Original Article

Postoperative oral nutritional supplementation after major gastrointestinal surgery: a randomized controlled clinical trial

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Background and Objectives: This study aimed to evaluate the efficacy of post-operative oral nutrition supplementation after major gastrointestinal surgery. **Methods and Study Design:** A prospective randomized controlled trial was conducted to evaluate 174 subjects who were discharged within 2 weeks after major gastrointestinal surgery. The subjects in the study group were prescribed 400 ml/day of Encover® from the day of discharge for 8 weeks, but no supplementation was allowed in the control group. The primary endpoint was the weight loss rate at 8 weeks after discharge compared with the pre-operative weight, and the secondary endpoints included changes in body weight, body mass index, Patient-Generated Subjective Global Assessment score/grade, hematological/biochemical parameters, and adverse events evaluated at 2, 4, and 8 weeks after discharge. **Results:** The weight loss rate at 8 weeks after discharge did not differ between two groups (4.23±5.49% vs 4.80±4.84%, p=0.481). The total lymphocyte count, the level of total cholesterol, total protein, and albumin were significantly higher in the study group after discharge. Diarrhea was the most frequent adverse event, and the incidence of adverse events with a severity score of ≥3 did not differ between groups (2.3% vs 1.2%). **Conclusions:** The utility of routine oral nutritional support after major gastrointestinal surgery was not proven in terms of weight loss at 8 weeks after discharge. However, it can be beneficial for early recovery of biochemical parameters.

Key Words: oral nutritional supplements, nutritional support, gastrointestinal surgery, weight loss, postoperative nutrition

INTRODUCTION

Patients who undergo major gastrointestinal surgery are frequently at risk of malnutrition, due to not only the disease itself, which may cause obstruction or hyper metabolic status, but also the treatment processes and postoperative functional deterioration of the gastrointestinal tract.[1-3] Several studies have shown that preoperative nutritional support is helpful in selected patients in terms of reducing post-operative complications.[4-8] However, the risk of malnutrition continues after surgery due to postop-

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erative gastrointestinal problems and the limitation of dietary intake after surgery, and it can impact long-term quality of life.[1,9]

It has been reported that weight loss is the most prominent during the period from four to twelve weeks after surgery.[10-12] Patients tend to gain weight after this period as their body weight stabilizes; however, many patients cannot reach their pre-operative weight. Within a few weeks after discharge from the hospital, patients must be provided with appropriate nutrition according to their individual recovery statuses to recover a normal quality of life with normal functioning. However, patients can be at risk of malnutrition due to deviation from daily dietary advice and postoperative gastrointestinal symptoms, which can be especially problematic if the patient's situation does not allow for proper support from family members.

An oral nutritional supplement (ONS) can be a good option for supplying nutrition during this period due to its ease of administration and balanced nutritional components. Beattie et al found that ONS administration was useful for the treatment of malnourished patients during the postoperative period in 2000.[13] However, the treatment process for operative patients has changed over the last 10 years, including an increase in laparoscopic surgery, improved postoperative pain control, early initiation of diet, and establishment of patient nutrition education programs. This progress may contribute to decreased metabolic rates during and after surgery with enhancement of nutritional recovery. This study was conducted to re-evaluate the efficacy of ONS administration in present practice for the treatment of patients who are at risk of malnutrition during the postoperative period following major gastrointestinal surgery.

METHODS

This study was a prospective, open-label, multicenter, randomized clinical trial performed in nine specialized surgical units in eight hospitals in Korea.[14] Patients with surgical gastrointestinal disease who needed major gastrointestinal surgery were screened for eligibility preoperatively. They were considered eligible if they met all of the following inclusion criteria: were male or female aged 20-80 years; were capable of being discharged from the hospital within 2 weeks after major gastrointestinal surgery; were capable of oral intake; had no history of preoperative radiotherapy or chemotherapy; and voluntarily agreed to participate in the trial and signed an informed consent form. Major gastrointestinal surgery was defined as resection of a part or all of the gastrointestinal organ, accompanied by reconstruction of bowel continuity, including partial or total gastrectomy, major colon and/or rectal resection, pancreaticoduodenectomy, etc. Any procedure with ileostomy was excluded from eligibility. The exclusion criteria included the need for parenteral nutrition after discharge; weight loss at the time of discharge of less than 5% compared to the preoperative body weight in a subject whose body mass index was more than 25; allergy to milk, wheat, soy beans, or salmon; residual macroscopic tumor in the abdominal cavity in cases of cancer; other malignancy needing treatment; and a doctor's judgment that the clinical trial was not suitable for the patient.

