

Perioperative Administration of Traditional Japanese Herbal Medicine *Daikenchuto* Relieves Postoperative Ileus in Patients Undergoing Surgery for Gastrointestinal Cancer: A Systematic Review and Meta-analysis

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Abstract. *Aim:* Although it has been widely demonstrated that administration of *Daikenchuto* (DKT), a traditional Japanese herbal medicine, improves gastrointestinal (GI) motility in patients undergoing abdominal surgery, few studies have investigated the efficacy of perioperative DKT administration for relief of postoperative ileus (PI) in patients undergoing surgery for GI cancer. Therefore, the aim of this study was to investigate whether perioperative administration of DKT relieves PI in patients with GI cancer. *Patients and Methods:* We performed a comprehensive electronic search of the literature (Cochrane Library, PubMed, the Web of Science and ICHUSHI) up to December 2016 to identify studies that had shown the efficacy of perioperative DKT administration for relief of PI in patients with GI cancer. To integrate the individual effect of DKT, a meta-analysis was performed using random-effects models to calculate the risk ratio (RR) and 95% confidence interval (CI), and heterogeneity was analyzed using I^2 statistics. *Results:* Seven studies involving a total of 1,134 patients who had undergone GI cancer surgery were included in this meta-analysis. Among 588 patients who received DKT perioperatively, 67 (11.4%) had PI, whereas among 546 patients who did not receive DKT perioperatively, 87 (15.9%) had PI. Perioperative administration of DKT significantly reduced the occurrence of PI (RR=0.58, 95% CI=0.35-0.97,

p=0.04, $I^2=48\%$) in comparison to patients who did not receive DKT or received placebo. Conclusion: The result of this meta-analysis suggests that perioperative administration of DKT relieves PI in patients undergoing surgery for GI cancer.

Daikenchuto (DKT) is a well-known traditional Japanese herbal (*kampo*) medicine for improvement of gastrointestinal (GI) function (1-4). DKT extract powder is manufactured from an aqueous extract containing 2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng radix, and 88.9% maltose syrup powder derived from rice (Tsumura & Co., Tokyo, Japan) (3). Because the medicinal effects of DKT have been established through a delicate balance of these three herbal ingredients over many centuries, DKT has not yet been fully accepted by all modern physicians, including those in both eastern (5) and western countries.

However, over the past decade, basic studies using animal models have revealed that the effects of DKT on GI function are mediated by cholinergic and serotonergic nerves (6). Several studies have demonstrated that DKT enhances GI motility both *in vitro* (7, 8) and *in vivo* (6, 9, 10), as well as increasing intestinal blood flow (2, 11), reducing the blood ammonia level after hepatectomy (12), and exerting anti-inflammatory effects (13, 14). Similarly, recent clinical studies have demonstrated that DKT improves not only GI motility after surgery (15, 16) but also attenuates the progression of adhesional bowel obstruction due to abdominal surgery (17, 18).

Although several randomized controlled trials (RCTs) have confirmed the effects of DKT (19), previously demonstrated in animal models (13, 20), for improving postoperative GI motility in patients undergoing abdominal surgery (21-25), few studies have investigated whether DKT reduces the occurrence of postoperative ileus (PI) in patients undergoing surgery for GI cancer as a primary end-point. Therefore, it seems reasonable to assume that, if DKT

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improves postoperative GI motility, this effect would also reduce the occurrence of PI.

In the present study, we performed a meta-analysis to investigate whether perioperative administration of DKT reduces the incidence of PI in patients undergoing surgery for GI cancer.

Materials and Methods

Search strategy. A systematic literature search was conducted using Cochrane Library, PubMed, the Web of Science, and the Japanese ICHUSHI medical database covering articles published up to December 2016. Therefore, the search was not restricted to English language publications. The search terms used were “*Daikenchuto*” (using English and Chinese characters), “DKT”, “TJ-100” and “TU-100”. Of those identified as potentially relevant, complete articles were retrieved and evaluated for inclusion. References from all the relevant articles were hand-searched for additional studies.

