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Clinical Original Article

Title: Impact of elemental diet on early recovery after laparoscopic colectomy: A randomized controlled trial

Short title: Elemental Diet in Lap Colon

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Keywords: elemental diet; laparoscopic colectomy; estimated minimum length of stay in hospital.

Abstract

Purpose: Amino acids-containing elemental diet (ED) does not require digestion for nutritional absorption. It is thus a good option for gastrointestinal malabsorption patients. Enhancement of recovery by perioperative ED in laparoscopic colectomy was verified through a randomized study.

Methods: Patients in the intervention arm was scheduled to receive commercially available ED from the day prior to surgery to the postoperative day (POD) 3. Control group received a conventional perioperative diet program. The primary endpoint was the ratio of the patients who had achieved "Estimated minimum length of stay after surgery" (emLOS) within 1 week, which is defined as the number of days necessary to reach all the five criteria for discharge, namely "Sufficient oral intake", "Sufficient pain control", "Withdrawal of intravenous alimentation", "No abnormal findings in routine examinations", and "No rise in fever".

Results: A total of 102 patients were randomized and 94 analyzed (ED 45, control 49). No morbidity was observed. The shorter achievement of emLOS (POD4 vs 7; p=0.018) and the earlier recovery of "Sufficient oral intake" (POD3 vs 4; p=0.034) were observed in ED group.

Conclusions: Perioperative ingestion of ED in laparoscopic colectomy is safe, and may enhance shorter hospital stay by supporting the acceleration of feeding. **(200 words)**

Introduction

In the past ten years, it has become generally accepted that perioperative nutritional management enhances outcomes after surgery. For elective surgery fasting prior to anesthesia is now limited to six hours for solids and two hours for clear carbohydrate drinks (CCD) [1, 2]. For postoperative oral intake after laparoscopic colectomy, the Enhanced Recovery After Surgery (ERAS®) protocol recommends oral intake at the earliest possible opportunity [3].

Despite the interest in perioperative nutritional management, adequate discussions concerning the optimal nutrient composition have yet to take place. To investigate an alternative perioperative nutritional management protocol for preoperative CCD ingestion and postoperative intake of oral nutritional supplements (ONS), we used a commercially available elemental diet (ED), Elental® (Ajinomoto Pharmaceutical, Tokyo, Japan) for this study. The composition of solution-prepared Elental® is 1 kcal/ml, 906 mOsm/kg, and a 300ml solution (1 package) contains 63.3g carbohydrates (provided as dextrin), 13.2 g amino acids (provided as 17 amino acids including 9 essential amino acids), 0.5g of fat, and vitamins and minerals. This amino acids-containing high-calorie and low-fat ED has a high nutritional absorbency without requiring digestion. Therefore it is recommended for digestive diseases [4], such as inflammatory bowel disease, acute pancreatitis, and short bowel syndrome. Based upon these facts, we hypothesized that perioperative nutritional management with ED would be beneficial for patients suffering from postoperative insufficiency of their digestive function [5]. Consequently, we

designed a randomized controlled trial (RCT) to determine whether ingestion of perioperative ED helps in accelerating the return of gastrointestinal functions and enhancing recovery in patients who underwent laparoscopic colectomy.

Methods

Study design

The protocol for this clinical trial “Multicenter study of the effect of Elemental diet for Perioperative nutrition in Laparoscopic colorectal Surgery (EPLAS)” was approved by the Ethics Committee of the Hokkaido University Graduate School of Medicine (IRB#011-0249) and registered on the UMIN Clinical Trials Registry (#000008154). This study was carried out by Gastroenterological Surgery II, Hokkaido University Hospital and ten affiliated hospitals; Sapporo Tonan Hospital KKR Medical Center, Hokkaido Gastroenterology Hospital, Obihiro-Kosei General Hospital, Steel Memorial Muroran Hospital, Japanese Red Cross Kitami Hospital, Hakodate Central General Hospital, Oji General Hospital, NTT East Sapporo Hospital, Japanese Red Cross Asahikawa Hospital, Kushiro City General Hospital. Ethics committee approval was given in all the centers and the trial was conducted based on ethical guidelines for clinical studies taking into consideration the patients’ human rights and privacy.

