain relief, continued studies are expected on, for example, whether tokishakuyakusan is also effective for patients not responding to analgesics and how patients indicated for tokishakuyakusan differ from those indicated for keishibukuryogan (桂枝茯苓丸) or shakuyakukanzoto (芍薬甘草湯).

12. Abstractor and date

Nakata H, 1 January 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Tanaka E, Saito H, Hiroi M. Kampo treatment for nonspecific complaints in climacteric women - comparison of clinical efficacy of Kampo medicine alone versus Kampo medicine combined with tofisopam -*. *Kampo Shinryo* 1997; 16: 22-4 (in Japanese).

1. Objectives

To compare the clinical effects of keishibukuryogan (桂枝茯苓丸) monotherapy with combined therapy (keishibukuryogan plus autonomic modulator).

2. Design

Randomized controlled trial (RCT).

3. Setting

The Department of Obstetrics and Gynecology, Oguni Municipal Hospital, Japan.

4. Participants

Forty-three women who visited the above institution with climacteric complaints between April 1994 and September 1995.

5. Intervention

Arm 1: oral administration of Tsumura Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals (n=21).

Arm 2: oral administration of Tsumura Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals and tofisopam 50 mg t.i.d. after meals (n=22).

6. Main outcome measures

Assessment of severity based on simplified menopausal index (SMI). Clinical efficacy evaluated according to the post-treatment SMI score: marked response (25 or less), moderate response (reduction of 35 or greater compared with the pretreatment score, even if the score was over 25), and slight response (reduction of 6–34). Time to onset of the clinical effect assessed on a three-point scale: within 1 week, 2 weeks, and 4 weeks after the initiation of the treatment.

7. Main results

The percentage of patients achieving marked responses was similar between arms (33.3% of arm 1 *vs.* 28.6% of arm 2), and the percentage achieving moderate responses was also similar between arms (40.9% *vs.* 36.4%, respectively). The clinical effect was observed within 1 week after the start of treatment in 14.3% patients in arm 1 and 36.4% in arm 2, and within 2 weeks in 33.3% and 40.9%, respectively (no significance test was reported).

8. Conclusions

Addition of tofisopam to keishibukuryogan for the treatment of nonspecific climacteric symptoms accelerated the onset of the clinical effect. Clinical benefits of the combination therapy are suggested.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two patients in arm 2 experienced sleepiness.

11. Abstractor's comments

In climacteric patients with undefined complaints, the combined therapy accelerates the onset of the effect, as compared with keishibukuryogan monotherapy. This conclusion may lead to improvement in the treatment of climacteric women. However, *sho* (証, pattern), which is the most important aspect of the Kampo medicine, was not considered in patient selection. The data therefore give a strong impression that tofisopam itself was effective for nonspecific climacteric symptoms. That is to say, a randomized controlled trial including patients whose *sho* is appropriate for keishibukuryogan could determine the true effect of keishibukuryogan monotherapy *vs.* keishibukuryogan combined with autonomic agents. In this study, 60% of patients treated with keishibukuryogan experienced at least a moderate response, and about half of patients became aware of improvement in symptoms within 2 weeks, even they were diagnosed with "climacteric complaints" not based on *shisin* (四診, four examinations) nor *sho*. Moreover, the combined therapy showed enhanced clinical efficacy. These results might be of benefit to clinical practice.

12. Abstractor and date

Ushiroyama T, 27 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Samukawa K, Ogita S. Climacteric disorders and medicinal ginseng*. *Chiryogaku* (*Biomedicine & Therapeutics*) 1994; 28: 57–62 (in Japanese).

1. Objectives

To evaluate the clinical effect of kojinmatsu (紅参末), tokishakuyakusan (当帰薬芍散), and their combination on climacteric disorders.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One facility (the Department of Obstetrics and Gynecology, Osaka City University Hospital), Japan.

4. Participants

One-hundred and thirteen patients diagnosed with climacteric disorders and 124 postmenopausal women with unidentified complaints but not yet seen by a physician.

5. Intervention

Study 1: therapeutic effects on climacteric disorders

Arm 1: CHEONG-KWAN-JANG Kojinmatsu (正官庄紅参末) 6 g/day (divided doses and time of administration not indicated) for 4 weeks (n=83).

Arm 2: KOTARO Tokishakuyakusan (当帰薬芍散) ryo Extract Granules 9 g/day (divided doses and time of administration not indicated) for 4 weeks (n=30).

Arm 3: CHEONG-KWAN-JANG Kojinmatsu (正官庄紅参末) 6 g/day + KOTARO Tokishakuyakusan (当帰薬芍散) Extract Granules 9 g/day (divided doses and time of administration not indicated) (n=61).

Study 2: preventive effects on those who are likely to visit a hospital for climacteric disorders in future.

Arm 1: CHEONG-KWAN-JANG Kojinmatsu (正官庄紅参末) 3 g/day (divided doses and time of administration not indicated) (n=36).

Arm 2: CHEONG-KWAN-JANG Kojinmatsu (正官庄紅参末) 6 g/day (divided doses and time of administration not indicated) (n=20).

Arm 3: KOTARO Tokishakuyakusan (当帰薬芍散) ryo Extract Granules 9 g/day (divided doses and time of administration not indicated) (n=34).

Arm 4: CHEONG-KWAN-JANG Kojinmatsu (正官庄紅参末) 3 g/day + KOTARO Tokishakuyakusan (当帰薬芍散) ryo Extract Granules 9 g/day (divided doses and time of administration not indicated) (n=34).

6. Main outcome measures

Improvement in clinical symptoms (decrease in Kupperman's index): marked improvement (80% or more decrease); moderate improvement (60–80% decrease); slight improvement (30–60% decrease); and no improvement (30% or less decrease). The evaluation in study 1 and study 2 was at 4 weeks and 8 weeks of treatment, respectively.

7. Main results

Study 1: Marked improvement occurred in a higher percentage of patients receiving kojinmatsu alone (18.1%) or kojinmatsu + tokishakuyakusan (19.7%) than in those receiving tokishakuyakusan alone (10.0%)(P<0.05). Moderate improvement occurred in a higher percentage of patients receiving the combination (47.5%) than in those receiving either tokishakuyakusan or kojinmatsu alone (33.3% and 28.9%, respectively) (P<0.01).

Study 2: Kojinmatsu alone tended to have a higher efficacy rate at 3 g/day than 6 g/day. Marked improvement occurred in considerably more subjects receiving the combination (32.4%) than in those receiving kojinmatsu 6 g/day alone (5.0%), although there was no significant difference due to the small sample size.

8. Conclusions

Kojinmatsu may improve the symptoms of climacteric disorders, and even more so when combined with tokishakuyakusan.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study concludes that the effect of kojinmatsu on climacteric disorders in postmenopausal women is both therapeutic and preventive, widening the clinical application of Kampo formulations. However, it does not mention whether subjects with unidentified complaints had *qikyo* (気虚, *qi* deficiency), which needs kojin, and how much they had *oketsu* (オ血, blood stasis), *kekkyo* (血虚, blood deficiency), or *suidoku* (水毒, water toxin), which needs tokishakuyakusan combination. In-depth studies taking into account Kampo concepts of pathogenesis are desired in future.

12. Abstractor and date

Ushiroyama T, 27 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Ota H. Positioning of Kampo therapy and hormone replacement therapy in treatment of climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2001; 18: 21-9 (in Japanese). Ichushi Web ID: 2002170744

1. Objectives

To compare hormone replacement therapy (HRT) and Kampo therapy as treatment of climacteric disorders.

2. Design

Randomized controlled trial (RCT).

3. Setting

None. The author belonged to the Department of Obstetrics and Gynecology, Tokyo Women's Medical University, Japan.

4. Participants

Ninety-six postmenopausal or ovariectomized patients with climacteric disorders.

5. Intervention

Arm 1: Kampo therapy (keishibukuryogan (桂枝茯苓丸), n=19; kamishoyosan (加味逍遙散), n=11; goshajinkigan (牛車腎気丸), n=8; tokishakuyakusan (当帰芍薬散), n=2; tokakujokito (桃核承気湯), n=2; kihito (帰脾湯), n=2; nyoshinsan (女神散), n=2) (n=46).

Arm 2: HRT (0.625 mg of conjugated estrogen and 2.5 or 5 mg of medroxyprogesterone acetate) (n=50).

No details indicated in the original paper.

6. Main outcome measures

Score on Keio modified menopause index, measured at baseline, 1, 6, and 12 months after the start of administration. Severity was defined as mild for 0–10 points, moderate for 10–20 points, and severe for 20–30 points, and response was defined as a change from severe to moderate, moderate to mild, or a score reduction by two-thirds in mild cases.

7. Main results

HRT improved the following 6 symptoms in 1 month: vasomotor manifestations; nervousness; low back and back pain; depression; insomnia; and headache. In contrast, Kampo therapy did not improve any symptoms in 1 month but improved the following 4 symptoms in 6 months: vasomotor manifestations; malaise; low back and back pain; and nervousness. Among Kampo medicines, only goshajinkigan was effective for low back and back pain.

8. Conclusions

The therapeutic effect of HRT is superior for hot flashes, perspiration, depression, and insomnia, whereas that of Kampo therapy is superior for malaise and chill.

9. From Kampo medicine perspective

The number of patients receiving keishibukuryogan (n=19), kamishoyosan (n=11), or tokishakuyakusan (n=2) was explained by the small number of cases with *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper outlines the characteristics of Kampo medicines and HRT. It recommends that Kampo medicine be administered in more responsive cases with specific symptoms. Subsequent publication of a study of individual Kampo medicines with more sensitive design is awaited.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Takamatsu K, Musha C, Okano H, et al. Study of usefulness of Kampo therapy for climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2002; 19: 111-6 (in Japanese) Ichushi Web ID: 2002193391

Takamatsu K. HRT and Kampo medicine*. *Nippon Konenki Igakukai Zasshi* (*The Journal of the Japan Menopause Society*) 2004; 12: 155-7 (in Japanese)

Takamatsu K, Makita K, Tanabe K, et al. HRT and Kampo medicine*. *Rinsho Kensa* (*The Journal of Medical Technology*) 2004; 48: 877-84 (in Japanese)

Takamatsu K, Tanabe K. Efficacy of Kampo medicine against climacteric disorders*. *Sanfujinka Chiryo* (*Obstetrical and Gynecological Therapy*) 2004; 89: 408-15 (in Japanese). MOL, MOL-Lib

Takamatsu K. Study of the usefulness of Kampo therapy for climacteric disorders – a randomized trial of three major Kampo medicines for treatment of gynecological disease–*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2006; 23: 35-42 (in Japanese). Ichushi Web ID: 2006288782

1. Objectives

To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-*sho*-based (非随証) Kampo medicines for gynecological disease.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Departments of Obstetrics and Gynecology, Tokyo Women's Medical University (1) and Keio University Hospital (2), Japan.

4. Participants

(1) Seventy women receiving ambulatory treatment for climacteric disorders between November 2000 and January 2002.
(2) One hundred women receiving ambulatory treatment for climacteric disorders between January 1993 and December 2000.

5. Intervention

Comparison of clinical efficacy of HRT and Kampo medicine

Arm 1: administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules, TSUMURA Kamishoyosan (加味逍遙散) Extract Granules or TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules before meals for 4–8 weeks (n=70).

Arm 2: continuous coadministration of 0.625 mg t.i.d. of Premarin (conjugated equine estrogen) and 2.5 mg of Provera (medroxyprogesterone acetete) before meals for 4–8 weeks (n=110).

Evaluation of the efficacy of non- *sho*-based therapy with three major Kampo medicines for gynecological disease.

Arm 1: administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules before meals for 4–8 weeks (n=23).

Arm 2: administration of 2.5 g t.i.d. of TSUMURA Kamishoyosan (加味逍遙散) Extract Granules before meals for 4–8 weeks (n=23).

Arm 3: administration of 2.5 g t.i.d. of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules before meals for 4–8 weeks (n=24).

6. Main outcome measures

Presence/absence and improvement of symptoms self-evaluated on a 4-point symptom severity scale using the Keio modified menopause index questionnaire.

7. Main results

Overall response rates for HRT and Kampo therapy were comparable (78.0% responders to HRT and 68.6% responders to Kampo therapy), although improvement was greater in patients receiving Kampo therapy (severity reduced by 2 or more points in 83.0% of patients receiving HRT and 21.4% of those receiving Kampo therapy). There was no difference in the percent who responded to the three non-*sho*-based therapies (65.2% were responders to tokishakuyakusan, 74.0% were responders to kamishoyosan, and 70.8% responders to keishibukuryogan). Kampo therapy was particularly effective for psychiatric manifestations including excitability, depression, irritation, anxiety, and brooding.

8. Conclusions

Using the same questionnaire, this study demonstrated that Kampo therapy has some effect on climacteric disorders, in particular, relieving subjective symptoms at almost the same rate as HRT and showing high efficacy against psychotic manifestations.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In this paper, the rate of symptom improvement after Kampo therapy was approx. one-quarter that after HRT and the three Kampo medicines had comparable efficacy, showing that non-*sho*-based Kampo therapy for "climacteric disorders" is limited. Thus, this study is valuable in that it supports the importance of the *zuisho* (随証, based on pattern) approach to Kampo therapy in the treatment of climacteric disorders.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 20 December 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Ogita Y, Fujimoto S, Ushiroyama T, et al. Efficacy of formulation TK-061 for various climacteric symptoms – comparison with Teikoku Keishibukuryogan Extract Granules*. *Rinsho Fujinka Sanka* (*Clinical Gynecology and Obstetrics*) 2002; 56: 799-810 (in Japanese). Ichushi Web ID: 2003004448

Ogita Y, Fujimoto S, Ushiroyama T, et al. Keishibukuryogan formulation TK-061 prepared with crude drug – verification of efficacy for various climacteric symptoms*. *Sanka to Fujinka* (*Obstetrics and Gynecology*) 2002; 69: 953-62 (in Japanese). Ichushi Web ID: 2003004359 MOL, MOL-Lib

1. Objectives

To investigate the equivalence between non-extracted keishibukuryogan (桂枝茯苓丸) and keishibukuryogan (桂枝茯苓丸) extract.

2. Design

Randomized controlled trial (RCT).

3. Setting

Twenty facilities (the Department of Obstetrics and Gynecology, Osaka City University School of Medicine, the Department of Obstetrics and Gynecology, Hokkaido University School of Medicine, the Department of Obstetrics and Gynecology, Osaka Medical College School of Medicine, et al.), Japan.

4. Participants

One-hundred and ninety-three patients who were diagnosed with climacteric disorders during a 1 year and 5 month period from November 1999 to March 2001, untreated with hormone replacement therapy within 4 weeks before the start of the study, and having body mass index (BMI) ≥20 and body fat <35%. (The per-protocol population included 158 out of these 193 patients).

5. Intervention

Arm 1: oral administration of 6 keishibukuryogan (桂枝茯苓丸) pills containing 5 ingredients (TK-061) t.i.d. (18 tablets/day), n=75.

Arm 2: oral administration of 2.5 g of TEIKOKU Keishibukuryogan (桂枝茯苓丸) Extract Granules (TKK-25) t.i.d. (7.5 g/day), n=83.

6. Main outcome measures

Simple Menopause Index (SMI) improvement rated on a 5-point scale; improvement in blood stasis score; changes in blood hormone concentrations; adverse events.

7. Main results

Response rate to TK-061 and TKK-25 were similar (55.8% *vs* 51.0%, respectively). Blood stasis score was decreased with time after the start of treatment to similarly reduced levels for both arms at week 8. Blood concentrations of estradiole (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) remained unchanged from baseline. The incidences of adverse drug reactions were similar: 22.4% with TK-061 and 23.2% with TKK-25. These adverse drug reactions disappeared naturally or were relieved by symptomatic therapy, suggesting that a causal relationship with treatment cannot be ruled out.

8. Conclusions

TK-061 is equivalent or superior to TKK-255 in increasing the SMI improvement rating, the primary endpoint. Both increase blood stasis score to a similar extent. In addition, neither affects the endocrine system.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events occurred in 22 patients receiving keishibukuryogan pills (22.4%) and 23 patients receiving keishibukuryogan extract granules (23.2%). No serious adverse events occurred. Adverse drug reactions occurred in 12 patients (12.2%) and 9 patients (9.1%), respectively. The global safety was “satisfactory” in 79 patients (80.6%) and 88 patients (88.9%), respectively.

11. Abstractor’s comments

This paper describes a clinical trial comparing keishibukuryogan pills to its extracted formulation, and demonstrates the efficacy of both for climacteric symptoms. Regrettably, however, *ganzai* (丸剤, pills), which proved more effective than the extract in the per-protocol population, is not on the NHI Drug Price list. For the moment, keishibukuryogan pill is only available as an OTC drug.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Koike K, Ohno S, Takahashi N, et al. Efficacy of the herbal medicine unkei-to as an adjunctive treatment to hormone replacement therapy for postmenopausal women with depressive symptoms. *Clinical Neuropharmacology* 2004; 27: 157-62. CENTRAL ID: CN-00490860, Pubmed ID: 15319700

1. Objectives

To evaluate the efficacy of unkeito unkeito (温経湯) for climacteric disorders with depressive symptoms.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One university hospital and one clinic, Japan.

4. Participants

Twenty-four women with climacteric disorders with depressive symptoms and unresponsive to hormone replacement therapy (HRT).

5. Intervention

Arm 1: administration of 7.5 g/day of TSUMURA Unkeito (温経湯) Extract Granules for 6 months followed by administration of 7.5 g/day of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules for 6 months, with 1-month washout between interventions (n=12).

Arm 2: administration of 7.5 g/day of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules for 6 months followed by administration of 7.5 g/day of TSUMURA Unkeito (温経湯) Extract Granules for 6 months, with 1-month washout between interventions (n=12).

HRT was continued in both arms.

6. Main outcome measures

Zung's Self-Rating Depression Scale (ZSDS), State-Trait Anxiety Inventory (STAI-1, 2).

7. Main results

Administration of unkeito produced significant improvement in ZSDS and STAI-1, 2 at 3 months, which persisted to 6 months. The improvement in ZSDS and STAI-1, 2 was significantly greater after unkeito than tokishakuyakusan at both 3 months and 6 months.

8. Conclusions

Unkeito is effective as an adjuvant therapy for climacteric disorders with depressive symptoms in patients unresponsive to HRT, and has superior efficacy to that of tokishakuyakusan.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

This study is a randomized cross-over trial of unkeito and tokishakuyakusan. It suggests that the mechanism of efficacy is the promotion of secretion of cytokine-induced neutrophil chemoattractant (CINC).

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Higuchi T, Tarakida A, Abe K, et al. Comparing the effects of hormone replacement therapy and kamishoyosan treatment on climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2009; 26: 18-23. Ichushi Web ID: 2009197632

Higuchi T, Iino K, Tarakida A, et al. A comparing the effects of kamishoyosan or HRT on climactericdisorders in postmenopausal women: results from a randomized controlled trial. *Nihon Josei Igaku Gakkai Zasshi* (*The Journal of Japan Society for Menopause and Women's Health*) 2012; 20: 305-12 (in Japanese).

1. Objectives

To evaluate effects of hormone replacement therapy (HRT) alone and in combination with kamishoyosan (加味逍遙散) on climacteric disorders.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Study Group for Treatment of Menopausal Unidentified Complaints, Hirosaki University Hospital and twenty other centers, Japan.

4. Participants

One hundred and three patients who were diagnosed with climacteric disorders at the above-mentioned institutions and sought treatment.

5. Intervention

Arm 1: KSS group: TSUMURA Kamishoyosan (加味逍遥散) Extract Granules 2.5 g t.i.d. orally before meals for 8 weeks (n=35).

Arm 2: HRT group: conjugated estrogen formulations or 17β-estradiol patch for 8 weeks (in patients with uterine preservation, medroxyprogesterone acetate was concomitantly administered) (n=34).

Arm 3: Arm 1 + Arm 2 (KSS/HRT group; n=34)

6. Main outcome measures

Changes in climacteric symptom rating scale developed by the Japan Society of Obstetrics and Gynecology (JSOG), at 4 and 8 weeks of treatment from baseline.

7. Main results

Since six participants dropped out of arm 1, 10 from arm 2, and five from arm 3, the efficacy analysis set consisted of a total of 82 patients. 'Dizziness' improved significantly (P<0.05) at Week 4 in arm 1 compared to arm 2. The rate of improvement for 'burning sensation in the head and upper body' was significantly higher (P<0.05) in arm 2 than in arm 1 and the rate for 'proneness to sweating' was significantly higher (P<0.01) in the HRT group than the KSS and the KSS/HRT groups. The KSS/HRT group demonstrated a significantly higher rate of improvement (P<0.05) than the KSS and HRT groups for nocturnal waking and tightness in the chest.

8. Conclusions

As therapies for climacteric disorder, HRT and kamishoyosan demonstrate differing effects for different symptoms. Given the choices for their application and combined use, it would seem that asking patients about the details of their symptoms and carefully analyzing them would be beneficial.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study compared the effects of kamishoyosan, the widely used conventional treatment for female climacteric disorder, and HRT, the standard therapy in Western medicine, and made certain evaluations. As speculated, the study reconfirmed that the effects of these therapies differ for different symptoms. That is, HRT demonstrates greater efficacy for vasomotor nerve disturbance symptoms, as diagnosed by Western medicine. Meanwhile, Kampo medical theory can explain the effects of kamishoyosan for hot flashes, palpitations, burning sensation, sweating in the upper body, and other symptoms. If possible, the authors should make their conclusions after using this study's protocols for comparison of kamishoyosan-pattern and non-kamishoyosan-pattern (非証) participants through rigorous pattern identification. My hope is that guidelines are formulated for appropriate usage with HRT according to Oriental medical principles and on the basis of diagnosis of the absence or presence of saiko-pattern or blood stasis, which would be relatively straightforward for a clinical physician. In terms of future practice, I also hope that the researchers take on the challenge of building the evidence base for proposing the incorporation of kamishoyosan into standard therapy in Japan for climacteric disorder.

12. Abstractor and date

Ushiroyama T, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Plotnikoff GA, Watanabe K, Torkelson C, et al. The TU-025 Keishibukuryogan clinical trial for hot flash management in postmenopausal women: result and lessons for future research. *Menopause* 2011; 18: 886–92. CENTRAL ID: CN-00810843, Pubmed ID: 21738077

1. Objectives

To evaluate the clinical effects of keishibukuryogan (桂枝茯苓丸) for hot flashes in menopausal American women.

2. Design

Randomized controlled trial (RCT).

3. Setting

Allina Center for Health Care Innovation (Minneapolis, MN, USA).

4. Participants

Participants were menopausal American women between 45 and 58 years with a hot flash score of at least 28 points/week (n=178).

5. Intervention

Arm 1: oral administration of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (12.5 g/day) for 12 weeks (n=57).

Arm 2: oral administration of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (7.5 g/day) for 12 weeks (n=62).

Arm 3: oral administration of placebo for 12 weeks (n=59).

6. Main outcome measures

The Greene Climacteric Index (GCI), Pittsburgh Sleep Quality Index (PSQI), and a hot flash scale score.

7. Main results

The hot flash scale score decreased significantly (P<0.001) in all groups 12 weeks after commencement of the study, however no significant difference was observed among the three groups. Similarly, no significant among-group difference was observed in the Greene Climacteric Index (GCI) or the Pittsburgh Sleep Quality Index (PSQI).

8. Conclusions

There is no difference between the effects of keishibukuryogan and placebo on overall climacteric disorder symptoms and sleep quality in American menopausal women.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The incidence of diarrhea was 1.7% in the placebo group, but approximately 20% in the keishibukuryogan groups.

11. Abstractor's comments

This study tested the effects of keishibukuryogan on climacteric disorder, a traditional therapy used in Japan, with the researchers asking menopausal American women to score their symptoms, chiefly hot flashes. keishibukuryogan has been one of the main therapeutic Kampo medicines used for climacteric disorder; it is the subject of many academic articles, and its clinical effects have been reported from a variety of perspectives. The present study found that keishibukuryogan extract preparation, compared to placebo, did not improve outcome in American women. However, keishibukuryogan is not necessarily the first choice for symptoms such as hot flashes, which frequently occur in estrogen-deficiency and climacteric disorder. This study might have demonstrated the superiority of estrogen preparations, which are chiefly Western drugs. However, the study did compare keishibukuryogan's effects on menopausal women whose hot flash score exceeded a certain number and its results do not appear to negate the use of keishibukuryogan in therapy for menopausal women, who suffer a variety of unspecified complaints (especially *oketsu* [瘀血, blood stasis] conditions). The authors say they hang their hopes on the emergence of more effective trial methods to test the effectiveness of traditional therapies such as Kampo. One hopes that the development of such research will revolve around RCTs that compare groups according to objective data based on *sho* (証, pattern).

12. Abstractor and date

Ushiroyama T, 31 December 2012.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Yoshimura A, Sawada K, Sasano T, et al. Effect of Japanese Kampo medicine therapy for menopausal symptoms after treatment of gynecological malignancy. *Obstetrics and Gynecology International* 2018: 1-6. Pubmed ID: 29805451

1. Objectives

To evaluate the effect of Kampo medicines kamikihito（加味帰脾湯）and kamishoyosan（加味逍遙散）on menopausal symptoms in gynecological cancer patients.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (Osaka University Hospital), Japan.

4. Participants

Patients who had menopausal symptoms after receiving treatment of gynecological malignancy between November 2012 and December 2015, and had a Kupperman Menopausal Index (KI) total score of 21 (Moderate) or more. Exclusion criteria were receiving Kampo preparations, herbal preparations, or hormone replacement therapy; a history of or being suspected of having aldosteronism; myopathy, or hypokalemia.

5. Intervention

Arm 1: KRACIE Kamikihito（加味帰脾湯）Extract Fine Granules 3.75 g b.i.d. (before or with a meal) for 8 weeks (n=18).

Arm 2: KRACIE Kamishoyosan（加味逍遙散）Extract Fine Granules 3.0 g b.i.d. (before or with a meal) for 8 weeks (n=15).

6. Main outcome measures

The treatment was given for 8 weeks. A KI questionnaire was used to assess subjective symptoms, and the KI total score and each domain score were examined. For the safety evaluation, any adverse events during the study period were evaluated.

7. Main results

Three patients in Arm 1 and 1 patient in Arm 2 were withdrawn from the study, and missing data were noted in 1 patient in Arm 1. Thus, the analysis of therapeutic efficacy was performed on 14 patients in Arm 1 and 14 patients in Arm 2. In both groups, the KI total scores before Kampo therapy (baseline) were significantly increased from the scores before anticancer therapy . After the start of Kampo therapy, the KI total scores decreased in both groups, and significantly improved from baseline at Weeks 4 and 8. Among the KI subscores, significant improvements were shown for 3 domains in Arm 1 and 6 domains in Arm 2.

8. Conclusions

Kampo therapy may contribute to the tailored medical management of patients with symptoms after receiving treatment for gynecologic malignancy, thus improving the patient's QOL.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two patients in Arm 1 had adverse events of unknown causality (i.e., diarrhea in 1 patient and joint pain in another patient).

11. Abstractor's comments

This clinical study is of interest in that it was designed to determine the effect of Kampo medicines on menopausal symptoms after treatment of cancer. Some menopausal symptoms after treatment of cancer are speculated to improve with the administration of Kampo medicines. This study compared two Kampo medicines of kamikihito and kamishoyosan, and showed that both were effective, with no significant difference between the two groups. As an RCT, however, adequate selection of the control group should be an issue. Further studies in more patients and the determination of similar effects of other Kampo medicines are awaited.

12. Abstractor and date

Kato Y, 1 September 2019.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Yasui T, Matsui S, Yamamoto S, et al. Effects of Japanese traditional medicines on circulating cytokine levels in women with hot flashes. *Menopause* 2011; 18: 85–92. CENTRAL ID: CN-00787935, Pubmed ID: 20647958

1. Objectives

To evaluate the effects of keishibukuryogan (桂枝茯苓丸) and kamishoyosan (加味逍遙散) on levels of circulating cytokines in patients with hot flashes.

2. Design

Quasi-randomized controlled trial (Quasi-RCT).

3. Setting

Outpatients Clinic, Department of Obstetrics and Gynecology, Tokushima University Hospital, Japan.

4. Participants

One hundred twenty women with vasomotor symptoms (hot flashes, night sweats, etc.) but no use of drugs affecting the immune system within the previous year, including 17 women who received bilateral ovariectomy within the previous year and 103 perimenopausal women who were menstruating regularly (n=7), menstruating irregularly within the previous 12 months (n=51), and no longer menstruating (last menses within the previous year; n=45).

5. Intervention

Participants who wanted to receive treatment were allocated to arm 2 (odd-number days) or arm 3 (even-number days). Participants who did not want treatment were allocated to arm 1.

Arm 1: follow up only, no treatment (n=40).

Arm 2: TSUMURA Keishibukuryogan Extract Granules (2.5 g t.i.d) for 6 months (n=40).

Arm 3: TSUMURA Kamishoyosan Extract Granules (2.5 g t.i.d) for 6 months (n=40).

6. Main outcome measures

Hot flash symptoms (severe, moderate, or mild according to FDA hot flash assessment criteria); circulating levels of IL-1β, IL-5, IL-6, IL-7, IL-8, IL-10, TNF-α, MCP-1, and MIP-1β before and 6 months after administration.

7. Main results

Improvement rates in hot flashes were significantly higher in arm 2 and arm 3 compared to arm 1 ($P<0.01$). Comparisons before and after treatment in the hot flash improvement group showed that MCP-1, IL-8, and MIP-1β decreased significantly in arm 2 ($P<0.05$ for both), while IL-6, IL-8, and MIP-1β decreased significantly in arm 3 ($P<0.05$ for both).

8. Conclusions

Keishibukuryogan and Kamishoyosan improve hot flashes by lowering circulating levels of IL-8 and MCP-1, which are indicators of blood vessel inflammation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This article describes the therapeutic value and mechanism of action of keishibukuryogan and kamishoyosan in menopausal hot flashes. Animal research has shown that keishibukuryogan is effective for peripheral hot flashes mediated by calcitonin gene-related peptide, and kamishoyosan is effective for central hot flashes mediated by luteinizing hormone-releasing hormone; therefore, it may be possible to clarify the differences between keishibukuryogan and kamishoyosan by allocating participants according to their *sho* (証, pattern), using a medical questionnaire or the like. The outcomes of further research are anticipated.

12. Abstractor and date

Nakata H, 31 December 2012

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Takamatsu K, Fujii E, Mizuno H, et al. An investigation of the usefulness of nyoshinsan for climacteric disorder*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 95-100 (in Japanese).

1. Objectives

To verify the efficacy of nyoshinsan (女神散) for female climacteric disorder.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One center: Tokyo Women's Medical University Hospital, Japan.

4. Participants

Eighty-eight post-menopausal women referred to a menopausal outpatient clinic for climacteric disorder between November 2000 and January 2002.

5. Intervention

Arm 1: TJ-67 group: TSUMURA Nyoshinsan (女神散) Extract Granules (2.5 g t.i.d.) taken before meals (n=18).

Arm 2: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules (2.5 g t.i.d.) taken orally before meals (n=23).

Arm 3: TSUMURA Kamishoyosan (加味逍遙散) Extract Granules (2.5 g t.i.d.) taken orally before meals (n=23).

Arm 4: TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (2.5 g t.i.d.) taken orally before meals (n=24).

The administration period was 4–8 weeks, depending on the patient.

6. Main outcome measures

Objective evaluation of symptom changes and their details.

(Keio menopausal index questionnaire, Self-rating Depression Scale [SDS] questionnaire).

7. Main results

There was no significant difference in the overall results for climacteric disorder between arm 1 and arms 2 to 4 collectively, and between each arm. The effect on the psychiatric symptoms of nocturnal awakening and depression appeared to be strong in arm 1. The effect on symptoms least affected by treatment was about the same in arm 1 and in arms 2 to 4. 'Palpitations', the symptom most responsive to treatment in arms 2 to 4, was significantly less responsive to treatment in arm 1, while comparison with each formulation showed a significant difference to arm 2 and to arm 3. The raw SDS scores changed significantly in response to treatment in arms 2 to 4 collectively and also to arm 4 individually ($P<0.05$), but not in response to treatment in arm 1. Among the patients in arm 1 with a BMI of 18.5–23, nyoshinsan had a significantly greater effect on those with higher BMI ($P<0.01$).

8. Conclusions

Nyoshinsan and the three major conventional Kampo medications for women (tokishakuyakusan, kamishoyosan, and keishibukuryogan) have similar effects on female climacteric disorder. Therefore proactive inclusion of nyoshinsan into treatment options is recommended.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no potentially problematic adverse effects.

11. Abstractor's comments

This study investigated and compared the effects of nyoshinsan for treatment of female climacteric disorder with those of tokishakuyakusan, kamishoyosan, and keishibukuryogan, which are considered the three major conventional Kampo medications for women. Although it was a randomized controlled trial that did not take pattern identification into account, it is worth noting that 66.7% of the effects of nyoshinsan, tokishakuyakusan, kamishoyosan, and keishibukuryogan were confirmed. The finding of greater effectiveness in women with relatively high BMI suggests that effectiveness could be increased by prescribing these medications on the basis of Kampo diagnosis of deficiency/excess pattern. However, to compare the results for nyoshinsan with the results for the three major conventional Kampo medications for women, by using the results from this four-group comparative study, undeniably presents the problem of multiplicity: essentially, the study requires randomization between two groups, nyoshinsan and the three major conventional Kampo medications for women. Further study offers some promise.

12. Abstractor and date

Ushiroyama T, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on shoulder stiffness in climacteric women. *Climacteric* 2013; 16: 447-52. (in Japanese with English abstract) CENTRAL ID: CN-00920084, Pubmed ID: 23113540

1. Objectives

To verify the clinical efficacy of porcine placental extract on shoulder stiffness in climacteric women.

2. Design

Randomized controlled trial (RCT).

3. Setting

Kanazawa University Hospital and Sugita Clinic (2 institutions), Japan.

4. Participants

Sixty-six climacteric women with shoulder stiffness.

5. Intervention

Arm 1: Three capsules/day of porcine placenta extract (350 mg/capsule) p.o. for 12 weeks, followed by 6 capsules/day p.o. for 12 weeks (n=33).
Arm 2: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules p.o. for 24 weeks (n=33).

6. Main outcome measures

Degree of shoulder stiffness on a visual analogue scale (VAS).

7. Main results

Among 66 patients enrolled, 7 patients did not complete the study. The VAS score was significantly lower (at the end of the study: 76.4% reduction from baseline, $P<0.01$) in arm 1 than in arm 2.

8. Conclusions

Oral administration of porcine placenta extract is effective in improving prolonged shoulder stiffness in climacteric women.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the study period, administration of porcine placenta extract did not affect serum chemistry values, BMI, cardiovascular function, estradiol levels, or thyroid hormone levels, and did not cause abnormal uterine bleeding.

11. Abstractor's comments

Placenta extract is currently used as a supplement and advertised as a product effective in relieving menopausal symptoms. The present study evaluated the clinical efficacy of porcine placenta extract, focusing on shoulder stiffness in climacteric women. It deserves some appreciation. Placenta extract contains many bioactive substances, of which low molecular weight peptides, etc., are thought to enter the systemic circulation from the gastrointestinal tract and exert effects in target organs. Its mechanism of action, however, remains unknown. Prior treatment with tokishakuyakusan may also affect the results. It is hoped that the authors will also investigate the relationship and differences between biologics and Kampo.

12. Abstractor and date

Ushiroyama T, 6 June 2015, 5 October 2015.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on shoulder stiffness in climacteric women. *Climacteric* 2013; 16: 447-52. (in Japanese with English abstract) CENTRAL ID: CN-00920084, Pubmed ID: 23113540

1. Objectives

To verify the clinical efficacy of porcine placental extract on shoulder stiffness in postmenopausal women taking hormone replacement therapy.

2. Design

Randomized controlled trial (RCT).

3. Setting

Kanazawa University Hospital and Sugita Clinic (2 institutions), Japan.

4. Participants

Fifty-four postmenopausal women with shoulder stiffness taking hormone replacement therapy.

5. Intervention

Arm 1: Hormone replacement therapy (product unknown) for 3 months, followed by hormone replacement therapy + 3 capsules/day of porcine placenta extract (350 mg/capsule) p.o. for 12 weeks (n=27).

Arm 2: Hormone replacement therapy (product unknown) for 3 months, followed by hormone replacement therapy + TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules p.o. for 12 weeks (n=27).

6. Main outcome measures

Degree of shoulder stiffness on a visual analogue scale (VAS).

7. Main results

Four of 54 patients were withdrawn. The VAS score was significantly lower (at the end of the study: 64.8% reduction from baseline, $P<0.01$) in arm 1 than in arm 2.

8. Conclusions

In postmenopausal women taking hormone replacement therapy, oral administration of porcine placenta extract is effective in improving prolonged or treatment-refractory shoulder stiffness.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the study period, administration of porcine placenta extract did not affect serum chemistry values, BMI, cardiovascular function, estradiol levels, or thyroid hormone levels, and did not cause abnormal uterine bleeding.

11. Abstractor's comments

Placenta extract is currently used as a supplement and advertised as a product effective in relieving menopausal symptoms. The present study evaluated the clinical efficacy of porcine placenta extract, focusing on shoulder stiffness that is prolonged or refractory to treatment in climacteric women taking hormone replacement therapy. It deserves some appreciation. Placenta extract contains many bioactive substances, of which low molecular weight peptides, etc., are thought to enter the systemic circulation from the gastrointestinal tract and exert effects in target organs. Although the mechanism of action of porcine placenta extract remains unknown, its effectiveness in improving shoulder stiffness refractory to hormone replacement therapy suggests a mechanism that is not mediated by estrogen receptors. Prior treatment with tokishakuyakusan may also affect the results. It is hoped that the authors will also investigate the relationship and differences between biologics and Kampo.

12. Abstractor and date

Ushiroyama T, 6 June 2015, 5 October 2015.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on climacteric symptoms in peri- and postmenopausal women. *Climacteric* 2013; 16: 28-35. Pubmed ID: 22920723

1. Objectives

To evaluate clinical effects of porcine placental extract on climacteric symptoms in peri-postmenopausal women.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital and 1 clinic, Japan.

4. Participants

Seventy-six women with climacteric symptoms.

5. Intervention

Arm 1: TSUMURA Tokishaykuyakusan (当帰芍薬散) Extract Granules administered orally at 7.5 g/day for 24 weeks (n=38).

Arm 2: Porcine placental extract (350 mg/capsule) administered orally 3 capsules/day for 12 weeks followed by 6 capsules/day for 12 weeks (n=38).

6. Main outcome measures

Severity (scores) of climacteric symptoms assessed by the simplified menopausal index (SMI), Zung self rating depression scale (ZSDS), and Spielberger state-trait anxiety inventory (STAI).

7. Main results

Compared with the tokishaykuyakusan alone group (control), the porcine placental extract group had significantly lower SMI and scores on the ZSDS and STAI ($P<0.01$).

8. Conclusions

Porcine placental extract may be an effective option for the treatment of climacteric symptoms in peri-postmenopausal women.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the study period, porcine placental extract treatment did not affect other variables including serum chemistry levels and BMI and caused no adverse drug reactions.

11. Abstractor's comments

Placental extracts have been commercialized and used as a supplement to alleviate climacteric symptoms. This article is valuable because treatment effects of porcine placental extract on climacteric symptoms in peri-postmenopausal women were clinically evaluated using SMI, ZSDS score, and STAI score. Placental extract contains many bioactive substances, including low-molecular-weight peptides, which appear to be absorbed from the gastrointestinal tract into systemic circulation, where they affect targeted organs. However, their mechanisms are unknown. Although the influence of prior treatment with tokishaykuyakusan could not be ruled out, further studies on the relation and difference between these biopharmaceuticals and Kampo medicines are anticipated.

12. Abstractor and date

Ushiroyama T, 31 March 2017.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Ushiroyama T, Ikeda A, Kakuma K, et al. Comparing the effects of estrogen and an herbal medicine on peripheral blood flow in post-menopausal women with hot flashes: hormone replacement therapy and gui-zhi-fu-ling-wan (keishibukuryogan), a Kampo medicine. *The American Journal of Chinese Medicine* 2005; 33: 259-67. CENTRAL ID: CN-00528621, Pubmed ID: 15974485

1. Objectives

To compare the efficacy of keishibukuryogan（桂枝茯苓丸）and hormone replacement therapy (HRT) for relief of hot flashes and chills.

2. Design

Randomized controlled trial (RCT).

3. Setting

None. (The authors belonged to the Department of Obstetrics and Gynecology, Osaka Medical College.), Japan

4. Participants

Three-hundred and fifty-two postmenopausal patients with hot flashes untreated with HRT in the past 3 months and without past history of chronic diseases, aged 46–58 years. Patients with coronary artery anomaly, thrombotic diseases, cerebral infarction, hypertension, renopathy, and allergic conditions were excluded.

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Keishibukuryogan (桂枝茯苓丸) (TJ-25) t.i.d. (daily dose 7.5 g).
Arm 2: oral administration of 0.625 mg of Premarin and 2.5 mg of Provera s.i.d. (i.e., HRT).

6. Main outcome measures

Peripheral blood flow, measured pre- and post-administration by a laser Doppler velocimeter at 3 sites (jaw, finger tips, and toes).

7. Main results

Both HRT and keishibukuryogan reduced blood flow in the jaw and finger tips. Blood flow in the toes was increased by keishibukuryogan but unchanged by HRT.

8. Conclusions

Keishibukuryogan is effective for chills, especially in the legs, in patients with hot flashes. HRT is ineffective for chills. Although both HRT and keishibukuryogan are effective for hot flashes, the latter is more effective.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is a controlled trial of HRT and keishibukuryogan. It ensures objectivity by measuring hot flashes and chills in terms of blood flow. It would also be interesting to investigate how well these medicines change blood flow in patients without hot flashes.

12. Abstractor and date

Nakata H, 1 April 2008.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Matsuo A, Koike K, Hoshina Y, et al. Study of the efficacy of unkeito for depressive and anxiety symptoms during menopause that are refractory to hormone replacement therapy*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2005; 22: 70-4 (in Japanese). Ichushi Web ID: 2005235338

Koike K. A slight advantage of Kampo treatment for gynecological disease 4: Menopausal depressed mood and the herbal medicine Unkei-to. *Sanfujinka Chiryo* (*Obstetrical and Gynecological Therapy*) 2006; 92: 784-6 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the usefulness of Kampo medicine for treatment of depressive patients refractory to hormone replacement therapy (HRT).

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

None (the authors belonged to the Department of Obstetrics and Gynecology, Kanazawa University School of Medicine), Japan.

4. Participants

Twenty-four depressive outpatients who visited the menopause clinic and were unresponsive to 6 months of HRT.