A secondary screening was performed again after surgery when the screened patients were cleared for discharge from the hospital within 2 weeks after surgery. Subjects who satisfied all eligibility criteria were randomly assigned at a 1:1 ratio to the ONS group or the control group using a randomized block design with block sizes of four and six. The randomization sequence was created and protected by the Medical Research Collaborating Center at Seoul National University Hospital and was provided by website at the time of randomization. Randomization was stratified according to the institutes.

The subjects in the ONS group were instructed to take 2 packages per day (400 ml/day, 400 kcal/day) of an ONS (Encover®, EN Otsuka Pharmaceutical, Hanamaki City, Japan) from the day of discharge for 8 weeks. A placebo was not used in the control group because it could have reduced the subjects' oral intake and aggravated malnutrition. There were no limitations on the use of intravenous solutions, including glucose, amino acids, lipids, trace elements and vitamins, during the in-hospital period, but the use of any other intravenous or oral nutritional supplement was prohibited during the clinical trial period. Follow-ups were planned at 2, 4, and 8 weeks after discharge. Anthropometric measurements, biochemical tests, patient-generated subjective global assessments (PG-SGAs) and compliance surveys were performed before surgery and at each planned visit. The primary endpoint was the proportion of weight loss (in kg) at 8 weeks after discharge compared with the preoperative bodyweight (proportion of weight loss=[(preoperative body weight–body weight at 8 weeks after discharge)/preoperative body weight]×100 (%)). The secondary endpoints included changes in body weight (in kg) between the day of discharge and each follow-up visit, sequential changes in body mass index (BMI), the PG-SGA score/grade, and hematological and biochemical test results, and compliance with the ONS treatment, as determined using self-reporting documents and by counting of the number of remaining packages.

The planned sample size was 174 subjects, allowing for a 10% dropout rate and assuming an improvement in weight loss of up to 3% (standard deviation for each group=6.5%) with ONS administration. The rate of weight loss and standard deviation in the ONS group were expected to be 3.1% and 6.5%, respectively, according to Beattie et al.[13] The rate of weight loss in the control group was expected to be 6.1% based on previous reports of gastrectomy and colorectal surgeries.[10,11]

Primary efficacy analysis was based on a modified intention-to-treat population, which included all randomized subjects with at least one measurement after discharge who had taken the ONS at least one time, particularly those in the ONS group. Missing responses due to withdrawal from the treatment were handled for intention-to-treat analyses in the following two ways: complete data analysis and the multiple imputation method, using the responses at 2 and 4 weeks after discharge. Supportive analyses were also conducted using the per-protocol population, including the subjects who had completed all visits according to the protocol and took the ONS for 8 weeks with ≥50% compliance. Safety was monitored in

every randomized subject. The severity of complications was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

The normality assumption for continuous data was evaluated using a Q-Q plot and the Shapiro-Wilk normality test. Normally distributed data were summarized and compared using the mean±standard deviation and independent t-test; otherwise the median [min, max] and Wilcoxon rank sum test were used. A linear mixed effect model for repeated measures analysis was used to assess the differences in the parameters at 2, 4 and 8 weeks after discharge, with adjustment for preoperative differences. The model included the fixed effects of the preoperative parameters, the group (ONS or control), the visit and the interaction between the group and visit. Study participant was treated as a random effect. The insignificant interaction term between the group and visit was excluded in the model. The risk factors for proportion of weight loss at 8 weeks after discharge were verified using multiple linear regression models in exploratory analysis. The randomization group (ONS/control), age, sex, PG-SGA score/grade, extent of gastric resection (total/partial/non-gastric), length of hospital stay and method of surgery (laparoscopic/open) were considered as possible risk factors. Univariable and multivariable analyses with stepwise variable selection were performed. Interactions between any two risk factors in the multivariable model were tested. Graphical and residual analyses were performed to assess modelling assumptions. All reported p-values were two-sided. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

The study was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Approval for the study protocol was obtained from the independent ethics committee at each institute (the IRB reference number for the institution of the principal investigator is H-1301-116-460). This study is registered in clinicaltrials.gov (NCT01838109).

RESULTS

From August 2013 to March 2014, 174 patients (89 in ONS group, 85 in control group) were enrolled, and the trial ended with the last visit of the final subject in April 2014. From this sample, 168 (87 in ONS group, 81 in control group) and 146 subjects (68 in ONS group, 78 in control group) were selected for inclusion in intention-to-treat and per-protocol analyses, respectively.

The demographics and baseline nutritional/functional statuses did not differ between the two groups (Table 1). The numbers of operative procedures performed on the stomach, colorectum, and hepatobiliary system were 115, 46, and 6, respectively, with no significant differences between the two groups (p=0.914) (Table 2). Of 168 subjects, 164 (97.6%) underwent surgery due to malignant disease.

