



Study on the Efficacy of Daikenchuto on Bowel Motility after Laparoscopic Resection of Colorectal Cancer

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Abstract

Introduction: Daikenchuto is considered to have actions that promote gastrointestinal motility and inhibit inflammation. We examined the efficacy of Daikenchuto on bowel motility after laparoscopic resection of colorectal cancer.

Materials and Methods: The subjects were 64 patients (33 Daikenchuto, 31 non Daikenchuto group) who underwent laparoscopic resection of colorectal cancer at our department. From Day 2, Daikenchuto was administered to the Daikenchuto group at a dose of 15 g. On days 1 and 5, plain X-ray and blood sampling were performed, in addition to the application of a questionnaire survey for bowel function. The plain X-ray images were examined using Image J image analysis software to measure the gas volume in the intestine and determine the Gas Volume Score (GVS). We evaluated bowel function using the Japanese version of Gastrointestinal Symptom Rating Scale (GSRS) as a QOL score. We also examined the duration of the operation, intraoperative blood loss and initial emission of gas after the surgery, initial defecation, duration of postoperative hospitalization, inflammatory reaction, and hepatic function.

Results: There were no significant differences between the Daikenchuto and the non-administration groups regarding background factors, QOL score and GVS. There were no significant differences between the two groups for other factors.

Discussion: No significant difference was observed between the two groups regarding laparoscopic resection of colorectal cancer in this study. The results of this study may be due to the fact that the minimally invasive laparoscopic surgery results in a favorable postoperative course, with less bowel paralysis, compared with abdominal open surgery.

Keywords: Kampo medicine; Laparoscopic colorectal surgery; Daikenchuto

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Introduction

Recently, the mechanism of Kampo medicine is being elucidated, and it is becoming more and more interested in the world. Herbal medicines have been used in Japan for more than 1500 years and traditional Japanese medicines (Kampo medicines) are now fully integrated into the modern healthcare system. In total, 148 Kampo formulae are officially approved as prescription drugs and covered by the national health insurance system in Japan. However, despite their long track record of clinical use, the multi-targeted, multi-component properties of Kampo medicines, which are fundamentally different from Western medicines, have made it difficult to create a suitable framework for conducting well-designed, large-scale clinical trials. In turn, this has led to misconceptions among western trained physicians concerning the paucity of scientific evidence for the beneficial effects of Kampo medicines. Fortunately, there has been a recent surge in scientifically robust data from basic and clinical studies for some of the Kampo medicines, e.g. Daikenchuto (Tsumura & Co., Tokyo, Japan) [1].

Daikenchuto [2], (DKT), a Japanese herbal medicine containing *Zingiber siccatum* (processed ginger), Japanese pepper, and carrot, is considered to have actions that promote gastrointestinal motility and inhibit inflammation [3,4].

In the Japan, it is clinically used extensively in patients with symptoms such as abdominal bloating, and is used in many hospital surgical wards for postoperative paralysis of the bowel obstruction. Although there have been some reports on the relationship between DKT and bowel motility, there are almost no reports of cases with laparoscopic surgery. We examined the efficacy

Table 1: Patient's characteristics.

| Characteristic | DKT(+) (n=33) | DKT(-) (n=31) | P value |
|--------------------------------|---------------|---------------|---------|
| Age | 68.5 ± 9.0 | 61.2 ± 11.2 | <0.05 |
| Gender (Male:Female) | 19:14 | 20:11 | 0.62 |
| BMI | 23.6 ± 4.0 | 22.9 ± 2.3 | 0.4 |
| Location | | | |
| Cecum | 5 (15.1%) | 5 (16.1%) | 0.37 |
| Ascending colon | 10 (30.2%) | 4 (12.9%) | |
| Transverse colon | 1 (3.1%) | 4 (12.9%) | |
| Descending colon | 3 (9.1%) | 1 (3.2%) | |
| Sigmoid colon | 12 (36.3%) | 14 (45.2%) | |
| Rectum | 2 (6.2%) | 3 (9.7%) | |
| Types of procedure | | | |
| Ileocectomy | 3 (9.1%) | 1 (3.2%) | 0.87 |
| Right hemicolectomy | 11 (33.3%) | 8 (25.7%) | |
| Left hemicolectomy | 1 (3.1%) | 2 (6.5%) | |
| Partial colectomy | 4 (12.1%) | 4 (12.9%) | |
| Sigmoidectomy | 10 (30.2%) | 12 (38.7%) | |
| AR* | 3 (9.1%) | 2 (6.5%) | |
| LAR** | 1 (3.1%) | 2 (6.5%) | |
| Operative time (min) | 234.9 ± 34.5 | 26.36 ± 39.8 | <0.05 |
| Intraoperative blood loss (ml) | 27.1 ± 21.4 | 35.5 ± 21.8 | 0.07 |

*Anterior resection; **Low anterior resection

of DKT on bowel motility after laparoscopic resection of colorectal cancer.