5. Intervention

Arm 1: HRT combined with TSUMURA Unkeito (温経湯) 7.5 g t.i.d. for 6 months. Washout for one month. Then HRT combined with TSUMURA Tokishakuyakusan (当帰芍薬散) 7.5 g t.i.d. for 6 months (n=12).

Arm 2: HRT combined with TSUMURA Tokishakuyakusan (当帰芍薬散) 7.5 g t.i.d. for 6 months. Washout for one month. Then, HRT combined with TSUMURA Unkeito (温経湯) 7.5 g t.i.d. for 6 months (n=12).

Hormone replacement therapy (HRT): Continuous use of transdermal estradiol (1 patch/2 days) and medroxyprogesterone (5 mg/day for 10 days).

6. Main outcome measures

Changes in Self-Rating Depression Scale (SDS) and State Trait Anxiety Inventory (STAI) scores after 6-month treatment with the unkeito or tokishakuyakusan combination.

7. Main results

In arm 1, SDS depression score was significantly decreased ($P<0.01$, testing method not indicated). STAI state and trait anxiety scores were significantly improved ($P<0.01$, testing method not indicated).

8. Conclusions

HRT + unkeito combination therapy is effective for relief of HRT-refractory depression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper is based on the previously published "Koike K, Ohno S, Takahashi N, et al. Efficacy of the herbal medicine Unkei-to as an adjunctive treatment to hormone replacement therapy for postmenopausal women with depressive symptoms. *Clinical Neuropharmacology* 2004; 27: 157-62." This study demonstrated the efficacy of unkeito for depressive and anxiety symptoms refractory to HRT administered as treatment for climacteric disorders. However, something seems wrong with the definition of "depressive and anxiety symptoms refractory to hormone replacement therapy." Kampo medicine as treatment of depressive and anxiety symptoms would be better assessed in comparison with antidepressants and anxiolytics. In addition, the statement in the text that 3-month oral administration produced an effect lasting 6 months raises the concern that a 1-month washout in the cross-over comparison is sufficient. Future research is expected.

12. Abstractor and date

Nakata H, 1 April 2008, 8 April 2009, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Ushiroyama T, Sakuma K, Nosaka S. Comparison of effects of vitamin E and wen-jing-tang (unkei-to), an herbal medicine, on peripheral blood flow in post-menopausal women with chilly sensation in the lower extremities: a randomized prospective study. The *American Journal of Chinese Medicine* 2006; 34: 969-79. CENTRAL ID: CN-00577271, Pubmed ID: 17163586

1. Objectives

To compare the effects of unkeito (温経湯) and vitamin E on peripheral blood flow.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Osaka University Faculty of Medicine, Japan.

4. Participants

One hundred and eighty post-menopausal women (42–61 years old) with chilly sensation in the lower extremities and no treatment by hormone replacement within 3 months.

5. Intervention

Arm 1: administration of unkeito (温経湯) (TSUMURA Unkeito Extract Granules 7.5 g/day) for 8 weeks (60 patients; of these, 58 were included for analysis).
Arm 2: administration of vitamin E (tocopherol nicotinate 600 mg/day) for 8 weeks (60 patients; of these, 55 were included for analysis).
Arm 3: no treatment for 8 weeks (60 patients; of these 48 were included for analysis).

6. Main outcome measures

Items evaluated by questionnaire on a 4-point scale and submandibular, middle finger, and middle toe blood flow measured by Doppler.

7. Main results

Chilly sensation evaluated by questionnaire was significantly improved in arm 1. Doppler blood flow evaluation revealed improved peripheral blood flow in the lower extremities in arm 1 and arm 2. While vitamin E significantly increased middle finger blood flow, unkeito suppressed blood flow (that was originally too high) and increased poor blood flow.

8. Conclusions

Unkeito is superior to vitamin E in improving blood flow and reducing chill.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No special problems noted.

11. Abstractor's comments

This paper compared the ability of unkeito and vitamin E to improve peripheral blood flow. It concluded that unlike vitamin E, unkeito improves chill by increasing poor circulation and improves hot flushes by decreasing excessive blood flow, well characterizing the Kampo medicine.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Yasui T, Irahara M, Aono T. Studies on treatment with the combination clomiphene citrate and toki-shakuyaku-san. *Nippon Funin Gakkai Zasshi* (*Japanese Journal of Fertility and Sterility*) 1995; 40: 83-91 (in Japanese).

1. Objectives

To compare the effects of clomiphene monotherapy with those of tokishakuyakusan (当帰芍薬散) plus clomiphene for infrequent menses, anovular menstrual cycle, and amenorrhea.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The Department of Obstetrics and Gynecology of Tokushima University Hospital and related hospitals (13 institutions), Japan.

4. Participants

Ninety-three outpatients seen at the above institutions and diagnosed with infrequent menses, anovular menstrual cycle, or amenorrhea between January 1992 and March 1994.

5. Intervention

Arm 1: oral administration of clomiphene (50 mg) after meals for 5 days from day 5 of the menstrual cycle + TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals. If no ovulation occurred, clomiphene was increased by one tablet per day at each subsequent cycle (n=41).

Arm 2: oral administration of clomiphene (50 mg) after meals for 5 days from day 5 of the menstrual cycle. If no ovulation occurred, clomiphene was increased by one tablet per day at each subsequent cycle (n=52).

6. Main outcome measures

Ovulation and pregnancy as determined by confirmation of a period of high basal body temperature lasting 10 or more days, or increased progesterone level (≥10 ng/mL) in mid-luteal phase. Improvement in endocrine condition as indicated by blood levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone. Assessments were made after treatments for 3 or more cycles.

7. Main results

There were no significant between-group differences in the ovulation rates evaluated for each treatment arm at each cycle, as well as in the pregnancy rate for each arm. In patients who became pregnant, the number of cycles until pregnancy was significantly lower in the combination therapy group (1.86 cycles) than in the monotherapy group (3.82 cycles) (P<0.05). There were also no significant between-group differences during any treatment cycle in pituitary hormone and estradiol levels, the number of growing ovarian follicles, cervical mucus volume, endometrial thickness in the mid-luteal phase, and the period of high basal body temperature. Both the progesterone level and progesterone/estradiol concentration ratio in the preovulatory period were higher in the clomiphene monotherapy group than in the combination therapy group (P<0.05).

8. Conclusions

In patients with infrequent menses, anovular menstrual cycle, or amenorrhea, combination therapy, as compared with monotherapy, did not improve ovulation rate but did facilitate pregnancy, suggesting the normalizing effects of tokishakuyakusan on sex hormones in the ovary.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The present study compared the efficacy of combination therapy with tokishakuyakusan with the efficacy of clomiphene (used as a positive control with proven effects on abnormal menstrual cycles). The conclusion is that tokishakuyakusan could shorten the time until pregnancy and is therefore clinically applicable. From the point of view of western medicine, more detailed classification of the primary disease would be useful for the determination of indications for tokishakuyakusan in women with abnormal menstrual cycles who want to become pregnant. To compare the physiological and endocrine data, the combination therapy group should be subgrouped on the basis of *sho* (証, pattern). Subgroup analysis of the data is expected.

12. Abstractor and date

Ushiroyama T, 28 August 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Takushima Y, Michigami F. Clinical study of saireito on gestational edema and upper gastrointestinal symptoms. *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2010; 64: 709–15 (in Japanese). Ichushi Web ID: 2011072703 MOL, MOL-Lib

1. Objectives

To evaluate the effectiveness of saireito (柴苓湯) combined with either sojutsu (蒼朮, Atractylodes Lancea Rhizome) or byakujutsu (白朮, Atractylodes Rhizome) as constituent crude drugs for lower limb edema and functional dyspepsia-like gastrointestinal symptoms.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital, Japan.

4. Participants

Fifty women in the latter stage of pregnancy with lower limb edema not associated with hypertension requiring drug therapy, and gastrointestinal symptoms such as appetite loss.

5. Intervention

Arm 1: saireito (柴苓湯) extract granules (manufacturer not identified) 3.0 g t.i.d. combined with sojutsu (蒼朮, Atractylodes Lancea Rhizome) for 4 weeks (n=25).

Arm 2: saireito (柴苓湯) extract granules (manufacturer not identified) 4.05 g b.i.d. combined with byakujutsu (白朮, Atractylodes Rhizome) for 4 weeks (n=25).

6. Main outcome measures

Ankle edema (ankle circumference), plantar edema (plantar circumference), gastrointestinal symptoms (questionnaire).

7. Main results

Ankle circumference began to improve significantly 2 weeks after saireito administration in both arms 1 and 2 ($P<0.05$). Improvement of plantar circumference after 4 weeks was significant in Arm 2 but not in Arm 1. Epigastralgia and bloating after meals at the end of the 4-week period of administration ($P<0.05$), epigastric heat sensation after treatment for 3 weeks ($P<0.01$), heaviness in the stomach after treatment for 3 weeks ($P<0.05$), and upper gastrointestinal symptoms overall (including gastrointestinal symptoms) after treatment for 3 weeks ($P<0.05$) were significantly improved in Arm 2 only.

8. Conclusions

Saireito combined with sojutsu and saireito combined with byakujutsu are both effective for lower limb edema in pregnancy. Of these combinations, only saireito + byakujutsu improve epigastric symptoms significantly.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed.

11. Abstractor's comments

This is a quasi-randomized controlled trial in which medications were allocated in order of patient presentation. It is a significant clinical trial that compared the effects of byakujutsu or sojutsu with saireito for lower limb edema and epigastric symptoms in pregnancy. Before-after comparison demonstrated that only saireito combined with byakujutsu is effective for epigastric symptoms. This was probably a reflection of byakujutsu's capacity to promote gastrointestinal function. Therefore, the two different saireito formulae appear to be indicated for different patterns. A further study is recommended for comparison of groups in a randomized trial that includes a placebo group.

12. Abstractor and date

Okabe T, 1 December 2012.

15. Ante/Post-partum Diseases

References

Ushiroyama T, Araki R, Sakuma K, et al. Efficacy of the kampo medicine xiong-gui-jiao-ai-tang, a traditional herbal medicine, in the treatment of threatened abortion in early pregnancy. *American Journal of Chinese Medicine* 2006; 34: 731-40. CENTRAL ID: CN-00457564, Pubmed ID: 17080540

Ushiroyama T, Sakuma K, Nosaka S, et al. Clinical efficacy of kyukikyogaito for imminent abortion with uterine hemorrhage*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2006; 23: 100-3 (in Japanese). Ichushi Web ID: 2006303253

1. Objectives

To evaluate the efficacy of kyukikyogaito（キュウ帰膠艾湯）as a therapeutic drug for imminent abortion in patients with uterine hemorrhage.

2. Design

Randomized controlled trial (RCT).

3. Setting

None. (The authors belonged to the Department of Obstetrics and Gynecology, Osaka Medical College and the Department of Obstetrics and Gynecology, Takatsuki Red Cross Hospital.), Japan.

4. Participants

Seventy-two patients who visited the hospital with a complaint of uterine hemorrhage and were given a diagnosis of imminent abortion.

5. Intervention

Arm 1: bed rest and administration of 2.5 g of TSUMURA Kyukikyogaito (キュウ帰膠艾湯) Extract Granules (TJ-77) t.i.d. (n=36).

Arm 2: bed rest and administration of human chronic gonadotropin (hCG) (alternate-day administration of 5,000 U) (n=36).

6. Main outcome measures

EFS (echo free space), number of days to hemostasis.

7. Main results

Statistical analysis was carried out using the chi-square test and Wilcoxon's signed-rank test. Significantly fewer days were required for hemostasis and for EFS disappearance in arm 1 (both $P<0.0001$). EFS on day 7 of treatment was significantly smaller in arm 1 ($P<0.0001$).

8. Conclusions

Kyukikyogaito (TJ-77) shortens the time to hemostasis in patients with imminent abortion and uterine hemorrhage.

9. From Kampo medicine perspective

The explanation of the efficacy of kyukikyogaito for imminent abortion is based on the blood replenishing effect of toki, shakuyaku, and senkyu as well as the hemostatic effect of akyo and gaiyo.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper shows that EFS disappears significantly earlier in patients with imminent abortion after treatment with a Kampo medicine. Considering that in principle, bed rest is the only treatment for imminent abortion with no effective therapeutic method having been established, the effects of kyukikyogaito are worthy of attention. However, without significant differences in the final outcome of fetal mortality, kyukikyogaito is reasonably considered to have limited efficacy and to contribute to better patient QOL through a reduction in length of hospital stay, etc.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

References

Mizuno M, Sato K, Mori T, et al. Clinical evaluation of TSUMURA Tokishakuyakusan and ritodrine hydrochloride combination therapy in the management of threatened premature delivery*. *Sanka to Fujinka* (*Obstetrics and Gynecology*) 1992; 59: 469–80 (in Japanese).

1. Objectives

To objectively evaluate the usefulness of tokishakuyakusan (当帰芍薬散) combined with ritodrine hydrochloride in the management of threatened premature labor.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Thirty-six facilities nationwide including the Department of Obstetrics and Gynecology, University of Tokyo Hospital, Japan.

4. Participants

One hundred and forty-seven patients diagnosed with threatened premature labor (24 weeks to less than 37 weeks of pregnancy) at the above facility between June 1989 and August 1990 with a cervical dilation of <3.5 cm and effacement of <80%.

5. Intervention

Arm 1: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals, started before or at the start of ritodrine hydrochloride (Utemerin; UT) (pretreatment group; n=78).

Arm 2: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals, started after the occurrence of adverse reactions to UT (post-treatment group; n=69).

6. Main outcome measures

Improvement in uterine contraction and prolongation of gestation evaluated on a 5-point scale; effect on maternal heart rate, fetal heart rate, and adverse drug reactions to UT evaluated on a 5-point scale; safety evaluated on a 3-point scale based on intrapartum, neonatal, and puerperal findings and laboratory findings; and usefulness with regard to clinical efficacy and safety evaluated on a 5-point scale.

7. Main results

The pretreatment, compared with the posttreatment, allowed the UT drip rate to be significantly raised. The pretreatment significantly suppressed uterine contraction at 1 hr of UT administration. There were no significant between-arm differences in symptoms of threatened premature labor. At 2 hr of UT administration, significantly more pretreated patients (≥20%) than posttreated patients (10%) had no UT-associated palpitation (P<0.0001). Similarly, significantly fewer pretreated patients had increased heart rate, tremor, decreased blood pressure, headache, and facial flushing. Full term delivery occurred in 71.8% of the pretreatment group and 62.5% of the posttreatment group. There was no between-arm difference in style of delivery and neonatal or puerperal findings.

8. Conclusions

Tokishakuyakusan relieves the adverse reactions to ritodrine hydrochloride, thereby enabling administration of more ritodrine hydrochloride to suppress uterine contraction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although their incidence and severity are not mentioned, adverse drug reactions associated with UT administration were relieved in 86% and 90% of patients receiving tokihsakuyakusan pretreatment and posttreatment, respectively.

11. Abstractor's comments

This study demonstrated that tokishakuyakusan (a drug traditionally used to prevent abortion) relieves or suppresses the adverse drug reactions to ritodrine hydrochloride (a representative western medicine used for tocolysis to prevent abortion), thereby allowing maintenance therapy with ritodrine hydrochloride at higher levels. It shows that the fusion of oriental and western medicine can contribute to clinical practice. However, in principle, a tocolytic Kampo medicine should be started when pregnancy is diagnosed. Moreover, the effect of tokishakuyakusan should have been weak in patients who had already passed the stage of *mibyo* (未病, predisposition of disease) and been clinically diagnosed with threatened premature labor. Therefore, future studies should use a protocol starting in the first trimester and have an RCT design.

12. Abstractor and date

Ushiroyama N, 10 September 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Takushima Y, Inoguchi H, Study on usefulness of kyukichoketsuin for control of puerperium – comparison with methylergometrine maleate (1st report) -*. *Progress in Medicine* 2001; 21: 1535-42 (in Japanese). Ichushi Web ID: 2002032923 MOL, MOL-Lib

1. Objectives

To evaluate the usefulness of kyukichoketsuin（キュウ帰調血飲） for control of puerperium.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

None (authors belong to the Department of Obstetrics and Gynecology, Yamato Municipal General Hospital), Japan.

4. Participants

Forty-seven puerperants, who had a vaginal delivery after the 36th week of pregnancy and no abnormal bleeding of more than 1,000 mL, were randomized to receive either kyukichoketsuin or methylergometrine maleate.

5. Intervention

Arm 1: oral administration of 1 sachet (2.0 g) of TAIKODO Kyukichoketsuin (キュウ帰調血飲) Extract Granules (EK-230) t.i.d. (n=23)
Arm 2: oral administration of 1 tablet (0.125 mg) of Metenarin t.i.d. (n=24)

6. Main outcome measures

Uterine volume, length of uterine fundus, lower abdominal pain score, and amount of lactation during 1 to 5 days postpartum. Improvement in outcome measures compared between groups.
Adverse drug reactions: described symptoms.

7. Main results

Statistical analysis used *t*-test, chi-square test, and Wilcoxon's signed-rank test. There was no significant between-group difference in uterine volume or length of uterine fundus. Lower abdominal pain was significantly less frequent in patients receiving kyukichoketsuin on postpartum days 1 ($P<0.0028$), 2 ($P<0.0005$), and 4 ($P<0.0232$). Patients receiving kyukichoketsuin secreted significantly more milk on postpartum days 3 ($P<0.0345$), 4 ($P<0.0368$), and 5 ($P<0.0177$). Regarding safety, pain associated with uterine contraction was so severe in patients receiving Metenarin as to preclude continued treatment in 2 patients, whereas no adverse drug reactions occurred in the kyukichoketsuin group.

8. Conclusions

Kyukichoketsuin could be an alternative medication to methylergometrine maleate.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Treatment was discontinued in two patients receiving methylergometrine maleate because of severe lower abdominal pain (associated with uterine contraction), whereas no adverse drug reactions occurred in the kyukichoketsuin group.

11. Abstractor's comments

The routine use of postpartum methylergometrine maleate has been criticized and is now limited only to cases such as uterine subinvolution. Therefore, this paper highlighting the effect of kyukichoketsuin, which is associated with few adverse drug reactions, is meaningful. However, since this paper does not address the effect of suckling stimulation and breast massage on uterine contraction and lactation promotion, further investigation of the effectiveness of oral kyukichoketsuin is expected.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

References

Sakuma K, Ushiroyama T, Akise D, et al. Clinical efficacy of kyukichoketsuin for regulation of puerperal psychosomatic functions. *Sanfujinka no Shinpo* (*Advances in Obstetrics and Gynecology*) 2002; 54: 80-6 (in Japanese with English abstract). Ichushi Web ID: 2002151144 MOL, MOL-Lib

Ushiroyama T, Sakuma K, Souen H, et al. Therapeutic effects of kyuki-choketsu-in in restoring postpartum physical condition. *The American Journal of Chinese Medicine* 2003; 31: 437-44. CENTRAL ID: CN-00457564, Pubmed ID: 12943174

1. Objectives

To evaluate the efficacy and safety of kyukichoketsuin（キュウ帰調血飲）for puerperal psychosomatic disorder.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Osaka Medical College Hospital and associated facilities, Japan.

4. Participants

One-hundred and seventy-one women who had a normal delivery.

5. Intervention

Arm 1: daily administration of 6.0 g/day of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Fine Granules for up to 1 month from the day of delivery (n=85).
Arm 2: administration of 0.375 mg/day of ergometrine (n=86).

6. Main outcome measures

Length of uterine fundus, blood hemoglobin concentration, body temperature, and amount of lactation measured 1 to 6 days postpartum.
Lochia, lactation, and mental state evaluated by questionnaire.

7. Main results

In arm 1, uterine contraction on postpartum day 5 was significantly greater, blood hemoglobin concentration was significantly higher, and mean amount of lactation was significantly increased from postpartum day 4 onward. The number of patients with subjectively rated depression in arm 1 was approx. half that in arm 2.

8. Conclusions

Kyukichoketsuin is more effective than ergometrine for some patients with puerperal psychosomatic symptomatology.

9. From Kampo medicine perspective

The crude-drug components of kyukichoketsuin associated with oxytocic, lactogenic, or psychotropic activity are mentioned in the discussion.

10. Safety assessment in the article

No adverse drug reactions occurred in either arm.

11. Abstractor's comments

In Japan, randomization by the RCT-envelope method tends not to be maintained. This study suggests the partial efficacy of kyukichoketsuin for some patients with puerperal psychosomatic symptoms. Kyukichoketsuin is also known by a name of kyukihoketsuto and considered to be effective for various postpartum symptoms including *qiketsukyoson* (気血虚損, qi and blood deficiencies), *hiikyojaku* (脾胃虚弱, hypofunctioning of the spleen and stomach), *orofugyo* (悪露不行, lochiometra), *kyoketsukata* (去血過多, hypermenorrhea), *inshokusissetsu* (飲食失節, crapula), and *dokisosho* (怒気相衝, anger) (In: *Wanbinghuichun* [萬病回春]: *Recovery from All Ailments*).

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Wada H, Wada K, Motoyama K. Usefulness in postpartum control by kyukichoketsuin. *Sanfujinka no Sekai* (*World of Obstetrics and Gynecology*) 2003; 55: 1057-61. Ichushi Web ID: 2004022822

1. Objectives

To evaluate the clinical usefulness of kyukichoketsuin（キュウ帰調血飲） for “postpartum restoration”

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single facility (Wada Obstetric and Gynecologic clinic), Japan.

4. Participants

Sixty multiparas who visited the above facility between January and the end of December 2001 and had a normal delivery.

5. Intervention

Arm 1: administration of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Granules (EK-230) 2.0 g t.i.d. (before meals) from immediately to 2 weeks postpartum in 30 patients.
Arm 2: administration of methylergometrine maleate (MME) 0.125 mg t.i.d. (after meals) from immediately to 5 days postpartum in 30 patients.

6. Main outcome measures

Uterine subinvolution: evaluated based on the length of the uterine fundus at 1 and 4 days postpartum and the amount of lochia at 1 month postpartum.
Amount of lactation: evaluated based on the amount of lactation at 4 days postpartum and the amount of lactation expressed as a percentage of the lactation amount after the previous delivery.
Clinical symptoms: complaint of afterpains evaluated by interview.
Drug compliance: evaluated on a 4-point scale by interview.

7. Main results

There was no between-group difference in the length of uterine fundus (11.4±0.7 cm [kyukichoketsuin] *vs* 11.8±2.8 cm [MME]) at 4 days postpartum and lactation at 4 days postpartum. The lactation index (i.e., amount of lactation in relation to the amount for the previous delivery of 100) was 81.7±15.0 with MME and 136.7±71.0 with kyukichoketsuin, showing a lactation-promoting effect of kyukichoketsuin, although the difference was not significant. There were more complaints of afterpains in the MME group (46.7%) than in the kyukichoketsuin group (23.3%). Drug compliance was significantly higher in patients receiving kyukichoketsuin ($P<0.001$).

8. Conclusions

Compared with MME, kyukichoketsuin (“a medicine for postpartum restoration”) is a better restorer of postpartum health and some physiological functions in puerperants.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This study follows up a randomized study published in 2002 that verified the efficacy of kyukichoketsuin for “postpartum restoration” as described in *Wanbinghuichun* (萬病回春, *Recovery from All Ailments*) using objective parameters. The present results showing that kyukichoketsuin has clinical efficacy support the results of the previous study. The psychosomatic condition of postpartum health is referred to as “*qiketsukyoson* (気血虚損, qi and blood deficiencies)” in Kampo medicine, for which kyukichoketsuin is indicated. It is hoped that “*qiketsukyoson*,” a Kampo medical pathology, will be scientifically elucidated based on objective clinical parameters as in the present study.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 8 August 2009, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Narimatsu A, Ito A, Usefulness of kyukichoketsuin during puerperium. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicine*) 2001; 17: 1329-35 (in Japanese with English abstract). Ichushi Web ID: 2002057351 MOL, MOL-Lib

1. Objectives

To evaluate the clinical usefulness of kyukichoketsuin（キュウ帰調血飲）during puerperium.

2. Design

A randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Ogori-Daiichi General Hospital, Japan.

4. Participants

Eighty women who had normal vaginal delivery at the above facility between July 2000 and March 2001.

5. Intervention

Arm 1: postpartum administration of an oral antibiotic for 5 days + kyukichoketsuin（キュウ帰調血飲）（manufacturer not specified) 2.0 g t.i.d. before meals for 4 weeks, n=40.
Arm 2: postpartum administration of an oral antibiotic and methylergometerine maleate for 5 days, n=40.

6. Main outcome measures

Incidence of poor uterine contraction at 4 weeks postpartum, amount of milk sucked at 2 days postpartum, percentage of participants with ≥15 g/day of lactation, total amount of milk sucked, and incidences of “maternity blues” and depression at 5 days postpartum.

7. Main results

No poor uterine contraction or intrauterine infection occurred in either arm. Those receiving Kampo medicine suffered significantly less afterbirth pains (P<0.05). Kampo medicine suppressed the decrease in newborn weight in all participants, especially in primiparas (P<0.05). Postpartumly, kyukichoketsuin significantly reduced the frequency of hot flushes and twilight state. There was no between-arm difference in the incidence of maternity blues and no incidence of depression in either arm.

8. Conclusions

Kyukichoketsuin safely promotes the physical and mental restoration of puerperants, ultimately contributing to growth of newborns.

9. From Kampo medicine perspective

The increase in lactation is due to the ingredients of kyukichoketsuin (jio [地黄], toki [当帰], kobushi [香附子], chinpi [陳皮], and uyaku [烏薬]), which are also involved in nutritional fortification and physical reconditioning. In addition, kobushi and uyaku have a *qi*-conditioning effect and prevent postpartum depression.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This study verified the efficacy of kyukichoketsuin for “restoration of the postpartum psychosomatic condition” as described in *Wanbinghuichun* (萬病回春, *Recovery from All Ailments*). Although difference in uterine contraction should have been evaluated by measuring the length of the uterine fundus, the study should be praised for evaluating lactation by accurately measuring the amount of sucked milk. Biological evidence of the contribution of mental and physical factors to the restoration of puerperants should be sought. Scientific verification of the efficacy of kyukichoketsuin in various combinations (frequent in *Manbyokaishun*) is desired.

12. Abstractor and date

Ushiroyama T, 12 December 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Ushiroyama T, Sakuma K, Souen H, et al. Xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, stimulates lactation with increase in secretion of prolactin but not oxytocin in the postpartum period. *The American Journal of Chinese Medicine* 2007; 35: 195-202. CENTRAL ID: CN-00609546, Pubmed ID: 17436360

1. Objectives

To evaluate the postpartum lactation-promoting effect and safety of kyukichoketsuin (キュウ帰調血飲).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Osaka Medical College Hospital, Japan.

4. Participants

Eighty-two women who had normal spontaneous delivery.

5. Intervention

Arm 1: TAIKODO Kyukichoketsuin (キュウ帰調血飲) Extract Granules (Kanebo) 2.0 g t.i.d. for 6 days, n=41.

Arm 2: methylergometerine maleate 0.375 mg/day in 3 divided doses for 6 days, n=41.

6. Main outcome measures

Amount of lactation, blood prolactin concentration.

7. Main results

The amount of lactation was significantly increased in arm 1 on day 4 to 276.5±21.4 g (compared with 155.3±61.2 g in arm 2; $P<0.042$), on day 5 to 342.6±43.6 g (compared with 245.5±59.4 g in arm 2; $P<0.038$), and on day 6 to 413.7±68.1 g (compared with 293.3±98.5 g in arm 2; $P<0.046$). In addition, blood prolactin concentration was significantly elevated in arm 1 (compared with arm 2) on day 1 ($P<0.037$) and 6 ($P<0.0024$) after delivery.

8. Conclusions

Kyukichoketsuin may increase postpartum lactation.

9. From Kampo medicine perspective

Mentioned in discussion.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

While in Japan the RCT-envelope method of allocation often fails to maintain randomization, this study can suggest that kyukichoketsuin increases postpartum lactation. Kyukichoketsuin, also known as kyukihoketsuto, is considered to be effective for various postpartum symptoms including *qiketsukyoson* (気血虚損, qi and blood deficiencies), *hiikyojaku* (脾胃虚弱, hypofunctioning of spleen and stomach), *orofugyo* (悪露不行, lochiometra), *kyoketsukata* (去血過多, hypermenorrhea), *inshokusissetsu* (飲食失節, crapula), and *dokisosho* (怒気相衝, anger) (In: *Wanbinghuichun* ［萬病回春], *Recovery from All Ailments*).

12. Abstractor and date

Okabe T, 27 November 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Kawakami S, Nishimura J, Umeki M, et al. Kampo therapy for feeling of lactation deficiency*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 140-3 (in Japanese). Ichushi Web ID: 2004068785

1. Objectives

To evaluate a Kampo medicine effective for relieving the feeling of lactation deficiency.

2. Design

Randomized controlled trial (RCT).

3. Setting

None (authors belong to the Department of Obstetrics and Gynecology, Fukuda Hospital), Japan.

4. Participants

Seventy-two puerperants who complained of feeling of lactation deficiency at 4 to 6 days postpartum between September 2002 and February 2002.

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules t.i.d.
Arm 2: oral administration of 2.5 g of TSUMURA Juzentaihoto (十全大補湯) Extract Granules t.i.d.
Arm 3: oral administration of 2.5 g of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Fine Granules t.i.d.
Arm 4: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules and 2.5 g of TSUMURA Juzentaihoto (十全大補湯) Extract Granules combined t.i.d.
Arm 5: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules and 2.5 g of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Fine Granule combined t.i.d.
Arm 6: oral administration of 2.5 g of TSUMURA Kikyoto (桔梗湯) Extract Granules t.i.d.
Arm 7: breast massage.

6. Main outcome measures

Total score from a questionnaire evaluating the amount of breast milk, degree of breast engorgement, milk supplementation, and satisfaction on a 10-point scale.

7. Main results

At 3 weeks after treatment, the score in the juzentaihoto monotherapy group was significantly higher than those in the kyukichoketsuin monotherapy, kakkonto + juzentaihoto combination therapy, and kikyoto monotherapy groups, but not significantly different from that in the breast massage group.

8. Conclusions

Juzentaihoto is effective treatment for feeling of lactation deficiency.

9. From Kampo medicine perspective

Administration according to "*sho* (証, pattern)" is recommended.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is valuable because it demonstrates the differing effects among Kampo prescriptions on lactation after birth and the importance of therapy according to *sho*. However, given that there was no significant effect on lactation deficiency and no difference between juzentaihoto and breast massage, the present data fail to provide evidence for an effect of juzentaihoto as a stimulant of lactation. Further investigations including combined use with breast massage are expected.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010.

15. Ante/Post-partum Diseases

Reference

Fushiki H, Saeki A, Shiozaki A. Attempt to reduce adverse reactions associated with oral iron preparation for anemia in pregnancy by combination with rikkunshito (TJ-43)*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 2003; 20: 138-9 (in Japanese). Ichushi Web ID: 2004068784

1. Objectives

To evaluate whether rikkunshito (六君子湯) combined with oral iron can improve hemoglobin level and reduce adverse reactions associated with the administration of iron for anemia in pregnant women.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (one obstetrics and gynecology clinic), Japan.

4. Participants

One hundred and twenty pregnant women (duration of pregnancy ≥ 5 months) with a hemoglobin (Hb) level of less than 11.0 g/dL, a hematocrit (Ht) of less than 33%, and a mean corpuscular volume (MCV) of less than 85 μm^3.

5. Intervention

Arm 1: treatment with sodium ferrous citrate (50 mg) 1 tablet b.i.d., and rikkunshito (六君子湯) 2.5 g t.i.d. for 14 days in patients with a mean age of 28.2 (20 - 42) years and a mean gestational age of 28.7 (18 - 38) weeks.

Arm 2: treatment with sodium ferrous citrate (50 mg) 1 tablet b.i.d. for 14 days in patients with a mean age of 28.8 (20 - 38) years and a mean gestational age of 28.4 (18 - 37) weeks.

6. Main outcome measures

Post-treatment Hb level.

7. Main results

Increase in Hb from the pre-treatment level was significantly greater after the sodium ferrous citrate plus rikkunshito therapy (arm 1; 0.8 [2.4 to -0.9] g/dL) than after sodium ferrous citrate monotherapy (arm 2; 0.3 [2.1 to -1.2] g/dL) (P=0.002). Also, oral administration of sodium ferrous citrate was better tolerated in arm 1.

8. Conclusions

It was suggested that rikkunshito combined with oral iron for anemia in pregnancy is effective for reducing adverse reactions associated with the administration of iron.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions to rikkunshito treatment.

11. Abstractor's comments

Oral iron preparations are commonly associated with gastrointestinal adverse reactions. Thus, many patients stop the treatment. Great clinical relevance is suggested by the present results, which showed that treatment with iron could be continued in combination with rikkunshito. Although this study was classified as an RCT because of the random assignment, data necessary for the assessment of bias, including the presence or absence of blinding, were inadequate, and further assessment cannot be made. Further studies are expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Ushiroyama T, Sakuma K, Ueki M, Efficacy of the Kampo medicine xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, in the treatment of maternity blues syndrome in the postpartum period. *The American Journal of Chinese Medicine* 2005; 33: 117-26. CENTRAL ID: CN-00515344, Pubmed ID: 15844839

1. Objectives

To confirm the efficacy of kyukichoketsuin (キュウ帰調血飲) for the “maternity blues.”

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Osaka Medical College Hospital and associated facilities, Japan.

4. Participants

Two-hundred and sixty-eight puerperants who had a normal single delivery and no pregnancy toxemia, diabetes mellitus, premature rupture of the membrane, etc. They were randomized to either kyukichoketsuin group or control group.

5. Intervention

Arm 1: administration of 2.0 g of Kanebo Kyukichoketsuin (キュウ帰調血飲) t.i.d., n=134.
Arm 2: control group without treatment, n=134.

6. Main outcome measures

Four items (including mood swings, crying over 5 min, and irritation) as judged by questionnaire.
Depressive symptoms as judged on the Edinburgh Postpartum Depression Scale.
Maternity blues as judged on a self-rating maternity blues scale.

7. Main results

Within 3 weeks postpartum, the kyukichoketsuin group had significantly decreased incidences of moderate or severe depressive symptom, crying lasting over 5 minutes, irritation, and maternity blues. During 3 to 6 weeks postpartum, there was no significant difference between arms. The incidence of maternity blues, especially within 3 days postpartum, was decreased in the kyukichoketsuin group.

8. Conclusions

Kyukichoketsuin can be used to stabilize postpartum mood.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor’s comments

This study provides objective evidence for efficacy of kyukichoketsuin in the treatment of classic postpartum maternity blues. Maternity blues disappear within 3 weeks postpartum and are followed up without treatment in clinical practice. Thus, in emphasizing importance of postpartum care, this study seems significant. Further study results are expected.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010.

18. Symptoms and Signs

Reference

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Beneficial effect of Chinese traditional herbal medicine, mai-men-don-tang (Japanese name: bakumondo-to) on acute pain in patients with acute internalmedical disease: antitussive effect on elderly patients with post infectious persistent coughs, prospective, multicenter, randomized comparative trial between mai-men-dong-tang and forminoben hydrochloride. *Itami to Kampo* (*Pain and Kampo Medicine*) 2003; 13: 12-21 (in Japanese with English abstract). Ichushi Web ID: 2006247201

1. Objectives

To evaluate the efficacy of bakumondoto (麦門冬湯) for persistent cough after infection in the elderly.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two hospitals and three clinics, Japan.

4. Participants

Two-thousand and sixty-nine patients with intense dry cough persisting for 3 weeks or more after common cold syndrome, aged ≥ 65 years.

5. Intervention

Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract granules 3.0 g t.i.d. between meals (n=1,039).
Arm 2: administration of fominoben hydrochloride 160 mg in three divided doses between meals (n=1,030).

6. Main outcome measures

Antitussive effect
Salivation degree, skin temperature, joint pain
Pain improvement rating
Global improvement rating

7. Main results

The antitussive effect and reduction in sputum expectoration (as measured on a visual analogue scale [VAS]) was superior in arm 1 than arm 2. Improvement in the following items after treatment, compared with baseline, was significant only in arm 1: the amounts of salivation and lacrimation determined by Saxon's test and Schirmer's test; joint pain judged on a VAS; and skin temperature measured with an upper and lower extremity-patch-type skin temperature indicator.
On the global scale, improvement, principally in cough, was better in arm 1 than arm 2. The condition of 89.5% of patients in arm 1 and 46.9% in arm 2 was rated "improved or better," showing the significantly higher efficacy of bakumondoto.

8. Conclusions

Bakumondoto is effective for not only cough but other symptoms in the elderly.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The "total-disease-related symptoms," a scale for acute pain severity developed by the present authors, is not described but referenced to their previous paper. This, however, should be detailed since the title refers to pain severity. In addition, except for the global improvement rating, the specific numbers of patients are not indicated, except in the graphs, making evaluation of the efficacy for pain impossible.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010.

18. Symptoms and Signs

Reference

Irifune K, Hamada H, Ito R, et al. Antitussive effect of bakumondoto a fixed kampo medicine (six herbal components) for treatment of post-infectious prolonged cough: controlled clinical pilot study with 19 patients. *Phytomedicine* 2011; 18: 630–3. CENTRAL ID: CN-00790677, Pubmed ID: 21514123

1. Objectives

To evaluate the combined effects of bakumondoto (麦門冬湯) and a bronchodilator for prolonged cough following common cold.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT - envelope).

3. Setting

Six hospitals including Ehime University Hospital, Japan.

4. Participants

Twenty-seven adult patients who presented between February 2007 and March 2009 with prolonged cough for more than 3 weeks following a common cold. Patients whose prolonged cough was not attributable to common cold, and patients currently taking β2 stimulants or anti-cholinergic drugs were excluded.

5. Intervention

Ultimately, 20 patients were registered after exclusions for adverse events and allocation errors.

Arm 1: TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. before or between meals, and 50 μg Meptin® (n=9).

Arm 2: Meptin® 50 μg b.i.d. after breakfast and before bed (n=10).

Patients with severe cough received Medicon®, if requested.

6. Main outcome measures

Cough intensity on a 5-point scale and timing recorded in a cough diary, VAS (visual analogue scale) score for cough intensity and frequency, and sleep quality questionnaire.

7. Main results

A significant antitussive effect (based on cough diary data: arm 1, 11 subjects; arm 2, 8 subjects) was observed in arm 1 four and five days after administration (P<0.05). There was no significant difference between groups for sleep quality (questionnaire) or cough improvement (VAS).

8. Conclusions

Additional treatment with bakumondoto achieves earlier antitussive results in cases of prolonged cough that do not respond to centrally acting antitussives.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Meptin® (50 μg) caused palpitations or tremors in 6 participants and bakumondoto extract granules caused rash in 1.

11. Abstractor's comments

Irifune et al. cite the assertion by Fujimori et al. (1997) that bakumondoto is effective for prolonged cough after common cold, whereas standard antitussive drugs are not. They also conducted a trial to compare the antitussive effects of Medicon® and bakumondoto, finding that bakumondoto has more rapid effects. The present study is the first randomized controlled trial (RCT) to clarify bakumondoto's antitussive effects. The use of central antitussives containing codeine for long periods is not recommended because of their adverse effects. Thus, using bakumondoto, which has few adverse effects, is apparently advantageous. Meptin® (50 μg) results in frequent adverse effects when taken in combination, so further investigation into dosage, etc. is required.

12. Abstractor and date

Fujisawa M, 31 December 2012.

18. Symptoms and Signs

Reference

Nishi K, Takata K, Asano S, et al. Effects of goreisan suppository on vomiting in children - comparison with domperidone suppository -*. *Nihon Byoin Yakuzaishikai Zasshi* (*Journal of Japanese Society of Hospital Pharmacists*) 1998; 34: 1173-6 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the effects of goreisan (五苓散) suppository compared with domperidone suppository on vomiting in children.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Single institution (Hokuriku Central Hospital), Japan.

4. Participants

Twenty children who visited the outpatient department with a chief complaint of vomiting. Patients who required fluid resuscitation were excluded.

5. Intervention

Arm 1: intrarectal administration of goreisan (五苓散) (via suppository consisting of TSUMURA Goreisan [五苓散] Extract Granules [1 g] + VOSCO H-15 base [1 mL]) in patients who underwent examination on the second or fourth week of the month (n=13).

Arm 2: intrarectal administration of domperidone (via suppository containing 10–30 mg dependent on the body weight) in patients who underwent the examination on the first, third, or fifth week of the month (n=7).

6. Main outcome measures

Presence or absence of nausea and vomiting 30 minutes after the administration.

7. Main results

Improvement rates of nausea and vomiting were 92.3% in arm 1 and 71.4% in arm 2.

8. Conclusions

The effects of goreisan on vomiting in children are suggested.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions did not occur.

11. Abstractor's comments

This paper compares the effect of goreisan suppository with the effect of domperidone suppository on vomiting in children. It is generally difficult to conduct a clinical study in children. This study of the effects of the authors' original preparation of goreisan suppository is valuable because it was conducted in children. A definite conclusion was not drawn because the study design was not strictly an RCT and the number of patients enrolled was small. So future studies are expected to include a larger number of patients and employ a more sophisticated design.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

18. Symptoms and Signs

References

Yoshida M, Mizuno T, Mizoguchi F, et al. Efficacy of goreisan suppositories for vomiting in young children (2nd report) – a double-blind study of the hochuekkito suppository–*. *Wakan Iyaku Gakkaishi* (*Journal of Medical and Pharmaceutical Society for WAKAN-YAKU*) 1991; 7: 506-7 (in Japanese). Ichushi Web ID: 1993089053

Yoshida M. Efficacy of goreisan suppository for vomiting in young children*. *Toyoigaku* (*Japanese Journal of Oriental Medicine*) 2000; 28: 36-8 (in Japanese).

Yoshida M. Efficacy of goreisan suppository*. *Nihon Syhoni Toyo Igakkaishi* (*The Japan Pediatric Society for Oriental Medicine*) 2003; 19: 13-7. Ichushi Web ID: 2005266312

1. Objectives

To evaluate the efficacy and safety of goreisan (五苓散) for vomiting in young children.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

A single facility (the department of pediatrics of a hospital), Japan.

4. Participants

Thirty-five patients who vomited three or more times within 24 hr before visiting the pediatric department and experienced vomiting/nausea during the visit. One of these patients ejected the medicine immediately after insertion and was excluded, resulting in the inclusion of 34 patients (21 males and 13 females, aged 1 – 9 years with a mean of 3.9 years) for analysis.

5. Intervention

Arm 1: administration of a home-prepared suppository containing 1 g of TSUMURA Goreisan (五苓散) Extract Granules (n=16, 10 males and 6 females).

Arm 2: administration of a home-prepared suppository containing 1 g of TSUMURA Hochuekkito (補中益気湯) Extract Granules (n=18, 11 males and 7 females).