The primary endpoint, a body weight change (%) at 8 weeks after discharge compared to the preoperative weight, did not significantly differ between the two groups (Table 3). The difference in the weight loss rate between the two groups, as determined by intention-to-treat analysis with multiple imputations, was 0.71% (95% CI: -0.87%, 2.30%), indicating that the ONS was less effective than the hypothesis predicted. Analysis using a linear mixed effect model of body weight change at 2, 4, and 8 weeks after discharge did not reveal any significant differences between the two groups (Figure 1a). Insignificant results were also obtained from analyses of the subgroups, including the gastric operation group, colorectal

Table 1. Characteristics of ONS and control group

	ONS (n=87)	Control (n=81)	p-value
Age (min, max)	56 (23, 79)	57 (27, 77)	0.831‡
Male to female ratio	1.81 : 1	1.53 : 1	0.604§
Height (cm) (min, max)	164.4 (138, 178)	163.4 (145, 187)	0.838‡
Weight (kg), mean±SD	60.8±10.3	61.2±10.2	0.787¶
BMI, mean±SD	22.77±2.58	22.76±2.59	0.984¶
PG-SGA score, (min, max)	2 (1, 13)	2 (0, 11)	0.343‡
PG-SGA grade, n (%)			0.475††
A	59 (67.8%)	61 (75.3%)	
B	22 (25.3%)	17 (21.0%)	
C	6 (6.9%)	3 (3.7%)	
ASA score, n (%)			0.350††
1	52 (60.0%)	45 (55.6%)	
2	30 (34.5%)	33 (40.7%)	
3	2 (2.3%)	3 (3.7%)	
4	3 (3.5%)	0 (0%)	
5	0 (0.0%)	0 (0.0%)	
TSF, (min, max)†	16 (4, 34)	15 (4, 32)	0.780‡
MAC, (min, max)†	27 (15, 36.5)	21.8 (15.9, 27)	0.888‡
Length of stay	8 (5, 14)	7 (4, 14)	0.099‡
Laparoscopic, n (%)	70 (80.5%)	67 (82.7%)	0.706§

TSF: Triceps skin fold; MAC: mid-arm circumference; ONS: oral nutritional supplement; PG-SGA: patient-generated subjective global assessments; ASA: American Society of Anesthesiologists physical status classification.
The data for which the assumption of normality is valid are presented as the mean±standard deviation (SD); otherwise, the data are presented as the median [min, max]. The data for PG-SGA grade, ASA score, and number of laparoscopic surgery are presented as n (%).
†TSF and MAC were measured in 74 subjects in the ONS group and in 69 subjects in the control group.
‡Wilcoxon rank sum test, §Chi-square test, ¶t-test, ††Fisher's exact test.

Table 2. Operative procedures

	ONS (n=87)	Control (n=81)
Organ		
Gastric	61 (70.1)	54 (66.7)
Cancer	61 (100)	54 (100)
Benign	0	0
Colorectal	23 (26.4)	23 (28.4)
Cancer	23 (100)	22 (95.7)
Benign	0	1 (4.3)
Hepatobiliary	3 (3.4)	3 (3.7)
Cancer	2 (66.7)	1 (33.3)
Benign	1 (33.3)	2 (66.7)
Others (small bowel)	0	1 (1.2)
Procedures		
Total gastrectomy	10 (11.5)	13 (16.0)‡
Distal gastrectomy	40 (46.0)	34 (42.0)‡
Proximal gastrectomy	2 (2.3)	1 (1.2)
Pylorus-preserving gastrectomy	9 (10.3)	6 (7.4)‡
Right hemicolectomy	4 (4.6)	9 (11.1)‡
Left hemicolectomy	2 (2.3)†	0 (0.0)
Anterior resection	11 (12.6)	9 (11.1)
Low anterior resection	5 (5.7)	4 (4.9)
Total proctocolectomy	0	1 (1.2)
Colon segmental resection	1 (1.1)	0
Pancreaticoduodenectomy	1 (1.1)	2 (2.5)
Choledochal cyst excision	1 (1.1)	1 (1.2)
Extended cholecystectomy with hepaticojejunostomy	1 (1.1)	0
Small bowel segmental resection	0	1 (1.2)

ONS: oral nutritional supplement.
The values in parentheses are percentages.
†Distal pancreatectomy was combined in 1 case in the ONS group.
‡Benign mass excision, hiatal hernia repair, cholecystectomy (n=2), and adhesiolysis are combined in 5 cases in the Control group.