The meta-analysis and search strategy complied with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2010 (26). Therefore, the PICO criteria for this study were: Patients [P]: patients undergoing surgery for GI cancer; Intervention [I]: perioperative administration of DKT; Comparison [C]: Control group without perioperative administration of DKT or with perioperative administration of placebo; Outcome [O]: relief of PI in patients with GI cancer receiving DKT perioperatively.

Inclusion and exclusion criteria. The inclusion criteria were as follows: (i) RCTs or other comparative studies except for those with a retrospective design. (ii) Studies that provided data for evaluation of PI in patients undergoing surgery for GI cancer. (iii) Studies that provided data for calculating the risk ratio (RR) or standardized incidence ratios with 95% confidence interval (CI). (iv) Studies that provided the sample size and other appropriate data. (v) Articles had to be written in English or Japanese. (vi) All types of ileus stated in the articles were regarded as PI. Therefore, paralytic ileus was included as PI in the study.

The exclusion criteria were: (i) Non-reporting of predefined outcomes for two groups, such as patients with or without DKT, or inability to extract the number of outcome events from the published results. (ii) Surgery for urological, gynecological and pediatric malignancies or for non-malignancies, and surgery involving animal models. (iii) Articles that were letters, comments, correspondences, editorials and reviews. (iv) Studies for which the published articles had considerable overlap between authors, centers and participants.

Study selection and data extraction. The full text reviews were performed independently by the two authors (M.I. and N.S.) on the basis of the inclusion and exclusion criteria and PICO. Any disagreements were resolved by discussion and consensus. The same two authors also independently extracted the following information from each eligible article: the first author’s name, the year of publication, the nation in which the study was performed, the study design, the number of PI occurrences and sample size. If the necessary data could not be extracted from the publication, we contacted the original authors directly whenever possible.

Data synthesis and statistical analysis. Review Manager (ver. 5.3) for Windows (downloaded from <http://ims.cochrane.org/revman/download>) was used for this meta-analysis. Because there were six RCTs among the seven selected articles, a random-effect model was used rather than a fixed-effect model.

Dichotomous variables were analyzed by assessing the risk ratio (RR) of PI occurrence in patients treated with DKT compared with those who were not treated with DKT as a control group, along with the 95% confidence interval (95% CI). A RR of less than 1 favored patients who were treated with DKT.

Statistical heterogeneity was complemented with the I^2 statistic, which qualified the proportion of the total variation across studies that was due to heterogeneity rather than chance. The presence of publication bias was assessed by funnel plot. Forest plots were demonstrated in order by weight of each study. A p -value of less than 0.05 was considered statistically significant.

Ethical approval was not required because this was a meta-analysis of previously published literature.

Results

Study identification and eligibility. An electronic search yielded 661 articles, of which 165 were regarded as duplicated articles based on a title search. Among the remaining articles, 468 were excluded by title/abstract review on the basis of their selection criteria and PICO. The remaining 28 articles were screened using full text review, after which seven studies including a total of 1,134 patients were regarded as suitable for inclusion in the data synthesis. The selection process for exclusion is demonstrated in Figure 1.

Characteristics of included studies. Three out of the seven included studies involved patients who underwent colon or colorectal cancer surgery (21, 27, 28). Among the remaining four studies, two involved patients who underwent surgery for gastric cancer (23, 24) and two involved patients who underwent surgery for tumors of the pancreas head and periampullary tumors (29, 30). These seven studies comprised six RCTs (21, 23, 24, 27, 28, 30), and one prospective study (29). All studies originated from Japan: five were written in English (21, 23, 24, 29, 30) and two in Japanese (27, 28). Among the seven studies, two involved patients who all underwent open surgery (21, 27) and two studies included a proportion of patients who underwent laparoscopic surgery (23, 28). The basic characteristics of the seven included studies are shown in Tables I-III.

Association between perioperative administration of DKT and occurrence of PI after GI surgery. Data on occurrence of PI in patients undergoing surgery for GI cancer were available for all seven studies.

With regard to the daily dose of DKT administered, five studies recommended 15 g/day (21, 24, 28-30) and one recommended a half dose (7.5 g/day) (23). Only one study recommended a dose of 27 g/day (27), because DKT it was provided by another company and included a larger amount of maltose powder.