6. Main outcome measures

Complete response (disappearance of both vomiting and nausea); partial response (presence of nausea without vomiting); and no response (vomiting of supplied water).

7. Main results

The distribution of baseline characteristics (age, sex, underlying disease, frequency of vomiting, and complication with diarrhea) were similar between arms. Complete response, partial response, and no response were achieved in 12 (75%), 2, and 2 patients receiving goreisan, and in 5 (28%), 2, and 11 patients receiving hochuekkito, respectively. The difference between arm 1 and arm 2 was statistically significant ($P<0.05$).

8. Conclusions

Goreisan suppository reduces vomiting and nausea in young children more effectively than hochuekkito suppository.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

Goreisan is generally indicated for thirst, decreased urine output, and gastrointestinal diseases such as watery diarrhea and acute gastroenteritis with nausea, vomiting abdominal pain, headache, or edema. This study demonstrated the efficacy of goreisan suppository (in-home formulation) for reducing acute vomiting in young children. The usefulness has also been demonstrated in a multicenter, double-blind study, as mentioned below. Since the study period was in winter, the target diseases included common-cold-associated dyspepsia, winter diarrhea, vomiting, and common cold. Since it is generally difficult to administer a medicine orally or by drip infusion to young children with vomiting, the suppository is considered to be a clinically useful alternative dosage form. Therefore, it is very meaningful that this study demonstrated usefulness. However, this paper does not describe the methods of randomization and statistical analysis, which should be specified. In addition, another Kampo medicine and not a true placebo was used as the control, therefore it would be useful in the future to conduct a placebo-controlled study. Future development is expected. Notably, the formulation of goreisan extract is only approved for oral use, not for use in suppositories.

In the article by Yoshida (2003), a multicenter, case-series study with the same design and evaluation methods has also reported. The study population consisted of 87 patients (43 males and 44 females, aged 0 – 9 years with a mean of 2.4 years). Complete response was achieved in 72 patients (83%), and partial response in 2 patients. No difference in efficacy for underlying diseases was shown; complete response was achieved in 43 (88%) of 49 patients with winter infantile diarrhea, 22 (76%) of 29 patients with common-cold-associated diarrhea, and 5 (83%) of 5 patients with acute gastroenteritis. No difference in baseline characteristics was shown; there was no statistically significant difference in age, frequency of vomiting, complication with diarrhea, and use of enema between patients with complete or partial response, and patients with no response.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 8 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
18. Symptoms and Signs

References

Ohnishi S, Watari H, Sakuragi N, et al. Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: results of a randomized phase II study (JORTC KMP-02). *Journal of Gynecologic Oncology* 2017; 28: 1-10. doi: 10.3802/jgo.2017.28. e44 CENTRAL ID: CN-01403248, Pubmed ID: 28657216

1. Objectives

To evaluate the efficacy and safety of add-on rikkunshito（六君子湯）to antiemetics for nausea, vomiting, and anorexia in patients receiving cisplatin plus paclitaxel for uterine cervical or corpus cancer

2. Design

Randomized controlled trial (RCT)

3. Setting

Four institutions, Japan

4. Participants

Forty patients aged 20 years or older, with histologically diagnosed uterine cervical or corpus cancer, and with an ECOG Performance Status score of 0 to 2.

Patients were excluded if they had brain metastasis, seizure, unconsciousness, gastrointestinal obstruction, vomiting, or nausea of CTCAE (version 4.0) grade ≥3, or had received treatment within one month with steroids, androgens, progesterones, other herbal medicines, other medicines with the potential to increase appetite, or opioids.

Efficacy was analyzed in 19 patients in the rikkunshito group and 17 patients in the control group. Safety was analyzed in 20 patients in the rikkunshito group and 19 patients in the control group.

5. Intervention

Arm 1: oral administration of rikkunshito（六君子湯）(manufacturer unknown) 7.5 g (on days 0-13) plus antiemetics (n=20)

Arm 2: administration of antiemetics alone (n=20)

6. Main outcome measures

Nausea using a 100-mm visual analog scale (VAS) with 0–5 mm indicating “no nausea” and 5–25 mm indicating “no significant nausea”, the rate of complete control (CC) (i.e., no emesis, no rescue medication, and no significant nausea), and the rate of complete response (CR) (i.e., no emesis and no rescue medication) were assessed.

7. Main results

Two-tailed $P<0.20$ was considered significant. For the overall phase (0–120 hours), both the CC rate and the CR rate were significantly higher in the rikkunshito group ($P=0.175$ and $P=0.042$, respectively). When the overall phase was divided into acute (0–24 hours) and delayed (24–120 hours) phases, the CC and CR rates were similar between the two groups during the acute phase and significantly higher in the rikkunshito group during the delayed phase ($P=0.095$ for the CC rate, $P= 0.042$ for the CR rate). In terms of anorexia and nausea VAS scores, rikkunshito appeared to be effective from day 2 through day 6 (without significant difference), but no differences were shown between the groups from day 7 through day 13.

8. Conclusion

Rikkunshito provides an additive effect to antiemetic therapy for vomiting and anorexia.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

In the rikkunshito group, there was increased ALT in 2 patients (10.0%), increased AST in 1 patient (5.0%), and increased GGT in 1 patient (5.0%).

11. Abstractor’s comments

Severe gastrointestinal symptoms during chemotherapy may make chemotherapy completion difficult. In cancer therapy, whether chemotherapy is completed or not is important because it changes the prognosis. This study showed significant reductions of nausea and vomiting by add-on rikkunshito to antiemetics. Add-on use of rikkunshito is considered to be particularly effective in highly emetogenic anticancer drug therapy.

12. Abstractor and date

Nakata H, 1 June 2020.

18. Symptoms and Signs

Reference

Sakiyama T, Wada E, Inoue M, et al. Study of effectiveness of goreisan suppository. *Japanese Journal of Pediatric Oriental Medicine*. 2017; 30: 33-42 (in Japanese). Ichushi Web ID: 2018110205

1. Objectives

To evaluate the effectiveness and safety of goreisan（五苓散）suppository on vomiting in pediatric infectious diseases.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not stated.

4. Participants

Pediatric patients with a primary symptom of vomiting associated with acute gastroenteritis or other diseases. Patients were excluded if suppository administration was not desired by the patient or patient's guardian, or if 24 hours had passed since symptomatic onset (n=50).

5. Intervention

Arm 1: A suppository made from TSUMURA Goreisan（五苓散）Extract Granules 1 g was administered once. If vomiting showed no improvement 30 minutes later, one suppository of goreisan 1 g was additionally administered. (n=25)

Arm 2: A suppository made from lactose was administered once. If vomiting showed no improvement 30 minutes later, one suppository of goreisan 1 g was additionally administered. (n=25)

6. Main outcome measures

The frequency of vomiting after the suppository administration was assessed at 30 minutes, 1 hour, and 24 hours post dose. Other assessments included presence or absence of suppository re-administration and adverse effects of the suppository.

7. Main results

The analysis was conducted on 50 patients. Vomiting occurred within 30 minutes after suppository administration in 3 patients in Arm 1 and 3 patients in Arm 2, showing no significant difference. Vomiting occurred between 0.5 and 1 hour after the suppository administration in 3 patients in Arm 1 and 5 patients in Arm 2, showing no significant difference. Suppository re-administration was required in 3 patients in Arm 1 and 7 patients in 3 patients, showing no significant difference. Among the 10 patients given suppository re-administration, vomiting occurred within 24 hours after the re-administration in no patients in Arm 1 and 4 patients in Arm 2. Among the patients without suppository re-administration, vomiting occurred in 4 patients each in Arm 1 and Arm 2, showing no significant difference.

8. Conclusions

Goreisan 1 g suppository is likely to reduce vomiting episodes in pediatric patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In the goreisan group, no adverse reactions were noted. In the placebo group, 1 patient had watery stools after insertion of the suppository.

11. Abstractor's comments

This article describes an important RCT that evaluated the effectiveness of intestinal administration of goreisan, often used to treat pediatric vomiting. In this study, repeated vomiting occurred in fewer patients in the goreisan group than in the placebo group, but there was no statistically significant between-group difference. As the authors state in the article, the investigators in this study were attending physicians of the participants, and therefore the placebo effect was more likely to occur. This may have made it difficult to show significant intergroup differences. In addition, the sample size could be too small to detect significant differences. This study might serve as a pilot study and it is desired that larger studies to follow will address this issue.

12. Abstractor and date

Koike H, 9 November 2019.

18. Symptoms and Signs

Reference

Sasaki S, Oumi A, Kumeda M, et al. Evaluation of nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding. *Science of Kampo Medicine 2014 (in Japanese)*, 38: 263-6. Ichushi Web ID: 2015111016

1. Objectives

To evaluate the nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

One hospital.

4. Participants

Twenty-four patients with tube feeding.

5. Intervention

Arm 1: Administration of TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5g t.i.d. for 3 months (n=12).
Arm 2: Lactose 2.5g colored with decaffeinated coffee t.i.d. for 3 months (n=12).

6. Main outcome measures

Serum albumin value, prognostic nutritional index, area of the brachial muscle, controlling nutritional status (CONUT) score, rate of fever of 37°C or higher 3 months before and after the administration.

7. Main results

As 1 and 3 patients dropped out in arm 1 and in arm 2, respectively, 11 patients in arm 1 and 9 patients in arm 2 were studied. Serum albumin level was significantly higher in arm 1 than arm 2 at month 3 (P=0.032). There were no significant between-arm differences in prognostic nutritional index, area of the brachial muscle, CONUT score after administration, and rate of fever of 37°C or higher for 3 months before and after the administration.

8. Conclusions

Hochuekkito increases serum albumin levels in patients with tube feeding.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In the hochuekkito-administered group, 1 patient died, and in placebo-administered group, 2 patients died.

11. Abstractor's comments

This paper reports nutrition improvement after hochuekkito administration in patients with tube feeding. A number of retrospective studies have suggested the efficacy of hochuekkito and other Kampo medicines to improve nutrition rationally; however, this study was significant because it was an actual double-blind prospective study showing the efficacy of hochuekkito. In the study, the endpoints had not been defined either primary or secondary endpoints and designed to detect any endpoints with statistical significance among the 5 endpoints. Therefore, we have to admit that improvement in serum albumin level (the only endpoint with statistical significance) may be accidental. In addition, the number of patients in the study was insufficient and the investigators appeared to proceed through the trial in a disorganized undisciplined manner without knowing the appropriate duration of evaluation. Thus the trial is only important as an exploratory study, and a new trial with defined primary endpoints, appropriate number of patients, and appropriate evaluation period is anticipated as a next step.

12. Abstractor and date

Koike H, 31 March 2017.

18. Symptoms and Signs

Reference

Igarashi I. Clinical study of traditional Chinese medicine therapy for post-operative or post-traumatic swelling in lower extremities. *Seikeigeka* (*Orthopedic Surgery*) 1993; 44: 127–31 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) for posttraumatic or postoperative swelling in the lower extremities.

2. Design

Randomized controlled trial (RCT).

3. Setting

The department of orthopedic surgery of one hospital, Japan.

4. Participants

Sixty-four inpatients receiving treatment for trauma or edema in the lower extremities.

5. Intervention

Arm 1: oral administration of TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. between or before meals (n=38).
Arm 2: no administration of Kampo medicine (n=26).
Analgesics were used as appropriate, but anti-swelling drugs were not used.

6. Main outcome measures

Swelling ratios calculated using circumferences of bilateral thighs, lower limbs and feet, and the number of days required for swelling disappearance.

7. Main results

Swelling resolution required 13–105 days after surgery or trauma (mean, 59.4 days) in arm 2, and 0–64 days (mean, 15.8 days) in arm 1. Swelling ratio was significantly smaller in arm 1 than in arm 2 at 1–6 weeks postoperatively (postoperative 1–6 weeks, $P<0.05$; 2–5 weeks, $P<0.01$). Nineteen patients in arm 1 who started saireito preoperatively required 0–56 days (mean, 9.5 days) for postoperative swelling resolution, and 10 of them did not develop swelling.

8. Conclusions

Saireito is effective for posttraumatic or postoperative swelling in the lower extremities.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Saireito administration was not associated with adverse reactions or electrolyte imbalance.

11. Abstractor's comments

This clinically useful, interesting study investigated the efficacy of saireito for swelling in the lower extremities after trauma or surgery. However, some patients in arm 1 had no swelling. Furthermore, 10 of 19 patients who started saireito preoperatively did not develop swelling, indicating that 10 of 38 patients in arm 1 had no swelling at the beginning of the study. In contrast, all patients in Arm 2 had swelling at the beginning of the study. This suggests a considerable between-arm difference in the baseline distribution of patients who had swelling. Preoperative patients without swelling or postoperative patients with swelling should have been allocated appropriately to meet the study objectives. Nevertheless, the focus of this study is excellent, and increasing sample size and dividing subjects into appropriate groups at the start will improve the study.

12. Abstractor and date

Goto H, 13 September 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Yoshida M, Kitaoka H, Masui Y, et al. Effects of shakuyaku-kanzo-to on muscle cramp in diabetics. *Shinkei Chiryogaku* (*Neurological Therapeutics*) 1995; 12: 529-34 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for preventing muscle cramps in diabetic patients.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and multiple general hospitals, Japan.

4. Participants

Fifteen patients with non-insulin-dependent diabetes mellitus (NIDDM) in relatively good glycemic control who complained of muscle cramps two or more times a week.

5. Intervention

Arm 1: treatment with shakuyakukanzoto (芍薬甘草湯) extract granules (manufacturer, not specified) 7.5 g/day for 4 weeks (n=10).
Arm 2: treatment with eperisone hydrochloride 150 mg/day for 4 weeks (n=5).
Patients were followed up for 4 weeks after the completion of treatment; total follow-up period was 10 weeks.

6. Main outcome measures

Muscle cramps: improvement in frequency of muscle cramps was rated on a 5-point scale based on the post-treatment/pre-treatment ratio of the frequency; improvement in severity of muscle cramps was rated on a 5-point scale based on the change in pain scores (on a 4-point scale).

7. Main results

The improvement in the frequency of muscle cramps was “marked” in 20%, “moderate” in 70%, and “mild” in 10% for arm 1, and “moderate” in 60% and “no change” in 40% for arm 2. The improvement in the severity of muscle cramps was “marked” in 10%, “moderate” in 40%, “mild” in 30%, and “no change” in 20% for arm 1, and “mild” in 40% and “no change” in 60% for arm 2.

8. Conclusions

Shakuyakukanzoto is effective for preventing muscle cramps in diabetic patients and its efficacy is comparable or superior to that of eperisone hydrochloride.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred in shakuyakukanzoto-treated patients.

11. Abstractor’s comments

It is clinically significant that a multicenter RCT was attempted, although the sample size was small. However, the between-group comparison of improvement was insufficient. As for adverse drug reactions, the number of patients analyzed was limited in this study and therefore reevaluation in a larger population is desired.

12. Abstractor and date

Kogure T, 8 August 2008.

18. Symptoms and Signs

References

Kumada T, Kumada H, Yoshiba M, et al. Effects of Shakuyaku-kanzo-to (Tsumura TJ-68) on muscle cramps accompanying cirrhosis in a placebo-controlled double-blined parallel study. *Rinsho Iyaku* (*Journal of Clinical Therapeutics and Medicine*) 1999; 15: 499-523 (in Japanese with English abstract). Ichushi Web ID: 1999184114 MOL, MOL-Lib

Kumada T, Kiriyama I, Sone Y, et al. EBM-based Kampo therapy for gastrointestinal diseases 3. Efficacy of shakuyakukanzoto for "muscle cramps in the calves" associated with hepatic cirrhosis*. *Nihon Toyo Igaku Zasshi* (*Kampo Medicine*) 2003; 54: 536-8 (in Japanese) CiNii

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for relief of muscle cramp.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

A total of 23 nationwide facilities including university hospitals (departments of internal medicine and gastroenterology), Japan.

4. Participants

One-hundred and twenty-six patients with 2 or more episodes of muscle cramp weekly during the observation period (4 or more bi-weekly), aged ≥20 years and ≤70 years. These patients were also taking other drugs for a variety of problems including serious hepatic, renal, and cardiac diseases, pregnancy, hepatic failure, complications of hepatocellular carcinoma, electrolyte abnormality, and hypertension. After excluding 12 ineligible patients and 13 with incomplete data, 101 patients were included for statistical evaluation.

5. Intervention

Arm 1: administration of 7.5 g/day of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules in 3 divided doses (before meals) for 2 weeks following a 2-week observation period (n=65).

Arm 2: administration of the same dose of placebo granules at the same frequency for 2 weeks following a 2-week observation period (n=61).

6. Main outcome measures

Frequency of episodes of muscle cramp, duration of each episode, severity of pain (at completion of the study compared with baseline values determined during the observation period).

7. Main results

The percentage of patients with frequency of muscle cramp episodes rated "improved" or higher was significantly larger in the shakuyakukanzoto group than in the placebo group (67.3% *vs* 37.5%, respectively). The percentage of patients with improved final global rating, which takes duration of each episode and severity of pain into account, was significantly larger in the shakuyakukanzoto group (69.2% *vs* 28.6%, respectively). The percentage of patients with a utility rating of "useful" or higher was also significantly larger in the shakuyakukanzoto group (63.3% *vs* 34.1%, respectively).

8. Conclusions

Shakuyakukanzoto is a clinically useful Kampo formulation with excellent efficacy and safety for muscle cramp.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions occurred in 7 patients (14.3%) receiving shakuyakukanzoto and 2 patients (4.9%) receiving placebo. The main adverse drug reaction was pseudoaldosteronism in the shakuyakukanzoto group and gastrointestinal symptoms in the placebo group. No serious adverse drug reactions occurred.

11. Abstractor's comments

This original article re-evaluates shakuyakukanzoto. The larger total amount of kanzo, contained in shakuyakukanzoto, is associated with higher incidence of pseudoaldosteronism. Since in the present study incidence of adverse drug reactions tended to be higher in the sahkuyakukanzoto group, although there was no significant between-group difference in incidence, reduction in the dose is recommended in the future.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Nishizawa Y, Nishizawa Y, Amemori Y, et al. A randomized paralleled group comparison in multicenter cooperation: analgesic effect and safety with gosha-jinki-gan and shakuyaku-kanzo-to in the treatment of painful muscle cramps in patients with cirrhosis. *Itami to Kampo* (*Pain and Kampo Medicine*) 2000; 10: 13-8 (in Japanese with English abstract). Ichushi Web ID: 2002242334

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for muscle cramps in the calves.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned, Japan.

4. Participants

Seventy-five patients with painful muscle cramps in the calves (PMC) associated with hepatic cirrhosis.

5. Intervention

Arm 1: oral administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (GJG) 30 mg/kg t.i.d. for 12 consecutive weeks, n=38.

Arm 2: oral administration of 50 mg/kg/day of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (SKT) in 3 divided doses for 12 consecutive weeks, n=37.

6. Main outcome measures

PMC rating (overall QOL, visual analog scale pain [VAS-P], face rating scale), QOL (modified health assessment questionnaire [MHAQ]), overall well-being (quality of well-being score), and psychological well-being (face scale).

7. Main results

GJG was significantly superior to SKT in improving the PMC rating and various QOL measures. The number of days until resolution of PMC was significantly shorter in the GJG group than in the SKT group.

8. Conclusions

Goshajinkigan is effective and safe for PMC associated with hepatic cirrhosis and is superior to shakuyakukanzoto in efficacy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reaction symptoms and laboratory test abnormalities (increased AST, LDH, and CPK) were noted in 0 patients receiving goshajinkigan and 4 patients receiving shakuyakukanzoto, but these resolved after discontinuation of treatment.

11. Abstractor's comments

This paper suggests that goshajinkigan may be the first-choice drug for PMC associated with hepatic cirrhosis.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

18. Symptoms and Signs

Reference

Toda Y, Effect of peony and licorice decoction on muscle hardness of gastrocnemius in patients with osteoarthritis of the knee* *Seikei Igaku* (*Orthopedic Surgery*) 2015; 66: 521-4.

1. Objectives

To evaluate the preventive effect and safety of shakuyakukanzoto (芍薬甘草湯) for gastrocnemius muscle hardness in knee osteoarthritis patients doing exercises at home.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One orthopedic clinic, Japan.

4. Participants

Eighty-three people aged 50-years of more, diagnosed with medial knee OA based on the American College of Rheumatology diagnostic criteria, with K-L classification grade 2 or more by simple knee X-ray.(70 females and 13 males)

5. Intervention

Arm 1: Shakuyakukanzoto (芍薬甘草湯) extract granules (manufacturer not mentioned) 5.0g/day (2.5g b.i.d.) taken orally before morning and evening meals (n=42).

Arm 2: No administration of shakuyakukanzoto (芍薬甘草湯) (n=41).

Participants were allocated in order of clinic visit. Observation period 4 weeks. Both groups received sodium hyaluronate joint injections (5 times/w), and were instructed to repeat 8 times (1 set) an exercise in which participants squeeze a roll of paper with 80% of maximum muscle effort in knee extension, and to repeat 3 sets, 1 to 2 minutes apart.

6. Main outcome measures

Medial gastrocnemius muscle hardness (measured by Neutone TDM-NAI), rate of muscle hardness change, presence/absence of calf muscle cramp, knee function (Lequesne severity index).

7. Main results

4 participants dropped out of arm 1, and 3 from arm 2, leaving 38 subjects for analysis in the two groups. No significant difference in distribution was observed between groups in age, gender, years duration of condition, BMI, and pre-treatment muscle hardness, Lequesne severity index or K-L classification. Rate of muscle hardness change after 1 week: Significantly decreased in arm 1 (96.1±9.9%) compared to arm 2 (102.8±14.9%) (P=0.023). The same trend was present in week 4, but there was no significant difference (P=0.12). Fewer patients complained of calf muscle cramp in arm 1 (2 cases, 5.3%) compared to arm 2 (8 cases, 21.1%), but the difference was not significant (P=0.086). There was no significant difference between the 2 groups in Lequesne severity index improvement (P＝0.093).

8. Conclusion

Taking shakuyakukanzoto significantly decreases medial gastrocnemius muscle hardness in OA patients. It also tends to decrease the occurrence of calf muscle cramp.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

A number of participants in the shakuyakukanzoto group had to stop visiting the clinic (2 due to gastralgia, 1 due to eczema, and 1 due to busy schedule) and dropped out. The author did not mention the reasons for the dropouts from arm 2. There was no significant difference between groups in the dropout rate.

11. Abstractor's comments

A relatively large number of clinical trials have investigated the effect of shakuyakukanzoto on calf muscle cramp, yet few of them are randomized controlled trials, and the evidence level is still not high. Being a quasi-randomized controlled trial studying 83 subjects and presenting a high level of evidence, it is a paper with clinical significance. It also objectively sets out the effects of shakuyakukanzoto, given that it significantly decreased gastrocnemius muscle hardness 1 week after administration. However, as the authors mention, it is unfortunate that there was no significant difference in regard to complaints of calf muscle cramp. As it did tend to decrease calf muscle cramp, a repeat of this study with a larger number of participants is anticipated.

12. Abstractor and date

Kogure T, 28 December 2016.

18. Symptoms and Signs

Reference

Takao Y, Takaoka Y, Sugano A, et al. Shakuyaku-kanzo-to (Shao-Yao-Gan-Cao-Tang) as treatment of painful muscle cramps in patients with lumbar spinal stenosis and its minimum effective dose. *Kobe Journal of Medical Sciences* 2015; 61: 5: E132-7. CENTRAL ID: CN-01140769, Pubmed ID: 27363396

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for muscle cramps in patients with lumbar spinal stenosis

2. Design

Randomized controlled trial (RCT)

3. Setting

One university hospital, Japan

4. Participants

Thirty patients with lumbar spinal stenosis

5. Intervention

Arm 1: Oral administration of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 7.5 g (in 3 divided doses)/day for 2 weeks (n=16)

Arm 2: Oral administration of eperisone hydrochloride (dose not specified) for 2 weeks (n=14)

6. Main outcome measures

Frequency of muscle cramps at Week 2 of treatment. Time to maximum therapeutic response.

7. Main results

The frequency of muscle cramps decreased to ≤50% in 14 (87.5%) of the 16 patients in Arm 1, compared with 4 (28.6%) of the 14 patients in Arm 2. Maximum therapeutic response was achieved within 3 days in ≥50% of the patients in Arm 1.

8. Conclusions

The results suggest that shakuyakukanzoto is effective for muscle cramps in lumbar spinal stenosis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Dizziness was reported in an 80-year-old man with a history of cerebral infarction, and improved after discontinuation of shakuyakukanzoto. No other adverse events were noted.

11. Abstractor's comments

This study evaluated the efficacy and safety of shakuyakukanzoto, compared with eperisone hydrochloride, for muscle cramps in patients with underlying lumbar spinal stenosis. Although the article states that the study consisted of 3 arms (i.e., the above-stated two arms plus Arm 3 [n=28] to determine the minimum effective dose) and was conducted in a total of 58 patients who were randomized to these 3 arms, this randomization to Arm 3 was not further described. Furthermore, regarding the use of a chi-square test for intergroup comparison stated in Figure 2, it is unclear which groups were compared. In addition, it is questionable whether ANOVA used in Figure 3 was an appropriate statistical method. While there have been other reports on the efficacy of shakuyakukanzoto for muscle cramps, this is the first report to specifically evaluate it in patients with lumbar spinal stenosis. Thus, further clinical studies with sufficient sample size and scientifically valid design are warranted.

12. Abstractor and date

Motoo Y, 18 May 2020

18. Symptoms and Signs

Reference

Yoshikawa H, Ikeuchi T, Kai Y. Clinical effects of kyuki-kyogai-to and sairei-to for essential microscopic hematuria. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 1997; 6: 55-8 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of kyukikyogaito (芎帰膠艾湯) and saireito (柴苓湯) for essential microscopic hematuria.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the authors belong to Showa University Fujigaoka Hospital and Ryokuseikai Yokohama General Hospital), Japan.

4. Participants

Sixty-eight female patients with essential microscopic hematuria who had no subjective symptoms, showed hematuria on analysis of urine obtained by urethral catheterization (according to the criteria proposed by Kai et al.), and had no abnormal findings on urological examinations.

5. Intervention

Arm 1: treatment with TSUMURA Kyukikyogaito (芎帰膠艾湯) Extract Granules 3.0 g t.i.d. for 4 weeks (n=26).
Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 4 weeks (n=19).
Arm 3: no treatment (n=23).

6. Main outcome measures

The degree of microscopic hematuria induced by urethral catheterization.

7. Main results

The improvement in hematuria was “marked” in 34.6%, “moderate” in 38.5%, “unchanged” in 23.1%, and “worse” in 3.8% of patients in arm 1, compared with 0, 26.1, 52.2, and 21.7%, respectively, in arm 3; the improvement was significantly greater in arm 1 ($P<0.0002$). The improvement in arm 2 (26.3, 31.6, 42.1, and 0%) was significantly greater than that in arm 3 ($P<0.0045$). There was no significant difference in the improvement of hematuria between arm 1 and arm 2.

8. Conclusions

Kyukikyogaito and saireito are suggested to improve essential microscopic hematuria in women.

9. From Kampo medicine perspective

This issue was referred to in the discussion section.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor’s comments

This is a valuable controlled clinical trial that demonstrated the effects of kyukikyogaito and saireito on essential microscopic hematuria in women. As the authors point out, each prescription for two different *sho* (証, pattern) has a different mechanism of action. A higher efficacy will probably be demonstrated in an RCT of the treatment according to *sho*.

12. Abstractor and date

Okabe T, 26 August 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Suzuki Y, Machida T, Onodera S, et al. Clinical effects of sairei-to for essential hematuria. *Hinyoki Geka* (*Japanese Journal of Urological Surgery*) 1994; 7: 325–7 (in Japanese). Ichushi Web ID: 1994241013

1. Objectives

To evaluate the clinical efficacy of saireito (柴苓湯) for essential hematuria.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Urology and 2nd Department of Internal Medicine, Jikei University School of Medicine, and two other facilities, Japan.

4. Participants

Eighty-two outpatients seen in the above hospitals with a chief complaint of hematuria and diagnosed with essential hematuria.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 9.0 g/day group for 28 days (n=50).
Arm 2: control group (no treatment) (n=32).

6. Main outcome measures

Urinary sediments evaluated on a 5-point scale: 3+, 2+, 1+, ±, and –.

7. Main results

A significantly greater improvement was noted in arm 2 than in arm 1 ($P<0.01$).

8. Conclusions

Saireito is expected to exert a hemostatic effect in hematuria.

9. From Kampo medicine perspective

Association with shosaikoto (小柴胡湯), an anti-inflammatory agent, is mentioned.

10. Safety assessment in the article

One patient complained of nausea.

11. Abstractor's comments

This paper is suggests the possible efficacy of saireito for essential hematuria, but no therapeutic regimen has been established. However, considering the clinical significance of asymptomatic hematuria, an investigation of the possible efficacy of saireito for nephritis prevention would make this study more meaningful. Future results are expected.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

References

Shimizu Y, Yoshimura K, Soda T, et al. The effects of gosha-jinki-gan, a blended herbal medicine, and furosemide for nocturnal polyuria with elevated B-type natriuretic peptide: a crossover trial. *Neurourology and Urodynamics* 2010; 29: 833–4. CENTRAL ID: CN-00766683

Yoshimura K, Shimizu Y, Masui K, et al. Furosemide versus gosha-jinki-gan, a blended herbal medicine, for nocturnal polyuria: a randomized crossover trial. *Lower Urinary Tract Symptoms* 2012; 4: 77-81.

1. Objectives

To evaluate the effectiveness of goshajinkigan (牛車腎気丸) for nocturnal polyuria with elevated B-type natriuretic peptide (BNP).

2. Design

Crossover randomized controlled trial (RCT – cross over).

3. Setting

No information about location of the trial (the first author belongs to the Department of Urology, Kyoto University), Japan.

4. Participants

Twenty-four patients over 50 years with a nocturia frequency of more than three times/night, a nocturnal polyuria index of more than 35%, and serum BNP level of over 20 pg/mL.

5. Intervention

Arm 1: goshajinkigan (牛車腎気丸) (manufacturer not identified) 2.5 g t.i.d. for 4 weeks, then furosemide 20 mg q.d. (p.m.) for 4 weeks (n=14).

Arm 2: furosemide 20 mg once/day (p.m.) for 4 weeks, then goshajinkigan (牛車腎気丸) (manufacturer not identified) 2.5 g t.i.d. for 4 weeks (n=10).

6. Main outcome measures

International Prostate Symptom Score (IPSS), Pittsburgh Sleep Quality Index (PSQI), frequency volume chart (FVC), blood pressure, serum BNP, and total body water assessed before and after each administration.

7. Main results

Mean age of participants was 73.8 years (54–85 years). Nocturia frequency and volume decreased significantly with furosemide administration compared to goshajinkigan administration (both $P<0.05$). However, IPSS-7, IPSS-QOL, and nocturia frequency improved significantly with both goshijinkigan and furosemide in before/after comparisons ($P<0.05$, $P<0.01$, $P<0.05$ for the three measures respectively with goshajinkigan, and $P<0.01$ for all three measures with furosemide). IPSS-total and nocturia volume improved significantly only with furosemide (both $P<0.01$). Nocturia volume decreased markedly with furosemide administration but only slightly with goshijinkigan administration. PSQI scores and subjective sleep scores improved significantly only with furosemide (both $P<0.05$).

8. Conclusions

Furosemide is more effective for nocturnal polyuria associated with elevated BNP, but goshajinkigan may be almost as effective.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical study investigated the effectiveness of goshajinkigan for nocturnal polyuria associated with elevated B-type natriuretic peptide. By classifying the causes of subjects' condition (nocturnal polyuria), effective condition for using goshajinkigan can be identified. The paper subsequently published by Yoshimura et al (2012) includes 36 participants and reports similar results, but it describes in detail the research methods they employed. Goshajinkigan may be effective for patients with slight nocturnal polyuria symptoms or patients who cannot take furosemide due to its adverse effects, which include electrolyte disturbance. It is, therefore, a highly significant clinical study.

12. Abstractor and date

Goto H, 31 December 2012, 31 December 2013.

18. Symptoms and Signs

Reference

Sekiguchi Y, Miyai K, Noguchi K, et al. Study of effects of anti-heat shock protein 60 antibody by ba wei di huang wan and qing xin lian zi yin (II). *Wakan Iyakugaku Zasshi* (*Journal of Traditional Medicines*) 1998; 15: 326-7 (in Japanese). CiNii

1. Objectives

To determine the effects of hachimijiogan (八味地黄丸) and seishinrenshiin (清心蓮子飲) on anti-heat shock protein (HSP) 60 antibody.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Not mentioned (the authors are in the Department of Urology, Yokohama City Kowan Hospital), Japan.

4. Participants

Twelve patients with normal urinalysis who chiefly complained of urinary frequency, pain on urination, or incomplete emptying.

5. Intervention

Arm 1: treatment with TSUMURA Seishinrenshiin (清心蓮子飲) Extract Granules (dose, not specified) orally for 2 weeks → treatment with TSUMURA Hachimijiogan (八味地黄丸) Extract Granules (dose, not specified) orally for 2 weeks (n=7).

Arm 2: treatment with TSUMURA Hachimijiogan (八味地黄丸) Extract Granules (dose, not specified) orally for 2 weeks → treatment with TSUMURA Seishinrenshiin (清心蓮子飲) Extract Granules (dose, not specified) orally for 2 weeks (n=5).

6. Main outcome measures

General subjective symptoms and urinary symptoms were evaluated using the International Prostate Symptom Score (IPSS) questionnaire. The titer of anti-HSP60 antibody was measured in blood samples.

7. Main results

The titer of anti-HSP60 IgG1 antibody was significantly reduced compared with the pre-treatment level both in arms 1 and 2. No change was observed in the titer of anti-HSP60 IgG2 antibody in both arms. Overall, although there was no change in urinary subjective symptoms score after treatment in both arms, gender-specific analysis of these ratings showed significant improvements after treatment of the male patients of arm 1 and female patients of arm 2. The outcomes were compared between patients with subjective symptoms lasting one month or more and patients with subjective symptoms lasting less than one month. The titer of anti-HSP60 IgG1 antibody declined significantly from pre-treatment level both in arms 1 and 2 in patients with urinary frequency lasting one month or more, but not in patients with urinary frequency lasting less than one month. Then, the association between general subjective symptoms and anti-HSP60 antibody (IgG1) were examined. The anti-HSP60 antibody (IgG1) titer was significantly higher in patients who self-reported nervousness than in patients who didn't (P=0.028) and in patients who reported early waking than in patients who didn't (P=0.0074). Similarly, the anti-HSP60 antibody (IgG1) titer was significantly lower in patients who reported having a good night's sleep than in patients who didn't (P=0.0300), and in patients who reported stiff back (P=0.0390) or cold hands (P=0.0472) than in patients who didn't.

8. Conclusions

The reduction of the titer of anti-HSP60 antibody (IgG1) after the hachimijiogan and seishinrenshiin treatments varies depending on the gender and the duration of urinary tract symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical study evaluated the effects of hachimijiogan and seishinrenshiin treatments on anti-HSP60 antibody. It is the only study to examine the association between anti-HSP60 antibody and urological symptoms. However, the paper was published in abstract form, and many details are omitted. One of the points that might significantly influence the results is wash-out period, which was not specified. The authors stated "the titer of anti-HSP60 IgG1 antibody was significantly reduced compared with the pre-treatment level both in arms 1 and 2". If the drugs were switched without wash-out, the anti-HSP60 IgG1 titer would remain low because the first drug is still present and active at the time of cross-over. So the length of the wash-out period needs to be stated. In addition, the authors found "significant improvements in male patients of arm 1 and female patients of arm 2 after the treatment", but this remarkable result might not be fully appreciated because details, including male/female ratio, are not available. Publication of the details of this study is needed to obtain further valuable insights into the association between Kampo medicine and anti-HSP60 antibody.

12. Abstractor and date

Goto H, 17 September 2008, 6 January 2010, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Matsushita S, Ueda S, Ouchi Y, et al. Usefulness of Chotosan (TJ-47) for relieving the accompanying symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension*. *Geriatric Medicine* 1995; 33: 1333-41 (in Japanese). Ichushi Web ID: 1996118416

1. Objectives

To evaluate the efficacy and safety of chotosan (釣藤散) for relieving the symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Geriatrics, The University of Tokyo Hospital; Department of Geriatrics, Nippon Medical School Hospital; and five hospitals, Japan.

4. Participants

Twenty-two patients with sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension, and the accompanying symptoms, such as headache, heaviness of head, and dizziness.

5. Intervention

Arm 1: treatment with TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g t.i.d. orally between meals for 12 weeks (n=11).

Arm 2: treatment with dilazep hydrochloride 50 mg t.i.d. orally between meals for 12 weeks (n=11).

6. Main outcome measures

Subjective symptoms (headache, heaviness of head, dizziness, stiff shoulders, palpitation, chest distress, hot flashes, tinnitus, numbness, cold extremities, and fatigue), psychiatric symptoms disorientation, loss of memory, bad mood, depression, anxiety and irritation, deranged speech, and decreased motivation), and blood pressure measured at baseline and 4, 8, and 12 weeks from the start of the study.

7. Main results

Because one patient in arm 2 withdrew due to a staggering walk, 11 patients in arm 1 and 10 in arm 2 were included in the analysis of results. Headache, heaviness of head, dizziness, stiff shoulders, depression, and anxiety and irritation were significantly improved in arm 1 compared to arm 2. Blood pressure in the sitting position was lowered significantly from 156/91 mmHg at baseline to 142/84 mmHg at 12 weeks in arm 1. In contrast, no significant change in blood pressure was observed in arm 2 (149/84 mmHg at baseline to 146/82 mmHg at 12 weeks) and there was no between-arm difference. When the change in blood pressure was subjectively rated on a 4-point scale (1: lowered - 4: elevated), the improvement at 12 weeks was significantly better in arm 1 than in arm 2.

8. Conclusions

Chotosan, compared with dilazep hydrochloride, is more effective for relieving the symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension, as well as for lowering blood pressure.

9. From Kampo medicine perspective

To determine which pattern (*kyo-sho* [虚証, deficiency pattern], *chukan-sho* [中間証, intermediate pattern], or *jitsu-sho* [実証, excess pattern]) each participant had, diagnoses were made using the *jitsu-sho* scoring system of the *kyo-jitsu* assessment. All the participants were diagnosed as having *kyo-sho*, making it impossible to determine the efficacy of chotosan for these three different patterns. In addition, no correlation was revealed by stratified analysis of global improvement ratings according to the indication of chotosan, including severity measures of headache, heaviness of head, dizziness, stiff shoulders, palpitation, choking feeling in the chest, hot flashes, tinnitus, disorientation, memory decline. There was no correlation between the degree of blood pressure lowering and the *jitsu-sho* score or the *sho*-related measures.

10. Safety assessment in the article

One patient in arm 1 developed mild elevation of lactose dehydrogenase (LDH) after 12 weeks of treatment. One patient in arm 2 discontinued the treatment due to staggering walk.

11. Abstractor's comments

This is an innovative clinical study that attempted to evaluate the efficacy of chotosan based on a consideration of *sho*, and determined objectively the efficacy of chotosan for relieving the symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension. However, each arm included only 11 patients and even fewer patients were included in the analysis of symptom improvement. This may explain why a significant difference was not detected. Furthermore, dilazep hydrochloride, which was used as a control, may cause, although uncommonly, adverse reactions such as headache, dizziness, and palpitation. The selection of this drug as a control would seem to be inappropriate because its adverse reactions are also among the variables used to measure outcome. Yet this is a remarkable clinical study that demonstrated the efficacy of chotosan in spite of the small number of patients.

12. Abstractor and date

Goto H, 18 September 2008, 1 June 2010.

18. Symptoms and Signs

Reference

Nishizawa Y, Nishizawa Y, Fushiki S. Analgesic effects on headache in patients with spinal cord injury. *Nippon Zutsu Gakkaishi* (*Japanese Journal of Headache*) 1997; 25: 23-6. Ichushi Web ID: 2000154079

1. Objectives

To evaluate the efficacy and safety of chotosan (釣藤散) for relieving headache in patients with spinal cord injury.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Not mentioned (the first author belongs to a clinic), Japan.

4. Participants

Two hundred and fifty-one patients who complained of moderate or severe headache persisting for at least 6 months after spinal cord injury; had normal cognitive and communicative abilities; and had no other pain than headache.

5. Intervention

Arm 1: treatment with clonidine (9–13.5 μg) (n=33).
Arm 2: treatment with tizanidine (120–180 μg) (n=31).
Arm 3: treatment with chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=30).
Arm 4: treatment with loxoprofen (3.6–4.8 mg) (n=34).
Arm 5: treatment with clonidine (9–13.5 μg) + chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=31).
Arm 6: treatment with tizanidine (120–180 μg) + chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=29).
Arm 7: treatment with loxoprofen (3.6–4.8 mg) + chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=32).
Arm 8: treatment with lactose (90–120 mg) (n=31).

Test drugs were administered orally in capsules, 3 hours before meals, for 6 months. Other details, including the frequency of administration, were not available.

6. Main outcome measures

Headache evaluated on a Visual Analogue Scale for pain (VAS-P) for 8 hours starting from 30 minutes before the administration. After 6 months of treatment, pain and quality of life (QOL) determined using the McGill Pain Questionnaire and evaluated using a VAS and verbal descriptor scale. Clonidine concentrations in cerebrospinal fluid and plasma measured only in patients who received this drug.

7. Main results

A total of 221 (30 in arm 1, 29 in arm 2, 28 in arm 3, 25 in arm 4, 28 in arm 5, 27 in arm 6, 24 in arm 7, and 30 in arm 8) out of 251 participants were included in the efficacy analysis. VAS-P and QOL were significantly improved only in arms 1 and 5 compared with the control ($P<0.01$). Furthermore, the improvements in arm 5 were significantly greater than those in arm 1.

8. Conclusions

Chotosan enhances analgesic effect of clonidine for headache in patients with spinal cord injury.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects of clonidine were mentioned in the results section, but no details were given. Although 30 patients appear to have withdrawn during the 6-month treatment, no details were given either.

11. Abstractor's comments

This clinical study determined the effects of various drugs on headache due to spinal cord injury in 250 patients, and provided meaningful results which can be directly applied to clinical practice. The value of the paper would have been increased by inclusion of detailed descriptions of the administration method, adverse drug reactions, etc. As for study design, many ineffective control drugs were used in this study. From the perspective of ethics, the effects of those drugs should have been observed in a shorter-term study. Although this study was reported to be a "double blind test", the numbers of capsules administered varied between arms and some problems with blinding are suspected. Furthermore, results from the clinical evaluation of various drugs were reported along with the correlation of blood clonidine concentration and pain. Preferably, these results should have been described clearly and separately in the methods and results sections. Nonetheless, this is a meaningful clinical study that provided a lot of valuable data and clarified the efficacy of chotosan combination therapy.