Materials and Methods

This study is randomized controlled trial for the efficacy of Daikenchuto on bowel motility after laparoscopic resection of colorectal cancer. Approval of the study was obtained from the Ethical Committee of Juntendo University (No. 2009506).

Patients

The subjects were 64 patients (male: 34, female: 16, average age: 67.2 years old) who underwent laparoscopic resection of colorectal cancer at our department from March 2010 to September 2011 and three years after surgery, we observed the occurrence of adverse events related to bowel movement, such as intestinal obstruction. In this study, patients who did not provide informed consent and those experiencing small bowel fistula, intestinal obstruction, or anastomotic leakage were excluded. They were randomly allocated to the DKT (33 subjects) (DKT (+) group) and the non-administration groups (31 subjects) (DKT (-) group).

Experimental protocol

On day 2, DKT was administered to the DKT group at a dose of 15 g (3 times a day). The subjects in the non-administration group were allowed to drink water. On days 1 and 5, plain X-ray and blood sampling were performed, the Gas Volume Score (GVS) was measured in Days 1 and 5 of the plain X-ray, in addition to the application of a questionnaire survey using the Japanese version of Gastrointestinal Symptom Rating Scale (GSRS) as a QOL score (Table 1 & Figure 1) [5,6].

Measurement of gas volume score

The plain X-ray images were examined using Image J image

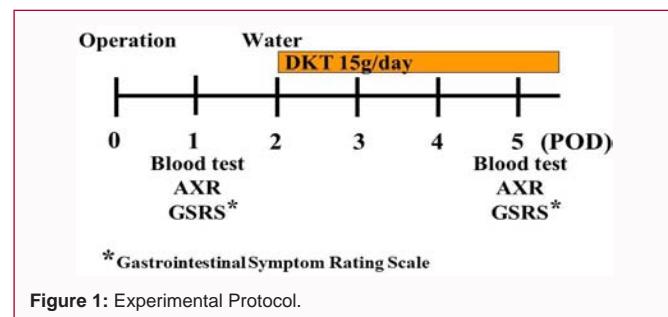


Figure 1: Experimental Protocol.

analysis software [7] to measure the gas volume in the intestine and determine the Gas Volume Score (GVS: number of pixels in the part equivalent to intestinal gas/number of pixels in the designated part) (Figure 2) [5].

Measurement of gastrointestinal symptom rating scale

The GSRS is a disease-specific instrument, developed, based on reviews of gastrointestinal symptoms and clinical experience, to evaluate common symptoms of gastrointestinal disorders. The GSRS can be administered in either self-report or interview format. The GSRS contains 15 common gastrointestinal symptoms and requires patients to rate the severity of symptom on a seven-point scale. The scores are calculated by taking the mean of the items completed within an individual scale, with higher scores indicating greater severity of symptoms. Highest score is seven, and lowest score is one [6].

Primary and secondary endpoints

In this clinical trial, co primary endpoints were

1. Gas Volume Score and
2. Gastrointestinal Symptom Rating Scale

Secondary primary points were initial emission of gas after the surgery, initial defecation, duration of postoperative hospitalization, inflammatory reaction, hepatic function and the incidence of postoperative small bowel obstruction within 3 years after surgery.

Statistical analysis

Statistical analysis was performed using the T test. 2 test was used for bivariate analysis (significance test between 2 groups). The significance level was considered to be p<0.05. Statistical analyses were conducted using SPSS II for Windows Version 11.0J (SPSS Inc.).

Results

Patients characteristics (Table 1)

Age: In the DKT (+) group, the age was 47 to 84 and the average was 68.5 years old.

On the other hand, in the DKT (-) group, the age was 37 to 82 years old and the average was 61.2 years old. It was younger with a significant difference in the DKT (-) group.

Gender: The DKT (+) group comprised 19 males (57.6%) and 14 females (42.4%) and the DKT (-) group consisted of 20 males (64.5%) and 11 females (35.5%), suggesting no significant differences between the groups.