Table 3. Weight loss rate at 8 weeks after discharge compared to preoperative body weight

		ONS	Control	*p*-value
Total				
ITT analysis (complete data analysis)	n	83	79	
	Mean±SD	4.23±5.49	4.80±4.84	0.481†
ITT analysis (multiple imputation)	n	87	81	
	Mean±SD	4.06±5.49	4.77±4.82	0.378†
PP analysis	n	68	78	
	Mean±SD	3.55±5.32	4.83±4.86	0.129†
Gastric				
ITT analysis (complete data analysis)	n	59	53	
	Mean±SD	6.23±4.60	6.67±4.23	0.599†
PP analysis		46	53	
	Mean±SD	5.65±4.43	6.67±4.23	0.246†
Colorectal				
ITT analysis (complete data analysis)	n	22	23	
	Median (min, max)	0.32 (-12.42, 5.16)	0.59 (-4.68, 12.57)	0.503‡
PP analysis	n	20	22	
	Median (min, max)	0.32 (-12.42, 4.38)	0.37 (-4.68, 12.57)	0.521‡
Hepatobiliary				
ITT analysis (complete data analysis)	n	2	2	
& PP analysis	Median (min, max)	0.37 (-2.44, 3.18)	2.40 (2.08, 2.73)	>0.999‡

ONS: oral nutritional supplement; ITT: intention-to-treat; PP: per-protocol.
The data for which the assumption of normality is valid are presented as the mean±standard deviation (SD); otherwise, the data are presented as the median [min, max].
†t-test, ‡Wilcoxon rank sum test.

operation group, and subjects with a poor preoperative nutritional status (PG-SGA grades B & C) (Figures 1b-d). However, the weight loss rates and the loss of BMIs in the ONS groups at 4 and 8 weeks after discharge were consistently less than those in the control groups.

Analysis of the hematologic and biochemical parameters using a linear mixed effect model revealed that the total lymphocyte count and total cholesterol, total protein, and albumin levels were significantly higher in the ONS group compared to the control group (Figure 2). The ONS group also exhibited a trend of superior recovery of the hemoglobin level following adjustments for preoperative