Patient eligibility

Patients meeting all of the following criteria were selected as subjects for this study: diagnosed

colorectal cancer located in the colon and the rectosigmoid, planned laparoscopic surgery, histologically-proven colorectal adenocarcinoma, expectation of a curative operation regardless of the stage of the cancer, sufficient physical function of the main organs, under 76 years of age, Performance Status (ECOG) [6] of 0 or 1, and voluntary written informed consent. Exclusion criteria of patients were as follows: neoplastic symptoms of ileus, bleeding, or perforation, preoperative treatment using chemotherapy, radiotherapy, or immunotherapy, severe or uncontrolled complications, risk of aspiration pneumonia due to neurological or neuromuscular disease, psychosis or psychiatric disorders judged by the investigator as disqualifying the patient from participating in the study, and any other reasons warranting non-inclusion. Exclusion criteria after initial registration and randomization were as follows: withdrawal by the patients, changes in the planned operative procedure such as conversion to open surgery, and any other reasons judged by the investigators as necessitating exclusion from the study.

Interventions

Patients in the intervention arm (ED group) received Elental®. Perioperative oral ED ingestion 900 mL with a bowel preparation diet on the day prior to surgery. On the day of the operation: 300ml preoperatively completed 2.5 hours before transportation to the operating room, and 300ml postoperatively that can be started 5 hours after operation and when the patient is able to maintain a sitting position. POD1 and POD2: 900 mL/day. POD3: 300-900 mL with the start of dietary intake of hospital food. The patients in the control group received a conventional perioperative diet program

(Table 1). The preoperative bowel preparation was the same in each group (oral administrations of 0.75% sodium picosulfate and sennosides).

Endpoints, sample size, and randomization

The primary endpoint was the ratio of the patients who had achieved an "Estimated minimum length of stay in hospital after surgery" (emLOS) of less than one week, which is defined as the number of days required to fulfill all five criteria for discharge: "sufficient oral intake", "sufficient pain control", "withdrawal of intravenous alimentation", "no abnormal findings in routine examinations", and "no rise in fever". "Sufficient oral intake" was defined as regular hospital food accounting for over 80 % of oral intake nourishment. "Sufficient pain control" was defined as the withdrawal of the patients' epidural anesthesia and a subjective pain scale of 0 or 1 (0: "painless, 1: "slight", 2: "moderate", 3: "severe," 4: "worst") regardless of the usage of oral analgesic drugs. "No abnormal findings in routine examinations" was defined as postoperative laboratory data (WBC, Plt, Hb, TP, Alb, T-Bil, AST, ALT, Cr, and CRP) within the normal range or within the normal postoperative course as judged by the attending surgeon, and the absence of abnormal X-ray findings (e.g. ileus or pneumonia). "No rise in fever" was defined as a body temperature less than 38°C or equal to the patient's baseline. The secondary outcomes were safety, compliance of perioperative administration of ED, adverse events and complications, and length of stay in hospital after surgery (LOS). Subjective items such as pain scale and nausea were self-reported by patients using survey sheets and monitored by the attending nurses. Stool was categorized on the survey

sheets shown by check boxes as ‘diarrhea’, ‘soft feces’, ’normal feces’, and ‘hard feces’ and self-reported by patients. Routine perioperative examinations were scheduled at 4 points: preoperative, POD1, 4, and 7. The sample size setting was determined based on the result of a small scale pilot study (unpublished data; presented by T. Sasaki et al., at the 112th annual meeting of the Japan Surgical Society, 2012). Based on this study, emLOS within POD 7 for each group was hypothesized as 80% in the ED group and 50% in the control group respectively. To determine a clinically relevant of emLOS within POD7 (80% test power and α level of 0.05), 78 patients were required based on a power calculation. To allow for dropouts we planned to recruit 50 patients in each group. Random allocations performed by an independent statistician were completed before the surgery, using the minimization method to balance institution, sex, age, and location of the tumor.