DKT administration was started after surgery in all studies, except for two in which it was started before surgery (29, 30). Among the seven studies, DKT administration was

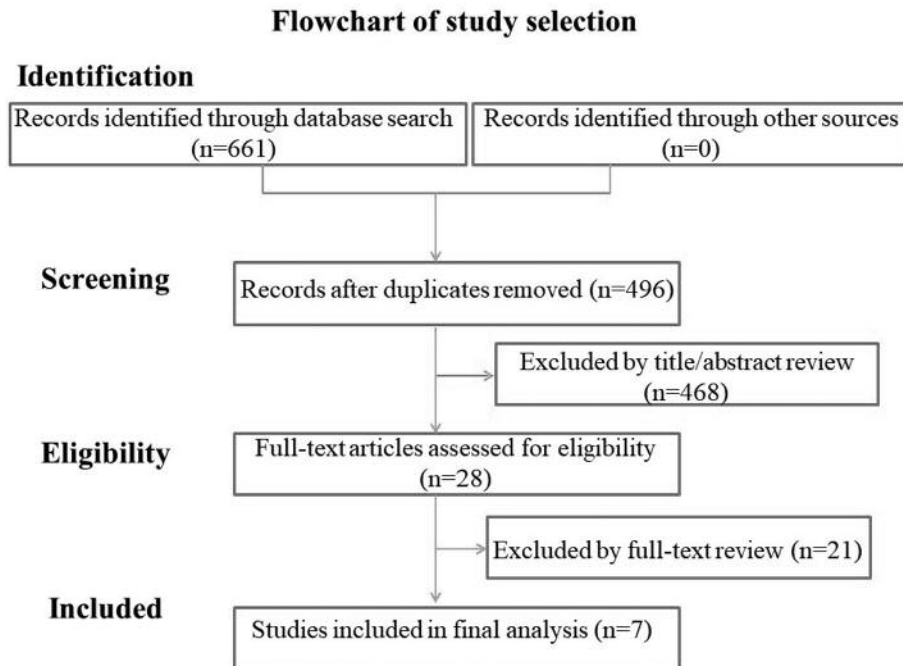


Figure 1. Flow diagram detailing search strategy and identification of studies used in data synthesis.

Table I. Basic characteristics of the included studies.

Author	Year	Nation	Language	Design	Center	Disease	Surgery	Procedure
Takagi <i>et al.</i> (27)	2007	Japan	Japanese	RCT	Single	CRC	Colectomy	Open
Fujii <i>et al.</i> (28)	2011	Japan	Japanese	Quasi-RCT	Single	CRC	Colectomy	L&O
Yoshikawa <i>et al.</i> (24)	2015	Japan	English	RCT	Multi	GC	TG	Undetermined
Akamaru <i>et al.</i> (23)	2015	Japan	English	RCT	Multi	GC	TG	L&O
Katsuno <i>et al.</i> (21)	2015	Japan	English	RCT	Multi	CC	Colectomy	Open
Okada <i>et al.</i> (29)	2015	Japan	English	Prospective	Single	PT	PD	Undetermined
Okada <i>et al.</i> (30)	2016	Japan	English	RCT	Multi	PT	PD	Undetermined

CC: Colon cancer; CRC: colorectal cancer; GC: gastric cancer; L&O: laparoscopic and open surgery; PT: pancreatic tumor (including periampullary tumors); PD: pancreatoduodenectomy; RCT: randomized controlled trial; TG: total gastrectomy.

Table II. Summary of administration of Daikenchuto (DKT) and endpoints of the included studies.

Author	Term of DKT administration	DKT dose, g/day	Investigated endpoints	Control	Study code
Takagi <i>et al.</i> (27)	Undetermined	27	A, B	None	None
Fujii <i>et al.</i> (28)	From 2 POD to first visit day after discharge	15	A, B, C, D, E	None	None
Yoshikawa <i>et al.</i> (24)	From 1 or 2 POD to 12 POD	15	A, B, C, E, F, G	Placebo	UMIN 000004693
Akamaru <i>et al.</i> (23)	Undetermined, 3 months	7.5	A, C, F, G, I	None	UMIN 000002090
Katsuno <i>et al.</i> (21)	From 2 POD to 8 POD	15	A, C, F, H	Placebo	UMIN 000001592
Okada <i>et al.</i> (29)	From preoperative day 3 to 7 POD	15	A, B, C, D, E	None	UMIN 000005056
Okada <i>et al.</i> (30)	From preoperative day 3 to 14 POD	15	A, B, C, D	Placebo	UMIN 000007975

Endpoint: A: occurrence of ileus, B: Occurrence of adverse effect, C: period until both gas and stool were passed, D: period of hospital stay after surgery, E: anti-inflammatory action, F: frequency of bowel movement, G: quality of life, H: stool form, I: quantity of bowel gas.