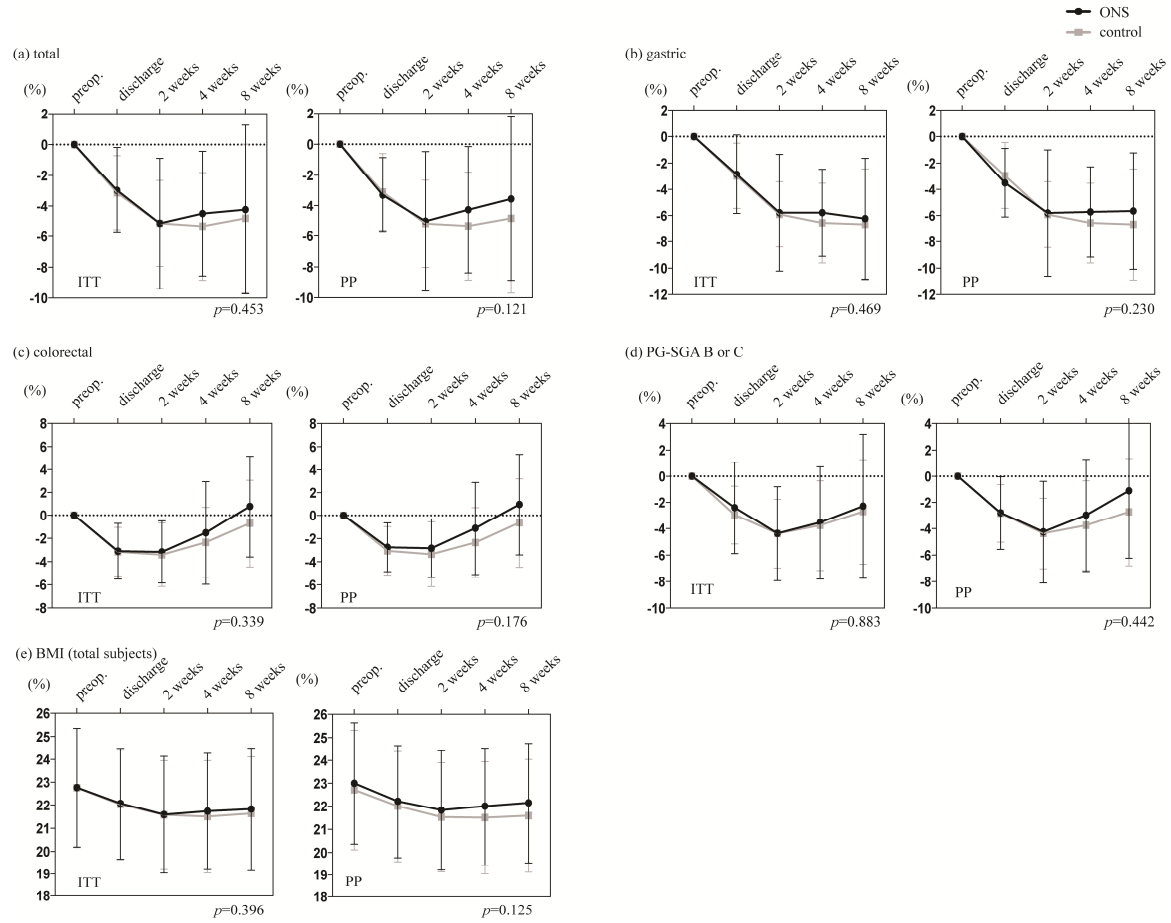

Figure 1. Weight loss (%) according to the follow-up time point. (a) Total subjects, (b) gastric operation subgroup, (c) colorectal operation subgroup, and (d) only subjects with a preoperative PG-SGA grade of B or C (ONS (n=28) and control (n=20) in ITT analysis, ONS (n=22) and control (n=19) in PP analysis). (e) Changes in body mass index. The *p*-values were calculated by mixed model analysis with adjustments for preoperative differences. ITT: intention-to-treat; PP: per-protocol; PG-SGA: patient-generated subjective global assessments; BMI: body mass index.

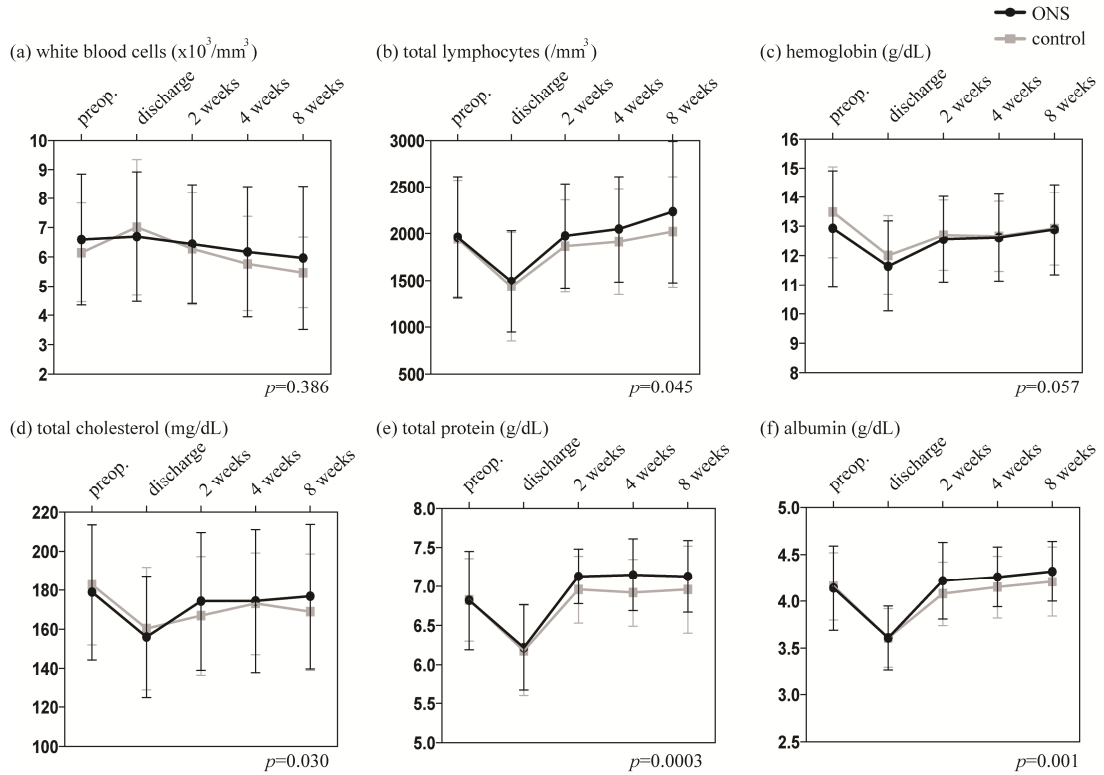

Figure 2. Changes in biochemistry test results. (a) White blood cell count, (b) total lymphocyte count, and (c) hemoglobin, (d) total cholesterol, (e) total protein, and (f) albumin levels. The *p*-values were calculated by mixed model analysis with adjustments for preoperative differences.

differences (least square mean± standard error : 12.85± 0.09 in the ONS group vs 12.61±0.09 in the control group, p=0.057).