12. Abstractor and date

Goto H, 22 September 2008, 6 January 2010, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

References

Seki H, Tateyama M, Sahara M, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization using the sealed-envelope method)*. *Shinryo to Shinyaku* (*Medical Consultation & New Remedies*) 1991; 28: 573–6 (in Japanese). Ichushi Web ID: 1992103222

Seki H, Okita N, Takase S, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization carried out using the sealed-envelope method)*. *Pharma Medica* 1993; 11: 288–91 (in Japanese). Ichushi Web ID: 1994170314

1. Objectives

To evaluate the efficacy and safety of goshuyuto (呉茱萸湯) for relieving chronic headache using keishininjinto (桂枝人参湯) as a control.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The department of neurology of one hospital, Japan.

4. Participants

Eighty-eight patients with chronic headache.

5. Intervention

Arm 1: oral administration of goshuyuto (呉茱萸湯) (manufacturer unknown) 2.5 g t.i.d. for 4 weeks (n=44).

Arm 2: oral administration of keishininjinto (桂枝人参湯) (manufacturer unknown) 2.5 g t.i.d. for 4 weeks (n=44).

6. Main outcome measures

Headache severity rated on a 4-point scale.

7. Main results

Headache severity was at least moderately improved in 56.8% and 38.6% of patients and at least slightly improved in 79.5% and 61.4% of patients in the goshuyuto (呉茱萸湯) group and keishininjinto (桂枝人参湯) group, respectively.

8. Conclusions

The effect of goshuyuto on chronic headache is comparable to that of keishininjinto.

9. From Kampo medicine perspective

Goshuyuto was expected to be effective in patients prone to obesity and constipation and with cold limbs, whereas keishininjinto was expected to be effective in lean patients prone to loose stool.

10. Safety assessment in the article

Mild increase in gamma-glutamyltranspeptidase (γ-GTP), glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) or prickly heat rash was noted in 3 patients in arm 1.

11. Abstractor's comments

This clinical study investigated the efficacy of goshuyuto for chronic headache using keishininjinto as a control and is excellent because it reviewed the *sho* (証, pattern) of the responsive group with the intention of elucidating the pathology of chronic headache according to Kampo concepts. Unfortunately, the results were not statistically significant. The failure to demonstrate a significant between-arm difference may be due to the use of only one measure of headache severity. Evaluating headache frequency, time to resolution, and frequency of use of as-needed drugs might have revealed differences in the efficacy of goshuyuto and keishininjinto. The names of the drug combinations and drug manufacturers should also have been specified. In addition, the *sho* (証, pattern) should have been used to identify the indications for goshuyuto and keishininjinto rather than to compare the indications for these medicines. Nevertheless, this clinical study is valuable because it considered the difficulty of using a placebo in patients with clinical complaints. The article by Seki et al (1991) was the interim report for this study.

12. Abstractor and date

Goto H, 14 September 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

References

Odaguchi H, Hanawa Y. Complementary alternative medicine in headache treatment*. *Igaku no Ayumi* (*Journal of Clinical and Experimental Medicine*) 2005; 215: 1137-40 (in Japanese) MOL, MOL-Lib

Odaguchi H, Wakasugi A, Ito H, et al. The efficacy of goshuyuto, a typical Kampo (Japanese herbal medicine) formula, in preventing episodes of headache. *Current Medical Research and Opinion* 2006; 22: 1587-97. CENTRAL ID: CN-00571314, Pubmed ID: 16870083

1. Objectives

To evaluate the efficacy of goshuyuto (呉茱萸湯) for relief of chronic headache and to evaluate the associated adverse drug reactions.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Three university-associated outpatient headache clinics, Japan.

4. Participants

Fifty-three patients with chronic headache that responded to goshuyuto orally administered for 4 weeks.

5. Intervention

Arm 1: oral administration of 7.5 g/day of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules for 12 weeks (n=28).

Arm 2: oral administration of the same dose of placebo granules indistinguishable in appearance, taste, and odor from goshuyuto for 12 weeks (n=25).

6. Main outcome measures

Headache severity, headache frequency, and severity of cold, menstrual cramps, and shoulder stiffness evaluated in all participants.

Surface temperature of fingers and toes, skin blood flow, deep body temperature, brain and femoral oxygen saturation, rigidity of the trapezius muscle, and blood serotonin concentration evaluated in some participants.

7. Main results

After a 12-week treatment, the number of days with headache was significantly decreased from baseline by 2.6 in arm 1 but remained unchanged in arm 2 (decreased by 0.3), showing significantly greater improvement in arm 1 than in arm 2. In addition, the number of doses of an analgesic taken was significantly decreased from baseline by 2.2 in arm 1 but remained unchanged (decreased by 1.4) in arm 2, indicating no between-arm difference. Comparison limited to migraine disclosed the same trend. There were no significant changes in the other parameters in both arms.

8. Conclusions

Goshuyuto decreases the frequency of headache episodes in patients with chronic headache, thereby reducing the number of analgesic doses.

9. From Kampo medicine perspective

This study considers *sho*, since its first stage involved selection of only goshuyuto-responders as "*sho* for goshuyuto," and these were enrolled in a double-blind, randomized controlled trial at the second stage.

10. Safety assessment in the article

No adverse drug reactions occurred except for increases in ALT, AST and γ–GTP in 1 patient receiving goshuyuto. These reactions persisted 3 months after drug discontinuation, suggesting possible development of fatty liver.

11. Abstractor's comments

In this study, goshuyuto was administered to 91 patients with chronic headache at its first stage to select responders (n=53) for a double-blind, randomized controlled trial at its second stage. Thus, it may be a groundbreaking study in that it focused on "*sho*." Besides headache, menstrual cramps and shoulder stiffness also tended to be improved by treatment with goshuyuto, warranting investigation with a larger sample size to clarify "goshuyuto-*sho*." More clinical studies in oriental medicine such as the present study are expected in the future.

12. Abstractor and date

Goto H, 1 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Satoh N, Sakai S, Kogure T, et al. A randomized double-blind placebo-controlled clinical trial of hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness, N of one and responder restricted design. *Phytomedicine* 2005; 12: 549-54. CENTRAL ID: CN-00524047, Pubmed ID: 16121514

1. Objectives

To evaluate the efficacy of hochuekkito (補中益気湯) for the elderly with weakness.

2. Design

Double-blind, randomized controlled trial (DB-RCT) in combination with N-of-1 trial restricted to hochuekkito-responders.

3. Setting

Five hospitals associated with Toyama Medical and Pharmaceutical University (now Toyama University), Japan.

4. Participants

Fifteen elderly patients (3 males and 12 females; age [mean ± SD], 78.4±7.8 years) with weakness satisfying the following 4 inclusion criteria: (1) complaint of discomfort and anorexia due to chronic debilitating disease; (2) no history of infection or vascular disorder within 1 month before the start of the trial; (3) no malignant diseases; and (4) aged ≥60 years and <90 years.

5. Intervention

Responders during the 2-week run-in period were randomly assigned to the following 3 arms:

Arm 1: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of placebo at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=4).

Arm 2: administration of placebo (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=5).

Arm 3: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=4).

Responders had to meet criterion (1) and one of the three other criteria (2) to (4): (1) good drug compliance; (2) subjective overall evaluation improved; (3) clinical symptoms improved; or (4) symptoms other than chief complaint improved.

6. Main outcome measures

36-item short-form health survey (SF36), profile of mood states (POMS), natural killer (NK) activity, interleukin (IL)-2-producing activity of peripheral lymphocytes, lymphocyte-proliferating activity, and lymphocyte cell-surface antigens.

7. Main results

PCS (physical component summary) of SF36 was significantly improved in the hochuekkito group ($P<0.05$). There were significant among-arm differences in 4 (anger-hostility, fatigue, tension-anxiety, confusion) of 6 subscales of the POMS ($P<0.01$, $P<0.05$, $P<0.01$, $P<0.05$, respectively). Lymphocyte cell-surface antigens, CD3-positive cells, and CD3/CD4 double-positive cells were significantly increased in the hochuekkito group ($P<0.05$).

8. Conclusions

Hochuekkito improves the QOL of elderly patients with weakness and activated their immune systems.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

The design of this study is very interesting, being a combination of RCT and N-of-1 trial. The authors mention that 15 candidates were registered and none dropped out; however, the actual number was 13 (four participants in arm 1, five in arm 2, and four in arm 3). The authors treated the participants as one group, with a washout period separating the interventions in each arm, and proceeded on a two-group basis by converting to a hochuekkito (補中益気湯) group (17 participants), and a placebo group (nine participants). The authors argue that they added an N-of-1 trial to a small-scale RCT; however, there is no before-after comparison for the N-of-1 trial, and it rather resembles a crossover trial (DB-RCT-crossover). Interpreting results from a complex design is difficult. Hopefully the authors will further develop their approach.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Ohno S, Suzuki T, Asaoka T, et al. Effects of Oriental medicine on lymphoid cells. *Kampo to Meneki-Allergy* (*Kampo and Immunoallergy*) 1995; 9: 78-86 (in Japanese with English abstract). Pubmed ID: 21724872

1. Objectives

To evaluate the effect of hochuekkito (補中益気湯) on lymphocytes.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One center: the Second Department of Internal Medicine, Saitama Medical University Hospital, Japan.

4. Participants

Thirty people who presented at an Oriental medicine outpatient clinic with fatigue.

5. Intervention

Arm 1: TSUMURA Hochuekkito (補中益気湯) Extract Granules group (n=15).
Arm 2: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules group (n=15).

6. Main outcome measures

Changes in leukocyte, neutrophil, and lymphocyte counts; response of lymphocytes to phytohemagglutinin (PHA) and concanavalin A (ConA) stimulation.

7. Main results

No changes in leukocyte or neutrophil count were observed. Lymphocyte count increased significantly in arm 1 ($P<0.05$). Lymphocyte count decreased with PHA and ConA stimulation in arm 2, and, conversely, lymphocyte count (particularly large-granular lymphocyte count) increased with ConA stimulation in arm 1.

8. Conclusions

Hachimijiogan and hochuekkito have different effects on the lymphocyte system *in vivo*.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One participant taking hochuekkito suffered constipation and three taking hachimijiogan suffered stomach discomfort, but no serious adverse effects were observed.

11. Abstractor's comments

While the significant increase in lymphocyte count in the hochuekkito group is the starting point for this study, the lymphocyte counts prior to treatment in the control group (hachimijiogan group) were widely scattered, which might explain the lack of any significant difference between the groups (Fig. 6 and Fig. 7). Increasing the number of participants in a future study may reduce between-group differences. Accordingly, it would be better to make the control group a no-treatment group, rather than a hachimijiogan group. Interestingly, the increase in the lymphocyte count (particularly large-granular lymphocyte count) and NK activity in the hochuekkito group suggests hochuekkito has an effect on tumor immune cells. Hopefully the authors will conduct a further study into the question of whether hachimijiogan and hochuekkito have similar activities, with an increased number of participants.

12. Abstractor and date

Nakata H, 31 December 2013.

18. Symptoms and Signs

Reference

Ishioka T. Comparison of the efficacy of goreisan and saireito for mild edema of the dorsum of the foot in elderly subjects stratified by physical strength*. *Kampo no Rinsho* (*Journal of Kampo Medicine*) 1997; 44: 1091-5 (in Japanese).

1. Objectives

To compare the efficacy of goreisan (五苓散) and saireito (柴苓湯) for mild edema of the dorsum of the foot in the elderly.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

A special nursing home, Japan.

4. Participants

Forty-three patients who were admitted to the nursing home, had no serious cardiac diseases, had a serum creatinine level within normal limits, and complained of mild persistent edema of the dorsum of the foot (9 males and 34 females, aged 66-94 years, mean age 83.1 years). Of these 43 patients, 21 were placed into a “moderate physical strength” subgroup and 22 into a “low physical strength” subgroup, on the basis of strength demonstrated during a balloon volleyball game played in the nursing home.

5. Intervention

Arm 1: treatment with TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. for 2 weeks, then switched, with no wash-out, to TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 2 weeks. The sample size was not reported.

Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 2 weeks, then switched, with no wash-out, to TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. for 2 weeks. The sample size was not reported.

6. Main outcome measures

Disappearance of edema after 2 weeks of treatment was rated as “moderate response”; marked reduction of edema as “mild response”; no change as “no response”; and symptomatic exacerbation requiring diuretics after 1 week, or marked exacerbation after 2 weeks of treatment as “worsening”. The two drugs were considered as “having comparable efficacy” when the extent of symptomatic changes during the first and the second 2 weeks were similar.

7. Main results

One patient was hospitalized with bronchitis on day 3 of the saireito treatment following the goreisan treatment. Consequently, the efficacy of goreisan but not saireito was evaluated in this patient. As a result, efficacy analysis population included 43 patients for goreisan and 42 for saireito. A “mild” or better response was obtained in 67% of the goreisan-treated and 62% of the saireito-treated patients; the difference was not significant. In the subgroup with moderate physical strength, there was no significant difference in the rate of response to goreisan (57%) and saireito (62%). In contrast, the rate of response to goreisan (77%) tended to higher than that to saireito (62%; $P<0.1$) in the subgroup with low physical strength.

8. Conclusions

Both goreisan and saireito results in a “mild” or better response in 60% or more of the elderly patients with mild edema of the dorsum of the foot. Notably, patients with low physical strength tended to be more responsive to goreisan.

9. From Kampo medicine perspective

The author argued that the classification “low physical strength” is almost identical to the definition of weak constitution in the clinical guidelines for the reevaluation of Kampo extract preparations, and that "low physical strength" and weak constitution are consistent with the Kampo concept of *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Although no individual patients developed abnormalities while taking the test drugs, a decrease in potassium level in all patients and an elevated serum creatinine level in the subgroup with low physical strength were observed. Subjective or objective symptoms were not reported.

11. Abstractor’s comments

This study was a cross-over trial conducted in a special nursing home. There are some problems with the study design, such as the absence of wash-out period and the non-blinded design. The development of further studies is expected.

12. Abstractor and date

Tsuruoka K, 25 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Kishida Y, Miki H, Nishii T, et al. Therapeutic effects of Saireito (TJ-114), a traditional Japanese herbal medicine, on postoperative edema and inflammation after total hip arthroplasty. *Phytomedicine* 2007; 14: 581-6. CENTRAL ID: CN-00609214, Pubmed ID: 17292595

1. Objectives

To investigate the efficacy and safety of saireito (柴苓湯) on postoperative edema and inflammation after total hip arthroplasty (THA).

2. Design

Randomized controlled trial (RCT).

3. Setting

Two departments (Department of Kampo Medicine and Department of Orthopaedic Surgery) of Osaka University, and one hospital, Japan.

4. Participants

Female patients who underwent THA because of unilateral osteoarthritis, n=17.

5. Intervention

Arm 1: Tsumura Saireito（柴苓湯）Extract Granules 9.0 g/day for 2 days before surgery and for 2 weeks after surgery, n=8.
Arm 2: no administration, n=9.

6. Main outcome measures

The circumference of the lower limb at three locations (the lower leg, ankle, and forefoot), Merle d'Aubigne hip score for clinical evaluation including pain, and serum C-reactive protein (CRP) level.

7. Main results

At three weeks after surgery, the circumference of the lower leg was less in arm 1 than in arm 2. The serum CRP level became negative by 2 weeks after surgery in 6 of 8 patients in arm 1 and in 0 of 9 patients in arm 2 (P<0.001).

8. Conclusions

Administration of saireito is suggested to reduce postoperative lower leg edema and inflammation after THA.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were reported in arm 1 and documented in arm 2.

11. Abstractor's comments

This study suggests the efficacy of saireito for postoperative lower leg edema after THA. In this trial, all patients had a pneumatic foot compression device and wore compression stockings concurrently to prevent postoperative lower leg swelling. This study also indicated that saireito is effective in decreasing postoperative inflammation. All patients received an intravenous infusion of prophylactic antibiotics for 4 days, subsequently oral antibiotics for 4 days, and nonsteroidal anti-inflammatory drugs (NSAIDs) for 1 week after surgery. However, CRP level remained positive in all subjects in arm 2, two weeks after surgery. In general, a few days' treatment with antibiotics should lead to a negative CRP level by two weeks after surgery. Further clinical studies with more patients and fewer concomitant therapies for knee replacement arthroplasty and bipolar hip arthroplasty are awaited and anticipated.

12. Abstractor and date

Okabe T, 11 December 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Nishida S, Eguchi E, Ohira T, et al. Effects of a traditional herbal medicine on peripheral blood flow in women experiencing peripheral coldness: a randomized controlled trial. *BMC Complementary Alternative Medicine* 2015; 15: 105.

1. Objectives

To evaluate the clinical effects of tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯) for peripheral coldness in women.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital and 1 hospital.

4. Participants

Fifty-eight women with peripheral coldness recruited online, etc. (aged 23-79).

5. Intervention

Arm 1: TSUMURA Tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯) Extract Granules (7.5g/day [2.5g t.i.d.] for 8 weeks) (n=28).
Arm 2: No administration (n=30).

6. Main outcome measures

Blood flow and peripheral skin temperature before cold bathing test, and 1 and 10 minutes after.

7. Main results

One participant could not be followed up and dropped out: 27 participants were analyzed in arm 1. Peripheral coldness was alleviated more in women in the tokishigyakukagoshuyushokyoto group than the control group. Although there was no difference in recovery of peripheral surface temperature between the tokishigyakukagoshuyushokyoto group and the control group, the rate of blood flow recovery was significantly higher in the tokishigyakukagoshuyushokyoto group ($P<0.007$).

8. Conclusion

The study suggests that tokishigyakukagoshuyushokyoto may alleviate coldness by improving peripheral blood flow in women.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This paper substantiates by cold bathing test the effects of tokishigyakukagoshuyushokyoto, a Kampo medication used for intense coldness since long ago, and whose effects have been enumerated in the texts. It has great significance for evidence building. Preferably, the authors would have scored the subjects' cold sensation, and dealt more fully with the relationship between recovery of peripheral temperature and blood flow, and the decreasing sensation of cold. Although accompanied by some difficulties, a double-blind RCT with placebo using the same evaluation methods is anticipated.

12. Abstractor and date

Ushiroyama T, 16 January 2017.

18. Symptoms and Signs

References

Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san, an oriental herbal medicine, in obese Japanese women with impaired glucose tolerance. *Clinical and Experimental Pharmacology and Physiology*, 2004; 31: 614-9. CENTRAL ID: CN-00505762, Pubmed ID: 15479169

Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san in obese Japanese women with IGT. *Rinsho Kampo Yakuri Kenkyukai Kaishi* (*Journal of the Society for Clinical Kampo Pharmacology*), 2004; 100th Memorial Issue: 19-22. Ichushi Web ID: 2006163538

Hioki C. The first randomized trial of bofutsushosan in obese patients with IGT. *Pharma Medica* 2007; 25: 43-8 (in Japanese) Ichushi web ID: 2008035994, MOL, MOL-Lib

Hioki C, Arai M. Bofutsushosan use for obesity with IGT: search for scientific basis and development of effective therapy with Kampo medicine. *Journal of Traditional Medicine* 2007; 24: 115-27. *Journal of Traditional Medicine* 2007; 24: 115-27. J-STAGE

1. Objectives

To evaluate the efficacy and safety of bofutsushosan (防風通聖散) in obese Japanese women with impaired glucose tolerance.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

An university hospital (Kyoto Prefectural University of Medicine), Japan.

4. Participants

Eighty-one obese women (mean body mass index, 36.5 kg/m^2) with impaired glucose tolerance were included. Patients with kidney, heart and/or liver disease, any metabolic or endocrine disease, psychiatric disorders, or cancer were excluded.

5. Intervention

Arm 1: treatment with TSUMURA Bofutsushosan (防風通聖散) Extract Granules for 24 weeks + low-calorie diet (1,200 kcal) + exercise therapy (300 kcal) (44 patients; of these, 41 were included for analysis).

Arm 2: treatment with placebo for 24 weeks + low-calorie diet (1,200 kcal) + exercise therapy (300 kcal) (41 patients; of these, 40 were included for analysis).

6. Main outcome measures

Body weight, the proportion of body fat (% weight), visceral and subcutaneous fat accumulation, systolic and diastolic blood pressure, heart rate, biochemical data (triglyceride, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, uric acid, glycosylated hemoglobin (HbA1c), and fasting glucose), and waist and hip circumference were measured before treatment, and after 12 and 24 weeks of treatment. Values for 2-h oral glucose tolerance test (OGTT) glucose, glucose area under the curve (AUC) 120, fasting insulin, insulin AUC120, and homeostasis model assessment of insulin resistance (HOMA-IR) were measured or calculated after 24 weeks.

7. Main results

Waist circumference decreased in both arms after 12- and 24-week treatment compared with before treatment. The decrease was significantly greater after 24 weeks in Arm 1 compared with Arm 2. There were significant differences in more measures after 24 weeks than after 12 weeks in both arms. In Arm 2, body weight, body fat (%), and subcutaneous fat decreased only after 24 weeks; systolic and diastolic blood pressure, triglyceride, and total cholesterol reduced after 12 and 24 weeks. In Arm 1, body weight, body fat (%), visceral and subcutaneous fat, systolic and diastolic blood pressure, biochemical data (LDL cholesterol, HDL cholesterol, uric acid, and insulin [fasting and AUC120]), 2-h OGTT glucose, and HOMA-IR improved after 24 weeks. The decrease in body weight in Arm 1 was associated with decreased visceral and subcutaneous fat but not with a decrease in adjusted resting metabolic rate, whereas the weight loss in Arm 2 was not associated with decreased visceral fat.

8. Conclusions

Bofutsushosan is useful in the treatment of obese patients with impaired glucose tolerance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no effect on cardiovascular or central nervous system in the two arms. Although no subject had steatorrhea, 3 subjects in the bofutsushosan arm discontinued treatment and withdrew from the study because of diarrhea. One subject in the placebo arm dropped out of the study owing to noncompliance.

11. Abstractor's comments

This DB-RCT (examining the efficacy and safety of bofutsushosan in obese Japanese women with impaired glucose tolerance) provides a high quality of evidence. Although body weight tended to decrease between 12 and 24 weeks of treatment in the placebo arm, it can still be concluded that the anti-obesity effect of bofutsushosan combined with diet and exercise therapies is more likely to persist potently. Further studies should be conducted to evaluate the effect of bofutsushosan monotherapy without diet and exercise therapies. Investigations with Kampo diagnostic considerations are also needed.

12. Abstractor and date

Namiki T, 15 Septmber 2007, 1 April 2008, 13 March 2009, 1 June 2010, 31 December 2013.

19. Injury, Poisoning, and Postoperative Pain

Reference

Nakae H, Yokoi A, Kodama H, et al. Comparison of the effects on rib fracture between the traditional Japanese medicine jidabokuippo and nonsteroidal anti-inflammatory drugs: a randomized controlled trial. *Evidence Based-Complementary and Alternative Medicine* 2012; 837958. Pubmed ID: 22888367

1. Objectives

To evaluate the effectiveness and safety of jidabokuippo (治打撲一方) on rib fracture.

2. Design

Randomized controlled trial (RCT).

3. Setting

Three centers (Akita University Hospital and 2 others).

4. Participants

Rib fractures were diagnosed by X-ray and CT images. Patients who could not ingest, who had multiple injuries, or who were examined 4 days or more after the injury occurred were excluded. Young patients under 15 years and pregnant women were also excluded. (n=170)

5. Intervention

Arm 1: TSUMURA Jidabokuippo (治打撲一方) (Dosage and daily frequency not mentioned.) (n=85)
Arm 2: NSAIDs (Loxoprofen, diclofenac sodium, lornoxicam, etodolac, meloxicam, celecoxib, naproxen) (Dosage and daily frequency not mentioned.) (n=85)
In both groups, administration continued until the visual analog scale (VAS) score for pain due to rib fracture were less than 50% of the pre-administration score.

6. Main outcome measures

The study compared the period until the visual analog scale (VAS) score for pain due to rib fracture were less than 50% of the pre-administration score. At the same time, it compared the medical costs required in the 2 groups.

7. Main results

In arm 1, 3 of the patients switched to NSAIDs because their symptoms did not improve, and 1 patient could take jidabokuippo because of its taste, so a total of 4 patients were excluded. In arm 2, 2 of the patients switched to jidabokuippo because their symptoms did not improve, 1 patient could not continue administration due to dyspepsia, and 1 patient discontinued administration before the VAS score fell below 50%, so a total of 4 patients were excluded. In each group 81 participants were analyzed. The median treatment periods were 7 days in arm 1 (7-77 days), and 14 days (5-77 days) in arm 2, meaning a significantly shorter period in arm 1 than arm 2 (P=0.0003). The median medical costs were 509.3 yen (339.5-5,601.8 yen) in arm 1 and 1,581.3 yen (468.3-10,256.4 yen) in arm 2, meaning a significantly lower amount in arm 1 than arm 2 ($P < 0.0001$).

8.Conclusions

Jidabokuippo is more effective in improving pain from rib fracture compared to NSAIDs, and the medical costs required are less.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Dyspepsia or other adverse effects were not observed in the jidabokuippo group, they were observed in 5 out of 85 patients in the NSAIDs group, however, there was no significant difference between the groups (P=0.0588).

11. Abstractor's comments

This clinical trial compared jidabokuippo to NSAIDs for their analgesic effect for pain from rib fracture, making it a valuable clinical trial examining the effects of a Kampo medication in the acute phase. However, the paper does not mention the drug dosages. Furthermore, while it was useful from a medical economy perspective, the medical costs of NSAIDs might be lower than jidabokuippo depending of the choice of NSAID. However, even after taking these points into consideration, jidabokuippo had few adverse effects, it did not require the combined use of gastric mucosal protective agents, etc., and appeared to effectively relieve pain from rib fracture. This clinical trial elucidated the effectiveness of Kampo medications in the field of orthopedics, suggesting further similar research into acute-phase pathologies and prescriptions is desirable.

12. Abstractor and date

Goto H, 18 May 2020.

19. Injury, Poisoning, and Postoperative Pain

Reference

Takeda N. Conservative therapy for fresh lateral ligament injury of the ankle joint – Comparison of a Western medicine and a Kampo medicine for pain and swelling*. *Kampo to Rinsho* (*Journal of Kampo Medicine*) 2010; 1: 128–32 (in Japanese). Ichushi Web ID: 2010218384

1. Objectives

To evaluate the efficacy of a Western medicine and a Kampo medicine (jidabokuippo [治打撲一方]) for pain and swelling after a fresh and isolated anterior talofibular ligament (ATFL) grade III injury.

2. Design

Randomized controlled trial (RCT).

3. Setting

One orthopedic clinic, Japan.

4. Participants

Thirty-five outpatients with grade III fresh ATFL isolated injury who received conservative therapy from April 2008 to March 2009.

5. Intervention

Treatment lasted approximately two weeks.
Arm 1: TSUMURA Jidabokuippo (治打撲一方) Extract Granules 2.5–7.5 g/day (n=17 [17 legs]).
Arm 2: loxoprofen sodium 60–180 mg/day (n=18 [18 legs]).
The dose was calculated per kg of body weight.

6. Main outcome measures

Pain (visual analogue scale [VAS]), swelling (average circumference at 5-cm centrally and peripherally from the ATFL rupture site).

7. Main results

Of 17 patients in arm 1, the pain had resolved within three weeks of trauma in 11 patients, within four weeks in 4, within six weeks in 1, and within 12 weeks in 1, and of 18 patients in arm 2, within three weeks in 12, within four weeks in 2, within six weeks in 2, and within 12 weeks in 2. The swelling had resolved within three weeks in 12 patients, within four weeks in 2, within six weeks in 2, and within 12 weeks in 1 in arm 1 and within three weeks in 9, within four weeks in 4, within six weeks in 3, and within 12 weeks in 2 in arm 2. A tendency toward earlier resolution of swelling was found in arm 1 at 2 weeks after trauma, and eventually disappeared.

8. Conclusions

The efficacy of the Western medicine and the Kampo medicine (jidabokuippo) for pain and swelling in grade III fresh ATFL isolated injury is comparable. The jidabokuippo treatment tends to resolve swelling earlier.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Clinical testing was not carried out and there were no adverse events.

11. Abstractor's comments

This paper is clinically significant because it compares the efficacy of loxoprofen sodium with that of jidabokuippo for pain and swelling in grade III fresh ATFL isolated injury in an RCT. Unfortunately, statistical analysis between groups was not sufficiently powerful to distinguish between the groups. However, from the viewpoint of primary care for grade III fresh lateral ligament injury of the ankle joint, the results of this paper are clinically quite significant, and further clinical study is anticipated.

12. Abstractor and date

Kogure T, 6 January 2011, 31 December 2013.

19. Injury, Poisoning, and Postoperative Pain

Reference

Nimura T, Yamada S, Ohwaki T, et al. Evaluation of the efficacy of Kampo therapy in patients with heat illness requiring hospitalization*. *Kampo Igaku* (*Kampo Medicine*) 2014: 38; 178-81 (in Japanese). Ichushi Web ID: 2015015844

1. Objectives

To evaluate the efficacy of Kampo therapy in patients with heat illness requiring hospitalization.

2. Design

Randomized controlled trial (RCT). However, the attending physicians were randomly assigned.

3. Setting

A department of internal medicine in a general hospital in Aichi Prefecture, Japan.

4. Participants

Thirty-four patients who were admitted to the hospital due to hyperthermia during the summer seasons (July to September) from 20xx to 20xx (2 years).

Hyperthermia was diagnosed and its severity was graded according to the severity classification (Classes I to III) of the Japanese Congress on Neurological Emergencies.

5. Intervention

Arm 1: Kampo arm (fluid replacement + Kampo medicine). Four physicians who routinely prescribe Kampo medicines were randomly assigned to this arm. (n=20)

Arm 2: Non-Kampo arm. Only fluid replacement was administered. Four physicians who do not routinely prescribe Kampo medicines were randomly assigned to this arm. (n=14)

6. Main outcome measures

Number of hospitalization days.

7. Main results

No inter-arm differences in age, sex, presence or absence of primary disease, laboratory data on admission, or severity of hyperthermia were found. Kampo medicines used in the Kampo arm were hochuekkito (n=17), rikkunshito (n=1), daikenchuto (n=1), and yokukansan (n=1). The hospitalization period was significantly shorter in the Kampo arm (5.1±3.7 days) than in the non-Kampo arm (15.8±16.1 days) for all hyperthermia severity Classes I to III ($P<0.05$) and for severity Class III (4.9±3.6 days in the Kampo arm vs. 20.5±18.5 days in the non-Kampo arm; $P<0.05$).

8. Conclusions

Kampo medicines shorten the period of hospitalization for hyperthermia.

9. From Kampo medicine perspective

No differences were found in effects of four Kampo medicines used in the study: hochuekkito, rikkunshito, daikenchuto, and yokukansan. According to the article, Kampo medicines (seishoekkito, hochuekkito, rikkunshito, ninjinto, goreisan, and ireito) had previously been used for treating summer fatigue and heat exhaustion, but not for hyperthermia requiring hospitalization.

10. Safety assessment in the article

One subject in each arm died in the study, but these deaths had no causal relationship with Kampo medicines.

11. Abstractor's comments

This study is important because the efficacy of Kampo medicines in subjects with hyperthermia requiring hospitalization was evaluated in an RCT. Since this article is a short report, the study methods and the results were not fully described. The study design was an RCT; however, the prescribing physicians (Arm 1: physicians who routinely prescribe Kampo medicines, Arm 2: physicians who do not routinely prescribe Kampo medicines) were randomly assigned to each study arm. Therefore, neither the physicians nor the subjects were blinded. As in the usual RCT design, which would preferable, just one Kampo medicine was used for evaluation and comparison between the Kampo and placebo control arms. The development of future studies is anticipated.

12. Abstractor and date

Tsuruoka K, 31 March 2017.

19. Injury, Poisoning, and Postoperative Pain

Reference

Takamura M, Effectiveness of Kampo extract preparations for the treatment of heat illness.* *Kampo to Saishinchiryo* (*Kampo & the Newest Therapy*) 2014; 23: 121-4 (in Japanese).

1. Objectives

To evaluate the effect of Kampo extract preparations as an adjunct to the standard therapy to shorten the symptom resolution time in patients with heat illness.

2. Design

Randomized controlled trial (RCT).

3. Setting

One clinic, Japan.

4. Participants

Eleven male patients with heat illness assessed as Class II (moderate) in severity, occurring at manufacturing sites of companies with around 3000 employees (including exterior and interior sites) between June and September in 2010 and 2011, who were able to drink water.

5. Intervention

For Kampo medicines, one packet (2.5 g) of TSUMURA Shyakuyakukanzoto (芍薬甘草湯) Extract Granules was used as a single dose for subjects with muscle cramp or myalgia. Otherwise, one packet (3.0 g) of TSUMURA Byakkokaninjinto (白虎加人参湯) Extract Granules was used as a single dose.

Arm 1: Cooling + oral rehydration solution (Otsuka OS-1) + saline infusion + Kampo extract preparation (n=5).

Arm 2: Cooling + oral rehydration solution (Otsuka OS-1) + saline infusion (n=6).

6. Main outcome measures

Time from onset to symptom resolution.

7. Main results

Symptoms in all subjects improved after treatment. Time to symptom resolution was significantly shorter in the Kampo arm (48.0±13.5 minutes vs 80.8±21.8 minutes; P=0.017). No significant difference in age, blood pressure, body temperature, fluid replacement, or total water requirement was found between the arms.

8. Conclusions

Adding shyakuyakukanzoto or byakkokaninjinto extract to the standard rehydration therapy (of cooling and salt and water supplementation) may shorten the time to symptom improvement in patients with heat illness.

9. From Kampo medicine perspective

In Kampo therapy, byakkokaninjinto is believed to be effective for treatment of the following symptoms: *etsu* (暍, summerheat stroke), sweating, feeling hot in the body and thirsty. Shyakuyakukanzoto is used for treatment of myalgia and muscle stiffening symptoms.

10. Safety assessment in the article

No adverse events were noted.

11. Abstractor's comments

This is an interesting clinical study because the addition of one packet of Kampo extract preparations to the standard therapy for heat illness significantly shortened the time to symptom resolution by 30 minutes. On the other hand, since the number of subjects was small and two types of Kampo medicines were used in the study, the results in this study should be reviewed in the future. Meanwhile, the author's efforts to obtain randomized data from a population requiring emergency medical attention, which is difficult in actual clinical settings, should be respected. Although each subject's *sho* (証, pattern) was not diagnosed, shyakuyakukanzoto and byakkokaninjinto were appropriate for heat illness. As stated by the author, shortening of the time to symptom resolution in patients with mild to moderate heat illness, which is estimated to affect 30,000 patients annually in Japan, is meaningful from a medical cost standpoint. Further development is anticipated in future studies assessing the efficacy and safety of Kampo medicines added to the standard therapy.

12. Abstractor and date

Fujisawa M, 31 March 2017.

19. Injury, Poisoning, and Postoperative Pain

Reference

Otake T, Kato I, Saito S, et al. The prophylactic effect of "gosyuyu-to" and "gorei-san" for post-spinal headache. *Pain Clinic* 1991; 12: 648-52 (in Japanese).

1. Objectives

To evaluate the efficacy of goshuyuto (呉茱萸湯) and goreisan (五苓散) for post-lumbar puncture headache (PLPH).

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the authors were affiliated with the Department of Anesthesiology, Isesaki Municipal Hospital), Japan.

4. Participants

Two hundred and ninety-five American Society of Anesthesiologists (ASA) PS I or II patients who underwent lumbar anesthesia.

5. Intervention

Arm 1: treatment with TSUMURA Goreisan (五苓散) Extract Granules 2.5 g orally 4 times, at night after surgery and in the morning, at noon, and in the evening of the following day (n=88).
Arm 2: treatment with TSUMURA Goshuyuto (呉茱萸湯) Extract Granules 2.5 g orally 4 times, at night after surgery and in the morning, at noon, and in the evening of the following day (n=93).
Arm 3: no treatment with Kampo medicine (n=114).
Indomethacin suppository was the only drug used for relieving postoperative wound pain.

6. Main outcome measures

Post-lumbar puncture headache (PLPH) severity was evaluated using a 5-point scale on days 1 (24 hours after the lumbar puncture), 2, 3, and 7.

7. Main results

The incidence of PLPH in all patients was 21.4%. Two-arm comparisons of the ratings of PLPH revealed significantly greater relief in arm 2 than arm 3 only on day 1 ($P<0.05$). Sex-specific analysis showed significantly greater relief in the female patients of arm 2 than of arm 3 on day 1 ($P<0.05$).

8. Conclusions

Goshuyuto seems to be effective for preventing and relieving headache after lumbar anesthesia or after intrathecal puncture during epidural block anesthesia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an interesting clinical study of the efficacy of goshuyuto and goreisan for relieving PLPH. It is a well-designed study with appropriate consideration given to clinical details including patient characteristics, interactions with indomethacin, type of puncture needle, and patient position. Since the incidence of PLPH is low and decreases over time, the small sample size may have contributed to the lack of a statistically significant difference in the outcome. In addition, if Kampo medicines had been administered for the duration of PLPH (about a week), differences among the three arms might have appeared on other days besides day 1. Despite the limited number of cases, this clinical study demonstrated the efficacy of goshuyuto. Future consideration of sample size and treatment duration would help to further clarify the efficacy of Kampo medicines for PLPH.

12. Abstractor and date

Goto H, 15 September 2008, 1 June 2010, 31 December 2013.

19. Injury, Poisoning, and Postoperative Pain

Reference

Isai H. Successful control of postoperative pain and hyperidrosis by Kampo medicine after thoracotomy for pulmonary disease. *Itami to Kampo* (*Pain and Kampo Medicine*) 1997; 7: 29-32 (in Japanese with English abstract).

1. Objectives

To evaluate the efficts of keishikajutsubuto (桂枝加朮附湯) and shakuyakukanzoto (芍薬甘草湯) on postoperative pain and hyperhidrosis following thoracotomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Twenty patients who underwent thoracotomy for pulmonary disease (lung cancer in 19 patients and spontaneous pneumothorax in 1 patient).

5. Intervention

All patients were given 4-6 mg of epidural morphine daily for 5 days after surgery. In addition, indomethacin, diclofenac sodium, or buprenorphine hydrochloride suppository was used at the discretion of each patient. Kampo medicine was administered for 4 weeks beginning on postoperative day 7.

Arm 1: control group (no Kampo medicine) (n=7).
Arm 2: TSUMURA Keishikajutsubuto (桂枝加朮附湯) Extract Granules 2.5 g t.i.d. (n=7).
Arm 3: TSUMURA Keishikajutsubuto (桂枝加朮附湯) Extract Granules 2.5 g t.i.d. + TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 g t.i.d. (n=6).

6. Main outcome measures

Dose of analgesics, wound pain, hyperhidrosis.

7. Main results

The dose of analgesic suppositories tended to decrease over the first 3 postoperative weeks in all 3 groups, but leveled out in Arm 1 and continued to decrease in Arms 2 and 3 at Weeks 4 and 5, resulting in a significantly higher level in Arm 1 than in Arms 2 and 3. Wound pain was well controlled in all 3 groups including Arm 1, where pain could be controlled by high doses of analgesics. Hyperhidrosis was almost resolved at Week 4 in Arm 2 and at Week 5 in Arm 3, but occurred significantly more often in Arm 1 than in Arms 2 and 3.

8. Conclusions

Kampo preparations administered after thoracotomy, particularly keishikajutsubuto plus shakuyakukanzoto, reduces the use of analgesics as well as the severity of hyperhidrosis. Therefore, this Kampo preparation is recommended after thoracotomy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were reported.

11. Abstractor's comments

In the Discussion, it was stated that while keishikajutsubuto is effective for wound pain, shakuyakukanzoto is effective for hyperhidrosis. This was also shown graphically.

12. Abstractor and date

Fujisawa M, 15 October 2008, 1 June 2010.

19. Injury, Poisoning, and Postoperative Pain

Reference

Miyazaki M, Yasui M, Ikenaga M, et al. The effect of Shakuyaku-kanzo-to (Tsumura TJ-68) on pain after hemorrhoidectomy – a prospective randomized study –. *Journal of the Japan Society of Coloproctology* 2012; 65: 313–7 (in Japanese with English abstract).

1. Objectives

To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) for pain after hemorrhoidectomy

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the first author belonged to the Department of Coloproctology, Dojinkai Dojin Hospital & the Department of Surgery, Osaka National Hospital), Japan.

4. Participants

Thirty-nine patients with hemorrhoids or mucosal prolapse who had undergone semi-closed hemorrhoidectomy.

5. Intervention

Arm 1: after hemorrhoidectomy, diclofenac sodium 25 mg t.i.d. plus TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 mg t.i.d. taken orally (n=18).

Arm 2: after hemorrhoidectomy, diclofenac sodium 25 mg t.i.d. alone taken orally (n=21).

In cases of poor analgesic action, both groups were permitted intramuscular injection of the painkillers pentazocine 15 mg plus hydroxyzine pamoate 25 mg, diclofenac sodium 50 mg suppository, or single-use loxoprofen sodium orally.

6. Main outcome measures

Pain score (maximum score for the day on a 10-point visual analog scale), type of pain (when resting, when defecating, when mobile), number of days till pain score fell below three, number of days till pain disappeared when resting, waking in the night due to pain, use of painkiller injection, additional use of nonsteroidal anti-inflammatory drugs (NSAIDs) by suppository or by mouth.

7. Main results

Excluding the day of surgery, pain scores were significantly lower in arm 1 compared to arm 2 on each day from the first to the ninth day after surgery ($P<0.05$). “Type of pain” results were not reported in the original paper. Significant differences between arm 1 and arm 2 were noted in the mean number of days till the pain score fell below three (2.1 vs 5.2; $P<0.05$) and use of painkiller injections (three times [17%] vs ten times [48%]; $P<0.05$) but not in the number of days till pain disappeared when resting, additional use of non-steroidal anti-inflammatory drugs (NSAIDs), or waking in the night due to pain.

8. Conclusions

Administration of shakuyakukanzoto in addition to NSAIDs is effective in improving pain after hemorrhoidectomy.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

No adverse effects of shakuyakukanzoto were observed.

11. Abstractor’s comments

This clinical study investigated the effectiveness of shakuyakukanzoto in addition to NSAIDs for pain after hemorrhoidectomy. While hemorrhoidectomy is excellent therapy, it is avoided because of the postoperative pain. This very interesting clinical study is intended to investigate whether that complication can be alleviated based on the unique idea of physicians. On the other hand, the pain score graphs imply that pain began to decrease in the shakuyakukanzoto group the day after surgery, even though there was no significant difference, which suggests a problem with the participant allocation method. Furthermore, while the mean pain scores were not significantly different immediately after surgery (5.7 without shakuyakukanzoto and 5.1 with shakuyakukanzoto), the difference was significant on the eighth day (2.4 and 2.1, respectively). It is also possible that variation had decreased by the eighth day; the mention of not just mean values but standard deviation suggests the possibility of deliberate emphasis on statistical differences. However, as the authors mention in the discussion, their treatment methods were relatively simple and potentially could alleviate pain, and should be further evaluated in a large-scale multi-center study.

