

Evidence Reports of Kampo Treatment (EKAT)

Appendix 2014

漢方治療エビデンスレポート(EKAT) Appendix 2014

6 June 2015

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

History of version upgrades

- 6 Jun. 2015: Kampo Chiryō Ebidensu Repoto Appendix 2014 (Evidence Reports of Kampo Treatment Appendix 2012)
- 31 Dec. 2013: Kampo Chiryō Ebidensu Repoto 2013 – 402 no RCT (Evidence Reports of Kampo Treatment 2013: 402 Randomized Controlled Trials)
- 31 Dec. 2012: Kampo Chiryō Ebidensu Repoto Appendix 2012 (Evidence Reports of Kampo Treatment Appendix 2012)
- 1 Oct. 2011: Kampo Chiryō Ebidensu Repoto Appendix 2011 (Evidence Reports of Kampo Treatment Appendix 2011)
- 1 Jun. 2010: Kampo Chiryō Ebidensu Repoto 2010 – 345 no RCT (Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials)
- 1 Jun. 2009: Kampo Chiryō Ebidensu Repoto 2009 – 320 no RCT (Evidence Reports of Kampo Treatment 2009: 320 Randomized Controlled Trials)
- 1 Apr. 2008: Kampo Chiryō 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 Jun. 2007: Kampo Chiryō 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 Jul. 2005: Kampo Chiryō niokeru Ebidensu Repoto (Evidence Reports of Kampo Treatment) (*Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2005: 56, EBM supplementary issue)
- 20 Sept. 2002: Kampo Chiryō 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
2015.6.6	Evidence Reports of Kampo Treatment, Appendix 2014 (EKAT appendix 2014)	From EKAT 2013 2013 (First half)	513 ²⁾	418 ^{1), 2)}	167
2013.12.31	Evidence Reports of Kampo Treatment, 2013 - 402 Randomized Controlled Trials	1986-2012 (First half)	494 ³⁾	403 ^{1), 3)}	159
2012.12.31	Evidence Reports of Kampo Treatment, Appendix 2012 (EKAT appendix 2012)	From EKAT 2011 2011 (First half)	457	379 ^{1), 4)}	150 ⁴⁾
2011.10.1	Evidence Reports of Kampo Treatment, Appendix 2011 (EKAT appendix 2011)	From EKAT 2010 2010 (First half)	432	360 ^{1), 5)}	-
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 ver1.1	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 meta-analysis

²⁾ Total of all references added in EKAT 2013 and EKAT Appendix 2014.

³⁾ Because literature search methods were improved in EKAT 2013, the additions subsequent to EKAT Appendix 2012 may not necessarily be references subsequent to the first half of 2011.

⁴⁾ Total of all references added or removed in EKAT 2010, EKAT Appendix 2011 and EKAT Appendix 2012.

⁵⁾ Total of all references added in EKAT 2010 and EKAT Appendix 2011.

Notes on the current version

The Task Force for Evidence Reports (ER -TF) of the Japan Society for Oriental Medicine (JSOM), Committee for Evidence-based Medicine (EBM) gathers comprehensive data on randomized controlled trials (RCTs) of Kampo formulations in Japan, compiles structured abstracts (SAs), and then publishes them as Kampo Chiryō Ebidensu Repoto (Evidence Reports of Kampo Treatment: EKAT). The Task Force for Evidence Reports was amalgamated with the Task Force for Clinical Practice Guidelines in June 2009 because RCTs of Kampo prescriptions were used for preparation of Clinical Practice Guidelines and it was considered that the relation between the two was strong. Nevertheless, it was determined that the Task Force for Evidence Reports return to activity as a separate body in June 2014 for project management reasons.

As indicated in "History of version upgrades" on the previous page, Kampo Chiryō Ebidensu Repoto 2013 - 402 no RCT- (EKAT 2013) was published on December 31, 2013, and included 402 RCTs and 1 meta-analysis published between 1986, when the specifications for the quality of Kampo formulations for prescription came into current effect, and the first half of 2012. Of the RCTs published in EKAT 2014 Appendix over about one year there are an additional 17 SAs (16 RCTs and one meta-analysis) and three revised SAs. Additionally, although references by Hirayama et al in 1990 and 1992 had been treated as separate RCTs and had separate SAs, it became clear that they were based on the same study, so the SAs were combined into one. This resulted in a decrease in the number of SAs by one. Furthermore, another SA was removed for reasons detailed below. The previous page presents a summary of the figures to do with the references and SAs in this Appendix.