BMI: In the DKT (+) group, the BMI of patients was 17.1 kg/m² to 35.3 kg/m² and averaged 23.6 kg/m². In the DKT (-) group, the BMI of patients was 17.3 kg/m² to 28.7 kg/m² and averaged 22.9 kg/m². In both groups, there were few obese patients. No significant differences were found between the groups by BMI.

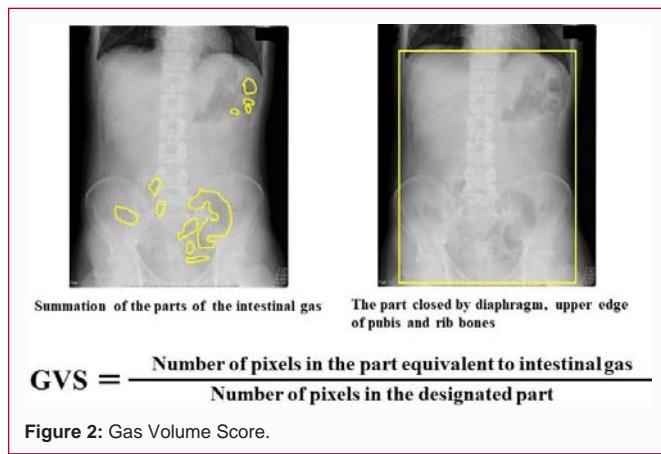


Figure 2: Gas Volume Score.

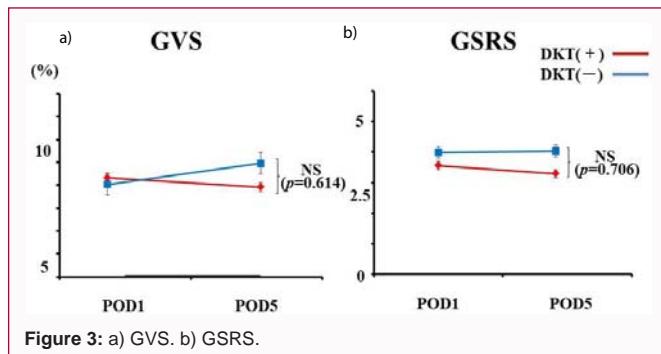


Figure 3: a) GVS. b) GSRS.

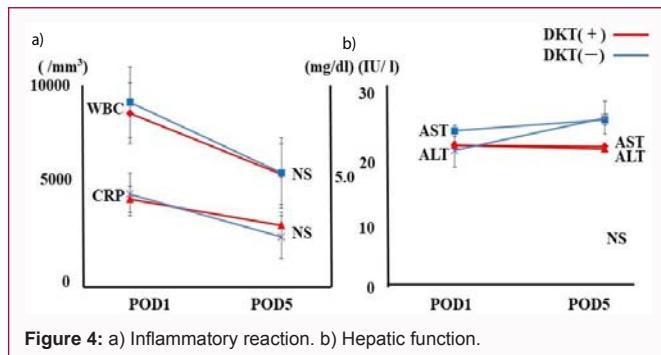


Figure 4: a) Inflammatory reaction. b) Hepatic function.

Location: For the location, in both groups, the sigmoid colon is the most numerous and 12 cases in the DKT (+) group (36.3%), 14 cases in the DKT (-) group (45.2%). For other locations, the DKT (+) group had 5 cases of cecum (15.1%), 10 on the ascending colon (30.2%), 1 case of transverse colon (3.1%), 3 descending colon (9.1%), and 2 rectal cases (6.2%). DKT (-) Group 5 cases (16.1%), 4 cases of ascending colon (12.9%), 4 cases of transverse colon (12.9%), 1 case of descending colon (3.2%), and 3 rectal (9.7%). There was no significant difference between the two groups for the location.

Type of procedure: In the DKT (+) group, 3 cases of ileocectomy in the group (9.1%), 11 cases of right hemicolectomy (33.3%), 1 case of left hemicolectomy (3.1%), 4 cases of partial colectomy (12.1%), 10 cases of sigmoidectomy (30.2%), 3 cases of anterior resection (9.1%), 1 case of low anterior resection (3.1%). On the other hand, DKT (-) group is 1 case of ileocectomy (3.2%), 8 cases of right hemicolectomy (25.7%), 2 cases of left hemicolectomy (6.5%), 4 cases of partial colectomy (12.9%), 12 cases of sigmoidectomy (38.7%), 2 cases of anterior resection (6.5%), 2 cases of low anterior resection (6.5%). There was no significant difference between the two groups.

