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Anti-Inflammatory Effect of the *Kampo* Japanese Traditional Medicine *daikenchuto* After Colorectal Resection

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Here we analyzed whether Daikenchuto (DKT) suppresses postoperative inflammatory reactions in patients who have undergone elective colorectal surgery. DKT is one of the most frequently prescribed traditional (*Kampo*) medicines in Japan. DKT is reported to have various beneficial effects on bowel disorders. It was recently reported that DKT also has an anti-inflammatory effect. Consecutive patients with colorectal cancer who underwent elective colorectal resection were separated into two groups. A total of 67 patients began a DKT regimen after surgery (DKT group) and 53 patients did not begin the DKT regimen after surgery (control group). We observed a steady postsurgery increase in the white blood cell (WBC) count of all patients on postoperative day 1 (POD 1), whereas the WBC count decreased at PODs 3 and 7. When we compared the WBC values of the DKT group (6147.2 $\pm$ 2217.3 per microliter) and control (7071.1 $\pm$ 2828.0 per microliter) groups on POD 7, we found significant differences ($P = 0.038$). There was no significant side effect due to DKT, except for one case of mildly impaired liver function. Our results suggest that DKT administration may have an anti-inflammatory effect during the postoperative period. Further studies are warranted to investigate the possibility of using DKT as a therapeutic agent based on its anti-inflammatory effect.

Key words: Daikenthuto – Inflammation – Colorectal surgery

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Traditional Japanese medicine, *Kampo*, is used to treat various disorders of the gastrointestinal tract in Japan, where *Kampo* medicines are integrated into the modern health care system.[1–3] Daikenchuto (DKT) is one of the most frequently prescribed traditional medicines in Japan. DKT consists of 3 different herbs: dried ginger rhizome, ginseng root, and xanthozylum fruit.[2] DKT is reported to have various beneficial effects on bowel disorders and to cause very few side effects.[2–7] It was reported that DKT stimulates gastrointestinal motility, increases gastrointestinal hormones (such as motilin), and increases intestinal blood flow.[8,9] DKT has thus been used to prevent postoperative adhesion and paralytic ileus after abdominal surgery.[10,11] Another beneficial effect of DKT was recently reported: an anti-inflammatory effect.[11–17] In animal models, it was found that DKT inhibited the production of inflammatory cytokines or suppressed colitis by an anti-inflammatory effect via the upregulation of endogenous adrenomedullin.[11–15] The objective of the present study was to analyze whether DKT can suppress postoperative inflammatory reactions in patients who had undergone elective colorectal surgery.

Patients and Methods

Consecutive patients with colorectal cancer who underwent elective colorectal resection at the Department of General Surgical Science, Graduate School of Medicine, Gunma University (Gunma, Japan), from 2010 to 2011 were identified for inclusion in this study. We separated the patients into 2 groups. A total of 67 patients who underwent elective colorectal resection began a DKT regimen after surgery (DKT group). A total of 53 patients who underwent elective colorectal resection did not begin a DKT regimen (7.5 g/d) after their surgeries (control group).

Patients who underwent a simple colostomy and colostomy closure were not included, nor were those with emergency operations. Data were collected retrospectively. Informed consent for study participation was obtained from all patients. Blood samples were obtained preoperatively and on postoperative days (PODs) 1, 3, and 7. With the exception of patients with intestinal stenosis, nasogastric tubes were not routinely used.

The clinical and surgical variables recorded for each patient included age, gender, location of tumor, stage of tumor, length of operation, intraoperative blood loss, laparoscopic surgery, serum C-reactive protein level, white blood cell (WBC) count, and length of hospital stay. The exact times of the patients' first passage of defecation were recorded.

Table 1 Patient and surgical characteristics

	Daikenchuto		
	Present	Absent	*P*
Age, y[a]	67.7 ± 10.4	67.5 ± 10.5	0.930
Sex, M/F, No.	32/35	34/19	0.108
Location, colon/rectum, No.	49/18	37/16	0.844
Laparoscopic surgery, No.	2	1	0.308
Depth of invasion, No.			
m/sm	21	12	
mp	6	7	
ss	32	21	
se/si	8	12	
Lymph node metastasis, No.	8	12	0.094
Operation time, min[a]	149.4 ± 56.2	154.1 ± 63.7	0.325
Blood loss, mL[a]	127.4 ± 164.8	126.8 ± 163.0	0.508
Hospital stay after surgery, d[a]	9.6 ± 5.2	9.7 ± 6.0	0.451
Time to defecation, d[a]	3.5 ± 1.3	3.9 ± 1.5	0.101

mp, muscularis propria; m/sm, mucosa/submucosa; se/si, penetration of serosa/invasion of adjacent structures; ss, subserosa.

[a]Values are expressed as mean ± SD.