Statistical analysis

Patients were analyzed according to intention-to-treat principles. StatFlex ver.6 software (Osaka, Japan) and JMP Pro11 software (Tokyo, Japan) were used for the statistical analysis. Continuous, normally distributed data were expressed as mean ± s.d., and statistical analysis was performed using unpaired *t* test. Non-normally distributed data were expressed as median (maximum-minimum range) and the Mann–Whitney *U* test was used. Fisher’s exact test was used for categorical data. *P* values presented are two tailed and $p< 0.050$ was considered statistically significant.

Results

A total of 102 patients were recruited and randomized, of whom 8 patients were withdrawn and 94 patients analyzed (Figure 1). There was no difference between the groups in baseline variables, clinical findings, or perioperative data (Table 2).

"Estimated minimum length of stay in hospital" and actual LOS

The clinical outcomes of emLOS, the criteria of discharge, and the actual LOS on each group are summarized in Table 3. The median of days to achieve emLOS was significantly shorter in the ED group compared to the control group (POD4 vs POD7, p=0.018). In the ED group, "Sufficient oral intake" was established on POD3, whereas the control group required 4 days to reach it (p=0.034). The significance of "Withdrawal of intravenous alimentation" (p=0.019) resulted from the different intravenous alimentation schedules within POD3 (Table 1). The median of actual LOS on each group was not significantly different (p=0.176): 9 days in the ED group and 10 days in the control group. Figure 2 shows the time-course of achievement of emLOS in each group. The primary endpoint for the ratio of patients who had achieved an emLOS of less than one week was not significant; the ratio of the patients who achieved the criteria on POD4 was significantly higher in the ED group (51% vs 29%, p=0.035), whereas no significant difference was observed after this period.

Figure 3 shows the time-course of oral intake of the meals supplied to each group. The ED group reached 80% oral intake on POD3, whereas the control group took 4 days to reach the same level. A

significant difference was observed on POD5 (100% vs 80%, p=0.025).

Adverse events and gut function outcomes

Postoperative morbidity was comparable between the groups (Table 4). The outcomes of the gut function are summarized in Table 5. A Significant shortening of the time to reach defecation was observed in the ED group (2.16±1.57) compared to the control group (3.10±1.61); p=0.005. Postoperative digestive symptoms, diarrhea, nausea, and vomiting during the administration of elemental diet to the ED group (from operation day to POD3) were not significantly different compared to the control group (Table 5).

Compliance of elemental diet

In the ED group, the percentage of the patient who adhered to the protocol was 44%. Twenty five patients were protocol-variant and 12 of them continued daily ingestion of ED but reduced the volume. The percentage of patients who ingested at least half the volume of ED of the protocoled dose during the protocoled period was 65% (Table 6).

Discussion

The length of stay in hospital after surgery is different in each country [7]: it depends on social conditions such as medical insurance systems and cultural factors. In this study, to assess the benefit of perioperative ED ingestion to the patient's recovery, we defined the criteria emLOS to indicate the