The PG-SGA scores at preoperative day, 2 weeks, 4 weeks, and 8 weeks were 3.14±2.62, 7.36±2.82, 5.35±3.07, and 3.71±2.48, respectively, in the ONS group and 2.74±2.32, 7.30±2.66, 5.46±2.92, and 3.65±2.40, respectively, in the control group. (p=0.989). The proportion of PG-SGA grades B or C at preoperative day, 2 weeks, 4 weeks, and 8 weeks were 32.2%, 90.7%, 71.8%, and 47.0%, respectively, in the ONS group, and 24.7%, 88.9%, 71.8%, and 45.5%, respectively, in the control group. PG-SGA scores/grades were the worst at 2 weeks after discharge, and the subjects exhibited gradual restoration of their PG-SGA scores/grades to levels similar to those observed preoperatively. There were no significant differences between the two groups.

Approximately 80% of the subjects showed compliance of ≥50%, and the colorectal surgery group showed better compliance than the gastric surgery group (Figure 3a). The compliance rate exhibited an increasing trend according to time (70.74±29.29%, 76.34±26.94%, and 77.65±29.2% for 2, 4, and 8 weeks after discharge, respectively). However, the subjects who underwent total gastrectomy showed a decreasing pattern of compliance between 4 and 8 weeks (Figure 3b). Body weight change was related to compliance with the ONS treatment (Figure 3c). The subjects with <50% compliance showed poorer recovery of body weight compared with those in the control group, and the body weight loss tended to continue to increase.

In linear regression analysis, which was an exploratory

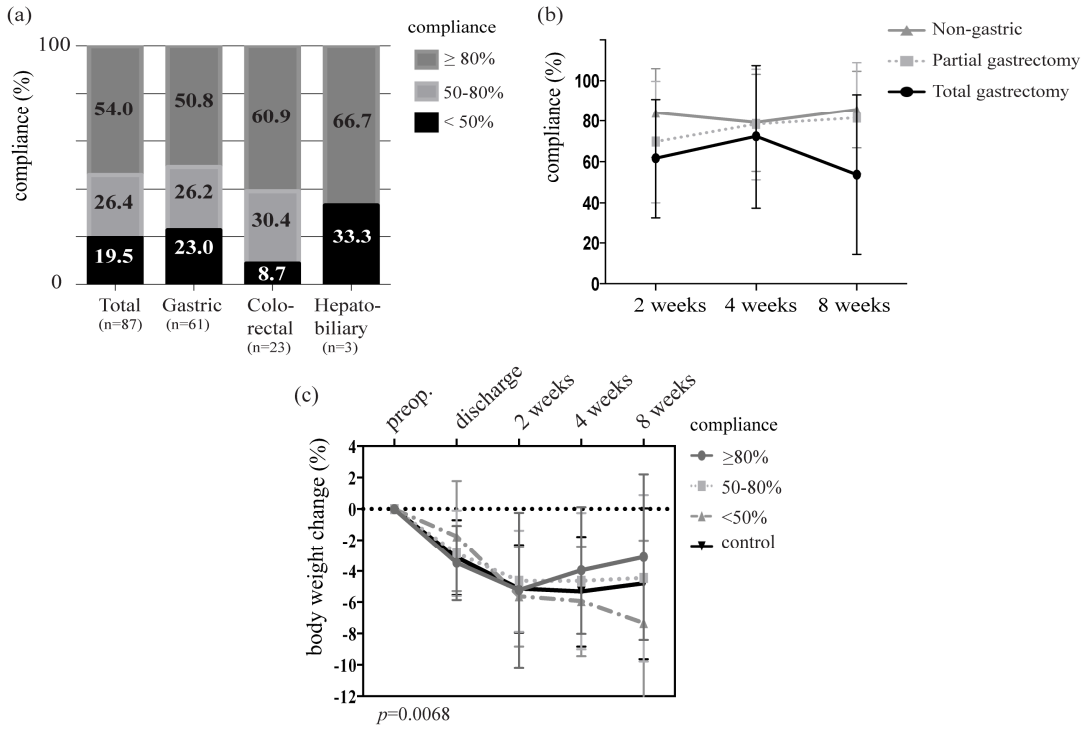

Figure 3. Factors related to compliance with ONS solution administration. (a) Compliance with oral nutritional supplement intake according to the type of surgery. (b) Change in compliance according to the extent of gastric resection. (c) Body weight change according to the total compliance with oral nutritional supplement intake. The p-values were calculated by analysis of linear trends in the order of <50%, control, 50-80%, and ≥80%.