Although the website has not been updated since EKAT 2013, the Google search engine available on the EKAT website allows users to search all SAs in both EKAT 2013 and the EKAT Appendix 2014. The society's past practice has been to make broad selections of references for EKAT on the principle of inclusiveness so as not to miss any RCT. This has meant that references were included in EKAT if they indicated the publisher's name and included content sufficient for an SA to be written, even if they were academic society articles or similar. But since 2010, the Novartis' Diovan scandal and the STAP cell falsification scandal have prompted heightened concerns about medical paper authorship and conflict of interest (COI). The society has found among Kampo prescription RCTs differences in the results and the numbers of patients in articles by journalists and the finished reference concerned, and in some cases it has not been possible to follow the link from the RCT in an article to the reference. In March this year, the Japanese Association of Medical Journal Editors, a part of the Japanese Association of Medical Sciences, published its *Medical Journal Editing Guidelines* (<http://jams.med.or.jp/guideline>).

Therefore, from EKAT Appendix 2014 on, the society will not include reports that are in article form and whose authors are clearly journalists. In addition, past SAs that were based on reports in article form will be revised when the finished reference is gathered, and if a reference is added to a past SA, the past SA will be removed and a new SA will be written.

The society again plans to publish them as an Appendix in the next EKAT and has decided to conduct the reference search at a different time from then on. In the past, the reference search has been conducted in November, however, differences have emerged between the EKAT name and the time of publishing, causing confusion. For example, because the reference search for this Appendix was conducted in November 2013, it does not include references in journals published in the latter half of 2013. Nevertheless, this Appendix is called EKAT Appendix 2014, which can be a cause for misunderstanding. To resolve this issue, the society plans to conduct the reference search for the next EKAT in April 2015, prepare SAs for references from most of the journals published in 2014, and publish the Japanese edition under the title EKAT Appendix 2015, before the end of 2015.

Fourth Phase (June 2013 -)
Task Force for Evidence Reports (ER-TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

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Yukio KANEKO	Kaneko Clinic (vice-trustee in charge of Committee for EBM)

Lists of Structured Abstracts

<<EKAT Appendix 2014: Structured Abstracts describing RCTs and the References Reporting Them>>

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

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
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. <i>Surgery Today</i> 2012; 42: 646-51.	RCT	I	10
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. <i>Hepato-Gastroenterology</i> 2012; 59: 2290-4.	RCT	N	11
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, 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. <i>Evidence-based Complementary and Alternative Medicine</i> 2013: 1-10.	RCT	N	12
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. <i>Psychiatry</i> 2013; 23: 130-8 (in Japanese with English abstract).	quasi-RCT	N	13
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. <i>American Journal of Respiratory and Critical Care Medicine</i> 2013; 187: A5694.	RCT	C	14
G62.9	To investigate the inhibitory effect of TSUMURA Goshajinkigan (牛車腎氣丸) Extract Granules(TJ-107) on oxaliplatin-induced peripheral neuropathy (OPN).	goshajinkigan (牛車腎氣丸)	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. <i>Cancer Chemotherapy and Pharmacology</i> 2013; 72: 1283-90.	DB-RCT	N	15
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. <i>Journal of Traditional Medicines</i> 2013; 30: 72-81.	DB-RCT	I	16
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. <i>Biomedicine & Aging Pathology</i> 2012; 2: 81-4.	RCT-cross over	N	17
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. 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. <i>Alimentary Pharmacology and Therapeutics</i> 2013; 37: 776-85.	DB-RCT	C	18
K59.8	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.* <i>Shokaki Geka (Gastroenterological Surgery)</i> 2013; 36: 1315-24.	RCT	N	19

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K91.0	To verify the inhibitory effect of goreisan (五苓散) on nausea and vomiting after surgery under general anesthetic.	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	20
K91.9	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	21
N95.1	To verify the clinical efficacy of porcine placental extract on shoulder stiffness in climacteric women.	porcine placental extract	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)	RCT	N	22
N95.1	To verify the clinical efficacy of porcine placental extract on shoulder stiffness in postmenopausal women taking hormone replacement therapy.	porcine placental extract	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)	RCT	N	23
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	24

Meta-analysis

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	25
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Revisions of Already Included References

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
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	26
			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-chiryō (Kampo & the Newest Therapy) 2013; 22: 113-19 (in Japanese).		N	
G62.9	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 Journal of Clinical Oncology 2011; 16: 322-7.	RCT	N	27
			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	