Table 2: Study endpoint.

| Characteristic | DKT(+) (n=33) | DKT(-) (n=31) | P value |
|---|---------------|---------------|---------|
| Initial emission of gas (POD) | 2.0 ± 1.0 | 1.7 ± 0.9 | 0.2 |
| Initial defecation (POD) | 4.2 ± 2.1 | 3.5 ± 1.6 | 0.19 |
| Postoperative hospital stay (day) | 11.0 ± 2.7 | 10.6 ± 3.0 | 0.27 |
| Postoperative intestinal obstruction ^a | 0 | 0 | - |

^apostoperative intestinal obstruction within 3 years after surgery

Operative time: In the DKT (+) group, the operative time was 164 min to 301 min, and the average time was 234.9 min. In the DKT (-) group, the operative time was 181 min to 338 min, and the average time was 263.6 min, and the operative time was longer in the DKT (-) group with a significant difference.

Intraoperative blood loss: In the DKT (+) group, the intraoperative blood loss was 6 ml to 110 ml, and the average time was 27.1 ml. In the DKT (-) group, the intraoperative blood loss was 6 ml to 85 ml and the average blood loss was 35.5 ml, and there was no significant difference between the two groups.

Study outcomes

GVS (%): In the DKT (+) group, the GVS of POD 1 was 0.6 to 24.8, and the average was 8.6. The GVS of POD5 was 0.8 to 14.2, and the average was 8.0. In the DKT (-) group, the GVS of POD 1 was 1.3 to 27.6, and the average was 8.2. The GVS of POD 5 was 1.9 to 21.9, and the average was 9.5 (Figure 3a).

Compared to the POD1, GVS decreased in the DKT (+) group in POD5, and it was mildly elevated in the DKT (-) group, although the peritoneal gas was clearly decreasing compared to the DKT (-) group in the DKT (+) group, but statistically no significant difference was observed ($p=0.614$).

GSRS: In the DKT (+) group, the average of GSRS on Day 1 was 1.0 to 3.4, and the overall average was 1.7. And the average of GSRS on Day 5 was 1.0 to 2.9, and the overall average was 1.6. In the DKT (-) group, the average of GSRS on Day 1 was 1.0 to 6.8, and the overall average was 1.8 and the average of GSRS on Day 5 was 1.0 to 6.4, and the overall average was 1.9 (Figure 3b).

Although the QOL score by GSRS is reduced in the DKT (+) group, it is believed that the QOL is improved in the DKT (-) group, and the quality of the DKT (+) group is increased, but no significant difference was found ($p=0.706$).

Initial emission of gas after the surgery: In the DKT (+) group, the initial emission of gas after the surgery was averaged POD2.0 in the range from POD1 to POD5. In the DKT (-) group, the initial emission of gas after the surgery was averaged POD1.7 in the range from POD1 to POD5. And there was no significant difference between the two groups.

Initial defecation: In the DKT (+) group, the initial defecation after the surgery was averaged POD 4.2 in the range from POD 1 to POD 9. In the DKT (-) group, the initial defecation after the surgery was averaged POD 3.5 in the range from POD 1 to POD 7. And there was no significant difference between the two groups.

Postoperative hospital stay: In the DKT (+) group, the average of the postoperative hospitalization period was 11.0 days from 8 days to 20 days. In the DKT (-) group, the average of the postoperative hospitalization period was 10.6 days from 8 days to 21 days. There was no significant difference between the two groups.

The incidence of postoperative intestinal obstruction within 3 years after Surgery: Patients in both groups were observed for three years after surgery, but no patients had developed intestinal obstruction that required treatment (Table 2).

Inflammatory reaction: As an evaluation of inflammatory responses, the WBC and CRP were examined.

In the DKT (+) group, the average of WBC on Day 1 was 3500/ μ l to 14600/ μ l, and the overall average was 8377/ μ l. The average of WBC on Day 5 was 1900/ μ l to 9300/ μ l, and the overall average was 5138/ μ l. In the DKT (-) group, the average of WBC on Day 1 was 920/ μ l to 15600/ μ l, and the overall average was 7867/ μ l. And the average of WBC on Day 5 was 2500/ μ l to 11400/ μ l, and the overall average was 5081/ μ l.