12. Abstractor and date

Goto H, 31 December 2013.

19. Injury, Poisoning, and Postoperative Pain

Reference

Fukuda Y, Azuma M, Novel pain reliever shakuyaku-kanzo-to after hemorrhoidectomy, *Journal of the Japan Society of Coloproctology*, 2014; 67: 324-9. Ichushi Web ID: 2014256564 J-STAGE

1. Objectives

To evaluate pre-and post-operative analgesic effects of shakuyakukanzoto (芍薬甘草湯) for treatment of pain after hemorrhoidectomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One clinic, Japan.

4. Participants

A total of 103 patients who visited the clinic after hemorrhoidectomy between April 2011 and September 2012.

5. Intervention

Arm 1: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules administered orally at 2.5 g t.i.d. before meals before and after hemorrhoidectomy for 14 days (n=34).

Arm 2: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules administered orally at 2.5 g t.i.d. before meals only after hemorrhoidectomy for 7 days (n=37).

Arm 3: No treatment with TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (n=32).

6. Main outcome measures

Maximum pain scored on a visual analogue scale (VAS).

7. Main results

Over a 7-day post-operative period, the pain VAS score was significantly lower in Arm 1 than in Arm 3 (P<0.05) on Day 2 after hemorrhoidectomy; in Arm 2 than in Arm 3 on Day 5 after hemorrhoidectomy (P<0.05); and in Arm 1 than in Arm 3 (P<0.05) on the day of hemorrhoidectomy. If VAS score of 3 or lower is defined as pain relief, the mean time to achieving pain relief was significantly shorter in Arm 1 than in Arm 3 (P<0.05). The degree of pain alleviation was higher in Arm 1 than in Arm 3 on Day 6, but not in Arm 2 than in Arm 3, although it tended to be higher in Arm 2.

8. Conclusions

Pre- and post-operative treatment with shakuyakukanzoto is effective for pain alleviation after hemorrhoidectomy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No evident adverse events were noted.

11. Abstractor's comments

This article demonstrated that continuous treatment with shakuyakukanzoto at the start of the pre-operative period is effective for post-operative pain alleviation. Although partial alleviation of pain was noted after the post-operative treatment, it is interesting that pre- and post-operative treatment was more effective. In general, since the effect of shakuyakukanzoto is apparent immediately after administration, it is also used as needed. As stated in the Discussion, careful monitoring is needed to prevent Glycyrrhiza-induced pseudoaldosteronism after continuous treatment. Since post-hemorrhoidectomy pain is most severe on the day of surgery, it is meaningful that oral administration of shakuyakukanzoto before the pain developed was more effective. Interestingly, mechanisms of pain development (increase in anal resting pressure and spasm of the anal sphincter) may explain why shakuyakukanzoto tended to be more effective in male and young subjects.

12. Abstractor and date

Nakata H, 31 March 2017.

19. Injury, Poisoning, and Postoperative Pain

Reference

Kuwamura A, Komasawa N, Kori K, et al. Preventive effect of preoperative administration of hange-shashin-to on postoperative sore throat: a prospective, double-blind, randomized trial. *Journal of Alternative Complementary Medicine* 2015; 21: 485-8.

1. Objectives

To evaluate the efficacy and safety of hangeshashinto (半夏瀉心湯) on postoperative sore throat and nausea.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

One hospital anesthesiology department, Japan.

4. Participants

Seventy adult females before surgery for benign gynecological disorder. Participants had been rated either class 1 (healthy apart from disorder for surgery) or class 2 (patients with mild systemic disease) on the American Society of Anesthesiologists physical status (ASA-PS), were scheduled for laparoscopic surgery under general anesthesia, and were expected to be hospitalized for at 24 hours after surgery. Gravida and women taking painkillers, anti-inflammatories, or other Kampo medications were excluded.

5. Intervention

Arm 1: Intervention group – TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules 2.5g per dose taken orally on the night before surgery and the morning of surgery, twice in total (n=35). The hangeshashinto was mixed with jelly.

Arm 2: Control group – Jelly only (n=35).

The pharmacy department prepared both the intervention drug and the placebo. Administration details were not revealed to the patients, anesthetists or nurses. Intratracheal intubation was carried out by an anesthetist with over 8 years experience, and the attending physician was not told the details of drug administration. A stomach tube was inserted immediately before surgery, and removed at the end of anesthesia.

6. Main outcome measures

The researchers recorded the presence/absence and severity of sore throat and nausea immediately after and at 3 and 24 hours after anesthesia awareness using a Numeric Rating Scale (NRS) for pain.

7. Main results

Incidence and severity of sore throat was significantly lower in arm 1 than arm 2 immediately after and 3 hours after surgery ($P<0.05$). However, there was no difference between arm1 and arm 2 for nausea.

8. Conclusion

Administration of hangeshashinto before general anesthesia significantly reduces sore throat after surgery in female patients undergoing laparoscopic surgery for a gynecological disorder. No effects are observed for hangeshashinto for postoperative nausea.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse event occurred during the clinical trial. The authors state that none of the symptoms that may be observed in hangeshashinto, namely edema, liver dysfunction, interstitial pneumonia and hypokalemia, was observed. According to the CONSORT flow chart in the original paper, there were no dropouts from this trial.

11. Abstractor's comments

A well designed DB-RCT. The authors precisely describe the method for determining the sample size. It can be understood from the paper that blinding was scrupulous and each person involved made independent assessments. The authors also describe in detail the stomach tube and intratracheal intubation associated with sore throat. And with the outcomes as well, the authors' use of NRS as criteria for assessment of pain is valid. The study design is therefore excellent, and the evidence for the results achieved is strong. If there is one thing that could be added, it might be more interesting to introduce a slightly longer term goal to the outcomes, for example, shortening of the period of hospitalization, etc. Further progress in this research is anticipated.

12. Abstractor and date

Tsuruoka K, 9 March 2017

19. Injury, Poisoning, and Postoperative Pain

Reference

Komasawa N, Yamamoto K, Ito Y, et al. Preoperative administration of jidabokuippo, a Kampo medicine, alleviates postoperative pain after tooth extraction with mandible bone removal under general anesthesia: a prospective, single-blind, randomized controlled trial. *Journal of Alternative and Complementary Medicine* 2018; 24: 1214-8. CENTRAL ID: CN-01702650, Pubmed ID: 29993259, UMIN ID: UMIN000019038

1. Objectives

To determine the efficacy and safety of preoperative administration of jidabokuippo（冶打撲一方） in treating postoperative pain after tooth extraction with mandible bone removal under general anesthesia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital (the author belongs to the Department of Anesthesiology and Oral and Maxillofacial Reconstructive Surgery, Osaka Medical College), Japan.

4. Participants

One hundred and fifty-six patients with an American Society of Anesthesiologists Physical Status class of 1 or 2 who were scheduled to undergo tooth extraction surgery under general anesthesia between February 2016 and March 2018. Patients were excluded if they were pregnant, used analgesics, anti-inflammatory drugs, or other Kampo formulations, or were scheduled to undergo only tooth extraction without mandible bone removal under general anesthesia.

5. Intervention

Arm 1: JDI group: TSUMURA Jidabokuippo（冶打撲一方）Extract Granules 7.5 g in three divided doses (at bedtime on the day before surgery, in the morning and around noon of the day of surgery) (n=30).

Arm 2: Control group: No administration of TSUMURA jidabokuippo Extract Granules (n=30).

In both Arm 1 and Arm 2, the surgery under general anesthesia was performed in the afternoon.

6. Main outcome measures

Primary endpoint: Severity of postoperative pain (measured using a numeric rating scale [NRS])

Secondary endpoints: Severity of postoperative nausea (measured using an NRS), number of patients who requested NSAIDs, time to the first NSAID request, number of additional NSAID administrations within 24 hours after anesthesia recovery.

7. Main results

Of the 156 patients screened, 96 patients were excluded because their surgery did not include mandible bone removal. The postoperative pain NRS score at 1 hour after anesthesia recovery did not significantly differ between the two groups. At 3 and 24 hours after anesthesia recovery, the postoperative pain NRS was significantly lower in Arm 1 (P<0.001 for both 3 and 24 hours). The number of patients who requested NSAIDs within 24 hours after anesthesia recovery was significantly lower in Arm 1 (21 patients in Arm 1 and 29 patients in Arm 2; P=0.006). The number of additional NSAID administrations within 24 hours after anesthesia recovery was significantly higher in Arm 2 (1.0±0.8 times in Arm 1 and 2.7±0.8 times in Arm 2; P<0.001). The time to the first NSAID request after anesthesia recovery was significantly longer in Arm 1 (6.5±3.4 hours in Arm 1 and 3.4±2.2 hours in Arm 2; P<0.001). The severity of nausea did not significantly differ between the groups.

8. Conclusions

Jidabokuippo administration before general anesthesia effectively decreased the severity of postoperative pain after anesthesia recovery in patients who underwent tooth extraction with mandible bone removal.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No side effects related to jidabokuippo, such as edema or hypokalemia, etc., were noted during the study.

11. Abstractor's comments

This large RCT evaluated the efficacy of preoperative administration of jidabokuippo on postoperative pain after tooth extraction with mandible bone removal under general anesthesia, and produced results that are clinically meaningful. The severity of postoperative pain was significantly lower in the jidabokuippo group at 3 and 24 hours after anesthesia recovery, though not at 1 hour after anesthesia recovery. The authors take a cautious approach to the clinical application of the treatment because this was not a placebo-controlled study. However, results of this clinical study provide adequate grounds for further clinical studies to confirm the efficacy of treatment, establish the therapeutic method, etc. Thus, future advances in the clinical research are awaited.

12. Abstractor and date

Kogure T, 11 September 2019.

19. Injury, Poisoning, and Postoperative Pain

Reference

Watanabe Y, Asai S, Hida A, et al. Regarding the utility of saireito against keloid and hypertrophic scars following surgery and injury. *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2012; 67: 245–9 (in Japanese). Ichushi Web ID: 2012256652, J-STAGE

1. Objectives

To evaluate the effectiveness and safety of saireito (柴苓湯) for keloid and hypertrophic scars following surgery, burn injury, and wound injury.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Department of Plastic and Reconstructive Surgery, Chukyo Hospital (1 center), Japan.

4. Participants

Fifty patients with confirmed subjective/objective symptoms including itchiness, tenderness, spontaneous pain, flushing, induration, or swelling of keloid and hypertrophic scars following surgery, burn injury, or wound injury.

5. Intervention

Allocation proceeded alternately in the order of consultation.

Arm 1: Kracie Saireito (柴苓湯) Extract Fine Granules 8.1 g/day in three divided doses orally before meals for at least 12 weeks (n=29).

Arm 2: no administration of saireito (柴苓湯) (n=21).

Compression, external preparations, and patches were applied depending on the symptom, but internal medicines such as tranilast were not given. Ointments containing steroids were used as appropriate in all patients. Compression gear was used for patients who had keloid and hypertrophic scars around limb joints.

6. Main outcome measures

Scar height and subjective/objective symptoms (itchiness, tenderness, spontaneous pain, flushing, induration, and swelling) were measured/evaluated on a 4-point scale (3: severe, 2: moderate, 1: mild, 0: none) at the start and in week 2, 4, 8 and 12 of the study.

7. Main results

The analysis included all 50 patients except those who took anti-allergy medicine during the study. In comparison to arm 2, arm 1 had significantly improved scores for itchiness and flushing starting on week 8 (week 8: $P<0.05$; week 12: $P<0.01$) and significantly improved scores for scar height, tenderness, spontaneous pain, induration, and swelling ($P<0.01$).

8. Conclusions

Saireito improves symptoms of keloid and hypertrophic scars following surgery, burn injury, or wound injury.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

No adverse effects of saireito were observed.

11. Abstractor's comments

This clinical study investigated the effectiveness of saireito for keloid and hypertrophic scars following surgery and injury. It is an advanced study that attempted to investigate the effects of saireito on pathological conditions with no effective therapy and which occur in large numbers of plastic surgery patients. The authors mention the number of patients whose results were analyzed but not the initial number of participants. Given that patients who took anti-allergy drugs were excluded from the analysis, the authors should have given the initial number of participants and the reasons for exclusion. Furthermore, because compression, external preparations, and patches were also used (depending on the symptom), mentioning the number of such cases would have clarified the details of the study. Additionally, the patient background table shows that 11 participants in the saireito group and only one in the no treatment group had scars due to wound injury. Since hypertrophic scars improve more readily than keloid scars, the authors should have considered whether any bias was attributable to the primary disease. Moreover, scar height improved from 1.5 mm to 0.5–1.0 mm; unless centimeters were misreported as millimeters, this is an extremely small change. Thus, the authors should have described their measurement methods. Yet, this clinical study is praiseworthy for being based on past reports and for detecting an effect of saireito on a pathological condition with no established treatment. Hopefully the authors will further evaluate its effectiveness in a multicenter study.

12. Abstractor and date

Goto H, 31 December 2013.

21. Others

Reference

Takayama S, Shiga Y, Kokubun T, et al. The traditional kampo medicine Tokishakuyakusan increases ocular blood flow in healthy subjects. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-8. doi: 10.1155/2014/586857 CENTRAL ID: CN-00993227, Pubmed ID: 24872835

1. Objectives

To evaluate the ability of tokishakuyakusan (当帰芍薬散) to increase ocular blood flow.

2. Design

Study 1: Double-blind, randomized controlled trial (cross-over) (DB-RCT cross-over).

3. Setting

A university department of ophthalmology, Japan.

4. Participants

Study 1: Thirteen healthy volunteers aged 20 to 70 years (mean age, 37.3±12.3 years; 6 males, 7 females) with intraocular pressure of ≤22 mmHg in both eyes (exclusion criteria: abnormal ocular fundus, history of ocular incisional surgery in either eye, history of systemic disease including hypertension and diabetes mellitus, and smoking history).

Study 2: Nineteen healthy volunteers (38 eyes) (mean age, 32.0±11.0 years; 8 males, 11 females).

5. Intervention

Study 1: Four Kampo medicines (TSUMURA Yokukansan [抑肝散] Extract Granules, TSUMURA Tokishakuyakusan [当帰芍薬散] Extract Granules, TSUMURA Keishibukuryogan [桂枝茯苓丸] Extract Granules, and TSUMURA Hachimijiogan [八味地黄丸] Extract Granules) at 5 g each were orally administered with 50 mL of warm water in a single arm. All subjects randomly received these 4 Kampo medicines in a blinded manner for 2 months. Subjects received 1 Kampo medicine, followed by at least 1 week of washout, and then received next Kampo medicine. Clinical tests were performed before and after administration (n=13).

Study 2: TSUMURA Tokishakuyakusan [当帰芍薬散] Extract Granules at 5 g was orally administered with 50 mL of warm water. Tests were performed at 15, 30, 45, and 60 minutes post-dose. After at least 1 week of washout, the control (50 mL of warm water) was administered to the same group (n=19) of subjects who were then evaluated in the same manner.

6. Main outcome measures

Intraocular pressure, blood pressure, pulse rate, and mean blur rate (MBR; a measure of ocular blood flow [OBF]) measured by laser speckle flowgraphy (LSFG) in both Studies 1 and 2.

7. Main results

Study 1: The four Kampo medicines did not cause intraocular pressure or blood pressure differences. The OBF was significantly increased 30 minutes after the administration of tokishakuyakusan (100% to 103.6%±6.9%; $P<0.01$).

Study 2: The OBF was significantly increased after the administration of tokishakuyakusan as compared with the control ($P<0.01$). In addition, intraocular pressure significantly increased from baseline to 30 to 60 minutes after the administration of tokishakuyakusan ($P<0.01$).

8. Conclusions

Tokishakuyakusan increases ocular blood flow irrespective of blood pressure and intraocular pressure in healthy volunteers.

9. From Kampo medicine perspective

The Kampo diagnostic questionnaire was used to reveal the conditions of "*qi* (気)," "blood," and "fluid" in subjects who received tokishakuyakusan in Study 2.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The results of Study 1 (which had a crossover design) showed that only one of the four Kampo medicines, tokishakuyakusan, increased the ocular blood flow. The results of Study 2 showed the ability of tokishakuyakusan to increase ocular blood flow over time. Furthermore, ocular blood flow was increased after tokishakuyakusan administration irrespective of blood pressure and intraocular pressure especially in subjects who met the *sho* (証, pattern) for tokishakuyakusan in accordance with Kampo diagnosis. Since the study uses a surrogate endpoint (i.e., ocular blood flow in healthy subjects) to determine outcome, the evidence provided by this study is still not clinically robust. However, this study has potential. RCTs with the true endpoint (i.e., ocular blood flow in patients) are anticipated as a next step.

12. Abstractor and date

Tsuruoka K, 31 March 2017.

21. Others

Reference

Saruwatari J, Hisaeda S, Higa Y, et al. The *in-vivo* effect of Bakumondoto (TJ-29), a traditional Japanese medicine used for treatment of chronic airway disease, on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activity in man. *Journal of Pharmacy and Pharmacology* 2004; 56: 1171-7. CENTRAL ID: CN-00490887, Pubmed ID: 15324486

1. Objectives

To evaluate the effect of bakumondoto (麦門冬湯) on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single facility (university), Japan.

4. Participants

Twenty-six healthy university students.

5. Intervention

Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. for 1 week followed by administration of the same dose of placebo at the same frequency for 1 week, with 2-week washout between both administration periods (n=13).

Arm 2: administration of placebo 3.0 g t.i.d. for 1 week followed by administration of the same dose of TSUMURA Bakumondoto (麦門冬湯) Extract Granules at the same frequency for 1 week, with 2-week washout between both administration periods (n=13).

6. Main outcome measures

Urinary cytochrome p450 1A2, xanthine oxidase, and *N*-acetyltransferase 2 activities (determined by a caffeine test).

7. Main results

There were no significant differences in urinary cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities on days 1 and 7 from baseline in either arm.

8. Conclusions

Caffeine test is a safe and noninvasive screening test for herb-drug interaction measuring the ratio of urinary caffeine metabolites (cytochrome p450 1A2, xanthine oxidase, *N*-acetyltransferase 2). Bakumondoto did not affect cytochrome p450 1A2 (a hepatic enzyme metabolizing theophylline), xanthine oxidase, or *N*-acetyltransferase 2 activity, suggesting the unlikeliness of interaction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred in the subjects receiving bakumondoto.

11. Abstractor's comments

Rather than examining data on the direct clinical effects of bakumondoto (麦門冬湯) extract granules, this study examines data on the effect of bakumondoto on urinary caffeine metabolites. The increase in Kampo medicine usage has raised interest in the interaction of Kampo with Western medicines. Hopefully this kind of research will progress further.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 31 December 2013.

21. Others

References

Ohnishi N, Yonekawa Y, Fumihara T, et al. Studies on interactions between traditional herbal and Western medicines, II. Lack of pharmacokinetic interaction between shoseiryu-to and carbamazepine in healthy volunteers. *TDM Kenkyu* (*Japanese Journal of Therapeutic Drug Monitoring*) 1999; 16: 399-404. Ichushi Web ID: 2000070928 MOL, MOL-Lib

Yonekawa Y, Ohnishi N, Kitano N, et al. Drug interaction with Kampo medicines (2): kinetic characteristics of carbamazepine combined with shoseiryuto in healthy volunteers. *TDM Kenkyu* (*Japanese Journal of Therapeutic Drug Monitoring*) 1999; 16: 191-2. MOL, MOL-Lib

1. Objectives

To evaluate the effect of shoseiryuto (小青竜湯) on blood carbamazepine concentration.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

None (authors belong to the Department of Hospital Pharmacy, Kyoto Pharmaceutical University), Japan.

4. Participants

Four healthy adult males.

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

Arm 1: administration of 9.0 g/day of TSUMURA Shoseiryuto (小青竜湯) Extract Granules in 3 divided doses before meals for 7 days and 200 mg of carbamazepine in the morning of day 4 (n=4).

Arm 2: administration of 200 mg of carbamazepine (n=4).

A two-week period intervened between the changeover from the arm 1 intervention to the arm 2 intervention.

6. Main outcome measures

Concentrations of carbamazepine and its metabolite carbamazepine-10,11-epoxide in blood sampled before, and 1.5, 4, 8, 24, 48, and 72 hr after administration of carbamazepine.

7. Main results

Combination with shoseiryuto did not affect the following parameters of carbamazepine and its metabolite carbamazepine-10,11-epoxide in blood: the maximum blood concentration; time to reach the maximum blood concentration; slope of the elimination phase; elimination half-life; area under the plasma concentration-time curve; and mean residence time.

8. Conclusions

Oral administration of shoseiryuto does not affect blood carbamazepine concentration.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study objectively demonstrated that combination of shoseiryuto does not affect blood carbamazepine concentration, which is susceptible to the effects of various drugs. This study does not evaluate the efficacy of the Kampo medicine, but is considered meaningful, given that Western and Kampo medicines are commonly combined in clinical practice.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Isobe H, Yamamoto K, Cyong JC. Effects of hachimi-jio-gan (ba-wei-di-huang-wan) on blood flow in the human central retinal artery. *The American Journal of Chinese Medicine* 2003; 31: 425-35. CENTRAL ID: CN-00457563, Pubmed ID: 12943173

1. Objectives

To evaluate the effect of hachimijiogan (八味地黄丸) on human central retinal artery.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single facility (the University of Tokyo), Japan.

4. Participants

Twelve healthy volunteers (6 males and 6 females; mean age, 26.0 years).

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.
Arm 1: single-dose administration of 27 g of Uchida no Hachimigan M (八味地黄丸) (n=12).
Arm 2: single-dose administration of 27 g of placebo (lactose) (n=12).

6. Main outcome measures

Systolic blood flow velocity, diastolic blood flow velocity, mean blood flow velocity, and vascular resistance of the central retinal artery, measured by ultrasonic diagnosis device before administration and every 15 min after administration for 60 min.

7. Main results

In arm 2, there were no changes from baseline in systolic blood flow velocity, diastolic blood flow velocity, mean blood flow velocity or vascular resistance of the central retinal artery. In arm 1, although vascular resistance did not change, there were increases in systolic velocity at 15 and 45 min, diastolic velocity at 45 min, and mean velocity at 30, 45, and 60 min. Group comparison revealed significantly higher systolic blood flow velocity at all postdose time points until 60 min, higher diastolic blood flow velocity at 45 min, and significantly higher mean blood flow velocity in the time period from 30 to 60 min in arm 1.

8. Conclusions

This study provides evidence that hachimijiogan increases the blood flow velocity of the central retinal artery.

9. From Kampo medicine perspective

When compared with hachimijiogan-non-responders (with unsuitable *sho*, n=9), hachimijiogan-responders (with suitable *sho*, n=3) had higher systolic, diastolic, and mean flow rates in the time period from 15 to 60 min (statistical analysis not performed due to the small sample size).

10. Safety assessment in the article

None.

11. Abstractor's comments

It was reported some time ago that hachimijiogan acts on the central nervous system to improve hypobulia in the elderly, and to improve eye symptoms. The present report showed an increase in blood flow rate of the central retinal artery, providing evidence for efficacy in improving visual acuity. Moreover, it was shown that intracerebral blood flow may also increase, suggesting effects on the central nervous system. Also, this report provides a valuable discussion from a Kampo medicine perspective of increased blood flow velocity in responders. However, a larger sample size will be necessary in the future. Another problem is that the systemic blood pressure was not indicated, making it impossible to determine whether the increase in blood flow velocity is attributable to a systemic or local reaction. Furthermore, since this RCT did not evaluate clinical efficacy and used single-dose administration, it is hoped that clinical research examining the persistent effects of long-term oral administration will be conducted.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Hamazaki K, Sawazaki S, Itomura M, et al. No effect of a traditional Chinese medicine, hochu-ekki-to, on antibody titer after influenza vaccination in man: a randomized, placebo-controlled, double-blind trial. *Phytomedicine* 2007; 14: 11-4. CENTRAL ID: CN-00576087, Pubmed ID: 16644196

1. Objectives

To assess the efficacy and safety of hochuekkito (補中益気湯) on antibody production after influenza vaccination.

2. Design

Double-blind, randomized, controlled trial (DB-RCT).

3. Setting

No description of the setting is available; the authors belong to the Division of Clinical Application, Institute of Natural Medicine, University of Toyama, Japan.

4. Participants

Of the 49 healthy males aged between 20 and 60 years who volunteered to enter this trial of hochuekkito, 36 were enrolled. None of the 36 had been taking any herbal medicine, hormone therapy, or anti-inflammatory drugs.

5. Intervention

Arm 1: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules 3.75 g b.i.d. before breakfast and supper for 14 days until the day prior to influenza vaccination, n=18.
Arm 2: administration of placebo (consisted mainly of cane sugar) 3.75 g b.i.d. before breakfast and supper for 14 days until the day prior to influenza vaccination, n=18.

6. Main outcome measures

Blood samples were taken at weeks 0, 1, 2, 4, and 12. Hemagglutination inhibition (HI) was used to measure influenza antibody titer, and a chromium (Cr)-release assay was used to measure natural killer (NK) activity.

7. Main results

Three subjects in arm 2 (because of common cold and diarrhea) and one subject in arm 1 (for a personal reason) dropped out of the study. There were no significant between-arm differences in postvaccination titer and NK activity.

8. Conclusions

Oral administration of hochuekkito for 14 days before influenza vaccination does not affect postvaccination antibody production.

9. From Kampo medicine perspective

Subjects not intending to use hochuekkito, as well as subjects with easy fatigability, a high susceptibility to colds, slow recovery from colds, a high susceptibility to other infections like herpes and wound infection, poor appetite, loose bowels, and somnolence especially after meals, were excluded from the study.

10. Safety assessment in the article

No adverse effects were observed.

11. Abstractor's comments

This is a high-quality, well-designed, and double-blind clinical trial to assess the effect of hochuekkito on antibody production after influenza vaccination. A similar report (Yamaguchi H et al., Assessment of the effect of hochuekkito extract on antibody response to influenza vaccination. *Kampo to Saishin-chiryo* [*Kampo & the Newest Therapy*] 2006; 15: 235-7 [in Japanese]) concluded similarly that oral administration of hochuekkito for 1 week after the vaccination has no effect on antibody production. On the other hand, as mentioned in the discussion of this paper, Takagi et al. reported that hochuekkito increased antibody production in old mice (Takagi et al. Antibody response of Kampo-hozai after infuluenza B immunization in old mice. *The Japanese Society for Vaccinology* 2002; 6: 72 [abstract in Japanese]). Considering that all the clinical trials were conducted with healthy subjects, further investigation in the elderly with decreased ability to produce antibodies is awaited. The design of this clinical trial, based on the result from basic studies, should be emulated by researchers who conduct clinical trials of Kampo medicines.

12. Abstractor and date

Goto H, 21 November 2008, 1 June 2010.

21. Others

Reference

Terashima Y, Hamazaki K, Itomura M, et al. Effect of a traditional Chinese medicine, maobushisaishinto, on the antibody titer after influenza vaccination: A randomized, placebo-controlled, double-blind trial. *Journal of Traditional Medicines* 2007; 24: 59-66. Ichushi Web ID: 2007258196 J-STAGE

1. Objectives

To evaluate the effect of maobushisaishinto (麻黄附子細辛湯) on antibody titer after influenza vaccination.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Two university hospitals, Japan.

4. Participants

One hundred and six healthy subjects aged 20–71 years.

5. Intervention

Maobushisaishinto (麻黄附子細辛湯) and placebo capsules were donated by Kotaro Pharmaceutical Co., Ltd. The following drugs were orally administered from day –14 to –1 of influenza vaccination (A/H1N1, A/H3N2, B). All subjects were vaccinated in late November, before the influenza season.
Arm 1: Kotaro Maobushisaishinto (麻黄附子細辛湯) Extract Capsules (6 capsules/day), n=23.
Arm 2: placebo capsules, n=24.

6. Main outcome measures

Serum hemagglutination inhibition titers were measured at weeks 0, 1, 2, 4, and 12.

7. Main results

After excluding 57 subjects with antibody titers of more than 1:80 and 2 subjects diagnosed with influenza during the study period (one in each arm), 23 and 24 subjects were enrolled for analysis. There was no significant between-arm difference in antibody titer against A/New Caledonia/20/99(H1N1), A/New York/55/2004(H3N2), and B/Shanghai/361/2002. However, anti-H3N2 virus antibody titer was significantly higher in arm 2 than in arm 1 at week 4. Subgroup comparisons (smokers *vs* non-smokers and older subjects [≥40 years old] *vs* younger subjects [<40 years old]) found no significant between-arm differences in antibody titers.

8. Conclusions

No adjuvant effect of maobushisaishinto on antibody titer after influenza vaccination is observed.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Previous studies have shown the adjuvant effect of maobushisaishinto on influenza vaccination in animals and in elderly subjects. This paper aims to verify this effect.

12. Abstractor and date

Fujisawa M, 15 January 2009, 1 June 2010.

21. Others

Reference

Sato Y, Katagiri F, Itoh H, et al. Bushi-richu-to raises calcitonin gene-related peptide, substance P, somatostatin, and vasoactive intestinal polypeptide levels in human plasma. *Journal of Health Science* 2007; 53: 615-21. Ichushi Web ID: 2008127570 J-STAGE

1. Objectives

To elucidate the mechanism of bushirichuto (附子理中湯) activity in raising gut-regulated peptide levels.

2. Design

Randomized crossover controlled trial (RCT-cross over).

3. Setting

Department of Clinical Pharmacy, Oita University Hospital, Japan.

4. Participants

Five healthy male volunteers recruited at the facility mentioned above, n=5.

5. Intervention

Arm 1: Kanebo Bushirichuto (附子理中湯) Extract Fine Granules (EK-410) 4.5 g was orally administered with 100 mL of water for 4 weeks.
Arm 2: placebo was orally administered with 100 mL of water for 4 weeks.
Each subject was administered these drugs with an interval of four weeks.

6. Main outcome measures

Blood samples were obtained before administration, and at 20, 40, 60, 90, 120, 180, and 240 min after administration of the test substances, and plasma levels of calcitonin gene-related peptide (CGRP), substance P, vasoactive intestinal polypeptide (VIP), somatostatin, and motilin-like immunoreactive substance (IS) were measured by enzyme immunoassay (EIA).

7. Main results

One dose of bushirichuto significantly increased CGRP, somatostatin, and VIP levels (which peaked at 40–60 min) and significantly increased substance P level (which peaked at 180 min). CGRP level increased 5.7-fold at 40 min (85.2±58.7 pg/mL in arm 1 *vs*. 14.9±1.9 pg/mL in arm 2) (P<0.01), somatostatin level increased 2.1-fold at 60 min (20.2±6.1 pg/mL in arm 1 *vs*. 9.8±2.1 pg/mL in arm 2) (P<0.01), VIP level increased 2-fold at 60 min (16.9±7.0 pg/mL in arm 1 *vs*. 8.3±1.4 pg/mL in arm 2) (P<0.01), and substance P increased 2-fold at 180 min (68.5±18.7 pg/mL in arm 1 *vs*. 34.3±17.9 pg/mL in arm 2) (P<0.01). On the other hand, plasma motilin-like IS level was unaffected during observation for 240 min after administration.

8. Conclusions

Administration of bushirichuto may reduce sensitivity to cold, gastrointestinal discomfort, and gastrointestinal dysfunction *via* increasing plasma levels of CGRP, somatostatin, VIP, and substance P.

9. From Kampo medicine perspective

The authors suggest that the taste and smell of bushirichuto may affect the kinetics of gut-regulated peptides.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Although this investigation had only a small number of subjects, the results helped us to reveal the mechanism of bushirichuto activity. As bushirichuto is an "*onchu-sankan*" (温中散寒) medicine which contains herbs (Aconiti tuber [附子] and Zingiberis siccatum rhizome [乾姜]) with strong anti-coldness ("*sankan*") activity, it is used for patients with "*hie*" (or a feeling of coldness in the body). However, the authors did not reveal whether the male volunteers had *kan-sho* (寒証, cold pattern). Most subjects treated with bushirichuto in clinical practice are frail women. From that point of view, to minimize the discrepancy between bushirichuto use in actual clinical practice and experimental study, clinical studies of "*sho*" in women with and without symptoms, and having the same study design as this trial, are awaited.

12. Abstractor and date

Ushiroyama T, 19 December 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Takahashi H, Nakao R, Hirasaka K, et al. Effects of single administration of Rokumi-gan (TJ-87) on serum amino acid concentration of 6 healthy Japanese male volunteers. *Journal of Medical Investigation* 2007; 54: 91-8. Ichushi Web ID: 2007295608 J-STAGE

1. Objectives

To evaluate effects of rokumigan (六味丸) on serum amino acid concentrations.

2. Design

Randomized crossover controlled trial (RCT-cross over).

3. Setting

Department of Internal Medicine, the Komatsushima Hospital, Japan.

4. Participants

Six healthy men (mean age 35.5 years), n=6.

5. Intervention

Arm 1: lactose 5 g administered once at 9:00, n=6.
Arm 2: Asahi amino GET 5 tablets (contains a similar amount of amino acids as 10 g of Tsumura Rokumigan (六味丸) Extract Granules) administered once at 9:00, n=6.
Arm 3: Tsumura Rokumigan (六味丸) Extract Granules (TJ-87) 10 g administered once at 9:00, n=6.
There was a washout period of 3 months between treatments.

6. Main outcome measures

Serum amino acid concentrations before and at 1, 2, 4, and 6 h after the intervention.

7. Main results

In arm 1, concentrations of Ala, Gly, and Ile were significantly decreased from pretreatment levels at 6 h, and Arg, Glu, His, Leu, Lys, Phe, Ser, and Val levels were unchanged. In arm 2, concentrations of Ala, Glu, Gly, Ile, Leu, and Ser were significantly decreased at 6 h, but Arg, His, Lys, Phe, and Val levels remained unchanged. In arm 3, the levels of Ala at 2 h and Gly and Ser at 1 h were significantly increased, but Arg, Glu, His, Ile, Leu, Lys, Phe, and Val levels remained unchanged. In all three arms, serum levels of Asn, Cys, Gln, Met, Pro, Thr, Trp, and Tyr were not determined, and Asp were undetectable.

8. Conclusions

Serum amino acid concentrations are higher after administration of rokumigan than after administration of a supplement containing a similar amount of amino acids.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

This interesting well-designed cross-over clinical trial investigates the entry of amino acids from rokumigan into the blood. Changes in the concentration of amino acids after rokumigan administration were compared with those after administration of lactose or an amino acid mixture containing almost the same amount of amino acids. Amino acid levels (e.g., the pretreatment Ala level) were widely dispersed in all three arms, suggesting possible measurement errors in serum level for some amino acids. To adjust for dispersion in the data, relative changes in amino acid concentrations were calculated and are shown in Fig. 1. However, symbols a, b, and c are not defined. Also, the amino acid mixture administered in arm 2 contains several ingredients besides amino acids such as beer yeast, and their influence on absorption should be considered. Importantly, this study found that administration of rokumigan increased amino acid levels in blood and suppressed the gradual decrease observed in other arms. This observation may have important pharmacologic implications. Further studies on several Kampo medicines are anticipated.

12. Abstractor and date

Goto H, 27 November 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Qi J, Toyoshima A, Honda Y, et al. Pharmacokinetic study on acetaminophen: interaction with a Chinese medicine. *Journal of Medical and Dental Sciences* 1997; 44: 31-5. CENTRAL ID: CN-00145359, Pubmed ID: 9385040

1. Objectives

To evaluate the effect of kakkonto (葛根湯) on the pharmacokinetics of acetaminophen.

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

No study site was specified (authors affiliated with the Department of Preventive Medicine, Division of Social Medicine, Medical Research Institute, Tokyo Medical and Dental University), Japan.

4. Participants

Nineteen healthy volunteers.

5. Intervention

Arm 1: single oral dose of PL glanules containing 150 mg of acetaminophen) in combination with TSUMURA Kakkonto (葛根湯) Extract Granules (containing 1250 mg of extract) (n=19).

Arm 2: single oral dose of PL (containing 150 mg of acetaminophen) (n=19).

There was a 1-week washout period.

6. Main outcome measures

Blood concentrations of acetaminophen (APAP) and APAP glucuronide (measured by high performance liquid chromatography [HPLC] before and 0.5, 1, 2, 3, and 4 hours after administration of APAP) were used to calculate the maximum blood concentration (C_{max}), time to C_{max} (t_{max}), half-life in blood ($t_{1/2}$), and area under the blood concentration curve (AUC).

7. Main results

There were no between-arm differences in C_{max}, t_{max}, $t_{1/2}$, or AUC of APAP or APAP glucuronide.

8. Conclusions

The pharmacokinetics of acetaminophen is not affected by concomitant administration of kakkonto.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were reported.

11. Abstractor's comments

This study measured blood acetaminophen concentration after coadministration of kakkonto with acetaminophen (which are commonly co-administered in clinical practice). Adverse reactions to acetaminophen were not affected by administration of kakkonto in combination with PL. In another study involving volunteers, however, it was reported that the blood APAP concentration was higher after co-administration of kakkonto (5 g; use of granules or extract bulk powder, not specified) in combination with APAP (12 mg/kg). In rats that received APAP (10 mg/kg) plus kakkonto (100 or 200 mg/day) for 1 week, the APAP level was significantly higher in the kakkonto (200 mg/day) group than in the distilled water group only at 0.25 hour after APAP administration. Therefore, since drug interaction may affect the blood acetaminophen concentration depending on the dose and/or treatment duration of kakkonto and acetaminophen, a randomized clinical study might have been more useful if co-administration was frequent. Nevertheless, the study was very valuable because it showed that the blood acetaminophen concentration was not affected by a single co-administration at commonly used doses.

12. Abstractor and date

Goto H, 19 September 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Shimakura K, Mineshita S, Sanaka M, et al. Effects of kakkonto on the pharmacokinetics of phenacetin in human serum and saliva*. *Rinsho Yakuri* (*Japanese Journal of Clinical Pharmacology and Therapeutics*) 1994; 25: 229–30 (in Japanese).

1. Objectives

To evaluate the effects of kakkonto (葛根湯) on the pharmacokinetics of phenacetin.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One university hospital, Japan.

4. Participants

Eleven healthy subjects.

5. Intervention

Arm 1: phenacetin 12 mg/kg (n=6).
Arm 2: phenacetin 12 mg/kg + TSUMURA Kakkonto (葛根湯) Extract Granules 2 sachets (containing 1250 mg of kakkonto dry extract / sachet) (n=5).
Crossed over with a 7-day or longer washout period between arms.

6. Main outcome measures

Blood and saliva concentrations of phenacetin and its metabolites, acetaminophen and glucuronide.

7. Main results

There were no between-arm significant differences in C_{max} (post-dose maximum blood concentration) and AUC (area under the blood concentration-time curve: a measure of efficacy reflecting the percent drug absorption or bioavailability) of acetaminophen in either blood or saliva. The time-course of acetaminophen concentration showed a tendency toward higher concentration in saliva in arm 2 than in arm 1, but no between-arm difference in concentration in blood.

8. Conclusions

Kakkonto seems to only slightly affect the pharmacokinetics of phenacetin, acetaminophen, or glucuronide.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study would have been probably designed to demonstrate kakkonnto combined with phenacetin increases the concentration of acetaminophen, a metabolite of phenacetin. Since the authors states that "at present, combination Kampo medicines containing western cold remedies and Kampo medicines such as kakkonto extract are commercially available, and some studies report the usefulness of Kampo medicines for drug efficacy of western medicines." In this study, concentration in saliva was measured because it was the focus of therapeutic drug monitoring at that time.

12. Abstractor and date

Fujisawa M, 15 October 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Fukushima M. Profiles of effects of traditional oriental herbal medicines on the central nervous system in humans - assessment of saiboku-to and saiko-ka-ryukotsu-borei-to using EEG and pharmacokinetics of herbal medicine-derived ingredients as indices -. *Seishin Shinkeigaku Zasshi* (*Psychiatria et Neurologia Japonica*) 1997; 99: 355-69 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of saibokuto (柴朴湯) and saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) on the central nerve system in humans.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single-center study in Department of Neuropsychiatry, Kansai Medical University, Japan.

4. Participants

Twelve healthy adult men.

5. Intervention

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 7.5 g q.d. for 1 day followed by 2.5 g t.i.d. for 8 days.
Arm 2: TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) 7.5 g q.d. for 1 day and 2.5 g t.i.d. for the following 8 days
Arm 3: lactose (placebo) 3 g q.d. for 1 day followed by 2.5 g t.i.d. for 8 days.
There was a washout period of 2 weeks or more between treatments.

6. Main outcome measures

Electroencephalogram (EEG) global field power (GFP) spectrum change.

7. Main results

For each individual, placebo-controlled data on GFP were used to calculate change due to treatment (i.e., the difference in GFP between before and after treatment). In Arm 1, there was an increase of 3.24 in the δ band 1 hour after administration ($P<0.01$) and an increase of 3.20 in the α_3 band 3 hours after administration ($P<0.01$). In Arm 2, there was no significant change in GFP 1, 3, or 6 hours after administration.

8. Conclusions

Saibokuto may have an effect on the central nervous system.

9. From Kampo medicine perspective

Mentioned in section “Subjects and Administration Method”.

10. Safety assessment in the article

Not documented.

11. Abstractor’s comments

In this article, saibokuto changed the EEG global field power in healthy adult men. This indicates that the GFP may be used as an objective measure of the central effect of saibokuto. In addition, the authors stated that the response to saibokuto varied among individuals. Further studies based on *sho* (証, pattern.syndrome) are awaited to validate the results of this study.

12. Abstractor and date

Okabe T, 29 August 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Hasegawa T, Yamaki K, Nadai M, et al. Lack of effect of Chinese medicines on bioavailability of ofloxacin in healthy volunteers. *International Journal of Clinical Pharmacology and Therapeutics* 1994; 31: 57-61. CENTRAL ID: CN-00102144, Pubmed ID: 8004359

1. Objectives

To evaluate the effect of Kampo medicines on bioavailability of ofloxacin (OFLX) in healthy volunteers.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single institution (Nagoya University School of Medicine), Japan.

4. Participants

Seven healthy male volunteers (age 23–30 years).

5. Intervention

Arm 1: treatment with OFLX 200 mg.
Arm 2: treatment with OFLX 200 mg + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g.
Arm 3: treatment with OFLX 200 mg + TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g.
Arm 4: treatment with OFLX 200 mg + TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g.
Test drugs were administered orally with 150 mL of water at 8:30 a.m. at one-week intervals.