K73.2	To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of 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. <i>Gastroenterologia Japonica</i> 1989; 24: 715–9.	DB-RCT	C&I	28
			Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis. <i>Kan-Tan-Sui</i> 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*. <i>Kan-Tan-Sui</i> 1992; 25: 551–8 (in Japanese).		I	
L20.9	To evaluate the efficacy and safety of hochuekkito (補中益氣湯) in patients with qikyo (氣虛, qi deficiency) associated with atopic dermatitis (AD).	hochuekkito (補中益氣湯)	Furue M, Tanaka Y, Kobayashi H, et al. Efficacy of Kanebo Hochuekkito in patients with atopic dermatitis with “qikyo” – a multicenter, double-blind trials*. <i>Arerugi (Japanese Journal of Allergology)</i> . 2005; 54: 1020 (in Japanese).	DB-RCT	N	29
			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. <i>Evidence-based Complementary and Alternative Medicine</i> 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 –*. <i>Nishinihon Hifuka (the Nishinihon Journal of Dermatology)</i> 2012; 74: 642-7 (in Japanese).		I	

List of Excluded References

(Appendix 2014)

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 (Japania 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).

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
C18.9	Evaluation of the anti-inflammatory effect and shortening of time until first flatus of daikenchuto (大建中湯) in colorectal cancer patients following laparotomy	daikenchuto (大建中湯)	Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto. * <i>Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai (5th Annual Meeting of the JGA)</i> . 2009; 9-10 (in Japanese)	6) Although included as structured abstract in the EKAT 2013, this study was excluded in the Appendix 2014 because it was reported in article form.	N
E88.9	Effect of bofutsushosan (防風通聖散) on metabolic syndrome	bofutsushosan (防風通聖散)	Wakasugi A. Kampo clinical research on metabolic syndrome*. <i>Uehara Kinen Seimei Kagaku Zaidan Kenkyu Houkokusyu</i> . 2012; 26: 105 (in Japanese)	5)	I
G47.8	Evaluation of the efficacy and safety of yokukansan (抑肝散) on REM sleep behavior disorder	yokukansan (抑肝散)	Shinobe R. <i>Efficacy of yokukansan on REM sleep behavior disorder (RBD) – comparison with clonazepam –</i> . <i>Kampo Igaku (Science of Kampo Medicine)</i> . 2013; 37: 22-5 (in Japanese)	6) Reported in article form.	N
G47.9	Effect of yokukansankachimpihange (抑肝散加陳皮半夏) on sleep in healthy adult males	yokukansankachimpihange (抑肝散加陳皮半夏)	Kambayashi T, Aizawa R, Hayashi Y, et al. <i>Effect of yokukansankachimpihange on sleep in healthy adult males*</i> . <i>Kampo Igaku (Science of Kampo Medicine)</i> . 2013; 37: 34-37 (in Japanese)	6) Reported in article form.	N
I25.9	Effect of Kampo medications on recovery of cerebrovascular function	keishibukuryogan (桂枝茯苓丸) tokakujokito (桃核承氣湯) 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. <i>Cerebrovascular diseases</i> . 2012; 34 Suppl 1: 36.	1)	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
J20.0	Tolerability and effect of EPs 7630 on 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. <i>Pediatrics International</i> 2012; 54: 219-26	2)	I
K51.2	Remission effect of a herbal preparation on ulcerative proctitis	Xilei San suppository	Fukunaga K, Ohda Y, Hida N, et al. Placebo controlled evaluation of Xilei San, a herbal preparation in patients with intractable ulcerative proctitis. <i>Journal of gastroenterology and hepatology</i> . 2012; 27: 1808-15.	2)	C
K91.3	Effectiveness of daikenchuto (大建中湯) on bowel motility and on 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). <i>Japanese Journal of Clinical Oncology</i> 2013; 43: 436-8	5)	N

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

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 5HT₃ 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

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.

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

4. Metabolism and Endocrine Diseases

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/m² before treatment to 33.7 ± 6.6 kg/m² after six months of treatment, while in arm 2 the scores were 34.9 ± 7.9 kg/m² before administration and 34.9 ± 8.1 kg/m² 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

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/m² 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.

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.

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

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

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.

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.

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 ($P<0.05$). 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 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. A future clinical trial involving the effectiveness of daikenchuto and its administration timing in the perioperative period is anticipated.

12. Abstractor and date

Okabe T, 6 June 2015

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

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

14. Diseases of the Musculoskeletal System and Connective Tissue

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.

13. Diseases of the Musculoskeletal System and Connective Tissue

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.

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.

Meta-analysis

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.

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-chiryō (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.

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

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 Kampo 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.

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.

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 –*. *Nishinohon Hifuka (the Nishinohon 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.