Table III. Summary of incidence of postoperative ileus (PI) according to administration of Daikenchuto (DKT) in the included studies.

Author	DKT			No DKT		
	Total, n	PI, n	No PI, n	Total, n	PI, n	No PI, n
Takagi <i>et al.</i> (27)	86	1	85	87	5	82
Fujii <i>et al.</i> (28)	57	1	56	40	4	36
Yoshikawa <i>et al.</i> (24)	96	3	93	99	2	97
Akamaru <i>et al.</i> (23)	41	1	40	40	2	38
Katsuno <i>et al.</i> (21)	174	20	154	162	25	137
Okada <i>et al.</i> (29)	30	6	24	15	11	4
Okada <i>et al.</i> (30)	104	35	69	103	38	65

performed within 14 days after surgery in three of them (21, 24, 29). Of the remaining four studies (23, 27, 28, 30), the term of DKT administration was only specifically defined in two studies (23, 30).

Among 588 patients who were administered DKT perioperatively, 67 (11.4%) had PI, whereas among 546 patients who did not receive DKT perioperatively, 87 (15.9%) had PI. Perioperative administration of DKT significantly reduced the occurrence of PI (RR=0.58; 95% CI=0.35-0.97; $p=0.04$; $I^2=48\%$) in comparison to patients who did not receive it (Figure 2a). The basic funnel plot of the studies included in this meta-analysis indicated no evidence of publication bias, in view of its symmetry (Figure 2b).

Discussion

The incidence of PI may be influenced by several perioperative factors. Hence, in order to minimize PI, several techniques have been developed in the field of abdominal surgery. Among them, an adhesion barrier film is frequently used for preventing adhesional ileus (31, 32). In fact, in this meta-analysis, an adhesion barrier film was used in about 80% of patients in one study (total gastrectomy for gastric cancer) (24) and in about 50% of patients in two studies (open colectomy for colon cancer and PD for periampullary tumor or tumor of the pancreas head) (21, 30). Therefore, if an adhesion barrier film really reduces the occurrence of adhesional ileus (32, 33), the effect of DKT would have been decreased in those two studies. Similarly, because there was a possibility that other studies may also have used an adhesion barrier film to prevent PI, the overall occurrence of PI in this meta-analysis may have been influenced by this factor.

Similarly, the spread of laparoscopic surgery has provided a number of benefits in the field of abdominal surgery. In particular, it is considered that laparoscopic surgery can reduce the incidence of PI in comparison to open surgery (34-37). Laparoscopic surgery with a small wound can reduce the occurrence of intra-abdominal adhesion.

Moreover, as the procedure is performed in the moist environment of the closed abdominal cavity, movement of the GI tract recovers sooner after surgery in comparison with open surgery performed in the dry atmosphere of the operation room.

In the study by Akamaru, about 40% of the patients underwent laparoscopic surgery (23). Similarly, the study by Fujii included patients who underwent laparoscopic surgery (28). Therefore, as laparoscopic surgery may reduce the incidence of PI, the effect of DKT in these two studies may also have been decreased (23, 28). In fact, although laparoscopic surgery is commonly employed in several types of abdominal surgery, a recent study that investigated the effect of DKT was designed in the setting of open surgery (25).