6. Main outcome measures

Blood concentration of OFLX and the percentage of OFLX excreted in 24-hour urine at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the administration; pharmacokinetic analysis.

7. Main results

There were no significant between-arm differences in bioavailability. The percentage of OFLX excreted in 24-hour urine in arm 1 (mean±SEM, 80.6±3.9%) was not significantly different from that after OFLX co-administration with shosaikoto (arm 2; 79.7±5.1%), rikkunshito (arm 3; 76.8±2.3%), or saireito (arm 4; 80.3±5.3%).

8. Conclusions

Kampo medicines have no significant effect on bioavailability of ofloxacin in healthy volunteers.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

It was speculated that those Kampo medicines studied don't have much effect on metabolism of quinolones and therefore can be safely co-administered with those agents. However, since this was an evaluation in healthy volunteers, it should be kept in mind that Kampo medicines might affect bioavailability in certain circumstances, such as in the disease state.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

21. Others

References

Niitsuma T, Fukuda T, Yamamoto S, et al. Effects of saibokuto and other saiko-zai (saiko-drugs) on prednisolone metabolism*. *Kampo to Meneki-Arerugi* (*Kampo and Immuno-allergy*) 1993; 7: 43–52 (in Japanese).

Homma M, Oka K, Ikeshima K, et al. Different effects of traditional Chinese medicines containing similar herbal constituents on prednisolone pharmacokinetics. *Journal of Pharmacy and Pharmacology* 1995; 47: 687–92. CENTRAL ID: CN-00120671, Pubmed ID: 8583374

1. Objectives

To evaluate the effects of shosaikoto (小柴胡湯), saibokuto (柴朴湯), and saireito (柴苓湯) on prednisolone metabolism.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Department of Clinical Pharmacology, Tokyo University of Pharmacy and Life Science, 3rd Department of Internal Medicine, Tokyo Medical University, Japan.

4. Participants

Twenty-two nonsmoking healthy males who took no drug that could affect glucocorticoid metabolism.

5. Intervention

Since allocation of patients by administration pattern to these treatment arms is not known, the treatment arms are described in terms of treatment regimen.

Study 1

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for 3 days. On the third study day, 10 mg prednisolone was administered orally in combination with the test preparation (n=6).

Arm 2: prednisolone 10 mg (n=6).

Age, 21.8±1.2 years; body weight, 63.8±6.8 kg

Study 2

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 g t.i.d. for 3 days. On the third study day, 10 mg prednisolone was administered orally in combination with the test preparation (n=9).

Arm 2: prednisolone 10 mg (n=9).

age, 23.5±1.5 years; body weight, 61.3±4.5 kg

Study 3

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 3 days (n=7)

Arm 2: prednisolone 10 mg (n=7)

Age, 22.4±1.9 years; body weight, 62.0±7.1 kg

Following a 2-week washout period, subjects were crossed over to the opposit arm.

6. Main outcome measures

Areas under the time-blood concentration curve (AUC) of prednisolone and prednisone, measured before and 1, 2, 4, and 6 h after treatment.

7. Main results

After the intervention, the AUC of prednisolone was significantly decreased to 0.94–0.78 $mgh L^{-1}$ in the shosaikoto group ($P<0.05$), significantly increased to 0.92–1.06 $mgh L^{-1}$ in the saibokuto group, and unchanged in the saireito group. After the intervention, the AUC ratio of prednisolone to prednisone, which reflects the activity of 11β-hydroxysteroid dehydrogenase (11-HSD), an *in vivo* steroid metabolic enzyme, was increased in the shosaikoto group ($P<0.01$), decreased in the saibokuto group ($P<0.01$), and unchanged in the saireito group.

8. Conclusions

Different types of saiko drugs affect steroid pharmacokinetics differently. 11-HSD activity is decreased, unaffected, and increased by saibokuto, saireito, and shosaikoto, respectively.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Kampo formulations have been used to stabilize medical conditions treated with steroids, with the aim of decreasing the use of steroids. This valuable study examined the effect of each saiko drug on steroid pharmacokinetics. An RCT in steroid-treated patients, but not healthy subjects as in the present study, would clarify the meaning of the present results.

12. Abstractor and date

Tsuruoka K, 26 April 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Hasegawa T, Yamaki K, Muraoka I, et al. Effects of traditional Chinese medicines on pharmacokinetics of levofloxacin. *Antimicrobial Agents and Chemotherapy* 1995; 39: 2135-37. CENTRAL ID: CN-00119767, Pubmed ID: 8540731

1. Objectives

To determine the pharmacokinetics of levofloxacin (Cravit®) when coadministered with hochuekkito (補中益気湯), rikkunshito (六君子湯), or juzentaihoto (十全大補湯), and to gain insights into the interactions between them.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Second Department of Internal Medicine, Nagoya University School of Medicine, Japan.

4. Participants

Eight male volunteers with no abnormal findings on medical history, routine blood biochemistry, and urinalysis.

5. Intervention

Since allocation of patients to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: treatment with levofloxacin 200 mg alone.
Arm 2: treatment with levofloxacin 200 mg + TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5 g.
Arm 3: treatment with levofloxacin 200 mg + TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g.
Arm 4: treatment with levofloxacin 200 mg + TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g.

All the 8 patients underwent arm 1 through arm 4 treatments, with a wash-out period of 7 days between treatments.

6. Main outcome measures

Concentrations of levofloxacin in blood and urine (determined by high-performance liquid chromatography).

7. Main results

All three Kampo formulations studied had no effect on metabolism of levofloxacin.

8. Conclusions

Kampo medicines have no effect on the pharmacokinetics of levofloxacin. Further investigations, including investigations of other Kampo formulations, are needed.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events occurred.

11. Abstractor's comments

This paper describes the effect of Kampo medicines on the pharmacokinetics of a typical antibiotic. It has been reported that Kampo medicines have considerable effects on the intestinal environment. The demonstration of no effect on the pharmacokinetics of at least one antibiotic in this study is of great significance, considering that western prescription medications and Kampo medicines are commonly coadministered in current clinical practice.

12. Abstractor and date

Nakata H, 10 January 2009, 31 December 2013.

21. Others

Reference

Ohnishi M, Hitoshi K, Katoh M, et al. Effect of a Kampo preparation, byakkokaninjinto, on the pharmacokinetics of ciprofloxacin and tetracycline. *Biological & Pharmaceutical Bulletin* 2009; 32: 1080–4. CENTRAL ID: CN-00704915, Pubmed ID: 19483319 J-STAGE

1. Objectives

To evaluate the effects of co-administered byakkokaninjinto (白虎加人参湯) on pharmacokinetics and renal excretion of antibiotics (tetracycline or ciprofloxacin.

2. Design

Randomized controlled cross-over trial (RCT-cross over).

3. Setting

Department of Pharmacy and Pharmacokinetics, Aichi Medical University and Faculty of Pharmacy, Meijo University, Japan.

4. Participants

Twenty healthy male volunteers (aged 23–36, mean 29.3 years).

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

Study 1

Arm 1: oral ciprofloxacin (Ciproxan tablet) 200 mg alone.

Arm 2: oral ciprofloxacin (Ciproxan tablet) 200 mg + byakkokaninjinto (白虎加人参湯) 3 g.

Each subject took Ciproxan immediately after taking byakkokaninjinto (白虎加人参湯) with 180 mL of water. After a 7-day wash-out period, the treatments were switched.

Study 2

Arm 1: oral tetracycline (Achromycin V capsule) 250 mg alone.

Arm 2: oral tetracycline (Achromycin V capsule) 250 mg + byakkokaninjinto (白虎加人参湯) 3 g.

The dosing and cross-over were performed in the same manner as Study 1.

The number of subjects in each arm is not specified.

6. Main outcome measures

Plasma and urinary concentrations of tetracycline and ciprofloxacin were measured by HPLC.

7. Main results

The peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of tetracycline and ciprofloxacin were significantly decreased by co-administration of byakkokaninjinto. The decrease in bioavailability of ciprofloxacin (15%) was smaller compared with that of tetracycline (30%). The co-administration of byakkokaninjinto significantly decreased urinary excretion rate of tetracycline, but not that of ciprofloxacin. Byakkokaninjinto had no effect on renal clearance of either antibiotic.

8. Conclusions

Byakkokaninjinto appears to reduce the absorption of tetracycline and ciprofloxacin.

9. From Kampo medicine perspective

In this study, it was assumed that byakkokaninjinto was used for treating heat exhaustion and febrile disease.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This highly suggestive study noted that co-administered byakkokaninjinto may reduce the absorption of tetracyclines and new quinolone agents (e.g., ciprofloxacin). The authors stated that this reduction may be due to the formation of chelates with Ca^{2+} contained in byakkokaninjinto. There remain some problems in the study design, such as small number of participants, inclusion of male subjects only, and no description of the number of subjects assigned to each arm. Yet the results of this study, if confirmed, mean that the co-administered byakkokaninjinto may delay the cure of infectious diseases, and therefore will have a strong impact on clinical practice. An RCT of byakkokaninjinto in patients with infectious diseases is desirable, but ethical aspects of such a trial must be considered. Alternatively, retrospective studies, including studies with a case-control design, might be of some help. Further studies on this topic are expected.

12. Abstractor and date

Tsuruoka K, 1 June 2010, 31 December 2013.

21. Others

Reference

Ogawa H, Xu F, Uebaba K, et al. Antioxidative potentiality of a Kampo formulation measured by an ex vivo study. *The Journal of Alternative and Complementary Medicine* 2009; 15: 267–74.

1. Objectives

To evaluate the antioxidative effect of bofutsushosan (防風通聖散) in healthy adults using the lag time of low-density lipoprotein (LDL) oxidation as the main yardstick.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

University of Toyama, Japan.

4. Participants

Eighteen healthy males (aged 22±3 years) selected from 38 males. The inclusion criteria were total cholesterol ≥180 and ≤220 mg/dL, triglyceride ≤170 mg/dL, high-density lipoprotein (HDL) cholesterol ≥40 mg/dL, LDL cholesterol ≤140 mg/dL). The subjects were randomly assigned to the following three arms.

5. Intervention

Arm 1: bofutsushosan (防風通聖散; Kanebo) 7.5 g/day.
Arm 2: placebo of bofutsushosan (防風通聖散; Kanebo) 7.5 g/day.
Arm 3: tablet containing a mixture of vitamin E (500 mg/day) and vitamin C (1000 mg/day).

6. Main outcome measures

Inhibitory effect on LDL oxidation induced by 2,2'-azobis (4-methoxy-2,4-dimethyl-valeronitrile); the lag time to oxidation (production of conjugated dienes), as a measure of antioxidative effect; plasma ephedrine, plasma baicalin, serum lipid peroxide, serum free fatty acids, urinary 8(OH)dG/creatinine levels, blood pressure, and heart rate.

7. Main results

The lag time tended to be longer, though not significantly longer, in arm 1 than arm 2 (P=0.08). There were no significant changes in levels of urinary 8(OH)dG/creatinine and serum lipid peroxide. In arm 1, a sympathomimetic response to the pharmacological action of ephedrine was observed.

8. Conclusions

Although not confirmed, the systemic antioxidative effect of bofutsushosan is suggested by this study.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This double-blind randomized controlled trial (DB-RCT) demonstrated the potential antioxidative effect of bofutsushosan on lipids. Drug administration in arms 1 and 2 was double-blinded, whereas it was unblinded in arm 3. So the study is an incomplete DB-RCT. Yet the outcomes are clinically highly suggestive. In the future, RCTs that involve patients with hyperlipidemia, compare Kampo medicines with standard medications, and use true endpoints to assess outcome are expected to be conducted.

12. Abstractor and date

Tsuruoka K, 1 June 2010.

21. Others

Reference

Yasui T, Yamada M, Uemura H, et al. Changes in circulating cytokine levels in midlife women with psychological symptoms treated with selective serotonin reuptake inhibitors and Japanese traditional medicine. *Maturitas* 2009; 62: 146–52.

1. Objectives

To compare the effects of kamishoyosan (加味逍遙散) and paroxetine in improving anxiety and depression as menopausal symptoms.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Tokushima University Hospital, Japan.

4. Participants

Seventy-six women with menopausal, psychological symptoms (such as anxiety and mild depression) who were recruited from among patients visiting the outpatient clinic of the Department of Obstetrics and Gynecology between November 2005 and October 2007. Subjects with major depression were excluded.

5. Intervention

Arm 1: paroxetine (paroxetine [GlaxoSmithKline] 10 mg/day for 6 months) (n=38).
Arm 2: Kamishoyosan (Tsumura Kamishoyosan Extract Granules 7.5 g/day for 6 months), (n=38).

6. Main outcome measures

The main outcome measures were serum levels of cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, TNF-α, IFN-γ, MCP-1, and MIP-1β) and climacteric symptoms assessed using Greene's climacteric scale.

7. Main results

The psychological, somatic, and vasomotor scores assessed using Greene's climacteric scale were improved in both arms, but improvement was greater in the paroxetine arm. Serum IL-6 levels decreased significantly compared with baseline in both arms, and showed significant positive correlations with Greene's climacteric scores. A significant decrease in IL-8, MIP-1β, and MCP-1 levels was also observed in the paroxetine arm.

8. Conclusions

The mechanism of the drug action of both paroxetine and kamishoyosan may involve IL-6, which therefore may be a useful marker of treatment. Though useful in treating menopausal symptoms, kamishoyosan is less effective than paroxetine.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Six of the 38 women in the paroxetine arm dropped out of the study because of the following adverse effects: headache, nausea, and uncomfortable gastrointestinal tract symptoms. One woman in kamishoyosan arm dropped out of the study because of bitter taste in the mouth and diarrhea, and two women dropped out because of no response to the drug.

11. Abstractor's comments

Kamishoyosan is often prescribed along with keishibukuryogan (桂枝茯苓丸) for treatment of menopausal symptoms. Although less effective than paroxetine, kamishoyosan was useful. Clinically, kamishoyosan and keishibukuryogan are prescribed based on *Kampo* findings, and the effectiveness of these drugs might be demonstrated if the subjects are treated on the basis of *Kampo* findings. However, it is interesting that improvement in somatic and psychological symptoms was correlated with serum IL-6 level. This correlation suggests a role of IL-6 in the mechanism of kamishoyosan.

12. Abstractor and date

Nakata H, 1 June 2010.

21. Others

Reference

Inotsume N, Fukushima S, Hayakawa T, et al. Pharmacokinetics of Ephedrine and Pseudoephedrine after oral administration of kakkonto to healthy male volunteers. *Rinsho Yakuri* (*Japanese Journal of Clinical Pharmacology and Therapeutics)* 2009; 40: 79-83. Ichusi Web ID: 2009308892

1. Objectives

To evaluate the pharmacokinetic profiles of serum ephedrine and pseudoephedrine after oral administration of kakkonto (葛根湯), and changes in biokinetics after different administered doses.

2. Design

Randomized controlled trial (cross over) (RCT-cross over)

3. Setting

One university, Japan.

4. Participants

Ten healthy male volunteers aged 23-26 years.

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

To examine the actual absorption under the conditions of administration after meals, following an overnight fast, kakkonto was given 1 hour after breakfast, and lunch was served 4 hours later. Blood samples were obtained before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug ingestion. The regimen was repeated in cross-over design after an interval of 2 weeks. Daily dose (7.5 g) of kakkonto contained 14.43 mg of ephedrine and 5.73 mg of pseudoephedrine.

Arm 1: Kanebo (now Kracie) Kakkonto (葛根湯) Extract Granule 2.5 g.

Arm 2: Kanebo (now Kracie) Kakkonto (葛根湯) Extract Granule 3.75 g.

6. Main outcome measures

Indices of the blood level-time curve of ephedrine and pseudoephedrine (maximum concentration [Cmax]), time to maximum serum concentration (tmax), area under the serum concentration-time curve (AUC), mean residence time (MRT), and terminal elimination rate constant (κ).

7. Main results

Serum ephedrine and pseudoephedrine concentrations were measured using a gas chromatograph-mass spectrometer. Standard curves were constructed based on quantitative analysis of deuterium labeled epinephrine and pseudoephedrine.

In Arm 1, the mean values of Cmax (ng/mL), tmax (h), AUC (ng・h/mL), MRT (h), and κ (/h) of ephedrine were 22.0, 3.0, 238.5, 9.8, and 0.1, respectively, and those of pseudoephedrine were 8.1, 3.0, 66.8, 7.4, and 0.2, respectively. The mean Cmax values of ephedrine and pseudoephedrine were 1.50- and 1.58-fold higher in Arm 2 compared with Arm 1, although the tmax did not differ significantly. The mean AUC values of ephedrine and pseudoephedrine in Arm 2 were 1.31- and 1.48- fold higher, respectively, than those in Arm 1, while the mean MRT and κ did not differ significantly.

8. Conclusions

The kinetic behavior of ephedrine and pseudoephedrine are largely linear at the doses examined.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a basic study evaluating the pharmacokinetics of ephedrine and pseudoephedrine contained in kakkonto in human serum. They were determined using high precision measurements such as gas chromatography, mass spectrometry, and deuterium labeling.

12. Abstractor and date

Fujisawa M, 1 June 2010, 31 December 2013.

21. Others

Reference

Munekage M, Kitagawa H, Ichikawa K, et al. Pharmacokinetics of daikenchuto, a traditional Japanese medicine (Kampo) after single oral administration to healthy Japanese volunteers. *Drug Metabolism and Disposition* 2011; 39: 1784-8. Pubmed ID: 21724872

1. Objectives

To analyze the blood kinetics of indicator components in daikenchuto (大建中湯).

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

Surgery Department, Kochi Medical School Hospital, Japan.

4. Participants

Nineteen healthy volunteers (including three volunteers who did not meet the criteria and were excluded).

5. Intervention

Groupings by administration pattern were not indicated, so the arms are described in terms of drug groups.
Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 2.5 g group (n=15).
Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules 5 g group (n=16).
Arm 3: TSUMURA Daikenchuto (大建中湯) Extract Granules 10 g group (n=16).

6. Main outcome measures

Hydroxyl-α-sanshool, hydroxyl-β-sanshool, 6-shogaol, 10-shogaol, ginsenoside Rb1, and ginsenoside Rg1 blood kinetics (AUC, C_{max}, $t_{1/2}$, t_{max}).

7. Main results

Hydroxyl-α-sanshool, hydroxyl-β-sanshool, 6-shogaol, and 10-shogaol reached t_{max} in 0.2–0.5 hours and were rapidly eliminated from the blood; however, ginsenoside Rb1 and ginsenoside Rg1 reached t_{max} in 1–4 hours and were more slowly eliminated from the blood. Increases in blood concentrations of hydroxyl-α-sanshool, hydroxyl-β-sanshool, 6-shogaol, and 10-shogaol were dosage dependent, but increases in blood concentrations of ginsenoside Rb1 and ginsenoside Rg1 were dosage independent.

8. Conclusions

Of the six indicator components in daikenchuto, increases in the blood concentrations of the sansho- and kankyo-derived components are dose dependent but increases in those of ginseng-derived components are dose independent.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Six adverse events (abnormal laboratory values) occurred in four participants, but a causal relationship with daikenchuto was excluded.

11. Abstractor's comments

The blood kinetics of six indicator components in daikenchuto extract were analyzed in this study. There are distinct differences between the blood kinetics of low molecular weight compounds such as hydroxyl-α-sanshool, hydroxyl-β-sanshool, 6-shogaol, and 10-shogaol, and high molecular weight compounds such as ginsenoside Rb1 and ginsenoside Rg1, which points to the complexity of the blood kinetics of Kampo preparations with their wide arrays of components. This paper suggests the possibility that prescriptions considered to be deficiency-pattern treating formulae or *hozai* (補剤) (because they contain a wide array of high molecular weight compounds) do not act in a dosage dependent manner.

12. Abstractor and date

Nakata H, 31 December 2013.

21. Others

Reference

Munekage M, Ichikawa K, Kitagawa H, et al. Population pharmacokinetic analysis of daikenchuto, a traditional Japanese medicine (Kampo) in Japanese and US health volunteers. *Drug Metabolism and Disposition* 2013; 41: 1256-63. CENTRAL ID: CN-0964576, Pubmed ID: 23545807

1. Objectives

To analyze the blood kinetics of indicator ingredients in daikenchuto (大建中湯).

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

Kochi Medical School Hospital, Japan, and a center in USA.

4. Participants

Healthy volunteers: 19 Japanese and 36 American.

5. Intervention

Since allocation of patients to treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.
Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 2.5 g (18 Japanese and 33 Americans).
Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules 5 g (19 Japanese and 34 Americans).
Arm 3: TSUMURA Daikenchuto (大建中湯) Extract Granules 10 g (19 Japanese and 33 Americans).

6. Main outcome measures

Hydroxyl-α-sanshool, hydroxyl-β-sanshool, 6-shogaol, 10-shogaol, and ginsenoside Rb1 blood kinetics.

7. Main results

The indicator ingredients, hydroxyl-α-sanshool, hydroxyl-β-sanshool, 6-shogaol, and 10-shogaol demonstrated blood kinetics in line with the one- or two-compartment model with bolus input; however, only ginsenoside Rb1 demonstrated blood kinetics in line with the one-compartment model with nonlinear extravascular input. Blood plasma hydroxyl-α-sanshool and hydroxyl-β-sanshool concentrations differed significantly between the Japanese and the Americans.

8. Conclusions

Of the indicator ingredients in daikenchuto, Japanese Pepper-/Processed Ginger-derived ingredients and Ginseng Radix-derived ingredients differed in blood kinetics. While concentrations of blood plasma hydroxyl-α-sanshool and hydroxyl-β-sanshool differed between Japanese and Americans, differences in BMI, age and race may also have an effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The blood kinetics of five indicator ingredients in daikenchuto extract were measured in this study. The blood kinetics of low molecular weight compounds such as hydroxyl-α-sanshool, hydroxyl-β-sanshool, 6-shogaol, and 10-shogaol, and that of high molecular weight compounds such as ginsenoside Rb1 differ vastly, pointing to the complexity of the blood kinetics of multicomponent Kampo preparations. Given that differences were observed between the blood concentrations of the ingredient sansho in the Japanese and the Americans, it may be important to adjust dosages according to circumstances, considering that the kinetics differ among ingredients, while taking race and physique into consideration. The Japanese study referred to in this report appears to be the identical study reported by Munekage M, Kitagawa H, Ichikawa K, et al. in *Drug Metabolism and Disposition* 2011; 39: 1874-8: Pharmacokinetics of daikenchuto, a traditional Japanese medicine (Kampo) after single oral administration to healthy Japanese volunteers.

12. Abstractor and date

Nakata H, 6 June 2015.

21. Others

Reference

Takayama S, Okitsu R, Iwasaki K, et al. The effect of warming the abdomen with herbal medicine or thermal therapy on superior mesenteric artery blood flow. *Kampo to Saishin Chiryo* (*Kampo & the Newest Therapy*) 2011; 20: 253-8 (in Japanese with English abstract). Ichushi Web ID: 2011349495

1. Objectives

To evaluate the effect of daikenchuto (大建中湯) and abdominal thermotherapy on blood flow through the superior mesenteric artery.

2. Design

Randomized controlled trial (RCT).

3. Setting

No mention of participating centers (the authors blong to the Advanced Course in Kampo Medicine, Department of Traditional Asian Medicine, Tohoku University), Japan.

4. Participants

Forty-three healthy volunteers with no cardiovascular or gastrointestinal disease.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (5 g) + distilled water (50 mL) group (n=14).
Arm 2: Abdominal warming group (n=15).
Arm 3: Distilled water (50 mL) group (n=14).

6. Main outcome measures

Comparison of changes in superior mesenteric artery blood flow monitored using a heat conduction control device at commencement of abdominal warming for 20 minutes, at oral administration of daikenchuto, and every 10 minutes (up to 50 minutes) after oral administration of distilled water.

7. Main results

Superior mesenteric artery blood flow was significantly increased in arms 1 and 2 compared to arm 3 ($P<0.01$ in both) but was not significantly different between arms 1 and 2.

8. Conclusions

The traditional medical therapy of abdominal warming increases superior mesenteric artery blood flow to the same extent as oral daikenchuto.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

It is significant that this study demonstrated with objective indicators that warm tonification (the Kampo medical concept of warming the body and tonifying qi) and warming (the therapeutic method used in acupuncture and moxibustion) both have the characteristic of increasing superior mesenteric artery blood flow. Further study is warranted to determine the significance of this increase.

12. Abstractor and date

Nakata H, 31 December 2013.

21. Others

Reference

Kitagawa H, Munekage M, Ichikawa K. et al. Pharmacokinetics of Active Components of Yokukansan, a Traditional Japanese Herbal Medicine after a Single Oral Administration to Healthy Japanese Volunteers: A Cross-Over, Randomized Study. *PloS One* 2015 7; 1-14.

1. Objectives

Pharmacokinetics of the blood concentration of active ingredients of yokukansan (抑肝散) in healthy subjects.

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

Two university surgery departments.

4. Participants

Healthy participants from 20- to 45-years, who had not taken any supplement containing yokukansan ingredients in the 3-7 days before start of the trial, and had no kidney disease, heart or vascular disease (n=21).

5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散) Extract Granules 2.5g→5g→7.5g/day once administered orally (n=8).
Arm 2: TSUMURA Yokukansan (抑肝散) Extract Granules 5g→7.5g→2.5g/day once administered orally (n=7).
Arm 3: TSUMURA Yokukansan (抑肝散) Extract Granules 7.5g→2.5g→5g/day once administered orally (n=6).
A 4-week washout period was allowed before changing the dosage.

6. Main outcome measures

Blood kinetics of Geissoschizine methyl ether (GM), Hirsuteine (HTE), and 18β-glycyrrhetinic acid (GA)

7. Main results

One participant dropped out of each of arms 1 and 3 after the first administration.
Results after taking orally 2.5g, 5g, and 7.5g respectively of TSUMURA Yokukansan (抑肝散) Extract Granules
GM: Cmax 2.5g=0.650ng/ml 5g=1.39ng/ml 7.5g=1.98ng/ml
AUC 2.5g=1.18ng/ml 5g=2.98ng/ml 7.5g=4.81ng/ml
HTE: Cmax 2.5g=0.138ng/ml 5g=0.305ng/ml 7.5g=0.450ng/ml
AUC 2.5g=0.277ng/ml 5g=0.833ng/ml 7.5g=1.50ng/ml
GA: Cmax 2.5g=57.7ng/ml 5g=84.3ng/ml 7.5g=108ng/ml
AUC 2.5g=690ng/ml 5g=1210ng/ml 7.5g=1670ng/ml

8. Conclusion

GM and HTE blood concentrations increased rapidly after taking yokukansan extract (0.5-1 hour), and rapidly reached their half-lives (2-3 hours). However, GA is an aglycone of GL. Absorption of GL directly was poor, and was not detected in blood. Yet, while GA, without glycosides, has greater absorption than GM or HTE, Tmax is slower than GM or HTE, 8 hours, and its half-life is long (11 hours).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse event was observed during the trial.

11. Abstractor's comments

This paper describes the pharmacokinetics of the active ingredients of yokukansan. Although the glycoside absorption rate is 8 times slower than alkaloids, its blood concentration was found to be 100 times greater. Although it is currently not understood how drug action is related to the fact that different ingredients reach blood concentration peaks at different times, the active ingredients in crude drugs are generally taken up into the blood in 1-8 hours, so when prescribing, the timing of administration must take those factors into account.

12. Abstractor and date

Nakata H, 2 February 2017.

21. Others

Reference

Kitagawa H, Munekage M, Matsumoto T, et al. Pharmacokinetic profiles of active ingredients and its *metabolites* derived from rikkunshito, a ghrelin enhancer, in healthy Japanese volunteers: A cross-over, randomized study. *PloS One* 2015; 10: 1-19.

1. Objectives

To analyze the pharmacokinetics of the active ingredients of rikkunshito (六君子湯) in healthy volunteers.

2. Design

Randomized controlled trial cross-over (cross over) (RCT-cross over).

3. Setting

One university department of medicine, Japan.

4. Participants

21 healthy participants. Ages 20-45, BMI 18-25. Participants had no liver, heart or vascular disease, and had not taken a supplement or pharmaceutical containing rikkunshito active ingredients. Pregnant or lactating women, and chronic alcohol or nicotine consumers were excluded.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules taken orally once in each of Period 1 (7.5g/day), Period 2 (2.5g/day), and Period 3 (5g/day) (n=7).
Arm 2: TSUMURA Rikkunshito (六君子湯) Extract Granules taken orally once in each of Period 1 (2.5g/day), Period 2 (5g/day), and Period 3 (7.5g/day) (n=7).
Arm 3: TSUMURA Rikkunshito (六君子湯) Extract Granules taken orally once in each of Period 1 (5g/day), Period 2 (7.5g/day), and Period 3 (2.5g/day) (n=7).

Participants took standard meals not containing active ingredients of rikkunshito from 3 days before the start of the trial. They fasted for 12 hours before taking the trial drug. Blood was sampled before taking the rikkunshito (0), then 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours, and the plasma was stored. A physician was in attendance.

6. Main outcome measures

Plasma concentrations of the 9 active ingredients contained in rikkunshito (Atractylodin, Atractylodin carboxylic acid, Pachymic acid, Heptamethoxyflavone, Naringenin, Nobiletin, Liquiritigenin, Isoliquiritinigenin, and 18β-Glycyrrhetinic acid), Cmax, AUC. 32 active ingredients determined by screening in preliminary tests. Atractylodin carboxylic acid was not screened, but was added to the trial as it is an Atractylodin metabolite.

7. Main results

One participant dropped out of arm 1 (after the second administration), and 2 dropped out of arm 2 (after the first and the second administrations). 1 participant dropped out of arm 1 and 1 from arm 2, leaving 19 subjects for analysis. The order of Cmax (7.5mg orally) was 18β-Glycyrrhetinic acid, Atractylodin carboxylic acid, Naringenin, Liquiritigenin, Heptamethoxyflavone, Pachymic acid, Isoliquiritinigenin, then Nobiletin. Tmax (7.5g) was 1 hour or less for Atractylodin carboxylic acid, Isoliquiritinigenin, Nobiletin, Atractylodin, and Heptamethoxyflavone and 3 hours or more for the other 4 active ingredients. Half-life (7.5g) was 10 hours or more for 18β-Glycyrrhetinic acid and Pachymic acid, and less than 10 hours for the other 7 active ingredients. There was dose dependency in the range 2.5-7.5g, for Cmax of Atractylodin and Atractylodin carboxylic acid and for AUC of 18β-Glycyrrhetinic acid and Atractylodin carboxylic acid.

8. Conclusion

The nine active ingredients of rikkunshito were pharmacokinetically analyzed after administration, finding the Cmax, Tmax, half-life and presence/absence of dose dependency of each ingredient.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two participants dropped out, but the reasons were not mentioned.

11. Abstractor's comments

This is an unprecedented paper setting out the pharmacokinetics of the active ingredients of rikkunshito after administration to healthy subjects in a rigorously designed study. Giving consideration to these pharmacokinetics and clinical effects under clinical trial may allow for rikkunshito's mechanisms of action to be elucidated. However, as the authors mention, it would be difficult to explain the effects of rikkunshito with one ingredient. In fact, the pharmacokinetics of each ingredient differ, and the effect of rikkunshito could be exerted through the synergic action of multiple ingredients.

12. Abstractor and date

Kogure T, 29 December 2016.

21. Others

Reference

Sadakane C, Watanabe J, Fukutake M, et al. Pharmacokinetic profiles of active components after oral administration of a Kampo medicine, shakuyakukanzoto, to healthy adult Japanese volunteers. *Journal of Pharmaceutical Sciences* 2015; 104: 3952-9.

1. Objectives

Comparative analysis of the plasma concentrations of components of shakuyakukanzoto (芍薬甘草湯) after administration of different doses

2. Design

Randomized controlled trial (cross-over) (RCT cross-over)

3. Setting

A clinic in Tokyo

4. Participants

The inclusion criteria were healthy Japanese adults aged 20–45 with a body mass index (BMI) between 18 and 25. The exclusion criteria were liver, cardiac or vascular diseases; intake of supplements containing components of shakuyakukanzoto or any medicine within 3–7 days before the first dose; allergy, and habitual use of alcohol or nicotine. Twenty subjects were included in the trial.

5. Intervention

Twenty subjects aged 21–42 were assigned randomly to two groups of 10 subjects.

Arm 1: 10 subjects. They were administered shakuyakukanzoto a single oral dose of 2.5 g in the first period. After a 7-day washout period, they were administered shakuyakukanzoto a single oral dose of 5 g in the second period.

Arm 2: 10 subjects. They were administered shakuyakukanzoto a single oral dose of 5 g in the first period. After a 7-day washout period, they were administered shakuyakukanzoto a single oral dose of 2.5 g in the second period.

6. Main outcome measures

The plasma concentrations of 6 active components of shakuyakukanzoto, i.e., albiflorin (ALB), paeoniflorin (PAE), glycycoumarin (GCM), isoliquiritigenin (ILG), glycyrrhetic acid (GA), and glycyrrhetic acid-3-*O*-monoglucuronide (3MGA), were measured by liquid chromatography-mass spectrometry. Based on these concentrations, the pharmacokinetic parameters were calculated, and linearity was assessed.

7. Main results

After oral administration of shakuyakukanzoto, all of the active components were detected in the plasma. ALB, PAE, GCM, and ILG were detected at an early stage. Time to maximum plasma concentration, t_{max}, after administration of 5.0 g were 2.00 hr for ALB, 3.00 hr for PAE, 0.500 hr for GCM, and 0.250 hr for ILG. Elimination half-life, $t_{1/2}$, of ALB (1.81 hr for 2.5 g and 1.76 hr for 5.0 g) and PAE (1.74 hr for 2.5 g and 1.73 hr for 5.0 g) were particularly short. Linearity was observed for the maximum plasma concentrations of GCM, ILG, and GA and for the area under the concentration-time curve of GA.

8. Conclusions

It was demonstrated for the first time in humans that active components of shakuyakukanzoto were absorbed into the blood after oral administration.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

Because it is written that the trial will be stopped if a serious adverse event occurs, and no subject dropped out, it is determined that there were no adverse events. It is argued in the paper that this study provides a basis for elucidating the mechanisms of common adverse events to Kampo medicines such as hypokalemia because the absorption of each component into the blood was confirmed.

11. Abstractor's comments

This is an important trial which proved for the first time in humans that active components of shakuyakukanzoto were absorbed into the blood after oral administration. All 6 components were absorbed into the blood after oral administration of both 2.5 g and 5 g. I expect this study will lead to more clinically relevant studies to identify, for example, the component or components that work against muscle cramp or abdominal pain, which shakuyakukanzoto is known to be effective against.

12. Abstractor and date

Tsuruoka K, 22 April 2017

21. Others

Reference

Endo Y, Ishihara Y, Tsuno S, Matsuda A, et al. Pharmacokinetic Interaction Study of Ranitidine and Daijokito in Healthy Volunteers. *Yonago Acta Medica* 2016; 59: 111-7. CENTRAL ID: CN- 01178387, PubMed ID: 27493481

1. Objectives

To verify the effect of daijokito (大承気湯) on the pharmacokinetics of ranitidine.

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

Not mentioned. (The author belongs to a university drug therapy department.)

4. Participants

Seven healthy males.

5. Intervention

Arm 1: Ranitidine (300mg) taken after fasting, then after at least 5 days, ranitidine (300mg) and TSUMURA Daijokito (大承気湯) Extract Granules (2.5g) taken after fasting (n=4).

Arm 2: Ranitidine (300mg) and TSUMURA Daijokito (大承気湯) Extract Granules (2.5g) taken after fasting, then after at least 5 days, ranitidine (300mg) taken after fasting (n=3).

6. Main outcome measures

Changes in ranitidine blood concentration over time, up to 12 hours after administration.

7. Main results

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) up to 12 hours after ranitidine administration were significantly lower when daijokito was taken compared to when daijokito was not taken.

8. Conclusions

Daijokito lowers ranitidine blood concentration.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No clinically significant adverse reaction was observed in blood tests, vital signs, or physical findings.

11. Abstractor's comments

There have been few findings on the interactions of Kampo and Western medications and there is little awareness in clinical practice of the effects of Kampo medications on Western medications, and vice versa. Against that background, the results indicated by this research are important. While the reduction in plasma drug concentration is not directly connected to the reduction in clinical effect, practitioners must be aware of the possibility that when a Kampo medication is administered the blood concentration of an important therapeutic drug might not reach the clinically required concentration and thereby might have no effect. Similar studies of frequently used Kampo preparations other than daijokito are desirable. In current clinical practice, very large numbers of patients are being administered multiple drugs, not only Kampo medications, whose blood concentrations are difficult to infer: this is a problem. The results of this research point to the constant need in clinical practice to curb the numbers and types of Kampo and Western medications used to the minimum required, and to vigilantly assess whether the anticipated effects are being achieved or not.

12. Abstractor and date

Koike H, 18 May 2020.

21. Others

Reference

Arai M, Sato H, Shirota F. An investigation into the relief of colonoscopy pain provided by shakuyaku-kanzo-to. *Nihon Toyo Igaku Zasshi* (*Japanese Journal of Oriental Medicine*) 1994; 44: 385-90 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) for relieving pain during colonoscopy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

Thirty-eight patients (30–60 years old) who underwent total colonoscopy.

5. Intervention

Arm 1: oral administration of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 5.0 g before the examination (n=18).
Arm 2: no treatment (n=20).
Diazepam 10 mg was injected intramuscularly 5 minutes before the examination in both arms.

6. Main outcome measures

Subjective symptoms (visual pain score: VPS), systolic blood pressure, heart rate, and examination time.

7. Main results

VPS was significantly lower in arm 1 (4.89±0.42 *vs.* 6.20±0.34; $P<0.05$). There were no between-arm differences in the systolic blood pressure, heart rate, and examination time.

8. Conclusions

Shakuyakukanzoto relieves pain during colonoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper is of clinical significance in that it demonstrated the efficacy of shakuyakukanzoto for relieving pain during colonoscopy in an RCT. The study would be more meaningful if it employed a design involving administration of placebo, such as lactose, instead of no-treatment.

12. Abstractor and date

Kogure T, 8 August 2008.

21. Others

References

Imazato S, Kai S, Koizumi K, et al. A Clinical Study of shakuyaku-kanzo-to (Kampo) as a preparation for double contrast barium enema. *Therapeutic Research* 1997; 18: S505-10 (in Japanese). MOL, MOL-Lib

Imazato S, Kai S, Koizumi K, et al. A clinical study of shakuyaku-kanzo-to (Kampo) as a preparation for double contrast barium enema. *Kampo Igaku* (*Science of Kampo Medicine*) 1998; 22: 87–92 (in Japanese).

1. Objectives

To evaluate the effectiveness of Shakuyakukanzoto (芍薬甘草湯) for complaints and distress related to pre-enema treatment.

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

Sixty patients who visited the hospital to undergo an enema X-ray examination..

5. Intervention

Arm 1: modified Brown method + TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 g before evening meal and sleep on the day before examination, and in the morning before examination (n=30).

Arm 2: modified Brown method (n=30).

6. Main outcome measures

Subjective symptoms (questionnaire).

7. Main results

Subjective symptom scores in arm 1 and arm 2 were 96.7% and 46.7% (respectively) for “not so much” abdominal pain the night before; 86.7% and 6.7% for “usual” sleep the night before; 90% and 66.7% for “no problems” referring to distress associated with enema examination pretreatment when visiting the hospital; and 66.7% and 0% for “easier than last time” referring to a previous occasion. Daily stool frequency was reduced in arm 1 (time range: 0~6 AM).

8. Conclusions

Shakuyakukanzoto reduces distress associated with enema examination pretreatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned. The examination itself was reported to have no ill effects and barium adhesion was reported to be satisfactory in arm 1.

11. Abstractor’s comments

This RCT is worthy of praise for having evaluated the effects of shakuyakukanzoto on pain and distress associated with pretreatment for the barium enema X-ray examination using a large number of participants. The evidence could have been made easier to understand by giving subjective symptoms numerical values and by comparing the two groups in greater detail.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010, 31 December 2012.

21. Others

Reference

Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). *Therapeutic Research* 1989; 10: 1637–43 (in Japanese with English abstract).
Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). *Current Therapy* 1989; 7: 749-54 (in Japanese).
Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). *Current Therapy* 1990; 8: 805-10 (in Japanese).

1. Objectives

To clinically evaluate the efficacy of a new colon preparation for colonoscopy using daiokanzoto（大黄甘草湯）.

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital (the author belongs to the Department of surgery, Hokota hospital), Japan.

4. Participants

Sixty patients undergoing colonoscopy for lower gastrointestinal complaints.

5. Intervention

Arm 1: TSUMURA Daiokanzoto（大黄甘草湯）Extract Granules 7.5 g/day from 2 days before colonoscopy (n=30).
Arm 2: Modified Brown method (n=30).

6. Main outcome measures

Degree of colonic irrigation (3-point scale), comprehensive evaluation (physician's impression, 4-point scale).

7. Main results

The degree of colonic irrigation was rated good in 90% (27 patients) and 30% (9 patients), fair in 10% (3 patients) and 60% (18 patients), and poor in 0% (0 patients) and 10% (3 patients) of patients in Arm 1 and Arm 2, respectively. Comprehensive evaluation was excellent in 83.3% (25 patients), good in 6.7% (2 patients), fair in 10% (3 patients) and poor in 0% (0 patients) of patients in Arm 1.

8. Conclusions

Daiokanzoto is superior to the modified Brown method of colonic preparation for colonoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No patients in Arm 1 had nausea, vomiting, or abdominal pain but 1 patient had bloated feeling, while 6, 2, 6, and 1 patient in Arm 2 had nausea, vomiting, abdominal pain, and bloated feeling, respectively.

11. Abstractor's comments

This study deserves praise for developing a new pretreatment method for colonoscopy using daiokanzoto and performing an RCT that compared it with the conventional method. However, statistical analysis of the data is warranted since the study's between-arm comparison was insufficient.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010, 22 November 2019.

21. Others

Reference

Saida Y, Takase M, Okumura C, et al. Efficacy of combined use of shakuyakukanzoto in pretreatment for large bowel endoscopy – prospective randomized trial*. *Nihon Daicho Kensa Gakkai Zasshi* (*Journal of the Japan Society of Colon Examination*) 2003; 20: 34-7 (in Japanese). Ichushi Web ID: 2005123565

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) combined with polyethylene glycol solution (PEG) in pretreatment for large bowel endoscopy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

None (authors belong to the Department of Colon and Rectal Surgery, Tohokamagaya Hospital), Japan.

4. Participants

Seventy patients who were scheduled to undergo large bowel endoscopy between November 2000 and March 2001 and gave informed consent to participate in this trial.