hypothetical minimal length of stay for each patient. emLOS represents the number of postoperative days required to fulfill all these five criteria: “Sufficient oral intake”, “Sufficient pain control”, “Withdrawal of intravenous alimentation”, “No abnormal findings in lab data and X-ray”, and “No rise in fever”. These criteria are those used to decide when to discharge a patient. They are based on objective data derived from the patient’s medical chart and examinations, the patient's own statements, and subjective assessments by medical personnel. In this study, emLOS demonstrated a significant difference between the groups as indicators of patients’ recovery after surgery. On the contrary, the actual LOS did not show any significant difference. Recently, Fiore et al. [8, 9] reported two articles describing criteria for hospital discharge following colorectal surgery using both the Delphi technique and systemic review. The criteria mentioned in the literature are: oral intake, recovery of the lower gastrointestinal function, adequate pain control, adequate mobility, absence of evidence of complications or untreated medical problems. The emLOS covers these criteria except mobility. To improve the emLOS as a more precise criterion, simple and objective index measures of a patient's mobility such as “No requirement for nursing care for dietary intake, excretion, dressing, and taking a shower” should be added as components of the assessment.

Although the safety of two-hours fasting after ingestion of CCD prior to the induction of anesthesia is based on the knowledge that CCD is less retained within the stomach [1, 2], the length of fasting after administration of amino acid is controversial. Lobo et al. [10] reported that ONS containing 15g of

glutamine with 50g carbohydrate dissolved with water to a total volume of 300 ml or 400ml prolonged gastric empting compared to 400ml of standard CCD (preOp®) containing an equal weight of carbohydrates, and recommended at least 3 hours preoperative fasting for protein or fat containing clear liquids. However, Awad et al. [11] compared three isocaloric-isovolumetric (410ml and 207kCal) solutions; standard CCD (preOp®), amino acid containing solution (36g carbohydrate+15g glutamine), and lipid containing solution (36g carbohydrate+7g lipid). Their study demonstrated that glutamine and lipid supplementation did not prolong gastric emptying, and that the glutamine-containing supplement reduced the glucose response compared to the others. Gastric emptying of Elental® is known to be more rapid than standard ONS [12], but the actual clearance time from the stomach had not been examined previously. Therefore, we conducted a pilot study to confirm the safety of ED ingestion. Clearance from the stomach was confirmed by three healthy volunteers: the absence of residual liquid within the stomach 2.5 to 3 hours after 300ml of oral ingestion was confirmed using an endoscope. Based on this result, we designed the protocol with 2.5 hours fasting after ingestion of ED prior to transportation to the operating room. As a result, no adverse event concerning the safety of ED ingestion was observed. No ED-related preoperative adverse event nor incident during induction of anesthesia was reported. Incidence of postoperative vomiting and ileus were not statistically different in both groups (Table 4, 5). We conclude that preoperative ingestion of this particular ED, 300ml of Elental®, by patients with a normal physical condition not less than 2.5 hours prior to anesthesia is safe.

Compliance to the protocol is another issue. The percentage of patients in the ED Group who adhered to the protocol was 44% (Table 6). Although almost all patients complied with the protocol before surgery, only about the half of them adhered the postoperative ED-ingestion schedule. The taste of the solution or the volume of ingestion may partly explain the low compliance. Other possible reason for the high protocol-variant rate might be the occurrence of diarrhea. Although the ratio of diarrhea recorded on the study was not significantly different between the groups (ED 51% vs Control 31%, p=0.059), this might have been high enough to reduce the volume of ED due to patients' requests or decisions by the medical staff. Therefore to develop the postoperative ingestion program of ED in clinical practice, the optimization of the volume and the concentration of the solution to minimize diarrhea is necessary to keep patients on ED.

Our clinical trial has some limitations. This study had not been designed based on the ERAS® protocol [3]. The first kick-off-meeting for the study had been held on 2009, then after the completion of the pilot study, the RCT was started. At that time, ERAS had not been fully adopted as a clinical practice. To confirm the merit of perioperative ED ingestion, rather than the conventional perioperative diet program, the updated ERAS® protocol with preoperative CCD and postoperative ONS should be compared. The study was not designed as to assess the metabolic aspects such as the elevation of blood glucose level, insulin response, or nitrogen balance, and muscle strength after perioperative administration of ED that have already been demonstrated by the ingestion of CCD [13-16]. Further

investigation is also needed to discuss the significance of ED as a perioperative supplemental feeding option. Recent studies have argued in favor of perioperative ONS with “enhancing” specific amino acids administration such as Glutamine to improve the cumulative nitrogen balance and decrease postoperative infectious morbidity [17]. The merit or necessity of ED as “all-inclusive” nutritional elements over ONSs “enhancing” specific amino acids is an issue to be investigated.