Table 4. Risk factors for weight loss analyzed using the linear regression model

Parameter	Univariable analysis		Multivariable analysis†	
	β coefficient (95% CI)	p-value	β coefficient (95% CI)	p-value
Group, ONS	-0.58 (-2.18, 1.03)	0.481		
Age	-0.07 (-0.14, 0.001)	0.053		
Sex, women	2.14 (0.51, 3.78)	0.011	1.85 (0.50, 3.20)	0.008
PG-SGA grade (ref=A)				
C	-4.72 (-8.14, -1.29)	0.007	-1.04 (-3.87, 1.79)	0.469
B	-2.45 (-4.30, -0.60)	0.010	-1.99 (-3.54, -0.45)	0.012
Procedure (ref=CR and HBP)				
Total gastrectomy	9.68 (7.62, 11.74)	<0.001	8.88 (6.80, 10.97)	<0.001
Partial gastrectomy	5.41 (3.99, 6.83)	<0.001	5.04 (3.59, 6.48)	<0.001
Length of stay	-0.71 (-1.11, -0.31)	0.001		
Type of surgery (ref=open)	-2.75 (-4.87, 0.64)	0.011		

CR: colorectal surgery; HBP: hepato-bilio-pancreatic surgery; ONS: oral nutritional supplement; PG-SGA: patient-generated subjective global assessments.
†R-squared=0.429.

Table 5. Incidence rates of adverse events

	ONS			Control		
	2 wks	4 wks	8 wks	2 wks	4 wks	8 wks
Adverse event						
Diarrhea	10 (11.5)	5 (5.7)	6 (6.9)	5 (6.2)	2 (2.5)	8 (9.9)
Abdominal discomfort	3 (3.4)	1 (1.1)	0	1 (1.2)	0	0
Abdominal pain	8 (9.2)	5 (5.7)	2 (2.3)	6 (7.4)	1 (1.2)	1 (1.2)
Nausea	6 (6.9)	3 (3.4)	5 (5.7)	1 (1.2)	5 (6.2)	3 (3.7)
Vomiting	5 (5.7)	6 (6.9)	5 (5.7)	5 (6.2)	5 (6.2)	2 (2.5)
Severity grade						
1	29 (33.3)	18 (20.7)	16 (18.4)	12 (14.8)	12 (14.8)	14 (17.3)
2	1 (1.1)	2 (2.3)	2 (2.3)	5 (6.2)	1 (1.2)	0
3	2 (2.3)	0	0	1 (1.2)	0	0
4/5	0	0	0	0	0	0
Relationship with ONS						
Highly probable	2 (2.3)	0	0	0	0	0
Probable	2 (2.3)	1 (1.1)	0	0	0	0
Possible	10 (1153)	5 (5.7)	3 (3.4)	0	0	0
Unlikely	1 (1.1)	3 (3.4)	3 (3.4)	0	0	0
Not related	17 (19.5)	11 (12.6)	12 (13.8)	18 (22.2)	13 (16.0)	14 (17.3)

The values in parentheses are percentages.

analysis, female gender, PG-SGA grade A, gastrectomy (especially total gastrectomy), open surgery and a shorter length of hospital stay were found to be risk factors for weight loss in univariate analysis (Table 4). Female gender, PG-SGC grade A (compared with B), and gastrectomy were independent risk factors in multivariable analysis. The length of hospital stay and method of surgery did not significantly differ after adjusting for the type of surgery.

The proportions of subjects who experienced any adverse event were 37.1% (33 subjects, 70 events) and 25.9% (22 subjects, 44 events) in the ONS and control groups, respectively (Table 5). The most frequent adverse event in both groups was diarrhea, and the incidence rates of events with a severity grade of ≥3 were 2.3% (2 subjects) and 1.2% (1 subject) in the ONS and control groups, respectively.

DISCUSSION

This study aimed to evaluate the efficacy of ONS intake over 8 weeks after discharge for the patients who have undergone major gastrointestinal surgery. Unlike the previous study conducted by Beattie et al., who recruited only malnourished patients, we intended to evaluate the benefits of the routine use of an ONS to treat patients who had undergone various types of gastrointestinal surgery because the treatment process for major gastrointestinal surgery itself can put most patients at risk of malnutrition. This hypothesis is supported by the results of this study indicating that 90% of the subjects became PG-SGA grade B or C at 2 weeks after discharge. The first several weeks after the date of discharge is considered the most vulnerable period for post-operative malnutrition because the gastrointestinal functions of patients are not completely recovered and because they do not receive daily nutritional advice after discharge from the hospital. Therefore, this period was selected as the time when an ONS might be the most beneficial for patient recovery.