5. Intervention

Arm 1: oral administration of shakuyakukanzoto (芍薬甘草湯) (2.5 g t.i.d.) starting from lunchtime on the day before endoscopy (n=37).
Arm 2: non-treatment (n=33).
Endoscopy was performed by an experienced specialist.

6. Main outcome measures

Frequency of defecation on the day of endoscopy, time until defecation, presence or absence and severity of abdominal pain associated with pretreatment, presence or absence and severity of nausea, pretreatment condition (residue), and time required to reach cecum.

7. Main results

Frequency of defecation and time until defecation were 6.9±2.5 times and 234±36 min, respectively, in arm 1 and 7.6±3.4 times and 171±30 min, respectively, in arm 2, showing reduced frequency and extended time until defecation in arm 1, although there were no significant differences between arms. The incidence and score of abdominal pain were 11% and 0.6±0.4, respectively, in arm 1 and 12% and 0.5±0.4, respectively, in arm 2, showing no difference between arms. Nausea was more prevalent in arm 1 with the incidence of 33%, compared with 12% in arm 2, although there was no difference in nausea score between arms. Pretreatment score and time required to reach cecum were 0.9±0.8 and 7.9±5.4 min, respectively, in arm 1 and 0.7±0.8 and 7.9±5.5 min, respectively, in arm 2, showing no difference between arms.

8. Conclusions

Shakuyakukanzoto combined with PEG tends to slightly suppress the cleansing of the bowel needed prior to large bowel endoscopy and may induce nausea, suggesting its ineffectiveness in such pretreatments.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

To achieve adequate intestinal lavage in preparation for large intestine endoscopy, a large amount of PEG has to be swallowed. In terms of efficacy and patient satisfaction, however, currently available pretreatments are not always useful. Focusing on this issue, the present study is meaningful. To further enhance the quality of this clinical research, however, the control should be a placebo that has no effect on bowel motility rather than no treatment. With no other useful concomitant drugs available, it is hoped that new drugs and useful approaches will be investigated.

12. Abstractor and date

Arai M, 23 February 2007, 30 October 2007, 1 June 2010.

21. Others

Reference

Ai M. Assessment of the antipasmodic effect of peppermint oil and Shakuyaku-kanzon-to (TJ-68); a Chinese herbal medicine on the clonic wall. *Medical Tribune Online* (*Digestive Disease Week: DDW*) 2005: 10-1 (in Japanese).

1. Objectives

To evaluate the efficacy of directly sprayed shakuyakukanzoto (芍薬甘草湯) on large bowel spasm.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (university), Japan.

4. Participants

One-hundred and thirty-one patients scheduled to undergo large bowel endoscopy for polyp surveillance, etc.

5. Intervention

Arm 1: shakuyakukanzoto (芍薬甘草湯) group (0.5 g of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extra Granules dissolved in physiological saline to make 50 mL [concentration: 10 g/L]).
Arm 2: peppermint oil group (0.4 mL of peppermint oil and 0.05 g of sorbitan fatty acid ester dissolved in water to make 50 mL [concentration: 8 mL/L]).
Arm 3: Physiological saline group.
In all arms, conventional fluoroscopy (CF) was performed in the left lateral position, and the contraction ring in the gastric antrum was sprayed, kept 1 cm from the tip of the endoscope inserted 20–25 cm from the anus.

6. Main outcome measures

Contraction ring lumen area (presented as the number of pixels on videotaped digital images of contraction-relaxation motions of the contraction ring during the 3-min period beginning before and ending after each drug was sprayed), and area under the expanded area-time curve.

7. Main results

Lumen area was significantly larger in the shakuyakukanzoto group and peppermint oil group than in the physiological saline group. The area under the expanded area-time curve was also significantly larger in both treatment groups than in the physiological saline group. There was no difference in outcome measures between the shakuyakukanzoto group and peppermint oil group.

8. Conclusions

Shakuyakukanzoto and peppermint oil have comparable large intestinal wall-relaxing activity.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Direct spray of large intestinal wall with shakuyakukanzoto may be applicable as an antispastic in the CF test.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

21. Others

Reference

Sugihara N. Effectiveness of shakuyaku-kanzo-to as a pretreatment for upper digestive tract endoscopic examination*. *Kampo Shinryo* 1999; 18: 17-9 (in Japanese).

1. Objectives

To evaluate the efficacy of pretreatment with shakuyakukanzoto (芍薬甘草湯) for upper gastrointestinal tract endoscopy.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Single facility (clinic), Japan.

4. Participants

Fifty-eight subjects who underwent endoscopy.

5. Intervention

Arm 1: shakuyakukanzoto (芍薬甘草湯) group (oral administration of 80 mg of dimethicone syrup followed by 5.0 g of shakuyakukanzoto (芍薬甘草湯) extract granules) (n=11).

Arm 2: anticholinergic drug group (oral administration of 80 mg of dimethicone syrup followed by subcutaneous injection of 40 mg of scopolamine butylbromide) (n=28).

6. Main outcome measures

Symptoms during endoscopy (pain evaluated subjectively on a visual analogue scale), peristalsis (Niwa's classification).

7. Main results

Among those under 70 years, the anticholinergic drug was significantly superior to shakuyakukanzoto in suppression of peristalsis, but was more frequently associated with experience of pain/discomfort.

8. Conclusions

Shakuyakukanzoto provides as much pain relief as the anticholinergic drug.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Of 58 subjects, only 39 were actually assigned to either group (arm 1, n=11; arm 2, n=28). This sample size seems to be slightly too small to evaluate efficacy.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

21. Others

Reference

Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, a herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Digestive Endoscopy* 2005; 17: 50-3. CENTRAL ID: CN-00575598, Ichushi Web ID: 2006000780

1. Objectives

To evaluate the efficacy of daikenchuto (大建中湯) combined with polyethylene glycol solution (PG solution) in pretreatment for large bowel endoscopy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

None (authors belong to the 3rd Department of Surgery, Toho University School of Medicine), Japan.

4. Participants

Two-hundred and eighty-five patients who underwent total large bowel endoscopy between January and December 2001, gave informed consent to participate in this trial, and remained after excluding those under 18 years old, pregnant women, and other ineligible patients.

5. Intervention

Arm 1: combination of PG solution and TSUMURA Daikenchuto (大建中湯) Extract Granules (oral administration of 2.5 g each at 12:00 and 21: 00 on the day before and 7:00 on the day of large bowel endoscopy) (n=144).
Arm 2: PG solution alone (n=141).
Endoscopy was performed by an experienced specialist.

6. Main outcome measures

Frequency of defecation on the day of endoscopy, time until defecation, presence or absence of abdominal pain, abdominal score, presence or absence of nausea, nausea score, pretreatment score, and time required to reach the ileocecal area.

7. Main results

The PG solution/daikenchuto combination group and PG solution group defecated 7.9±3.1 times and 7.7±3.6 times, respectively, and required 3.3±1.6 hr and 3.0±1.5 hr until defecation, respectively. The incidence of abdominal pain (score) was 17% (0.17±0.38) and 15% (0.15±0.35), respectively, and the incidence of nausea (score) was 24% (0.28±0.55) and 21% (0.21±0.43), respectively. Thus, there were no significant between-group differences in these parameters. Pretreatment score was significantly improved in the PG solution/daikenchuto combination group (0.28±0.52 *vs* 0.81±0.77 in the PG solution group; $P<0.01$). The time required to reach the ileocecal area was also significantly reduced in the PG solution/daikenchuto combination group (6.4±3.6 min *vs* 7.3±4.0 min in the PG solution group; $P=0.04$).

8. Conclusions

PG solution/daikenchuto pretreatment for large bowel endoscopy is a more patient-friendly effective method for facilitating insertion (compared with pretreatment with PG solution alone) and does not increase the level of uncomfortable symptoms such as abdominal pain, nausea, and frequent defecation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This randomized controlled trial demonstrated that daikenchuto combined with PG solution is superior to PG alone in the preparation of the large intestine for endoscopy. This study has a large sample size and is well designed, but fails to explain pretreatment score and abdominal pain score. It has been presented in a previous report "Saida Y. The 15th Surgery and Kampo Medicine Study Meeting 1. Efficacy of combined use of daikenchuto in pretreatment for large bowel endoscopy - 6 prospective studies -*. *Progress in Medicine* 2005; 25: 3058-9 (in Japanese)."

12. Abstractor and date

Arai M, 10 March 2007, 30 October 2007, 1 June 2010, 31 December 2013.

21. Others

Reference

Ai M, Yamaguchi T, Odaka T, et al. Objective assessment of the antispasmodic effect of Shakuyaku-kanzo-to (TJ-68), a Chinese herbal medicine, on the colonic wall by direct spraying during colonoscopy. *World Journal of Gastroenterology* 2006; 12: 760-4. CENTRAL ID: CN-00563124, Pubmed ID: 16521190

1. Objectives

To evaluate the efficacy and safety of direct spraying of shakuyakukanzoto (芍薬甘草湯) on the colonic mucosa for suppression of bowel movement during colonoscopy.

2. Design

A randomized controlled trial (RCT).

3. Setting

Not specifically mentioned (the authors belong to one university hospital), Japan.

4. Participants

One-hundred and ten patients with suspected intestinal hemorrhage, acute abdomen due to acute enteritis, inflammatory bowel disease, or a history of abdominal surgery, and treated with an oral drug affecting bowel movement, who visited our hospital between July 2002 and March 2004.

5. Intervention

Arm 1: spray of 0.5 g/50 mL of a solution of TSUMURA Shakuyakukanzo (芍薬甘草湯) Extract Granules in physiological saline maintained at 36℃ over the area of spasms in the intestine, 10 mm apart (n=51).

Arm 2: spray of physiological saline maintained at 36℃ in the same manner as arm 1.

Colon preparation involved oral administration of Magcorol (59 g/250 mL) on the day before colonoscopy and 2 L of Niflec on the day of colonoscopy. No sedatives were used during colonoscopy (n=50).

Five patients in arm 1 and 4 patients in arm 2 were excluded from the study population because of poor or incomplete bowel preparation.

6. Main outcome measures

Lumen area (pixels) × time (min), determined before and after spraying over the area of spasms.

7. Main results

Before spraying, there was no significant difference between arms. After spraying, the area × time value was significantly larger in arm 1.

8. Conclusions

Direct spray of shakuyakukanzoto is effective for suppression of bowel movement during colonoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no complications throughout the study period.

11. Abstractor's comments

This is an excellent study because it quantifies bowel movement by monitoring digital images over time, enabling objective evaluation.

12. Abstractor and date

Kogure T, 27 January 2009.

21. Others

Reference

Mizukami T, Maruyama K, Yamauchi H, et al. Assessment of antispasmodic effect of herbal medicine, Shyakuyakukanzoto (TJ-68) on colonoscopy – Using colonoscopy insertion technique "collapsing method" –. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2006; 15: 69-76 (in Japanese). Ichushi Web ID: 2006142071

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) solution in preparation for colonoscopy used with the water method of distension.

2. Design

A quasi-randomized controlled trial (quasi-RCT).

3. Setting

Not mentioned (the authors belong to one specialty hospital), Japan.

4. Participants

Forty-two males undergoing colonoscopy who gave consent to participate in the study.

5. Intervention

Arm 1: intrarectal injection of a solution of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (1.25 g/100 mL) instead of water used in preparation for colonoscopy used with the water method, simultaneously performed with colonoscope insertion (n=21).

Arm 2: intramuscular injection of butylscopolammonium bromide (Buscopan) (20 mg/mL/A), simultaneously performed with colonoscope insertion (n=21).

One patient in each arm was considered unresponsive because of failure to achieve spasmolysis during the test and was excluded.

6. Main outcome measures

Duration of spasmolysis determined by measuring the time between the first and second appearance of colonic ring contractions.
Pulse rate measured before and 10 min after endoscope insertion.
Pain evaluated on a 5-point scale.

7. Main results

There was no significant difference in duration of spasmolysis or pain scale score between arms. Percent increase in pulse rate from before to 10 min after insertion was significantly larger in arm 2. Spasmolytic effect persisted until completion of the test in 68.8% of subjects in arm 1 and 25.0% of subjects in arm 2, showing a significant between-arm difference.

8. Conclusions

Shakuyakukanzoto solution in preparation for colonoscopy, used with the water method, prolongs spasmolysis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This excellent paper suggests the potential of a Kampo medicine as a bowel pretreatment for colonoscopy. Evaluation of spasmolysis by colonoscopy is limited to the visual field. Combined use of fluoroscopy may enable observation to be extended to the whole intestine. Studies on the effects of distension methods other than the water method during colonoscopy are expected.

12. Abstractor and date

Kogure T, 26 January 2009, 1 June 2010.

21. Others

Reference

Saida Y, Nagao J, Nakamura Y, et al. Dai-kenchu-to and mosapride in combination with precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Nihon Daicho Kensa Gakkai Zasshi* (*Journal of the Japan Society of Colon Examination*) 2005; 22: 145-8 (in Japanese). Ichushi Web ID: 2007146750

1. Objectives

To evaluate the bowel cleansing effect of precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage solution (PG solution) combined with daikenchuto (大建中湯) and mosapride.

2. Design

Randomized controlled trial (RCT).

3. Setting

None (the authors belong to the Third Department of Surgery, Toho University School of Medicine and/or Tohokamagaya Hospital), Japan.

4. Participants

Two hundred and twenty-two patients (155 males and 67 females) who underwent colonoscopy between April 2004 and October 2004 and gave informed consent, including consent to disclose relevant information.

5. Intervention

Arm 1: treatment with 2 L of polyethylene glycol (PG) solution plus daikenchuto (大建中湯) (7.5 g; manufacturer, not specified) (n=116).

Arm 2: treatment with 2 L of PG solution plus daikenchuto (大建中湯) (7.5 g; manufacturer, not specified) and mosapride (15 mg; 3 tablets) (n=106).

PG solution was administered orally for about 2 hours, at least 6 hours prior to the colonoscopy. Daikenchuto (大建中湯) and mosapride were administered in three divided doses, starting at noon one day before colonoscopy.

6. Main outcome measures

Number of bowel movements, duration time of defecation, presence and severity of abdominal pain and nausea, ease/difficulty of taking the combined medication, adequacy of bowel preparation, and cecal intubation time.

7. Main results

The mean number of bowel movements was significantly higher in arm 2 (7.8) than in arm 1 (7.0). Defecation time tended to be slightly longer in arm 2 (3 h 18 min) than in arm 1 (2 h 59 min). No between-arm differences in abdominal pain (13% of patients in arm 1 and 17% in arm 2) and nausea (24% and 25%, respectively) were observed. The percentage of patients who reported that taking the combined medication was “difficult” or “slightly difficult” was significantly higher in arm 2 (38%) than in arm 1 (28%). No between-arm differences in mean bowel preparation scores (0.9 in both arms) and median cecal intubation times at colonoscopy (6 minutes in both arms) were observed.

8. Conclusions

The addition of mosapride offers no benefit to precolonoscopy bowel preparation with PG solution plus daikenchuto alone.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This paper follows up a previous paper that discussed the efficacy of precolonoscopy bowel preparation with PG solution plus daikenchuto: Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, an herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Digestive Endoscopy* 2005; 17: 50-3. The present trial had a large sample size and was well-designed. There are yet some drawbacks, including the following: 1) possible dependence of some results on skills of the colonoscopist is not mentioned; and 2) the method used for scoring bowel preparation quality was not described. Further studies, like this one, are anticipated.

12. Abstractor and date

Arai M, 19 January 2009, 1 June 2010.

21. Others

Reference

Arai J, Nakajima S, Fujinuma S, et al. A comparative study of bowel preparation for barium enema using divided administrations of powdered magnesium citrate with mosapride or DAIKEN CHUTOU. *Nihon Daicho Kensa Gakkai Zasshi* (*Journal of the Japan Society of Colon Examination*) 2002; 19: 170-3 (in Japanese). Ichushi Web ID: 2003041591

1. Objectives

To evaluate the effectiveness of daikenchuto (大建中湯) in bowel preparation for barium enema X-ray study.

2. Design

Randomized crossover controlled trial (RCT).

3. Setting

Ohashi Hospital, Toho University School of Medicine, Japan.

4. Participants

Forty-five patients who underwent barium enema X-ray study on an outpatient basis between March and August 2001.

5. Intervention

Arm 1: conventional bowel preparation plus oral administration of daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. on the day before the X-ray examination (n=24).

Arm 2: conventional bowel preparation plus oral administration of mosapride citrate 10 mg t.i.d. on the day before the X-ray examination (n=21).

6. Main outcome measures

The number and amount of fecal residues and the adherence of barium.

7. Main results

No significant between-arm differences were observed in the number and amount of fecal residues or in the adherence of barium.

8. Conclusions

Daikenchuto is suggested to be as effective as mosapride citrate in bowel preparation for barium enema X-ray study.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper compares the effectiveness of daikenchuto with that of mosapride citrate in bowel preparation for barium enema X-ray study. Prokinetic agents combined with conventional bowel preparation for barium enema X-ray decreases the number and amount of fecal residues and improves the adherence of barium. The authors of the present paper concluded that daikenchuto is as effective as a prokinetic agent. The effectiveness of daikenchuto in preparation for lower gastrointestinal endoscopy has been suggested in a previous report and the usefulness of shakuyakukanzoto has already been demonstrated. The use of Kampo medicines in this field is expected to increase in the future.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010.

21. Others

References

Fujinami H. Assessment of diminished persistalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): randomized placebo-controlled trial. *Nikkei Medical* (*Supplement*) 2010; 8: 34 (in Japanese).

Fujinami H, Kudo T, Nakayama Y, et al. Assessment of diminished peristalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): a randomized, placebo-controlled trial. *Gastrointestinal Endoscopy* 2010; 71: AB227.

1. Objectives

To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) as premedication for ERCP in suppressing duodenal peristalsis.

2. Design

Randomized controlled trial (RCT).

3. Setting

No. 3 Department of Internal Medicine, Toyama University Hospital, Japan.

4. Participants

Thirty patients undergoing ERCP (20 males, 10 females; mean age 66.5 years).

5. Intervention

Arm 1: shakuyakukanzoto group: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 5.0 g dissolved in 50 mL warm water (n=10).
Arm 2: anticholinergic group: scopolamine butylbromide solution 20 mg/mL intravenous injection (n=10).
Arm 3: placebo group: warm (37°C) water 50 mL (n=10).
The liquids in arm 1 and arm 3 were sprayed directly into the duodenum through an endoscope.

6. Main outcome measures

Assessment by DVD image analysis of the time required to stop peristalsis (RT: seconds) and period of cessation of peristalsis (DT: minutes).

7. Main results

Peristalsis stopped in 8/10 patients in arm 1, 10/10 in arm 2, and 0/10 in arm 3. RT was 76.0±23.9 in arm 1 and 42.4±6.1 in arm 2. DT was 11.3±4.2 in arm 1 and 14.9±5.3 in arm 2. There was no significant difference in RT and DT between these groups.

8. Conclusions

Shakuyakukanzoto is effective as premedication for ERCP in suppressing duodenal peristalsis. Its effects are similar to scopolamine butylbromide solution 20 mg/mL intravenous injection.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In clinical terms, this is a highly significant clinical trial because it assessed peristalsis in three groups during actual ERCP. Anticholinergics are generally used to reduce peristaltic action for upper gastrointestinal endoscopy and ERCP, but they are contraindicated for patients with ischemic heart disease, prostatic hypertrophy, glaucoma, etc. Such patients cannot take anticholinergics. Shakuyakukanzoto appears to be a very safe premedication that will reliably suppress peristalsis in such patients.

12. Abstractor and date

Kogure T, 31 December 2012.

21. Others

References

Fujinami H, Kajiura S, Nishikawa J, et al. The influence of duodenally-delivered Shakuyakukanzoto (Shao Yao Gan Cao Tang) on duodenal peristalsis during endoscopic retrograde cholangiopancreatography: a randomised controlled trial. *Chinese Medicine* 2017; 12: 3: 1-6. doi: 10.1186/s13020-016-0125-6. Pubmed ID: 28077962

1. Objectives

To evaluate the inhibitory effect of intraduodenal administration of shakuyakukanzoto（芍薬甘草湯）on duodenal peristalsis during endoscopic retrograde cholangiopancreatography (ERCP)

2. Design

Randomized controlled trial (RCT)

3. Setting

One university hospital (department of internal medicine), Japan

4. Participants

Twenty-eight patients undergoing ERCP

5. Intervention

Arm 1: TSUMURA Shakuyakukanzoto（芍薬甘草湯）Extract Granules 5.0 g dissolved in 50 mL of warm water (concentration, 100 mg/mL), endoscopically sprayed once towards the major papilla of the duodenum (n=15)

Arm 2: Warm water as placebo sprayed in a similar manner (n=13)

6. Main outcome measures

Duodenal peristalsis was assessed using a 4-grade scoring system: +0 = no peristalsis and easy cannulation; +1 = slight peristalsis and easy cannulation; +2 = moderate peristalsis and difficult cannulation; +3 = severe peristalsis and impossible cannulation.

Primary endpoint: Duodenal peristalsis inhibition rate (i.e., proportion of patients with inhibition of grade +0 or +1 peristalsis).

Secondary endpoints: Required time (RT [seconds]) from dosing to inhibition of peristalsis, and stop duration time (DT [minutes]) of peristalsis

7. Main results

The analysis was conducted on 10 patients in Arm 1 and 9 patients in Arm 2, after exclusion of 5 patients in Arm 1 and 4 patients in Arm 2 who had no evident duodenal peristalsis at duodenoscopy. In Arm 1, duodenal peristalsis was inhibited in 8 (80%) of the 10 patients, and the RT was 76.0 ± 23.9 seconds and the DT was 11.3 ± 23.9 minutes. In Arm 2, inhibition of duodenal peristalsis occurred in no patients (0%), with RT and DT not measurable.

8. Conclusion

Endoscopic spraying of shakuyakukanzoto as premedication for ERCP inhibits duodenal peristalsis and allows easy cannulation.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Serum potassium was measured for detection of pseudoaldosteronism, but showed no significant difference between the two groups. No safety issues were noted.

11. Abstractor's comments

This is the first report of an RCT demonstrating that endoscopically sprayed shakuyakukanzoto solution in ERCP can inhibit duodenal peristalsis and permits easy cannulation. Typically, premedication before ERCP uses intravenous anticholinergic agents or glucagon, but adverse reactions to these agents can be problematic especially in elderly patients. If endoscopically sprayed shakuyakukanzoto is effective, the approach is of great significance. The reported mean time to the onset of action was 1+ minutes and mean duration of action was 11 minutes, which seem quite acceptable in clinical practice. However, since the sample size was small in this study, confirmation in a larger sample is warranted. In addition, since the warm water described as the placebo must be obviously different in appearance from shakuyakukanzoto solution, in a strict sense the warm water should probably be described as the "control" rather than the "placebo". It may also worth conducting an RCT using an intravenous anticholinergic agent as a control.

12. Abstractor and date

Motoo Y, 1 June 2020.

21. Others

Reference

Kita T, Sumino M. The effect of dosage frequency of ethical Kampo extract formulations on drug compliance – a comparison of twice a day and three times a day prescriptions. *Igaku to Yakugaku* (*Japanese Journal of Medicine and Pharmaceutical Science*) 2011; 66: 117–22 (in Japanese). Ichushi Web ID: 2011300492 MOL, MOL-Lib

1. Objectives

To assess whether differences in ethical Kampo extract formulation dosage and dosing frequency have an effect on compliance and patient satisfaction.

2. Design

Crossover randomized controlled trial (RCT – cross over).

3. Setting

Not specified (the authors are from the Center for Environment, Health and Field Sciences, Chiba University.), Japan.

4. Participants

One hundred and five outpatients who had been taking ethical Kampo extract formulation for chronic disease or symptoms for more than one month, whose condition had stabilized, and who gave their consent.

5. Intervention

Kracie KB - stick packages (twice a day) and Kracie EK - stick packages (three times a day) containing the same ethical Kampo extract formulation as currently being taken. Administered for one week each.
Arm 1: three times a day for the first week, then twice a day for the second week (n=54).
Arm 2: twice a day for the first week, then three times a day for the second week (n=55).

6. Main outcome measures

Questionnaire on dosing circumstances (timing, whether dosing was missed, and how often dosing was missed), patients' satisfaction with frequency and dosage (5-step scale: satisfied, slightly satisfied, no change, slightly dissatisfied, dissatisfied), and lifestyle (which suits lifestyle better, twice a day or three times a day) during each period.

7. Main results

In arm 1, dosing was missed in 36 of 54 participants during the first week (three times a day) and 15 of 54 participants in the second week (twice a day), which meant a significant difference (P<0.0001). Similarly, there was a significant difference in missed dosing in arm 2 (P<0.001). The mean amount and proportion of left-over medication was 2.0±2.2 packages and 9.4±10.4%, respectively, during the three-times-a-day period and 0.4±0.8 and 2.8±6.0% respectively during the twice-a-day period. There was a significant difference in the proportion of left-over medication between the periods (P<0.0001). Participants missed their medication most often around midday (63 participants, 87.5%) during the three-times-a-day period. Thirty-nine participants (72.2%) were satisfied or slightly satisfied in arm 1, where dosage frequency decreased in the second week, while 36 participants (65.5%) were satisfied or slightly satisfied in arm 2, where dosage frequency increased in the second week. Ninety-four participants (86.2%) chose the twice-a-day medication for consistency with lifestyle, while 6 participants chose the three-times-a-day medication (5.5%) and 9 (8.3%) were indifferent.

8. Conclusions

Reducing the frequency of Kampo extract preparation dosing from three to two times a day decreases missed dosing, and therefore is an effective means of improving compliance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This RCT employed different dosing frequencies in the intervention and measured outcomes in terms of dosing compliance and satisfaction. This trial is, therefore, very instructive in that it demonstrates that such an approach can be used in an RCT. It also has great clinical significance in the sense that doctors' prescribing behavior can change patients' dosing compliance. Researchers should be encouraged to develop further research along these lines, perhaps by including symptoms among the outcomes.

12. Abstractor and date

Tsuruoka K, 31 December 2012.

21.Others

References

Horii C, Okonogi A, Okubo T, et al. Studies on bioequivalence of kakkonto decoction and its extract preparation (I)*. Shoyakugaku zasshi 2014; 68: 9-12.
Horii C, Okonogi A, Okubo T, et al. Study of the equivalence of kakkonto (葛根湯) extract formulation and decoction (II). *Natural Medicines* 2015; 69: 59-65.

1. 1. Objectives
To select the Pharmacopeia indicator components for evaluation of the equivalence of kakkonto (葛根湯) extract formulation and decoction.

2. Design
Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting
Public recruitment of healthy volunteers from a clinical study registry of a university hospital medical information network center, Japan.

4. Participants
Six healthy volunteers.

5. Intervention
Since the method of allocation to treatment arms was not described in the article, the treatment arms are described in terms of treatment regimen.
Arm 1: Administration orally of kakkonto (葛根湯) decoction (of Pueraria Root 8 g, Ephedra Herb 4 g, Jujube 4 g, Cinnamon Bark 3 g, Peony Root 3 g, Glycyrrhiza 2 g, and ginger 1 g heated and extracted in 500 mL of water, filtered through 4 layers of gauze, and adjusted to 250 mL), washout for 2 weeks, and finally administration of Kracie Kakkonto (葛根湯) Extract Fine Granules 7.5 g (n=6).
Arm 2: Administration orally of Kracie Kakkonto (葛根湯) Extract Fine Granules 7.5 g, washout for 2 weeks, and administration of its decoction (n=6).

6. Main outcome measures
Blood concentrations of ephedrine and pseudoephedrine from mao (麻黄, ephedra herb), puerarin and daidzein from kakkon (葛根, pueraria root), glycyrrhizic acid and liquiritin from kanzo (甘草, glycyrrhiza), and peoniflorin from shakuyaku (芍薬, peony root) at 15, 30, 60, 120 and 240 minutes after administration.

7. Main results
No between-group difference was found in the rates of absorption based on MRT parameters, AUC, Cmax, Tmax, and blood concentrations after taking puerarin from kakkon and ephedrine and pseudoephedrine from mao. At the same time, there was a tendency toward large variation between subjects in the daidzein from kakkon, glycyrrhizic acid and liquiritin in kanzo, and the peoniflorin from shakuyaku.

8. Conclusion
Analysis of blood concentrations of the several pharmacopoeia indicator components contained in kakkonto, namely ephedrine and pseudoephedrine from mao and puerarin from kakkon, suggests they may be indicator components for the equivalence of kakkonto extract formulation and decoction.

9. From **Kampo medicine perspective**
None.

10. Safety assessment in the article
Not mentioned.

11. Abstractor's comments
This study was conducted to evaluate the equivalence of Kampo extract with decoction, the predominant form of this Kampo treatment in daily use. When ephedrine and pseudoephedrine, the main ingredients in kakkonto, were selected as indicator ingredients, their post-dose blood concentrations and absorption rates were similar between the extract and decoction formulation. These results suggested that the various drug formulations prescribed in clinical settings were equally effective and that these indicator ingredients selected from the Japanese Pharmacopeia may be used to show the equivalence between formulations. This study is a pilot study of just six subjects assigned to two groups. , Considering the differences in treatment response between individuals, an increased number of study subjects will be required to obtain more generalizable results. ePilot studies, such as this study, which evaluate pharmacokinetics of Kampo crude ingredient absorption, are of major importance to clinicians who need to anticipate the possible effects of Kampo medicines in daily practice. Further studies are anticipated.

12. Abstractor and date
Ushiroyama T, 31 March 2017.

21. Others

Reference

Horii C, Okonogi A, Studies on bioequivalence of shoseiryuto decoction and its extract preparation (I), *Shoyakugaku zasshi* (*Journal of Natural Medicines*) 2014; 68: 65-9. Ichushi Web ID: 2014391859 MOL, MOL-Lib

1. Objectives

To evaluate the bioequivalence of shoseiryuto (小青竜湯) extract and its decoction.

2. Design

Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting

A university hospital medical center, Japan.

4. Participants

Six volunteers recruited publicly.

5. Intervention

Since the method of treatment assignment was not apparent from the article, treatment arms are defined by drug formulation.

Arm 1: Kracie Shoseiryuto (小青竜湯) Extract Fine Granules at 6.0 g for 2 weeks.

Arm 2: Shoseiryuto (小青竜湯) decoction (Ephedra Herb 3 g, Peony Root 3 g, Processed Ginger 3 g, Glycyrrhiza 3 g, Cinnamon Bark 3 g, Asiasarum Root 3 g, Schisandra Fruit 3 g, and Pinellia Tuber 6 g)

6. Main outcome measures

Blood concentrations of ephedrine and pseudoephedrine (indicator constituents of Ephedra Herb).

7. Main results

There was no significant difference in blood concentrations of ephedrine and pseudoephedrine between Arm 1 and Arm 2 at each timepoint.

8. Conclusions

Concentrations of the indicator constituents in Ephedra Herb seem to be equivalent between the shoseiryuto decoction and shoseiryuto extract.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No special problems were noted.

11. Abstractor's comments

This article showed no significant difference in blood levels of ephedrine and pseudoephedrine between the decoction and extract. As mentioned in the Discussion in this article, however, additional comparisons including comparison of paeoniflorin of Peony Root and glycyrrhizic acid of Glycyrrhiza and an examination of the influence of absorption and metabolism would make this article's results more meaningful. However, even though the decoction and extract produced the same blood levels of the indicator constituents of Ephedra Herb, the efficacy of the extract was not fully demonstrated.

12. Abstractor and date

Nakata H, 31 March 2017.

21. Others

Reference

Ueda T, Yamashita K, Nakamori Y, et al. Study of the MRSA carriage-preventing effect of Hochuekkito (TJ-41): 1st report*. *Progress in Medicine* 1999; 19: 1000-3 (in Japanese). MOL, MOL-Lib

1. Objectives

To evaluate the effects of hochuekkito (補中益気湯) on prevention of MRSA carriage, prevention of *Pseudomonas aeruginosa* carriage, prevention of infection development, neutrophil count, and C-reactive protein (CRP) value.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (Osaka University Hospital ER), Japan.

4. Participants

Twenty patients with trauma (aged 16 years or older) who were hospitalized in the above facility for at least 1 week.

5. Intervention

Arm 1: hochuekkito group (補中益気湯) (n=8 [2/10 enrolled were excluded]; male: female = 3:1; mean age, 46.8 years; injury severity score [ISS], 26.1).
Arm 2: non-treatment group (n=12; male: female = 3:1; mean age, 31.2 years; ISS, 24.0).

6. Main outcome measures

Incidences of MRSA and *Pseudomonas aeruginosa* colonization and infection, CRP level, and neutrophil count.
Bacteriological examination of nasopharyngeal swabs, sputum, midstream urine, feces, and wound scraping was performed on the 1st, 3rd and, 7th day of hospitalization.

7. Main results

There was no significant between-arm difference in neutrophil count and CRP level. Meningitis occurred in 0 of 2 treated patients and 4 of 5 untreated patients. There was no difference in the incidence of pneumonia. MRSA was detected in 1 of 8 treated patients and 4 of 12 untreated patients, although the difference was not significant. *Pseudomonas aeruginosa* was detected in 1 of 8 treated patients.

8. Conclusions

Hochuekkito tends to prevent MRSA carriage and infections in trauma patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a valuable RCT performed in an emergency setting. As admitted by the authors in the text, the timing of hochuekkito administration varied. Specification of the method, duration of hochuekkito administration, and presence or absence of blinding, would increase the reliability of this assessment. More results from their study, now underway with a new protocol, are expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

21. Others

Reference

Fujii S, Fukushi Y, Yamaguchi E, et al. A study of the addition of tokishakuyakusan during in-vitro fertilization cycles*. *Sanfujinka Kampo Kenkyu no Ayumi* (*Recent Progress of Kampo Medicine in Obstetrics and Gynecology*) 1997; 14: 121-5 (in Japanese).

1. Objectives

To evaluate the effect of ovarian stimulation by tokishakuyakusan (当帰芍薬散) (used during in vitro fertilization and embryo transfer [IVF-ET] cycles) on follicular growth, luteal function, pregnancy rate, and abortion rate.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Department of Obstetrics and Gynecology, Hirosaki University Hospital), Japan.

4. Participants

Ninety-three patients who were diagnosed as infertile at the above-mentioned institution between April 1995 and September 1996 and underwent ovarian stimulation using gonadotropin-releasing hormone (GnRH) agonist (long protocol).

5. Intervention

Arm 1: IVF-ET with ovarian stimulation using GnRH agonist (long protocol) and hMG, combined with oral administration of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals.

Arm 2: IVF-ET with ovarian stimulation using GnRH agonist (long protocol) and human menopausal gonadotropin (hMG).

6. Main outcome measures

The following measures were compared between two arms: number of dosing days and total dose of hMG as an ovarian stimulant, endometrial thickness at the last dose of hMG, number of retrieved oocytes, number of fertilized oocytes, fertilization rate, number of transferred embryos, number of cancelled transfer cycles per oocyte retrieval, pregnancy rate, abortion rate per pregnancy; blood concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), estradiol (E), and progesterone (P); and P/E ratio.

7. Main results

There were no between-arm differences in the number of dosing days and total dose of hMG as an ovarian stimulant, endometrial thickness at the last dose of hMG, number of retrieved oocytes, number of fertilized oocytes, and fertilization rate. There were trends toward higher number of transferred embryos and lower number of cancelled transfer cycles per oocyte retrieval in arm 2. There were no between-arm differences in pregnancy rate per oocyte retrieval and abortion rate per pregnancy. The blood estradiol concentration was relatively high in arm 2 throughout the treatment cycles. No significant differences were observed in the blood concentrations of PRL and progesterone and P/E ratio. The blood FSH concentration was significantly higher in arm 2 at the time of oocyte retrieval ($P<0.01$).

8. Conclusions

During IVF-ET cycles (GnRH agonist-long protocol), oral tokishakuyakusan was not found to have a clear clinical significance, but it reduced the total dose of hMG required to induce follicular growth, suggesting that this drug may stimulate secretion of FSH at the times of human chorionic gonadotropin (hCG) administration and oocyte retrieval.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The authors of this paper concluded that during IVF-ET cycles, combined tokishakuyakusan has no clear clinical significance. Yet it is noteworthy that, in IVF-ET, which we can consider an example of highly-advanced medical technology, tokishakuyakusan significantly reduced the dose of the drug used for ovarian stimulation, tended to reduce the rate of cancelled embryo transfer cycles per oocyte retrieval (to one fifth), and increased the number of transferred embryos. In this study, a sufficient number of cycles for clinical evaluation were administered, but rates of pathological conditions that require oral tokishakuyakusan were not compared between the two arms. Subgroup analyses would have been needed for, at least, cases with *oketsu* (瘀血, static blood) and *suidoku* (水毒, disorder of body fluid metabolism). I hope that the true clinical value of tokishakuyakusan-combined therapy will be found in future prospective studies that compare the effects according to the pathological conditions (with or without *ketsu-kyo* [血虚, blood deficiency], *oketsu*, or *suidoku*) with rigorous oriental medical diagnoses.

12. Abstractor and date

Ushiroyama T, 10 September 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

21. Others

References

Kaido T, Shinoda M, Inomata Y, et al. Effect of herbal medicine daikenchuto on oral and enteral caloric intake after liver transplantation: A multicenter, randomized controlled trial. *Nutrition* 2018 54: 68-75. Pubmed ID: 29747091

1. Objectives

To evaluate the efficacy and safety of daikenchuto（大建中湯）to enhance oral and enteral caloric intake after liver transplantation

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

Fourteen institutions including university hospitals, Japan

4. Participants

A total of 112 patients with end-stage liver disease.

Inclusion criteria: Patients aged ≥20 years who met the indication criteria for liver transplantation at each study center.

Exclusion criteria: Uncontrollable acute infection other than in the liver, uncontrollable malignant disease other than hepatocellular carcinoma, severe postoperative adhesions, use of psychotropic, gastrointestinal prokinetic, or other Kampo medicines, current pregnancy or lactation.

5. Intervention

Arm 1: administration of TSUMURA Daikenchuto（大建中湯）Extract Granules 15.0 g/day (5 g three times daily orally immediately before meals or enterally via tube every 8 hours) (n=57)

Arm 2: administration of placebo 15.0 g/day (5 g three times daily orally immediately before meals or enterally via tube every 8 hours) (n=55)

In both Arms 1 and 2, the treatment was given from postoperative day (POD) 1 to POD 14.

6. Main outcome measures

Primary endpoints: total oral/enteral caloric intake at POD 7, abdominal distension, abdominal pain (numeric rating scale [NRS]).

Secondary endpoints: 1) chronological changes in total oral or enteral caloric intake, 2) chronological changes in abdominal distension and abdominal pain, 3) elapsed time from extubation to first postoperative defecation, 4) quality of life (QOL) assessment using the Gastrointestinal Symptom Rating Scale (GSRS) score, 5) liver regeneration rate between POD 14 and POD 21, 6) incidence of sepsis, 7) incidence of acute cellular rejection, 8) rate of discharge from the hospital within 2 months after liver transplantation, 9) portal vein flow volume and velocity.

7. Main results

Since 2 patients in Arm 1 and 6 patients in Arm 2 dropped out of the study, the analysis was conducted in 55 patients in Arm 1 and 49 patients in Arm 2. Arm 1 and Arm 2 did not significantly differ in total caloric intake (972.6±595.3 kcal in Arm 1 and 966.0±615.7 kcal in Arm 2; P=0.957), abdominal distension (3.5±2.9, 3.2±2.8; P=0.609), and abdominal pain (3.4±2.5, 3.0±2.3; P=0.530). As for chronological changes, the total caloric intake at PODs 3, 5, 7, 10, and 14 did not significantly differ between the two arms. However, between POD 3 and POD 10, the rate of increase in the caloric intake was significantly higher in Arm 1 (P=0.023). No significant intergroup differences were shown in the chronological changes in abdominal distension or abdominal pain, elapsed time from extubation to first postoperative defecation, QOL, liver regeneration rate, incidence of sepsis, incidence of acute cellular rejection, discharge rate within 2 months after liver transplantation. On the other hand, the portal vein flow volume was significantly higher in Arm 1 than in Arm 2 at POD 10 and POD 14 (P=0.047, P=0.025). The portal vein flow velocity at POD 14 was significantly higher in Arm 1 than in Arm 2 (P=0.014). In a subgroup analysis conducted on 70 patients (i.e., 37 in Arm 1 and 33 in Arm 2) in whom oral or enteral nutrition was started within 3 days postoperatively, the total caloric intake between POD 3 and POD 7 was significantly higher in Arm 1 than in Arm 2 (P=0.014). The portal vein flow volume was significantly higher in Arm 1 between POD 0 and POD 14 (P=0.010), and the portal vein flow velocity and volume were significantly higher in Arm 1 at POD 14 (P=0.032 and P=0.030, respectively).

8. Conclusion

Administration of daikenchuto after liver transplantation may enhance total oral and enteral caloric intake in the early postoperative period, in which involvement of increased portal vein flow volume and velocity is suggested.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

There was no significant difference in the frequency of grade ≥3 major complications between the daikenchuto group and the placebo group.

11. Abstractor's comments

This is a highly objective article describing an analysis from a DB-RCT (14 study centers) on the effect of daikenchuto in enhancing oral/enteral caloric intake in patients who underwent liver transplantation. As the authors described, unfortunately no significant intergroup difference was shown in total caloric intake as a primary endpoint. However, a subgroup analysis among the patients with early resumption of oral/enteral caloric intake showed significantly higher caloric intake in the daikenchuto group. Follow-up of this finding is awaited.

12. Abstractor and date

Kogure T, 1 June 2020.

13. Structured Abstracts

(10 abstracts describing meta-analysis)

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, HepatoBiliary-Pancreatic Diseases

Reference

Zhang L, Cheng Y, Li H, et al. Meta-analysis of randomized controlled trials on the efficacy of daikenchuto on improving intestinal dysfunction after abdominal surgery. *Annals of Surgical and Treatment Research* 2018; 95: 7-15. Pubmed ID: 29963534

1. Objectives

To assess the efficacy of daikenchuto（大建中湯）in improving intestinal dysfunction after abdominal surgery.

2. Data source

PubMed, the Cochrane Library, and Embase: relevant trials up to February 10, 2017.

3. Study selection

Randomized controlled trials (RCTs) focused on daikenchuto for intestinal dysfunction in patients after abdominal surgery.

4. Data extraction

The databases were searched to identify RCTs with preoperative or postoperative administration of daikenchuto compared with placebo or no-treatment as a control, using the following key words: “Daikenchuto” or “Dai-kenchu-to” or “Dai-ken-chu-to” or “DKT” or “TJ-100” or “N100” or “TU-100”. Two reviewers separately conducted literature retrieval, data extraction, quality assessment, and statistical analysis, with inconsistency resolved by discussion and by the chief reviewer. A statistician in the author group performed the statistical analysis and reviewed the statistical section. Data analyses were conducted using RevMan version 5.3.