In conclusion, this study is the first RCT that investigates perioperative ingestion of ED in laparoscopic colectomy. Perioperative ingestion of ED is safe, and may shorten hospital stay by helping the acceleration of bowel movement and promoting postoperative feeding. To confirm the advantage of perioperative ED compared to both preoperative CCD and early feeding with supplemental ONS, further examination with a well-designed RCT is necessary.

Conflict of Interest Statement

Toshiaki Shichinohe and his co-authors have no conflict of interest.

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Table 1. Protocol Schedule of Infusion, Ingestion, and Oral Intake for Each Trial Group

	ED group	**Control group**
Day-2	low residue diet	
Day-1	bowel preparation diet	
	ED 900ml	PPN (A/N)
Day0 (pre ope)	ED 300ml*	NPO PPN (A/N)
Day0 (post ope)	ED 300ml† +water-drinking PPN 1000mL	NPO PPN 2000mL
POD1-2	Water-drinking	
	ED 900mL PPN 500mL	PPN 2000mL
POD3	rice gruel (half-watery)	
	ED 300-900mL	PPN 1000mL
POD4 ~	rice gruel (medium-solid) ~ normal diet	

ED; elemental diet. PPN; peripheral parenteral nutrition. NPO; nil per os. A/N; as needed.

*Preoperative ED should be completed 2.5 hours before transportation to the operating room.

†Postoperative ED can be started 5 hours after operation when the patient can maintain a sitting position.

Table 2. Patients' Characteristics and Baseline Data

	ED group (*n*=45)	**Control group (*n*=49)**	***P***
Age (years)	63±10	64±9	0.569
Sex ratio (M:F)	24:21	24:25	0.686
Body mass index (kg/m^2)	23.6±3.6	23.7±3.2	0.854
Performance status (PS0/1)	45/0	47/2	0.496
History of open abdominal surgery	8 (18)	12 (24)	0.461
Preexisting comorbidities	15 (33)	21 (43)	0.399
Tumor location (C/A/T/D/S/RS)	6/12/4/2/16/5	6/16/2/6/15/4	0.667*
Primary tumor (clinical; Tis/T1/T2/T3/T4)	0/10/13/22/0	0/18/10/21/0	0.638*
Regional lymph node (clinical; N0/N1-2)	37/8	39/10	0.798
Distant metastasis (clinical; M0/M1)	45/0	49/0	1.000
Stage (clinical; 0/I/IIA,B/IIIA,B,C/IV)	0/22/15/8/0	0/26/13/10/0	0.971*
Operation time (min)	194.1±73.2	192.7±54.1	0.912
Bleeding (mL)	30.7±70.0	16.3±31.4	0.195
Drain placement	15 (33)	21 (43)	0.399
Resection type (R0/1-2)	45/0	48/1	1.000

Values in parentheses are percentage *chi-squared test

Table 3. Clinical Evaluation

	ED group (*n*=45)	**Control group (*n*=49)**	***P***
"Estimated minimum length of stay in hospital" (longest number of the days of a-e)	4 (3-25)	7 (4-27)	0.018
a. "Sufficient oral intake"	3 (3-10)	4 (3-25)	0.034
b. "Sufficient pain control"	3 (0-7)	3 (0-20)	0.570
c. "Withdrawal of intravenous alimentation"	4 (3-25)	4 (3-23)	0.019
d. "No abnormal findings in routine examinations"	4 (1-11)	7 (1-27)	0.200
e. "No rise in fever"	2 (1-8)	2 (0-17)	0.401
Length of stay in hospital (actual)	9 (5-29)	10 (7-68)	0.176

Data are median (range). Statistical analysis was done by Mann-Whitney *U* test.