Despite the fact that the effect of DKT would have been decreased by several clinical background factors such as usage of an adhesion barrier film and performance of laparoscopic surgery, the results of this meta-analysis clearly indicated that perioperative administration of DKT reduced the incidence of PI in patients undergoing surgery for GI cancer. In fact, among the 7 studies selected for this meta-analysis, only one, which investigated the effect of DKT in patients undergoing pancreaticoduodenectomy (PD), demonstrated a significant difference in the occurrence of paralytic ileus between patients who received and did not receive DKT (29). Although it was not specifically stated whether or not an adhesion barrier film had been used, PD is commonly performed by open surgery and it is regarded as one of the most invasive forms of abdominal surgery. Therefore, it is acceptable that the effect of DKT would be more noticeable in patients undergoing complicated and highly invasive surgical procedures such as PD. However, a recent double-blind, randomized, placebo-controlled trial showed that DKT did not improve recovery from paralytic ileus after PD (30).

Hepatic resection is also regarded as one of the most invasive procedures in the field of abdominal surgery. However, a recent study which investigated the efficacy of

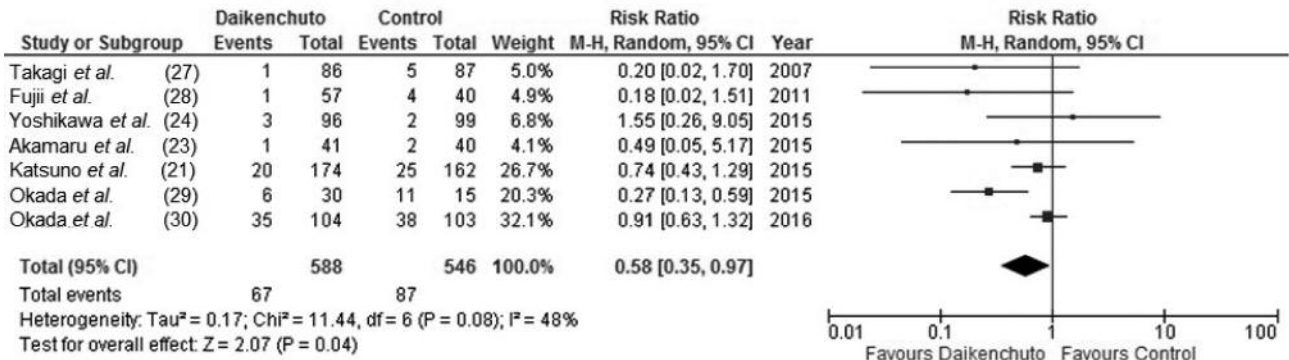
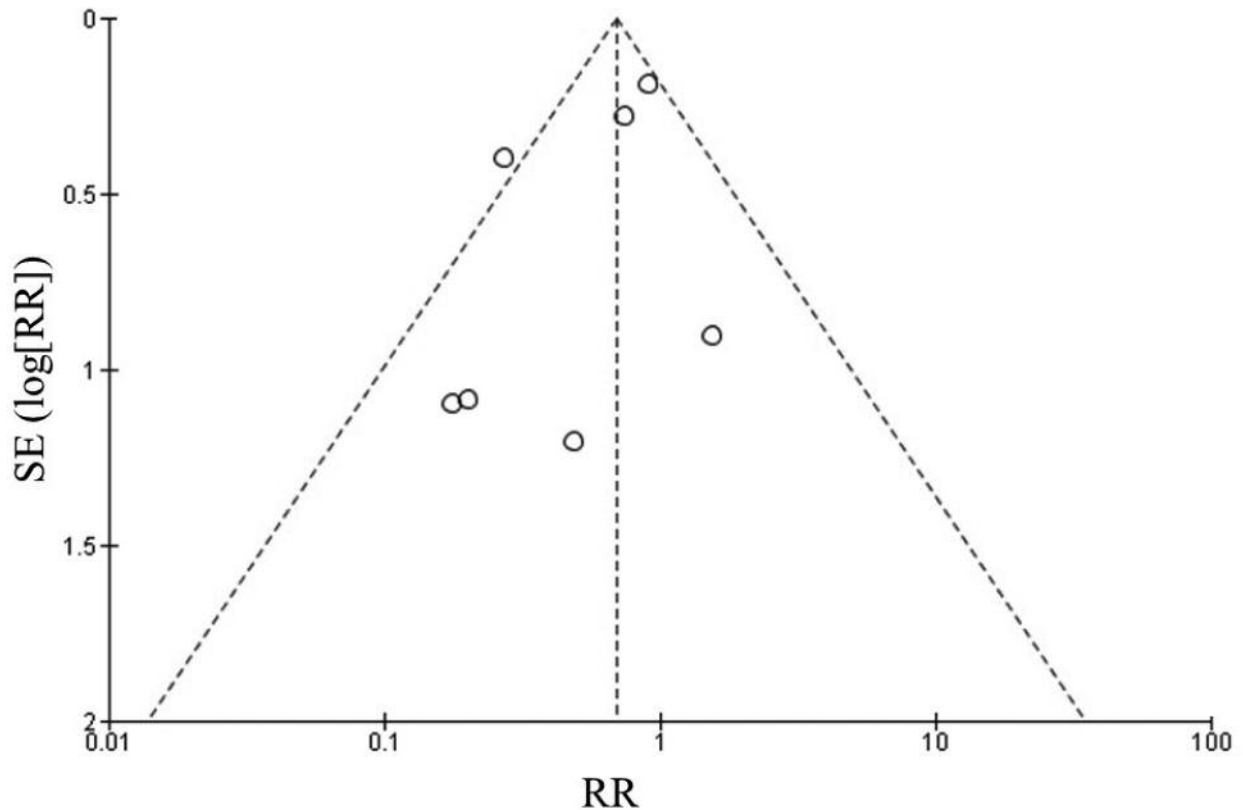
a**b**