In the DKT (+) group, the average of CRP on Day 1 was 0.1 mg/dl to 10.3 mg/dl, and the overall average was 3.9 mg/dl and the average of CRP on Day 5 was 0.2 mg/dl to 8.1 mg/dl, and the overall average was 2.7 mg/dl. In the DKT (-) group, the average of WBC on Day 1 was 0.7 mg/dl to 8.8 mg/dl, and the overall average was 4.2 mg/dl. And the average of WBC on Day 5 was 0.4 mg/dl to 13.7 mg/dl, and the overall average was 3.4 mg/dl (Figure 4a).

In both groups, the value of the WBC and CRP decreased and the inflammatory response was reduced, but there was no significant difference between the two groups.

Hepatic function: We investigated the value of AST and ALT, which were used as evaluation of liver function.

In the DKT (+) group, the average of AST on Day 1 was 11 U/l to 68 U/l, and the overall average was 21.4 U/l. And the average of AST on Day 5 was 9 U/l to 33 U/l, and the overall average was 18.0 U/l. In the DKT (-) group, the average of AST on Day 1 was 10 U/l to 35 U/l, and the overall average was 21.8 U/l. And the average of AST on Day 5 was 11 U/l to 160 U/l, and the overall average was 24.5 U/l.

In the DKT (+) group, the average of ALT on Day 1 was 7 U/l to 74 U/l, and the overall average was 18.3 U/l and the average of ALT on Day 5 was 6 mg/dl to 40 mg/dl, and the overall average was 17.5 U/l. In the DKT (-) group, the average of ALT on Day 1 was 7 U/l to 32 U/l, and the overall average was 17.0 mg/dl. And the average of ALT on Day 5 was 6 U/l to 191 U/l, and the overall average was 25.1 U/l.

In the DKT (+) group, the AST, the alt decreased mildly, and the DKT (-) group AST and ALT were also mildly elevated. DKT (+) Group was considered to have suppressed hepatic dysfunction, but no significant difference was observed (Figure 4b).

Discussion

Although Kampo medicine has not been elucidated in many fields, many things are being elucidated, and it has been used in many areas, and the interest has been gathered around the world. Daikenchuto is the most frequently prescribed traditional Japanese medicine in Japan. The formulation is composed of extract granules of Japanese pepper, processed ginger, ginseng radix, and maltose powder derived from rice. The standard dosage of DKT is 15 g/day, and the water-soluble nature of DKT, due to its high maltose content, makes this dosage possible. The “(to)” character of DKT indicates water solubility, “(chu)” denotes gastrointestinal tract, “(ken)” connotes reconstruction, and “(dai)” implies maximal effect. These characters translate as, “to reconstruct strongly the diseased gastrointestinal

tract to the health [8].” In 2009, the effect of the postoperative ileus of Daikenchuto was reported [8]. Papers on many Kampo medicines have been reported. There have been a lot of reports about the Daiken that we are researching. In the field of gastric and esophagus, the gastrointestinal dysfunction and the preventive effect against ileus have been reported after total gastrectomy [9]. The inflammatory response of patients after hepatectomy was suppressed in the liver surgery area. It also stimulates defecation and improves oral ingestion [4]. In the area of basic research, it has been reported that there is an action to prevent neutrophils accumulation in the Sinus Occlusion syndrome [10].

As for the lower gastrointestinal tract, the same as this study is reported more than other fields. Maintenance of digestive function in patients with colorectal cancer resection and improvement of abdominal bloating in patients after hepatectomy and colorectal motility, such as lowering the re-operation rate and recurrence rate of ileus after colon resection [11-13]. Recently, there is a report that the Daikenchuto is effective for the prevention of the anastomotic leakage [14].

DKT has been reported to decrease the bowel gas volume by stimulating colonic motility [15], and it is reported that the reduction of constipation and the decrease in GVS was obtained when using DKT for patients with chronic constipation and constipation in stroke patients. It is thought that GVS decreases due to the promotion of intestinal motility [15,16].

Although there are not many reports of the normal value of GVS, the value of the GVS in the control group is $3.33\% \pm 1.3\%$ according to the report of Koide et al. [17]. In this study, it is thought that the higher the report is due to the postoperative intestinal palsy.