Table 4. Operative Morbidity and Mortality

	ED group (*n*=45)	**Control group (*n*=49)**	***P***
Any complication	9 (20)	11 (22)	0.806
Anastomotic leakage	0 (0)	3 (6)	0.243
Ileus	1 (2)	3 (6)	0.618
Wound infection	3 (7)	5 (10)	0.716
Intra-abdominal abscess	1 (2)	1 (2)	1.000
Bleeding	2 (4)	0 (0)	0.227
Fistula	0 (0)	1 (2)	1.000
Thrombosis, Pneumonia, Stroke	0 (0)	0 (0)	1.000
Others	2 (4) Meniere's disease 1, Neurogenic bladder 1	1 (2) Urinary tract infection 1	0.605
Complications require reoperation	1 (2) Ileus 1	3 (6) Ileus 2, Leakage 1	0.618
Mortality	0 (0)	0 (0)	1.000

Values in parentheses are percentage.

Table 5. Intestinal Movement and Digestive Symptoms

	ED group (*n*=45)	**Control group (*n*=49)**	***P***
Intestinal movement, time to appearance after operation (days)			
Bowel sound	0.76±0.80	1.04±0.90	0.122
Flatus	1.24±0.91	1.51±0.94	0.167
Defecation	2.16±1.57	3.10±1.61	0.005
Digestive symptoms observed during Day0 to POD3			
Diarrhea	23 (51)	15 (31)	0.059
Nausea	13 (29)	15 (31)	1.000
Vomiting	7 (16)	5 (10)	0.542

ED; elemental diet. Values in parentheses are percentage. Data are mean±s.d. for continuous variables.

Unpaired *t* test is used for continuous variables and Fisher's exact test for categorical data.

Table 6. Compliance of Oral Intake of Elemental Diet

	Protocoled ED (ml)	**Actual volume of ED (ml)**	**Adherence**	
			100%	**>50%**
Total	3300~4200	3011±1128	20 (44)	29 (65)
Day-1	900	847±195	41 (91)	43 (96)
Day0 (pre ope)	300	280 ±76	42 (93)	42 (93)
Day0 (post ope)	300*	188±137	25 (56)*	29 (64)*
POD1	900	612±367	24 (53)	31 (69)
POD2	900	599±365	23 (51)	31 (69)
POD3	300~900	485±355	35 (78) †	35 (78) †

ED; elemental diet. Values in parentheses are percentage. *Postoperative ED is not obligation.

†Calculates 300ml as 100%

Figure legends

Figure 1. CONSORT Flow Diagram

ED; elemental diet.

Figure 2. Time-Course of Achievement of “Estimated minimum length of stay in hospital”

ED; elemental diet group. *p=0.035, Fisher’s exact test

Figure 3. Time-Course of Oral Intake

ED; elemental diet group. Plots indicates median, lower quartile (Q1), and upper quartile (Q3). *p=0.025, Mann–Whitney U test.

