Daikenchuto improved perioperative nutritional status of the patients with colorectal cancer: A prospective open-labeled randomized exploratory study

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Abstract: *Background and aims:* The aim of this study is to exploratively evaluate the effect of Tsumura Daikenchuto Extract Granules (DKT, TJ-100) on abdominal symptoms, body weight, and nutritional function following colorectal cancer surgery. *Methods:* The subjects included 20 patients for curative resection of colorectal cancer. A TJ-100 administration group ($n = 10$) and non-administration group ($n = 10$) were randomized and compared. In the administration group, TJ-100 was administered from 2 days prior to surgery up to 12 weeks following surgery. The endpoints included body weight gain, Gastrointestinal Symptom Rating Scale (GSRS), and blood biochemical factors. For the purpose of observing safety, drug adverse events were evaluated including liver function tests. *Results:* Excluding one patient, we compared 9 cases in the administration group and 10 cases in the non-administration group. No obvious adverse events were observed in any of the cases. In the comparison of body weight gain, the TJ-100 administration group showed significantly higher values at 2, 4, and 12 weeks following the surgery. There was a tendency for lower stable GSRS scores in the administration group overall, with no statistically significant difference. *Conclusion:* It is suggested that TJ-100 can be safely administered in the perioperative period for cases undergoing colorectal cancer surgery, potentially preventing weight loss during the early postoperative period.

Keywords: Daikenchuto, TJ-100, colorectal cancer, nutrition, surgery

Introduction

Recently, as general perioperative management for abdominal surgery, it is recommended to ingest water and meals from the early postoperative period. However, the gastrointestinal function declines in the early postoperative period and we have experienced many patients who could not undergo postoperative management following clinical paths. By resolving this problem and further speeding up the recovery of gastrointestinal function, minimization of postoperative weight loss and nutritional disorders can be expected.

Tsumura Daikenchuto Extract Granules (DKT, TJ-100) is a traditional herbal medicine agent that has clinical effects on intestinal obstruction after laparotomy [1] and is used widely in the gastroenterological area. TJ-100 is composed of four crude compounds, including dried ginger rhizome, ginseng root, rice gluten, and Zanthoxylum fruit [2]. The effect of each component of TJ-100 on blood flow and mobility in the gastrointestinal tract is examined [3, 4]. It was reported that TJ-100 increases portal blood flow (PBF) in the early period after oral administration in humans [5]. A previous article reported that an increase of the PBF leads to enhance liver regeneration. In our previous experiment, through continuous monitoring of portal venous flow in rats, we showed that TJ-100 has the potential to protect the liver by increasing PBF when the liver has either normal or mild to moderate dysfunction [6].

However, there have been no studies that observed the dynamic change of recovery in response to TJ-100 administration in patients undergoing laparoscopic colectomy. In particular, no reports are currently available for nutritional and physical changes. The aim of this study is to evaluate the effect of TJ-100 on abdominal symptoms, body weight, and nutritional status accompanying the decline of gut motor function following colorectal cancer surgery.

Materials and Methods

The subjects included 20 patients for whom curative resection of colorectal cancer was deemed possible and who underwent laparoscopic surgery in the Department of Surgery, Nagasaki University Hospital. Eligibility criteria included laparoscopic surgery for colorectal cancer and age over 20 years old with performance status of 0 or 1. Exclusion criteria included history of open surgery or peritonitis, complication of inflammatory disease, or allergy to TJ-100. As this study was planned as exploratory research, a TJ-100 administration group (10 cases) and a non-administration group (10 cases) were randomized with random number table and compared. In the administration group, TJ-100 was administered from 2 days prior to surgery up to 12 weeks following surgery, excluding the day of surgery and the following day. The endpoints, which were measured over time, included body weight gain, Gastrointestinal Symptom Rating Scale (GSRS), and blood biochemical factors (serum albumin, serum total protein, prealbumin, and total cholesterol). The GSRS is evaluated in a questioning format, which has 15 items for symptoms and a 7-point graded Likert-type scale where 1 represents absence of trouble/some symptoms and 7 represents very troublesome symptoms. For the purpose of observing safety, drug adverse events were evaluated, including liver function tests.