In the GVS which evaluated the intestinal movement by the image analysis by the abdominal simple X-ray, it was decreased by the DKT (+) group. On the other hand, it was thought that the amount of gas was decreased by the effect of the intestinal movement promotion by the Daikenchuto because the rise was admitted in the DKT (-) group of the hot water, but the statistically significant difference was not found. The reason for this is that the accuracy of the image evaluation of gas and the amount of gas in the case are varied. The reason why the intestinal movement was evaluated as a method of evaluating intestinal movement by using the radiation non-permeability mark is a minimum, and the burden to the patient is considered as the reasons for evaluating the bowel movements by analyzing the amount of colon gas [18]. Despite the GSRS evaluation of intestinal motility by QOL scores in this study was performed in the DKT (+) group improves QOL, to even have a slight deterioration in the DKT (-) group, and did not significantly in evaluation of QOL score by question thinking for the had a variation on the questions of personal interpretation, score was inconsistent. There was no significant difference between the DKT (+) group and the DKT (-) group even in the number of days until the initial emission of gas and the initial defecation after the surgery. There is a report that there was no significant difference in the QOL evaluation by the first defecation, GSRS, and fACT-C for the clinical effect of Daikenchuto in the laparotomy for colonic cancer [18].

In the evaluation of postoperative inflammatory responses, the WBC and CRP values were measured, but there was no significant difference in the number of POD1 in both groups as the POD5 elapsed. In this study, there was no significant difference between the two groups of CRP, but there was a report that a rapid rise was

observed on the 3 POD in the DKT (-) group [18]. There is also a report that the inflammatory response by bacterial translocation was suppressed in the basic research [19].

Although many have not been elucidated before, there have been many reports about the mechanism of Daikenchuto. The secretion promoting action of 1) Digestive tract peptide hormone in the intestinal motility is activated the transient receptor potential cation channel subfamily V member 1 (TRPV1) channel to speak on the sensory nerve cells of 2) Intestinal tract, and the digestive tract smooth muscle is contracted, Promoting the secretion of serotonin (5-HT) by activating the transient receptor potential ankyrin 1 (TRPA1) channel present on the chromium affinity cells of the 3) Intestinal epithelium promotes the secretion of substance p to enhance the digestive tract motility and promotes the advantage of acetylcholine. Acetylcholine shrinks the digestive tract smooth muscle cells and enhances the digestive tract movement. The intestinal motility is enhanced by inhibiting the KCNK9 channel of 4) The intestinal motility is enhanced by inhibiting the KCNK9 channel of 5) Intestinal nerve cells and cajal-mediated cells [1,20-22].

By activating the TRPV1 channel and the TRPA1 channel for intestinal blood flow increase, the secretion of Calcitonin Gene-Related Peptide (CGRP) and Adrenomedullin (ADM) is promoted, and vascular expansion and blood flow increase in the intestinal tract are generated [23,24]. As for the anti-inflammatory action, it is reported that the secretion of ADM is promoted by TRPV1 channel activation, and inflammatory cytokines suppress inflammation [25]. The usefulness of Enhanced Recovery after Surgery (ERAS) in colorectal cancer surgery has been reported since before. In consideration of the effects of the intestinal motility and anti-inflammatory effect of Daikenchuto in the past, the paper presentation is not allowed, but it may be possible to contribute to the ERAS protocol in the future [26]. Although Daikenchuto has been reported to be efficacious for postoperative bowel motility in cases that had undergone abdominal operation for colorectal cancer, no significant difference was observed between the Daikenchuto and the non-administration groups regarding laparoscopic resection of colorectal cancer in this study. In consideration of laparoscopic and laparotomy cases for colorectal cancer, the recovery of postoperative bowel movement was early, and there was also a report that the number of days to the first exhaust gas and the number of hospital days were short [27-29]. The results of this study may be due to the fact that the minimally invasive laparoscopic surgery results in a favorable postoperative course, with less bowel paralysis, compared with abdominal surgery. And moreover, it was thought that it was necessary to examine it by the oral method, the preoperative or the postoperative long-term administration in the future because it was a study of the early bowel movement by the oral treatment only for several days after the postoperative examination. Moreover, it is thought that it had a significant difference in the DKT (+) group, and that the operation time was short with a significant difference and the influence of the bowel movement between both groups was not a little. In the future, it is necessary to consider the case matching. The Protocol for the study of gastrointestinal symptoms of Daikenchuto in the laparoscopic colorectal after postoperative treatment has also been reported, as in the present study [30]. In the future, it was thought that it was necessary to consider the accumulation of the case and the method of administration of Daikenchuto and the evaluation of the new bowel motility. Moreover, the Daikenchuto of the hot water which I used for this study is 15 g and many powders, and there

is a peculiar bitterness of the Kampo medicine. In this study, it was thought that the examination of the dosage type and the amount of the oral was necessary in the future though the case which was difficult to take was not admitted, and the deterioration of the compliance of the oral was feared.

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