Fig.1

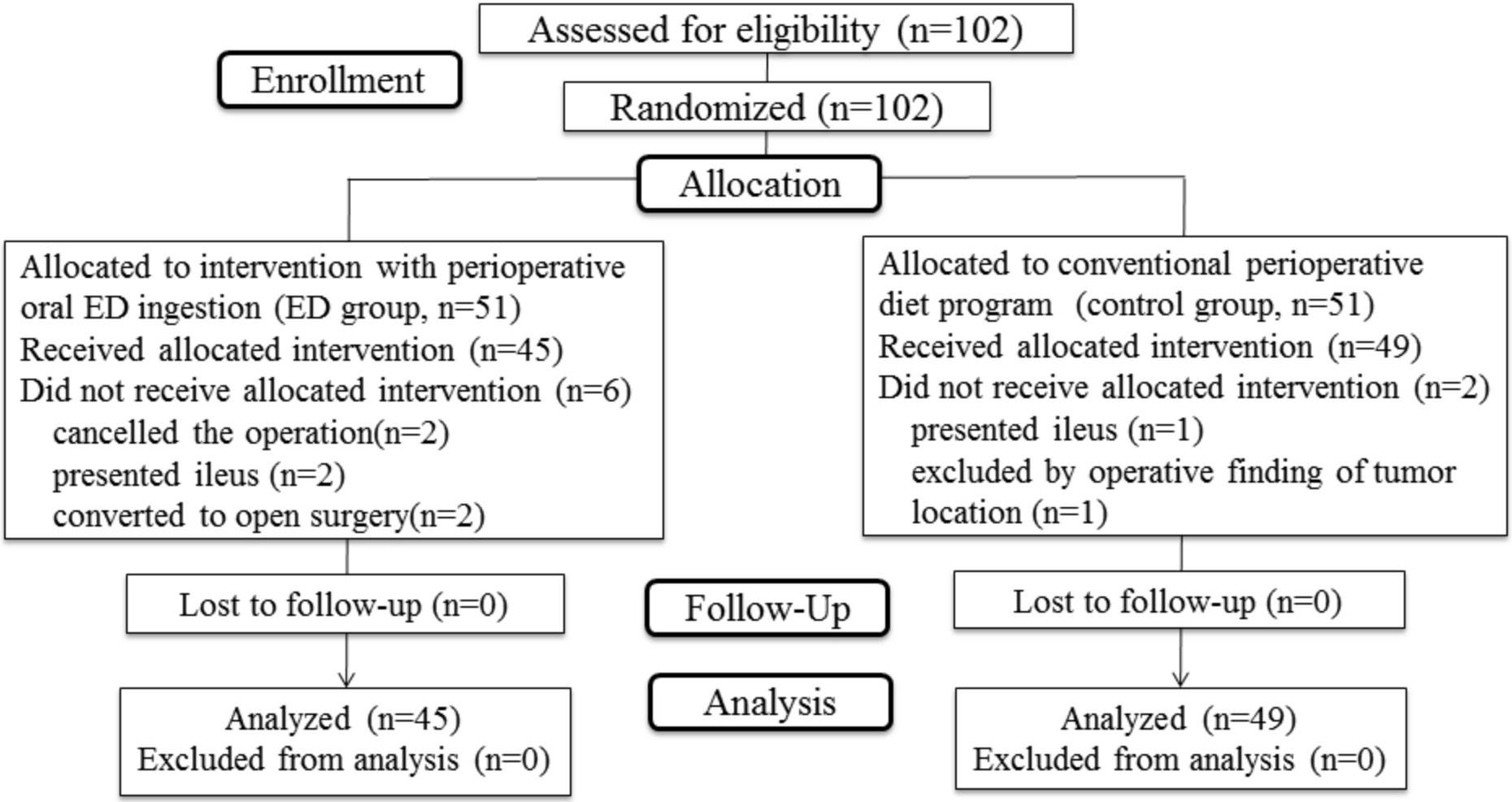

Assessed for eligibility (n=102)
Enrollment
Randomized (n=102)
Allocation
Allocated to intervention with perioperative oral ED ingestion (ED group, n=51)
Received allocated intervention (n=45)
Did not receive allocated intervention (n=6)
cancelled the operation(n=2)
presented ileus (n=2)
converted to open surgery(n=2)
Allocated to conventional perioperative diet program (control group, n=51)
Received allocated intervention (n=49)
Did not receive allocated intervention (n=2)
presented ileus (n=1)
excluded by operative finding of tumor location (n=1)
Lost to follow-up (n=0)
Follow-Up
Lost to follow-up (n=0)
Analysis
Analyzed (n=45)
Excluded from analysis (n=0)
Analyzed (n=49)
Excluded from analysis (n=0)