Statistical analysis was performed by non-parametric method for two group comparisons and analysis of variance method for time course comparison. This study adheres to CONSORT guidelines and includes a completed CONSORT checklist. The study was carried out from February 2012 to October 2014 and was registered in the UMIN Clinical Trials Registry (UMIN000006413).

Ethics

The protocol for this research project has been approved by a suitably constituted ethics committee of Nagasaki University Hospital (no. 11012489-4), and it conforms to the provisions of the Declaration of Helsinki. All informed consent was obtained from the subjects.

Results

Enrolled patient characteristics were described in *Table I*. There were no statistical significant differences in the background data. Excluding one patient in the administration group who wanted to discontinue participation because of the taste, we compared nine cases in the administration group and eight cases in the non-administration group *(Fig. 1)*. No obvious adverse events were observed in any of the cases. In the comparison of body weight gain, the TJ-100 administration group showed significantly higher values at 2, 4, and 12 weeks following the operation *(Fig. 2)*.

Although there was a tendency for lower stable GSRS scores in the administration group, it did not show statistically significant difference *(Fig. 2)*. In the evaluation of blood biochemical factors, the level of serum total protein on the third postoperative day was significantly lower in the administration group, with no difference found between the two groups in terms of other items such as serum prealbumin and total cholesterol levels *(Fig. 3)*.

Discussion

In this study, we demonstrated the maintenance and gain of body weight in patients undergoing colectomy in a prospective manner with the administration of TJ-100. Although this study did not use a placebo, this

Table I Patients' characteristics

	TJ-100 group ($n=9$)	Control group ($n=8$)	
Age	69 (61–88)	75 (56–88)	n.s.
Gender (male/female)	2/8	5/3	n.s.
Location (A/T/D/S/R)	1/1/1/4/2	3/0/1/1/3	n.s.
Stage (I/II/III/IV)	3/6/0/0	1/1/6/0	n.s.
Operative methods (open/lap)	0/9	0/8	n.s.

TJ-100: Tsumura Daikenchuto Extract Granules

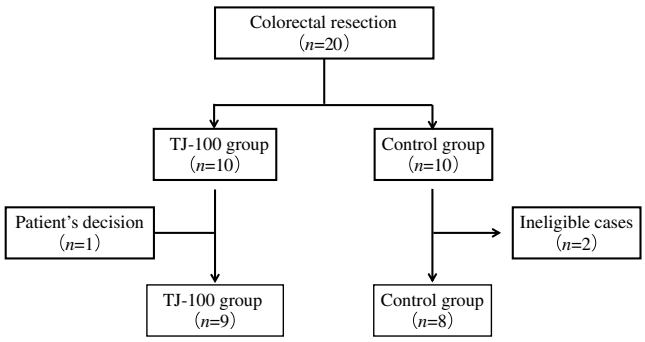

Fig. 1. Registration status of the patients

prospective open-label interventional study, even with a small number, still provides significant value as a pilot exploration.

There was a tendency for lower stable GSRS scores in the TJ-100-administered group. However, no statistically significant difference was observed in the scores between the two groups. GSRS score is generally used for the evaluation of upper gastrointestinal function. Therefore, this could be one of the reasons that there were no statistical differences between the two groups of patients undergoing colorectal surgery in this study, not upper GI