In contrast with the previous study, we failed to demonstrate the efficacy of the ONS in reducing body weight loss. This result can be partly explained by the lower body weight loss rate of the control group (approximately 4.8%) compared with the expected rate (6.1%) based on previous studies.[10,11,13] The improvement in the control group compared with previous studies may be explained by the development of laparoscopic surgery, better perioperative care and the effects of patient education. Despite the absence of a significant difference in weight loss between the ONS and control groups, we found consistent trends of increased body weight and earlier recovery from 2 weeks after discharge in the ONS group in subgroup analyses, as shown in Figure 1. The patients who underwent colorectal surgery returned to their preoperative weights at 8 weeks, which is in accordance with Smedley,[15] but a pattern of early recovery could also be identified in the ONS group.

On the other hand, the ONS group exhibited superior restoration of biochemical parameters such as the total lymphocyte count and the cholesterol, protein, and albumin levels (Figure 2). These results indicated that the use of an ONS post-operatively could be helpful for maintaining immunologic function and that it could facilitate anabolic processes by minimizing negative nitrogen balances because it provided more balanced nutrition, including proteins, compared with a diet lacking an ONS. The improvements in the biochemical parameters tended to begin at 2 weeks after discharge, which was earlier than the time point at which the differences in body weight emerged (4 weeks after discharge).

Multivariable analysis using a linear regression model revealed that female gender, PG-SGA grade A, and gastrectomy were risk factors. The greater weight loss of the patients with PG-SGA grade A again implied that the effects of major surgery on the nutritional status were not limited to patients with preoperative malnutrition. Thus, nutritional status should be more closely monitored in female patients undergoing total gastrectomy.

We found that body weight loss was inversely correlated with compliance with the ONS treatment and that subjects with compliance of <50% experienced consistent

weight loss (Figure 3d). It was difficult to determine whether the increased recovery of body weight in the subjects with high compliance was due to effects of the ONS or whether the high compliance reflected a general capacity for oral intake. We could not perform detailed analysis of diets other than the ONS, which may have provided information about this distinction, due to technical limitations, which is one weakness of this study. For both hypotheses, less than 50% compliance with the ONS treatment could be regarded as indicative of a high risk of malnutrition. In the clinical setting, <50% compliance with an ONS treatment could be used as a reference indicating poor intake or malnutrition instead of a complex and time-consuming diet analysis. More frequent follow-ups or additional nutritional support could be planned for these patients accordingly.

Another weakness of this study was that we could not completely blind the subjects by administering placebos because a placebo without nutritional content could have reduced the intake of other foods and have resulted in unethical malnutrition in the control group. We also could not completely control the nutritional education program at each institute. Further, the process of the clinical trial itself could have influenced the behavior of the subjects in the control group by reminding them about the importance of postoperative oral intake. Another weakness is that we could not perform measurements of more sensitive and accurate biochemical markers reflecting the acute nutritional status, such as pre-albumin, retinol-binding protein, or transferrin.[16,17] All of these parameters are meaningful only with adjustments of the pre-operative levels. Because enrolment of the subjects was performed at the time of discharge, we had technical difficulties with obtaining non-routine samples for research purposes before enrolment. However, we believe that more general biochemical markers, including the total lymphocyte count and total cholesterol, total protein and albumin levels, can still meaningfully represent the nutritional status in a time frame of 2-8 weeks after discharge.

It is unclear whether the improvements in the biochemical parameters demonstrated in this study would be continued over the long-term. Considering previous reports demonstrating that body weight stabilizes after this period and remains similar over the long term, we cautiously hypothesize that early nutritional support may be helpful for adaptation and for the reestablishment of neurohormonal homeostasis over the longterm.[10,11,18,19] These issues may be addressed by long-term follow-ups of the subjects.

In conclusion, the utility of routine postoperative ONS administration after major gastrointestinal surgery was not proven in terms of weight loss at 8 weeks after discharge. However, postoperative ONS administration did contribute to the improved recovery of some biochemical parameters, such as the total lymphocyte count and total cholesterol, serum protein, and albumin levels compared with the control group during the early time period after discharge in patients who had undergone major gastrointestinal surgery.

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AUTHOR DISCLOSURES

JW Pharmaceutical provided research funding and investigational products (oral nutritional supplements) to conduct this clinical trial. All processes involved in conducting the trial, including the study design, collection, analysis and interpretation of data, the writing of the report, and the decision to submit the article for publication, were made by the investigators independent from JW Pharmaceutical.

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