5. Main results

The literature search identified 435 publications. After exclusion of duplicate studies, etc., 220 studies were screened, of which 23 studies were reviewed for full text analysis. Of these, after exclusion of studies involving irrelevant populations or interventions, quasi-RCTs, and cross-over RCTs, 9 RCTs were eligible and included in the final analysis. In the 9 studies, there were 618 patients in the daikenchuto group and 594 patients in the control group. Among these 9 RCTs, 6 reported the time to first postoperative flatus, and 6 reported the time to first postoperative bowel movement. In these studies, daikenchuto significantly shortened the time to first postoperative flatus ($P = 0.001$) with significant heterogeneity between studies ($P = 0.004$), and the time to first bowel movement ($P < 0.001$) compared with control without heterogeneity.

6. Conclusions

Daikenchuto improves intestinal dysfunction after abdominal surgery.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

Not stated.

9. Abstractor’s comments

This meta-analysis of RCTs using Japanese Daikenchuto Extract Granules (prescription drug) assessed the efficacy of daikenchuto in improving intestinal dysfunction after abdominal surgery, and has a high evidence level. The authors did not use the term “Kampo medicine” but used “traditional herbal medicine,” which is unfortunate considering the values of Japanese traditional Kampo medicine and one of its basic formulations, Daikenchuto Extract Granules. In addition, as the authors state in the article, the results should be interpreted with caution, given that the studies included in the analysis involved patients who underwent a variety of surgeries and different surgical approaches, as well as treatment with daikenchuto regimens varying in dosage, method of administration, and duration of treatment, and as few as 9 studies were analyzed. Daikenchuto is the most common Kampo formulation used in Japan. Publication of additional articles would allow similar meta-analyses in the future.

10. Abstractor and date

Motoo Y, 28 August 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, HepatoBiliary-Pancreatic Diseases

Reference

Kono T, Shimada M, Nishi M, et al. Daikenchuto accelerates the recovery from prolonged postoperative ileus after open abdominal surgery: a subgroup analysis of three randomized controlled trials. *Surgery Today* 2019: 1-8. Pubmed ID: 30805720, UMIN ID: UMIN 000026292

1. Objectives

To analyze whether daikenchuto（大建中湯）accelerates the recovery from prolonged postoperative ileus after open abdominal surgery.

2. Data source

Three randomized controlled trials (RCTs) of JFMC39 (colon), JFMC40 (liver), and JFMC42 (gastric cancer) that assessed the effect of daikenchuto on prolonged postoperative ileus.

3. Study selection

A secondary analysis was conducted on the three multicenter RCTs supported by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) assessing the effect of daikenchuto on prolonged postoperative ileus after open abdominal surgery.

4. Data extraction

Of a total of 862 randomized patients with colon, liver, or gastric cancer who underwent open abdominal surgery, 122 patients were excluded from the respective studies for ineligibility or other reasons (i.e., 50 patients in JFMC39 [colon] including 32 patients who were considered to be ineligible for continuing the study, 22 patients in JFMC40 [liver] including 15 patients who were considered to be ineligible for continuing the study, and 50 patients in JFMC42 [stomach] including 15 patients who were considered to be ineligible for continuing the study). The remaining 740 patients were eligible for efficacy analysis. Of these patients, 410 patients with no bowel movement before the first meal after surgery (main analysis cohort), and the remaining 330 patients (non-main analysis cohort) were included in the subgroup analysis.

5. Main results

Main analysis cohort
Arm 1: Daikenchuto（大建中湯）15 g (n=214)
Arm 2: Placebo 15 g (n=196)
Non-main analysis cohort
Arm 1: Daikenchuto 15 g (n=158)
Arm 2: Placebo 15 g (n=161)
In the main analysis cohort, the time from the end of surgery to the first bowel movement was significantly shorter in the daikenchuto group. In the non-main analysis cohort, the time from the end of surgery to the first bowel movement did not differ between the two groups.

6. Conclusions

Daikenchuto significantly accelerated the recovery from prolonged postoperative ileus following open abdominal surgery.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

None.

9. Abstractor's comments

The key point of this subgroup analysis of 3 RCTs is that it showed the effectiveness of daikenchuto in patients with impaired intestinal motility after open abdominal surgery. On the basis of the primary endpoint, that is, the time from the end of surgery to the first bowel movement, daikenchuto was effective for prolonged postoperative ileus.

10. Abstractor and date

Nakata H, 31 October 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Ishizuka M, Shibuya N, Nagata H, et al. Perioperative administration of traditional Japanese medicine daikenchuto relieves postoperative ileus in patients undergoing surgery for gastrointestinal cancer: a systemic review and meta-analysis. *Anticancer Research* 2017; 37: 5967-74. Pubmed ID: 29061775

1. Objectives

To conduct a meta-analysis to determine the efficacy of perioperative daikenchuto (大建中湯) (DKT) administration for relief of postoperative ileus (PI) in patients undergoing surgery for gastrointestinal (GI) cancer

2. Data source

Cochrane Library, PubMed, the Web of Science, and ICHUSHI (literature published up to December 2016) were searched to collect relevant articles, using the search terms of daikenchuto, TJ-100, and TU-100.

3. Selection of study

Inclusion criteria: 1) RCTs or other comparative studies except for those with a retrospective design; 2) description of the evaluation of PI in GI cancer; 3) description of the data on the risk ratio (RR) or standardized incidence ratios (with 95% confidence interval); 4) description of sample size; 5) written in Japanese or English; 6) any types of PI (including paralytic ileus).

Exclusion criteria: 1) non-reporting of a control group, or inability to extract the number of outcome events; 2) surgery for urological, gynecological, or pediatric malignancies or non-malignancies, surgery on animal models; 3) letters, comments, correspondences, editorials, or reviews; 4) studies for which published articles had considerable overlap between authors, centers, and participants.

4. Data extraction

Full text reviews were performed independently by two authors on the basis of the inclusion and exclusion criteria and PICO criteria. Any disagreements were resolved by discussion. The same two authors also independently extracted the following information from each eligible article: first author's name, year of publication, country of the study, study design, number of PI occurrences, and sample size. If required data could not be obtained, the original authors were contacted.

5. Main results

The search yielded 661 articles, of which 165 were regarded as duplicate articles and thus excluded. Additional 468 articles were also excluded by title/abstract review and PICO. The remaining 28 articles were reviewed in full-text, of which 7 articles (6 RCTs and 1 prospective study; n=1134) were applicable to this study and thus included in this meta-analysis.

Arm 1: administration of DKT (n=588); Dose 15 g/day in 5 studies, 7.5 g/day in 1 study, and 27 g/day in 1 study

Arm 2: no administration of DKT (n=546)

PI occurred in 67 patients (11.4%) in Arm 1 and 87 patients (15.9%) in Arm 2, showing significant reduction of PI occurrence in Arm 1 compared with Arm 2 (RR=0.58; 95% CI, 0.35–0.97; P=0.04; I^2=48%).

6. Conclusion

Daikenchuto significantly reduces postoperative ileus in GI cancer patients.

7. From Kampo medicine perspective

None

8. Safety assessment in the article

Not mentioned.

9. Abstractor's comments

Daikenchuto is the Kampo medicine most commonly studied regarding its efficacy as an inhibitor of GI motility and for the prevention of ileus. This is a clinically meaningful and valuable article describing a meta-analysis showing the efficacy of daikenchuto for postoperative ileus in GI cancer patients. Evidence-based Kampo medicine has long been advocated, but evidence from meta-analyses has been limited. With increases in RCTs, further systematic reviews are desired.

10. Abstractor and date

Kogure T, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Hoshino N, Ganeko R, Hida K, et al. Goshajinkigan for reducing chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *International Journal of Clinical Oncology* 2018; 23: 434-42. Pubmed ID: 29270698

1. Objectives

To assess the efficacy and safety of goshajinkigan（牛車腎気丸）for chemotherapy-induced peripheral neuropathy (CIPN)

2. Data source

Scopus, Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, ICHUSHI

3. Selection of study

RCTs (other than cross-over or quasi-RCTs) that compared goshajinkigan with a control for CIPN

4. Data extraction

Titles and abstracts of the studies identified by the literature search were independently screened by two researchers (other than those who performed the literature search). Data were then extracted and entered into the Review Manager software, version 5.3.

5. Main results

Five RCTs were included in the analysis, consisting of 1 study of docetaxel for breast cancer, 1 study of paclitaxel for breast cancer, and 3 studies of FOLFOX (oxaliplatin-based) for colorectal cancer. As a primary endpoint, the efficacy of goshajinkigan was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) in 4 RCTs, which did not show preventive effect of goshajinkigan against grade ≥2 and ≥3 CIPN compared with the controls (no administration of goshajinkigan). The efficacy was evaluated using the Neurotoxicity Criteria of Debiopharm (DEB-NTC) in 3 RCTs (including 2 RCTs that also used CTCAE), where goshajinkigan showed a tendency to reduce the risk of grade ≥2 and ≥3 CIPN compared with the controls (no administration of goshajinkigan). As a secondary endpoint, 1 RCT evaluated CIPN subjectively on a visual analogue scale (VAS) and reported significant improvement with goshajinkigan. Goshajinkigan had no influence on hematotoxicity in 3 RCTs and tumor response in 2 RCTs. The risk of bias was assessed in the 5 studies. Three RCTs used a computer random number generator. Two RCTs used central registration. Two RCTs included a placebo arm and were reported to be double-blinded. Two RCTs followed all enrolled patients. Of the remaining 3 studies, 2 studies excluded only a few patients. Four studies were registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR).

6. Conclusion

Goshajinkigan tended to prevent persistence but not severity of CIPN.

7. From Kampo medicine perspective

None

8. Safety assessment in the article

In five RCTs that reported on adverse events, there were no serious adverse events.

9. Abstractor's comments

This is the first meta-analysis of the efficacy and safety of goshajinkigan for CIPN for which currently no effective treatment exists. CTCAE or DEB-NTC can be used to assess CIPN severity and persistence, with the former being superior for severity assessment and the latter for persistence assessment. This meta-analysis revealed that goshajinkigan tended to reduce the risk of CIPN compared with the controls when the DEB-NTC was used for assessment, but had no significant effect when the CTCAE was used for assessment. However, since the pathogenesis of CIPN can primarily involve either axonopathy (caused by taxanes) or neuronopathy (caused by platinum-based drugs), and since the severity and the time to resolution can differ depending on the pathogenesis, the analysis of CIPN irrespective of pathogenesis may be somewhat impractical. Also, since CIPN can only be measured subjectively, RCTs using objective parameters such as serum biomarkers are desired. Further, these published RCTs had high risk of bias, which should be addressed in the future.

10. Abstractor and date

Motoo Y, 1 June 2020.

2.Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Kuriyama A, Endo K. Goshajinkigan for prevention of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Supportive Care in Cancer* 2018; 26: 1051-9. Pubmed ID: 29280005, CRD42017062691

1. Objectives

To examine whether goshajinkigan（牛車腎気丸）prevents chemotherapy-induced peripheral neuropathy (CIPN) in patients receiving neurotoxic chemotherapy.

2. Data source

PubMed, EMBASE, Ichushi, the Cochrane Central Register of Controlled Trials: EMBASE was searched up to August 10, 2017, and all other databases up to August 15, 2017.

3. Study selection

Randomized controlled trials (RCTs) that assessed the efficacy and safety of goshajinkigan for prevention of CIPN in cancer patients undergoing neurotoxic chemotherapy were included.

4. Data extraction

The analysis included RCTs in patients aged ≥18 years with solid cancers who received neurotoxic chemotherapy including taxanes, vinca alkaloids, and platinum agents, and received goshajinkigan as “prophylactic” intervention against CIPN. The analysis excluded studies that examined goshajinkigan as a “treatment” in patients with CIPN. The search terms were: “goshajinkigan”, “gosha-jinki-gan”, “go-sha-jinki-gan”, “niu-che-shen-qi-wan”, and “TJ-107”. Two review authors independently conducted a literature search, data extraction, and analysis.

5. Main results

The analysis included 5 RCTs involving 397 patients. The primary outcomes were incidence of CIPN, response to chemotherapy, and adverse events related to goshajinkigan. The secondary outcomes were the proportion of patients that completed chemotherapy and disease control. When evaluated with Neurotoxicity Criteria of Debiopharm (DEB-NTC), goshajinkigan was associated with significantly reduced incidence of CIPN of grade ≥1 (risk ratio [RR] 0.43; 95% CI, 0.27 to 0.66) and grade 3 (RR 0.42; 95% CI, 0.25 to 0.71), but not grade ≥2. When assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE), goshajinkigan was not associated with reduced incidence of CIPN. Goshajinkigan did not improve response to chemotherapy.

6. Conclusions

Goshajinkigan is unlikely to prevent CIPN in patients undergoing neurotoxic chemotherapy. Given the low quality and insufficient amount of the evidence, use of goshajinkigan as standard of care is not currently recommended.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

Goshajinkigan was well tolerated based on one RCT.

9. Abstractor’s comments

This notable article describes a meta-analysis focused on the preventive effect of goshajinkigan on chemotherapy-induced peripheral neuropathy, which is difficult to manage even with modern medicine. However, it is problematic that studies of taxanes and platinum agents were not separated (3 studies of oxaliplatin, 1 study of paclitaxel, and 1 study of docetaxel). The primary pathology of neuropathy differs between these drugs, as taxanes cause damage to neuronal axons, while platinum agents cause damage to neuronal cells. Furthermore, although this article states that the results differed between the two assessment criteria (i.e., DEB-NTC vs. CTC-AE), there is a well-known inconsistency between results obtained using DEB-NTC, which prioritizes the duration of symptoms, and those obtained using CTC-AE, which prioritizes the severity of symptoms. Although the authors state the conclusion based on the results obtained using CTC-AE, one RCT with taxane-class anticancer drugs showed significant reduction of CIPN grade and incidence of CIPN after prophylactic administration of goshajinkigan, and thus it is inappropriate to conclude that this meta-analysis negates the efficacy of prophylactic administration of goshajinkigan. In addition, in terms of response to chemotherapy, not only potentiation but also a possibility of decrease should be considered. A re-analysis is desired at least after multiple similar RCTs with taxane-class anticancer drugs are published.

10. Abstractor and date

Motoo Y, 31 August 2019.

5. Psychiatric/Behavioral Disorders

Reference

Matsunaga S, Kishi T, Iwata N. Yokukansan in the treatment of behavioral and psychological symptoms of dementia: an updated meta-analysis of randomized controlled trials. *Journal of Alzheimer's Disease* 2016; 54: 635-43. PubMed: 27497482

1. Objectives

To evaluate by meta-analysis the effectiveness and safety of yokukansan (抑肝散) for behavior and psychological symptoms of dementia (BPSD).

2. Data sources

PubMed, the Cochrane Library database, PsycINFO, and clinical trial registries (ClinicalTrials.gov, ISRCTN, the WHO portal), all data sourced before April 20, 2016.

3. Research selection

Randomized controlled trials (RCTs) comparing yokukansan with usual treatment or placebo for BPSD in dementia patients were collected.

4. Data sampling

Searches were conducted using keywords such as the following: "dementia" OR "Alzheimer's" OR "Alzheimer" OR "Lewy" AND "Yokukansan" OR "Yigansan". Two of the authors checked the various inclusion and exclusion criteria, and independently analyzed the results using Review Manager (RevMan) ver 5.3.

5. Main outcome measures

The primary outcome measure for effectiveness was overall Neuropsychiatric Inventory (NPI) score; the primary outcome measure for safety was discontinuation of treatment for any reason; and the secondary outcome measure was NPI subscale (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/emotional instability, aberrant motor activity, nighttime behavior changes, eating changes).

6. Main results

Five RCTs (control groups: 4 RCTs with a no-yokukansan-administration group, and 1 RCT with a placebo group) were included in the meta-analysis. Overall NPI scores for a total of 381 BPSD patients were significantly lower in yokukansan groups compared to control groups (P=0.003). Yokukansan was useful for the BPSD sub-scores delusions, hallucinations, and agitation/aggression. However, yokukansan did not demonstrate effectiveness for Alzheimer's disease on either the overall BPSD score or the subscales. Of the cognitive functions, yokukansan improved activities of daily life (ADL), but did not improve mini-mental state examination (MMSE) scores.

7. Conclusions

Yokukansan is an effective and safe therapeutic drug for BPSD, excluding Alzheimer's disease.

8. From Kampo medicine perspective

None.

9. Safety assessment in the article

There was no significant difference between yokukansan groups and control groups for frequency of adverse effects, discontinuation due to adverse effects, or discontinuation of therapy for any reason.

10. Abstractor's comments

This meta-analysis of the effectiveness and safety of yokukansan, frequently used in clinical settings, is an important report. However, the authors have done the same meta-analysis of the groups in 4 RCTs (Hum Psychopharmacol 2013; 28: 80-6), this time adding the placebo group, which wasn't in the previous meta-analysis. The results are the same: yokukansan was verified to be effective for BPSD, excluding Alzheimer's disease. As the authors also mention, there were a number of problems: they analyzed a small number of RCTs, there were few patients registered to participate in the RCTs, and in particular, the blinding bias risk was high, the periods of yokukansan administration were short (from 4 - 12 weeks), and the concomitant use of antidementia and antipsychotic agents may have affected the results. The authors mention that research outside Japan is desirable, but achieving that goal is not simple. A question for future research is why the effectiveness of yokukansan differs by dementia type.

11. Abstractor and date

Motoo Y, 18 May 2020.

5. Psychiatric/Behavioral Disorders

Reference

Imai H, Takeshima N, Oda H, et al. Choto-san versus placebo for patients with dementia: systematic review and meta-analysis. *Psychogeriatrics* 2017; 17: 466-78. PROSPERO 2015: CRD42015027029, Pubmed ID: 28589702, Ichushi Web ID: 2018244046

1. Objectives

To assess the effectiveness and acceptability of choto-san（釣藤散）in the treatment of adults with cognitive impairment.

2. Data source

Cochrane Central Register of Controlled Trials, PubMed, the International Clinical Trials Registry Platform, the Japan Medical Abstract Society, the China National Knowledge Infrastructure: Relevant trials up to October 12, 2015.

3. Study selection

Randomized controlled trials (RCTs) evaluating chotosan（釣藤散）compared with placebo for cognitive impairment in dementia patients.

4. Data extraction

English language databases were searched using the following key words: “dementia” or “cognitive impair*” and “choto-san” or “cho-to san” or “chotosan” or “gouteng*” or “uncaria”. The Japanese database was searched using the following key words: “dementia/TH” or “dementia/AL” or “cognitive/AL” and “impair*/AL” or “釣藤散/TH” of “choto-san/AL” or “cho-to/AL” and “san/AL” or “釣藤散/TH” or “chotosan/AL” or “gouteng*/AL” or “カギカズラ属/TH” or “uncaria/AL”. The Chinese database was searched using the following key word: “gouteng”. Two review authors independently assessed the selected trials. RavMan was used for the meta-analysis.

5. Main outcome measures

Primary endpoints: Short-term (defined as 3 to 12 months) global improvement; improvement of behavioral and psychological symptoms of dementia (BPSD); number of dropouts.
Secondary endpoints: Improvement of cognitive function, activity of daily living (ADL), burden of caregivers, quality of life (QOL).

6. Main results

The meta-analysis included 3 RCTs. Of these, all used placebo as the control. Two were studies on vascular dementia, and the other was on Alzheimer’s dementia. The short-term (3–12 months) global improvement (n=199) did not significantly differ between the chotosan and control groups. Improvement of BPSD was not evaluated in any RCTs. The number of dropouts among the total of 219 patients did not differ between the chotosan and control groups. The short-term (3–12 months) cognitive function was significantly higher in the chotosan group (P=0.03). None of the RCTs reported long-term (defined as >1 year) outcomes of cognitive function. ADL (n=199) and caregiver burden (n=20) showed no significant differences between the chotosan and control groups. No study reported short-term improvement in QOL.

7. Conclusions

Chotosan can be one of the choices for the treatment of vascular dementia as it is well tolerated.

8. From Kampo medicine perspective

None.

9. Safety assessment in the article

The number of dropouts due to adverse effects and the number of patients who experienced adverse effects showed no significant differences between the chotosan and control groups.

10. Abstractor’s comments

This important article describes a meta-analysis of the efficacy of chotosan in dementia patients. In terms of the primary endpoints, short-term global improvement showed no significant difference, while no studies reported outcomes of BPSD. However, among the secondary endpoints, chotosan was more effective than placebo for short-term improvement of cognitive function, a core component of dementia, and this analysis result appeared to be important. Unfortunately, this meta-analysis included studies on different conditions (vascular dementia and Alzheimer’s dementia). More advanced research is desired in the future, such as evaluation of the efficacy of chotosan for core symptoms of Alzheimer’s dementia, which has not been studied.

11. Abstractor and date

Koike H, 9 November 2019.

5. Psychiatric/Behavioral Disorders

Reference

Kongpakwattana K, Sawangjit R, Tawankanjanachot I, et al. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. *British Journal of Clinical Pharmacology* 2018; 84 (7): 1445-56. Pubmed ID: 29637593, CRD42017056722

1. Objectives

To determine the most efficacious and acceptable treatments of agitation (including yokukansan（抑肝散） in dementia.

2. Data source

MEDLINE, EMBASE, PsycINFO, CENTRAL, Clinicaltrials. gov (-7th February 2017)

3. Study selection

Randomized controlled trials (RCTs) of treatments to alleviate agitation in people with all-types dementia, compared with either placebo or other medications were performed, and agitation was assessed using one of the following: the Cohen-Mansfield Agitation Inventory (CMAI); the Neuropsychiatric Inventory–Agitation subscale score (NPI-A); the Behavioural Pathology in Alzheimer's Disease rating scale–Aggression/agitation subscale score (BEHAVE-AD-A); or the Neurobehavioral Rating Scale–Agitation subscale score (NBRS-A).

4. Data extraction

Two reviewers independently selected articles using the above-mentioned databases. Search terms included “dementia,” “agitation,” along with other related terms. The quality of the included studies was assessed using the revised Cochrane Risk of Bias Tool for Randomized Trials. Data were pooled using meta-analysis. The primary outcome of efficacy was the 8-week response rate, defined as the proportion of people with a 50% reduction from baseline agitation score. The secondary outcome was treatment acceptability, defined as treatment continuation for 8 weeks.

5. Main results

Thirty-six RCTs comprising 5585 participants (30.9% male; mean ± standard deviation age, 81.8 ± 4.9 years) were included. In terms of 8-week response, dextromethorphan/quinidine (odds ratio [OR] 3.04; 95% confidence interval [CI], 1.63–5.66), risperidone (OR 1.96; 95% CI, 1.49–2.59), and selective serotonin reuptake inhibitors as a class (OR 1.61; 95%CI, 1.02–2.53) were found to be significantly more efficacious than placebo. Haloperidol appeared less efficacious than nearly all comparators. Yokukansan (OR 1.44; 95%CI, 0.84–2.38) showed no significant difference from placebo. Most treatments had noninferior treatment continuation compared to placebo, except oxcarbazepine, which was inferior.

6. Conclusions

Risperidone, serotonin reuptake inhibitors as a class, and dextromethorphan/quinidine demonstrated evidence of efficacy for agitation in dementia, although findings for dextromethorphan/quinidine were based on a single RCT. The findings do not support prescribing haloperidol due to lack of efficacy, or oxcarbazepine due to lack of acceptability.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

Not stated.

9. Abstractor’s comments

This article describes a systematic review and network meta-analysis of RCTs of multiple pharmacological treatments for alleviating agitation in dementia. Among the 36 RCTs included in the meta-analysis, there were 3 studies of yokukansan. Yokukansan was not significantly more efficacious compared with placebo. Given that there were 11 RCTs of risperidone, which showed significant difference, accumulation of RCTs of yokukansan in the future may lead to demonstration of efficacy.

10. Abstractor and date

Goto H, 21 September 2019.

6.Nervous System Diseases (including Alzheimer's Disease)

Reference

Matsuda Y, Kishi T, Shibayama H, et al. Yokukansan in the treatment of behavioral and psychological symptoms of dementia: a systematic review and meta-analysis of randomized controlled trials. *Human Psychopharmacology* 2013; 28: 80-6. Pubmed ID: 23359469

1. Objectives

To perform a systematic review of the efficacy and tolerability of yokukansan (抑肝散) in the treatment of behavioral and psychological symptoms of dementia (BPSD).

2. Data source

PubMed (-2012), the Cochrane Library (-2012), PsyINFO (-2012).

3. Study selection

Randomized controlled trials (RCTs) comparing yokukansan and conventional medications in patients with BPSD were collected. Reviews, non-RCTs, and experimental studies not conducted in humans were excluded.

4. Data extraction

Necessary information was retrieved from the above databases using the keywords “dementia” and “Yokukansan.” Two persons individually conducted a literature search, and another two confirmed the inclusion and exclusion criteria, respectively. Unpublished data were provided by two researchers. The neuropsychiatric inventory (NPI) score, which is a known measure of BPSD, was used as the primary outcome, and NPI subscores (delusion, hallucination, agitation/aggression, discomfort, anxiety, apathy, irritability/instability, euphoria, disinhibition, and unusual motor behavior) were used as the secondary outcomes. Cognitive function was evaluated by the Mini-Mental State Examination (MMSE), and activities of daily living (ADL) was evaluated by the Barthel index and Disability Assessment for Dementia (DAD). For the meta-analysis, Cochrane Collaboration’s Review Manager (RevMan) ver 5.0 was used.

5. Main results

Forty-six articles were collected, and 42 (6 reviews, 19 non-RCTs, and 17 animal studies) were excluded. Thus, the results of four studies were meta-analyzed. A total of 236 subjects (sample size range: 15 to 106) with a mean age 78.6 years were studied for a mean of 6 weeks. Two of the studies included patients with Alzheimer-type dementia, vascular dementia, and dementia with Lewy bodies, and the other two included only patients with Alzheimer-type dementia. Compared to conventional medications, yokukansan improved the total NPI score (P=0.0009, weighted mean difference [WMD] = –7.20, I^2=0%) and NPI subscores (delusion, hallucination, and agitation/aggression) (P<0.00001–0.0009) to a significantly greater extent. Yokukansan also improved ADL (P=0.04, standardized mean difference [SMD] = –0.32, I^2=0%) but not MMSE score. The discontinuation rates were similar between yokukansan and conventional medications.

6. Conclusions

Yokukansan improves the NPI score of BPSD and ADL score with good tolerability.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

One subject in the yokukansan group developed extrapyramidal symptoms, which were improved by reducing sulpiride (concomitant drug). Two subjects in the yokukansan group developed hypokalemia.

9. Abstractor’s comments

This meta-analysis with RevMan is a good systematic review (SR), the first SR of EKAT, and a welcome effort to promote evidence-based medicine in the field of Kampo. This study of yokukansan as a treatment for BPSD is also a hot, timely topic in clinical practice. Since the comprehensiveness of the search is a key point of SRs, the authors should disclose the search expressions to further improve the quality. They should also use a flowchart to show adopted and rejected trials with inclusion and exclusion criteria. They should provide more detailed information on conventional medications. I hope their research will be further improved.

10. Abstractor and date

Tsuruoka K, 6 June 2015.

2.Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Kuriyama A, Endo K. Goshajinkigan for prevention of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Supportive Care in Cancer* 2018; 26: 1051-9. Pubmed ID: 29280005, CRD42017062691

1. Objectives

To examine whether goshajinkigan（牛車腎気丸）prevents chemotherapy-induced peripheral neuropathy (CIPN) in patients receiving neurotoxic chemotherapy.

2. Data source

PubMed, EMBASE, Ichushi, the Cochrane Central Register of Controlled Trials: EMBASE was searched up to August 10, 2017, and all other databases up to August 15, 2017.

3. Study selection

Randomized controlled trials (RCTs) that assessed the efficacy and safety of goshajinkigan for prevention of CIPN in cancer patients undergoing neurotoxic chemotherapy were included.

4. Data extraction

The analysis included RCTs in patients aged ≥18 years with solid cancers who received neurotoxic chemotherapy including taxanes, vinca alkaloids, and platinum agents, and received goshajinkigan as “prophylactic” intervention against CIPN. The analysis excluded studies that examined goshajinkigan as a “treatment” in patients with CIPN. The search terms were: “goshajinkigan”, “gosha-jinki-gan”, “go-sha-jinki-gan”, “niu-che-shen-qi-wan”, and “TJ-107”. Two review authors independently conducted a literature search, data extraction, and analysis.

5. Main results

The analysis included 5 RCTs involving 397 patients. The primary outcomes were incidence of CIPN, response to chemotherapy, and adverse events related to goshajinkigan. The secondary outcomes were the proportion of patients that completed chemotherapy and disease control. When evaluated with Neurotoxicity Criteria of Debiopharm (DEB-NTC), goshajinkigan was associated with significantly reduced incidence of CIPN of grade ≥1 (risk ratio [RR] 0.43; 95% CI, 0.27 to 0.66) and grade 3 (RR 0.42; 95% CI, 0.25 to 0.71), but not grade ≥ 2. When assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE), goshajinkigan was not associated with reduced incidence of CIPN. Goshajinkigan did not improve response to chemotherapy.

6. Conclusions

Goshajinkigan is unlikely to prevent CIPN in patients undergoing neurotoxic chemotherapy. Given the low quality and insufficient amount of the evidence, use of goshajinkigan as standard of care is not currently recommended.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

Goshajinkigan was well tolerated based on one RCT.

9. Abstractor’s comments

This notable article describes a meta-analysis focused on the preventive effect of goshajinkigan on chemotherapy-induced peripheral neuropathy, which is difficult to manage even with modern medicine. However, it is problematic that studies of taxanes and platinum agents were not separated (3 studies of oxaliplatin, 1 study of paclitaxel, and 1 study of docetaxel). The primary pathology of neuropathy differs between these drugs, as taxanes cause damage to neuronal axons, while platinum agents cause damage to neuronal cells. Furthermore, although this article states that the results differed between the two assessment criteria (i.e., DEB-NTC vs. CTC-AE), there is a well-known inconsistency between results obtained using DEB-NTC, which prioritizes the duration of symptoms, and those obtained using CTC-AE, which prioritizes the severity of symptoms. Although the authors state the conclusion based on the results obtained using CTC-AE, one RCT with taxane-class anticancer drugs showed significant reduction of CIPN grade and incidence of CIPN after prophylactic administration of goshajinkigan, and thus it is inappropriate to conclude that this meta-analysis negates the efficacy of prophylactic administration of goshajinkigan. In addition, in terms of response to chemotherapy, not only potentiation but also a possibility of decrease should be considered. A re-analysis is desired at least after multiple similar RCTs with taxane-class anticancer drugs are published.

10. Abstractor and date

Motoo Y, 31 August 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Ishizuka M, Shibuya N, Nagata H, et al. Perioperative administration of traditional Japanese medicine daikenchuto relieves postoperative ileus in patients undergoing surgery for gastrointestinal cancer: a systemic review and meta-analysis. *Anticancer Research* 2017; 37: 5967-74. Pubmed ID: 29061775

1. Objectives

To conduct a meta-analysis to determine the efficacy of perioperative daikenchuto (大建中湯) (DKT) administration for relief of postoperative ileus (PI) in patients undergoing surgery for gastrointestinal (GI) cancer

2. Data source

Cochrane Library, PubMed, the Web of Science, and ICHUSHI (literature published up to December 2016) were searched to collect relevant articles, using the search terms of daikenchuto, TJ-100, and TU-100.

3. Selection of study

Inclusion criteria: 1) RCTs or other comparative studies except for those with a retrospective design; 2) description of the evaluation of PI in GI cancer; 3) description of the data on the risk ratio (RR) or standardized incidence ratios (with 95% confidence interval); 4) description of sample size; 5) written in Japanese or English; 6) any types of PI (including paralytic ileus).

Exclusion criteria: 1) non-reporting of a control group, or inability to extract the number of outcome events; 2) surgery for urological, gynecological, or pediatric malignancies or non-malignancies, surgery on animal models; 3) letters, comments, correspondences, editorials, or reviews; 4) studies for which published articles had considerable overlap between authors, centers, and participants.

4. Data extraction

Full text reviews were performed independently by two authors on the basis of the inclusion and exclusion criteria and PICO criteria. Any disagreements were resolved by discussion. The same two authors also independently extracted the following information from each eligible article: first author's name, year of publication, country of the study, study design, number of PI occurrences, and sample size. If required data could not be obtained, the original authors were contacted.

5. Main results

The search yielded 661 articles, of which 165 were regarded as duplicate articles and thus excluded. Additional 468 articles were also excluded by title/abstract review and PICO. The remaining 28 articles were reviewed in full-text, of which 7 articles (6 RCTs and 1 prospective study; n=1134) were applicable to this study and thus included in this meta-analysis.

Arm 1: administration of DKT (n=588); Dose 15 g/day in 5 studies, 7.5 g/day in 1 study, and 27 g/day in 1 study

Arm 2: no administration of DKT (n=546)

PI occurred in 67 patients (11.4%) in Arm 1 and 87 patients (15.9%) in Arm 2, showing significant reduction of PI occurrence in Arm 1 compared with Arm 2 (RR=0.58; 95% CI, 0.35–0.97; P=0.04; I^2=48%).

6. Conclusion

Daikenchuto significantly reduces postoperative ileus in GI cancer patients.

7. From Kampo medicine perspective

None

8. Safety assessment in the article

Not mentioned.

9. Abstractor's comments

Daikenchuto is the Kampo medicine most commonly studied regarding its efficacy as an inhibitor of GI motility and for the prevention of ileus. This is a clinically meaningful and valuable article describing a meta-analysis showing the efficacy of daikenchuto for postoperative ileus in GI cancer patients. Evidence-based Kampo medicine has long been advocated, but evidence from meta-analyses has been limited. With increases in RCTs, further systematic reviews are desired.

10. Abstractor and date

Kogure T, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, HepatoBiliary-Pancreatic Diseases

Reference

Kono T, Shimada M, Nishi M, et al. Daikenchuto accelerates the recovery from prolonged postoperative ileus after open abdominal surgery: a subgroup analysis of three randomized controlled trials. *Surgery Today* 2019: 1-8. Pubmed ID: 30805720, UMIN ID: UMIN 000026292

1. Objectives
To analyze whether daikenchuto（大建中湯）accelerates the recovery from prolonged postoperative ileus after open abdominal surgery.

2. Data source
Three randomized controlled trials (RCTs) of JFMC39 (colon), JFMC40 (liver), and JFMC42 (gastric cancer) that assessed the effect of daikenchuto on prolonged postoperative ileus.

3. Study selection
A secondary analysis was conducted on the three multicenter RCTs supported by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) assessing the effect of daikenchuto on prolonged postoperative ileus after open abdominal surgery.

4. Data extraction
Of a total of 862 randomized patients with colon, liver, or gastric cancer who underwent open abdominal surgery, 122 patients were excluded from the respective studies for ineligibility or other reasons (i.e., 50 patients in JFMC39 [colon] including 32 patients who were considered to be ineligible for continuing the study, 22 patients in JFMC40 [liver] including 15 patients who were considered to be ineligible for continuing the study, and 50 patients in JFMC42 [stomach] including 15 patients who were considered to be ineligible for continuing the study). The remaining 740 patients were eligible for efficacy analysis. Of these patients, 410 patients with no bowel movement before the first meal after surgery (main analysis cohort), and the remaining 330 patients (non-main analysis cohort) were included in the subgroup analysis.

5. Main results
Main analysis cohort
Arm 1: Daikenchuto（大建中湯）15 g (n=214)
Arm 2: Placebo 15 g (n=196)
Non-main analysis cohort
Arm 1: Daikenchuto 15 g (n=158)
Arm 2: Placebo 15 g (n=161)
In the main analysis cohort, the time from the end of surgery to the first bowel movement was significantly shorter in the daikenchuto group. In the non-main analysis cohort, the time from the end of surgery to the first bowel movement did not differ between the two groups.

6. Conclusions
Daikenchuto significantly accelerated the recovery from prolonged postoperative ileus following open abdominal surgery.

7. From Kampo medicine perspective
None.

8. Safety assessment in the article
None.

9. Abstractor's comments
The key point of this subgroup analysis of 3 RCTs is that it showed the effectiveness of daikenchuto in patients with impaired intestinal motility after open abdominal surgery. On the basis of the primary endpoint, that is, the time from the end of surgery to the first bowel movement, daikenchuto was effective for prolonged postoperative ileus.

10. Abstractor and date
Nakata H, 31 October 2019.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, HepatoBiliary-Pancreatic Diseases

Reference
Zhang L, Cheng Y, Li H, et al. Meta-analysis of randomized controlled trials on the efficacy of daikenchuto on improving intestinal dysfunction after abdominal surgery. *Annals of Surgical and Treatment Research* 2018; 95: 7-15. Pubmed ID: 29963534

1. Objectives
To assess the efficacy of daikenchuto（大建中湯）in improving intestinal dysfunction after abdominal surgery.

2. Data source
PubMed, the Cochrane Library, and Embase: relevant trials up to February 10, 2017.

3. Study selection
Randomized controlled trials (RCTs) focused on daikenchuto for intestinal dysfunction in patients after abdominal surgery.

4. Data extraction
The databases were searched to identify RCTs with preoperative or postoperative administration of daikenchuto compared with placebo or no-treatment as a control, using the following key words: “Daikenchuto” or “Dai-kenchu-to” or “Dai-ken-chu-to” or “DKT” or “TJ-100” or “N100” or “TU-100”. Two reviewers separately conducted literature retrieval, data extraction, quality assessment, and statistical analysis, with inconsistency resolved by discussion and by the chief reviewer. A statistician in the author group performed the statistical analysis and reviewed the statistical section. Data analyses were conducted using RevMan version 5.3.

5. Main results
The literature search identified 435 publications. After exclusion of duplicate studies, etc., 220 studies were screened, of which 23 studies were reviewed for full text analysis. Of these, after exclusion of studies involving irrelevant populations or interventions, quasi-RCTs, and cross-over RCTs, 9 RCTs were eligible and included in the final analysis. In the 9 studies, there were 618 patients in the daikenchuto group and 594 patients in the control group. Among these 9 RCTs, 6 reported the time to first postoperative flatus, and 6 reported the time to first postoperative bowel movement. In these studies, daikenchuto significantly shortened the time to first postoperative flatus ($P = 0.001$) with significant heterogeneity between studies ($P = 0.004$), and the time to first bowel movement ($P < 0.001$) compared with control without heterogeneity.

6. Conclusions
Daikenchuto improves intestinal dysfunction after abdominal surgery.

7. From Kampo medicine perspective
None.

8. Safety assessment in the article
Not stated.

9. Abstractor’s comments
This meta-analysis of RCTs using Japanese Daikenchuto Extract Granules (prescription drug) assessed the efficacy of daikenchuto in improving intestinal dysfunction after abdominal surgery, and has a high evidence level. The authors did not use the term “Kampo medicine” but used “traditional herbal medicine,” which is unfortunate considering the values of Japanese traditional Kampo medicine and one of its basic formulations, Daikenchuto Extract Granules. In addition, as the authors state in the article, the results should be interpreted with caution, given that the studies included in the analysis involved patients who underwent a variety of surgeries and different surgical approaches, as well as treatment with daikenchuto regimens varying in dosage, method of administration, and duration of treatment, and as few as 9 studies were analyzed. Daikenchuto is the most common Kampo formulation used in Japan. Publication of additional articles would allow similar meta-analyses in the future.

10. Abstractor and date
Motoo Y, 28 August 2019.

15. Ante/Post-partum Diseases

Reference

Koinuma M, Narikawa H, Kamei M, et al. Meta-analysis on the usefulness in postpartum control by kyukichoketsuin with methylergometrine maleate as control. *Nihon Toyo Igaku Zasshi* (*Kampo Medicine)* 2006; 57: 45-55 (in English with Japanese abstract). Ichushi Web ID: 2006097925 CiNii

1. Objectives

To evaluate the efficacy of kyukichoketsuin (キュウ帰調血飲) (KCL) in puerperal care in comparison with methylergometrine maleate (MME) by conducting a meta-analysis.

2. Data source

Articles in *Igaku Chuo Zasshi* (*Japana Centra Revuo Medicina*) (1983 – 2004) and Medline (1966 – 2004) were searched and collected using key words such as kyukichoketsuin, etc.

3. Selection of study

Inclusion criteria: 1) RCT; 2) original article; 3) study population consisting of puerperal primipara and pluripara who had normal delivery; 4) use of KCL as an intervention drug and MME as control; and 5) indices of therapeutic effect including length of uterine fundus, amount of lactation, and severity of afterbirth pains.

4. Data extraction

Data extraction was performed independently of data integration by a different researcher. Extracted data were baseline characteristics of subjects, sample size, method of randomization, method of blinding, method of administering the investigational and control drugs, dosage, number of daily doses, number of days of administration, concomitant drugs, and study endpoints. If study end points data were shown just graphically without numerical values, points on the graph with calipers were measured and converted graphical values to numerical values. The quality of selected RCTs was evaluated using the Chalmers' scoring system.

5. Main results

Of 44 RCTs gathered, 5 satisfied the selection criteria. One of these 5 overlapped and was excluded, leaving 4 RCTs for analysis. These RCTs were equivalent in quality. Analysis of three RCTs evaluating breast pain revealed that KCL significantly attenuated afterbirth pains compared with MME (combined odds ratio: 0.32 [95%CI, 0.17 – 0.60]). On day 5 after delivery, there was statistically significant difference in the length of the uterine fundus between groups treated with KLC and MME in 1 trial, but no difference based on the combined data from all 4 trials. On day 4 after delivery, neither data from individual trials nor the combined data showed significant differences in the length of the uterine fundus, suggesting comparable effect of KCL and MME on involution of the uterus. Combined data form 2 contradictory articles compared the amount of lactation on day 4 after delivery, one showed no difference and another showed that both KCL and MME increased the amount of lactation, demonstrated significantly less lactation with KCL (combined odds ratio: -8.20 [95%CI, -16.17 to -0.23]). Combined data on day 5 after delivery revealed that KCL increased the amount of lactation, although not significantly, showing the efficacies of KCL and MME for inducing lactation were similar.

6. Conclusions

Compared to MME, KCL is more effective in attenuating afterbirth pains. Analysis of safety is necessary.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

Not mentioned.

9. Abstractor's comments

The authors deserve praise for conducting a meta-analysis of RCTs restricted to Kampo medicine. As the point of meta-analysis is to gather data from all related studies, it would be better to provide the details of the gathering process; for example, whether the search was exhaustive and included a hand-search of textbooks, reference books, and specialists' opinions. Considering current movement towards evidence based medicine (EBM) in Kampo field, the authors' meta-analysis is epoch-making. It is expected that this study will stimulate further meta-analyses and systematic reviews of Kampo medicine studies.

10. Abstractor and date

Tsuruoka K, 19 February 2009, 1 June 2010.