We performed univariate statistical analyses using the χ^2 test for qualitative variables and the two-tailed Fisher exact test for some data, as well as unpaired, one-tailed *t*-tests. Differences were considered to be significant at $P < 0.05$.

Results

Table 1 summarizes the characteristics of the total population and the DKT and control groups of colorectal resection patients. The DKT group had 67 patients (32 males and 35 females), with a mean age of 67.7 ± 10.4 years, and the control group was 53 patients (34 males and 19 females), with a mean age of 67.5 ± 10.5 years. As can be seen in Table 1, the clinical characteristics of the two groups, including the operative time and blood loss, were similar.

A steady increase in all of the patients' WBC counts was observed on POD 1, whereas the WBC count decreased at PODs 3 and 7 (Fig. 1). When we compared the WBC values of the DKT group (6147.2 ± 2217.3 per microliter) and control group (7071.1 ± 2828.0 per microliter) on POD 7, we found a significant difference ($P = 0.038$). In the DKT group, C-reactive protein level had a tendency to decrease; however, there was no significant difference in C-

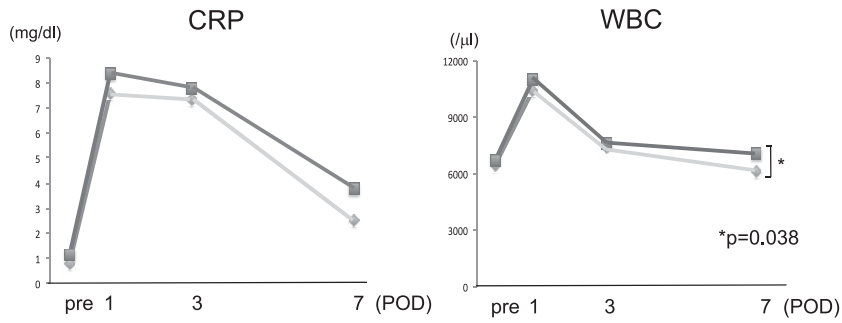

Fig. 1 The C-reactive protein levels (a) and WBC counts (b) of the DKT group and control group.

CRP, C-reactive protein; WBC; white blood cell: POD, post-operative day

reactive protein levels between the DKT group (2.5 ± 3.3 mg/dL) and the control group (3.7 ± 4.6 mg/dL; $P = 0.081$).

As for gastrointestinal recovery, the first defecation was relatively earlier in the DKT group compared with the control group (POD 3.5 ± 1.3 versus 3.9 ± 1.5, respectively), but the difference was not significant. The length of postoperative hospital stay was not significantly different between the two groups (9.6 ± 5.2 versus 9.7 ± 6.0 days, respectively). There were no significant side effects due to DKT, except for one case of mildly impaired liver function.

Discussion

Postoperative ileus is a relatively common condition after colorectal surgery. DKT has often been used in the treatment of postoperative ileus after gastrointestinal surgery. DKT stimulates gastrointestinal motility through a neural reflex involving presynaptic cholinergic and 5-HT3 receptors,[5–7] increasing the intestinal blood flow[10,11] and increasing gastrointestinal hormones, such as motilin.[8,9] It was recently reported that DKT has an anti-inflammatory effect[11–17]; DKT inhibited the production of inflammatory cytokines, including interferon-γ, interleukin-6, and tumor necrosis factor-α.[13,14] DKT also suppressed colitis by an anti-inflammatory effect via the upregulation of endogenous adrenomedullin[12] or via the downregulation of Th1 and Th17 responses.[15] In our present study, DKT administration also significantly suppressed postoperative inflammation following colorectal surgery, supporting the results of a previous study.[16,17] This result suggests that DKT administration may have an anti-inflammatory effect during the postoperative period.

This study has several potential limitations. The major limitation is the use of retrospective methods of data collection. Further laboratory and epidemiologic studies are necessary, and further studies should focus on the appropriate DKT regimen, including the duration of treatment and timing of the start of treatment.

One of the potential advantages of DKT administration is the recovery of bowel movement and shorter hospital stays; however, in the present study the time to defecation and the length of hospital stay were not significantly different between the DKT and control groups. The time to defecation was relatively shorter in the patients with DKT than the control patients, but not significantly so. The administration of DKT was initiated for patients with relatively delayed bowel movement after laparotomy in this study, and the time to defecation may have been affected by this. The length of hospital stay may also be affected by other factors, including medical, psychological, and social factors. Although the present findings showed no association between DKT and shorter time to defecation or length of hospital stay, the DKT administration was feasible and safe in patients who underwent colorectal surgery, which is clinically important.

In conclusion, DKT administration also significantly suppressed postoperative inflammation following colorectal surgery, as in previous studies.[16,17] This result suggests that DKT administration may have an anti-inflammatory effect during the postoperative period. The present results merit further investigation into the possibility of DKT as a therapeutic agent through its anti-inflammatory effect.

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