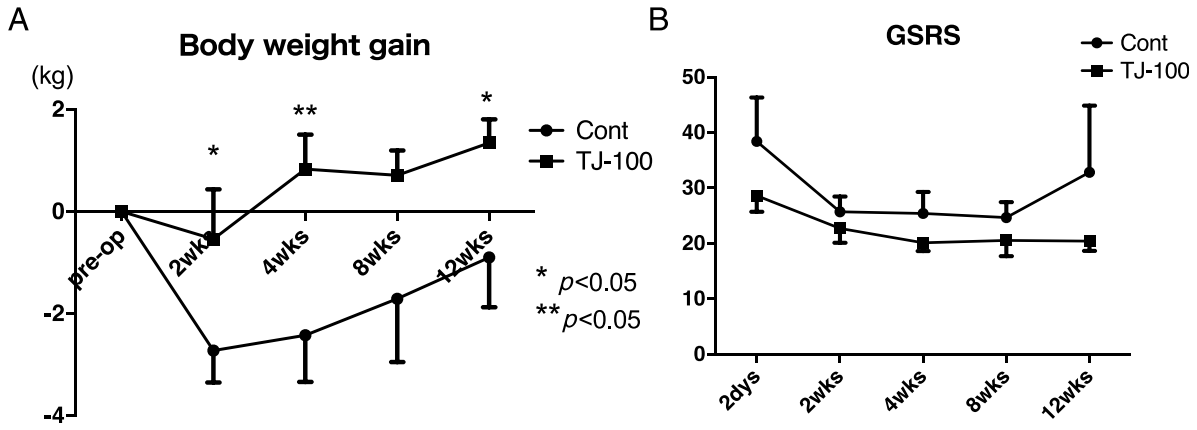

Fig. 2. Changes in (A) body weight and (B) GSRS score

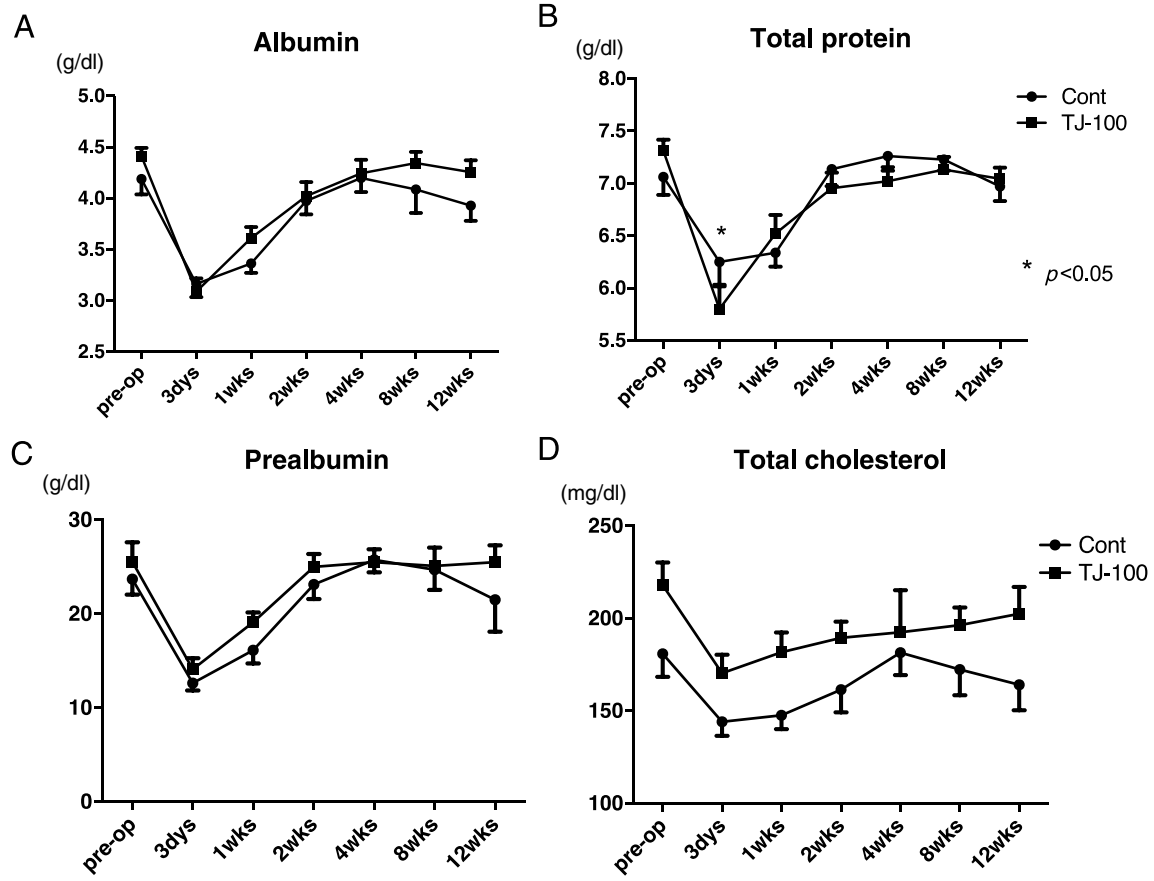

Fig. 3. Changes in proteins and cholesterol

surgery. A scoring system specialized to assess lower bowel function should be selected for studying cases following colorectal surgery.

As for the mechanism of the increase and maintenance and gain of body weight in the TJ-100 group, there are some possible reports to support our results. The positive effects of TJ-100 after esophageal cancer resection were reported in an open-label, randomized controlled trial after esophageal surgery [7]. It stated that TJ-100 plus nutritional agents enhanced recovery after esophageal surgery. It was mentioned that the mechanism was possibly synergistic effect of TJ-100 on nutritional supplements. In addition, recently, enhanced oral and enteral caloric intake after liver transplant surgery was reported with herbal medicine TJ-100 in a multicenter, randomized controlled trial possibly based on the same mechanism of TJ-100 [8]. In fact, in an *in vivo* animal study, TJ-100 was shown to have a stimulation effect on bowel peristalsis through the TRPA1 [9] and KCNK9 [10] channels. It also increases the blood to the bowel through the TRPA1 [9] and CGRP [11] channels.

It was reported that TJ-100 induced a dose-dependent increase in the intestinal blood flow [12]. Basically, the active ingredient in TJ-100 most attributable to this effect is dried ginger rhizome [13]. Our previous study demonstrated an increase in the PBF after intragastric administration of TJ-100 in the normal liver rat model [14]. Theoretically, increase of the intestinal blood flow volume should increase the volume of PBF. We are considering the possibility that there is an optimum density for TJ-100 to affect PBF; however, it is still unclear why TJ-100 increased small intestine blood flow in a dose-related manner but not PBF. We are continuing the investigation. Also with other herbal medicine, Rikkunshito (TJ-43) was proved to have stimulating effect on ghrelin excretion, which is not proven in TJ-100 [15].

There was a limitation regarding no significant difference in any parameters between the surgical approaches of laparoscopy and laparotomy. Although it has been reported that the laparoscopic approach provides better bowel movement after a surgery, these findings could be due to rather short and minimally invasive surgeries, even under the laparotomy approach. In addition, the number of each group in this study was not calculated and set from estimated improvement of nutritional status. It was indeed set as 10 patients in each group as exploratory prospective pilot study. Finally, we did not use placebo agents, so that phycological effects of TJ-100 on nutritional status were not completely eliminated. In conclusion, TJ-100 was safely administered in the perioperative period for patients undergoing colorectal cancer surgery, potentially preventing weight loss during the early postoperative period.

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Authors' contribution: FF designed the study, analyzed data, and wrote the initial draft of the manuscript. YT, KK, and YI especially contributed to interpretation of data and supervised the patient treatments. SI, KK, and MT especially participated in the discussion and assisted in the preparation of the manuscript. SE supervised the patient treatments and especially assisted in editing the manuscript.

Conflict of interest: The authors declare no conflict of interest.

Abbreviations

DKT, TJ-100 : Tsumura Daikenchuto Extract Granules
GSRS : Gastrointestinal Symptom Rating Scale
PBF : portal blood flow

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