Figure 2. a. Forest plot of the occurrence of postoperative ileus (PI) in patients with gastrointestinal cancer. b. Funnel plot analysis of patients with postoperative ileus.

DKT in patients undergoing hepatic resection (UMIN000003103) showed that there was no significant difference in the occurrence of PI between patients who received DKT (4/108, 3.7%) and those who did not (2/101,

2.0%) ($p=0.684$) (38). Because there is no need for GI reconstruction in most patients who undergo hepatic resection, the efficacy of DKT for preventing PI would be less noticeable in such patients.

With regard to administration of DKT, patients received DKT perioperatively within 14 days in three out of the seven studies (21, 24, 29), and in two studies the patients received DKT before surgery (29, 30). Therefore, although several studies revealed that DKT relieves the condition of patients with adhesional ileus (18, 20), relatively short-term administration of DKT may also be useful for prevention of PI including paralytic ileus.

With regard to the type of PI, only two studies defined paralytic ileus as delay of the first postoperative flatus beyond 72 hours after surgery, or the need for interventional therapy for ileus (29, 30). In addition, although only one study collected data on the occurrence of PI over a 3-year postoperative observation period (21), most studies investigated the occurrence of PI within a short perioperative period from surgery to discharge. Because most studies did not distinguish whether the PI was paralytic or adhesional, a long observation period will be required in future studies in order to improve the precision of collected data.

With regard to the risk of bias, although all studies were conducted in Japan, the I^2 value of 48% suggested that there was a moderate heterogeneity in this meta-analysis. In addition, although only seven studies were selected, the bilateral symmetry of the funnel plot indicated that the possibility of publication bias was low. Analysis of the ideal sample size on the basis of both absolute risk reduction and reduction of RR [occurrence rate of PI: with DKT=11.4%, without DKT=15.9%; absolute risk reduction 4.5%=15.9%-11.4%; RR reduction 28.3%=100%-(11.4%/15.9%)] demonstrated that a RCT including a total of 1,826 patients (913 patients with DKT and 913 patients without DKT) would be required to prove the same effect of this meta-analysis. Therefore, the results of this meta-analysis of seven studies with a relatively large sample of patients (n=1134) are considered clinically meaningful in comparison with a study involving an ideal sample size (n=1826).

After accumulation of a large amount of evidence from basic studies using animal models (39), several multicenter phase III trials have assessed the clinical efficacy of DKT for GI disorders after abdominal surgery in Japan (21, 23, 25, 40). However, because only a few studies have started to investigate the effects of DKT on GI motility in Western countries (2, 41), such studies should be continued in order to obtain concrete evidence for the efficacy of DKT in reducing PI in patients undergoing surgery for GI cancer (42) and to minimize the limitations of meta-analyses.

Although it is acceptable to employ multimodal strategies in order to reduce the occurrence of PI, perioperative administration of DKT could be considered a useful means of preventing PI in patients undergoing surgery for GI cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare in regard to this study.

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