Fig. 2

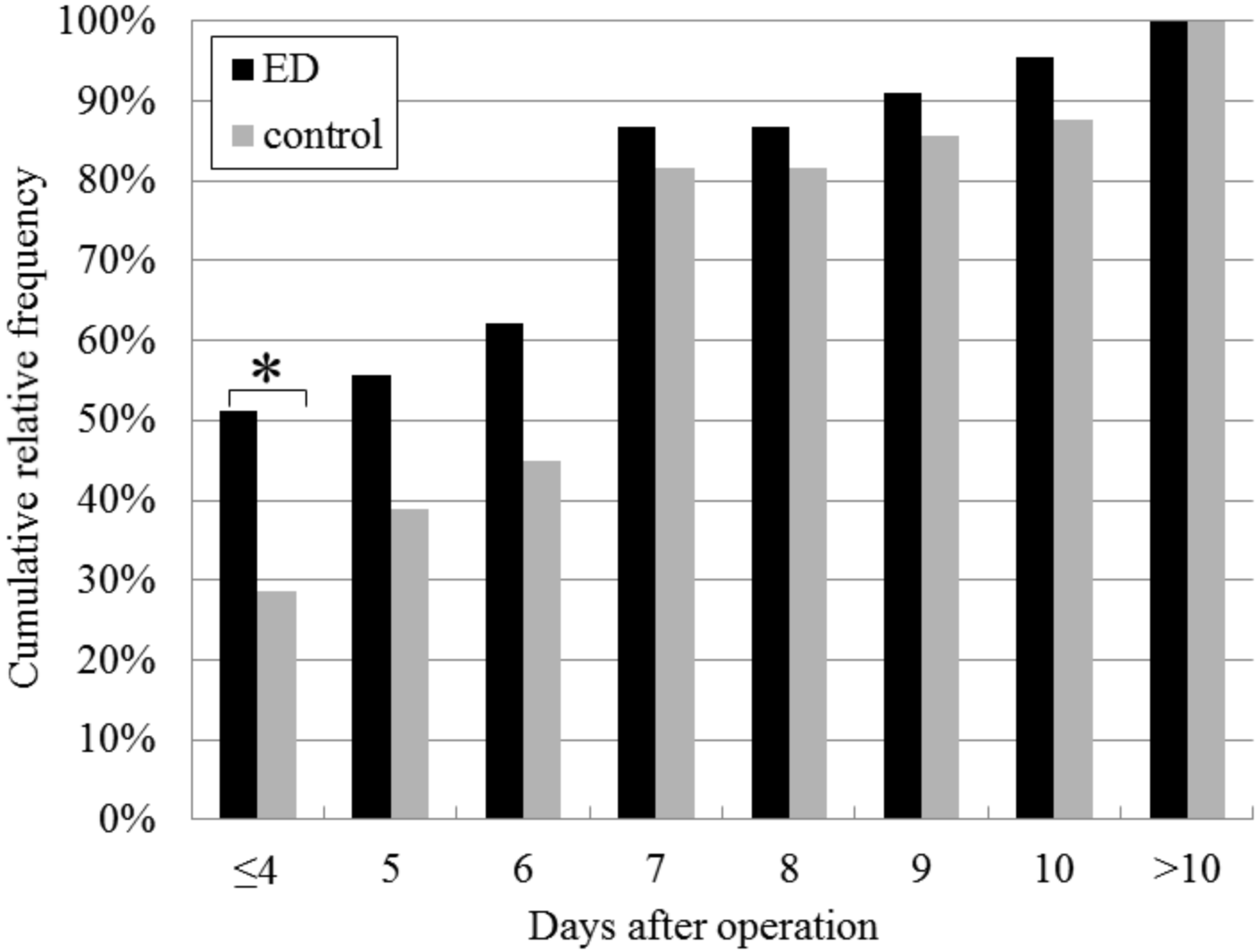
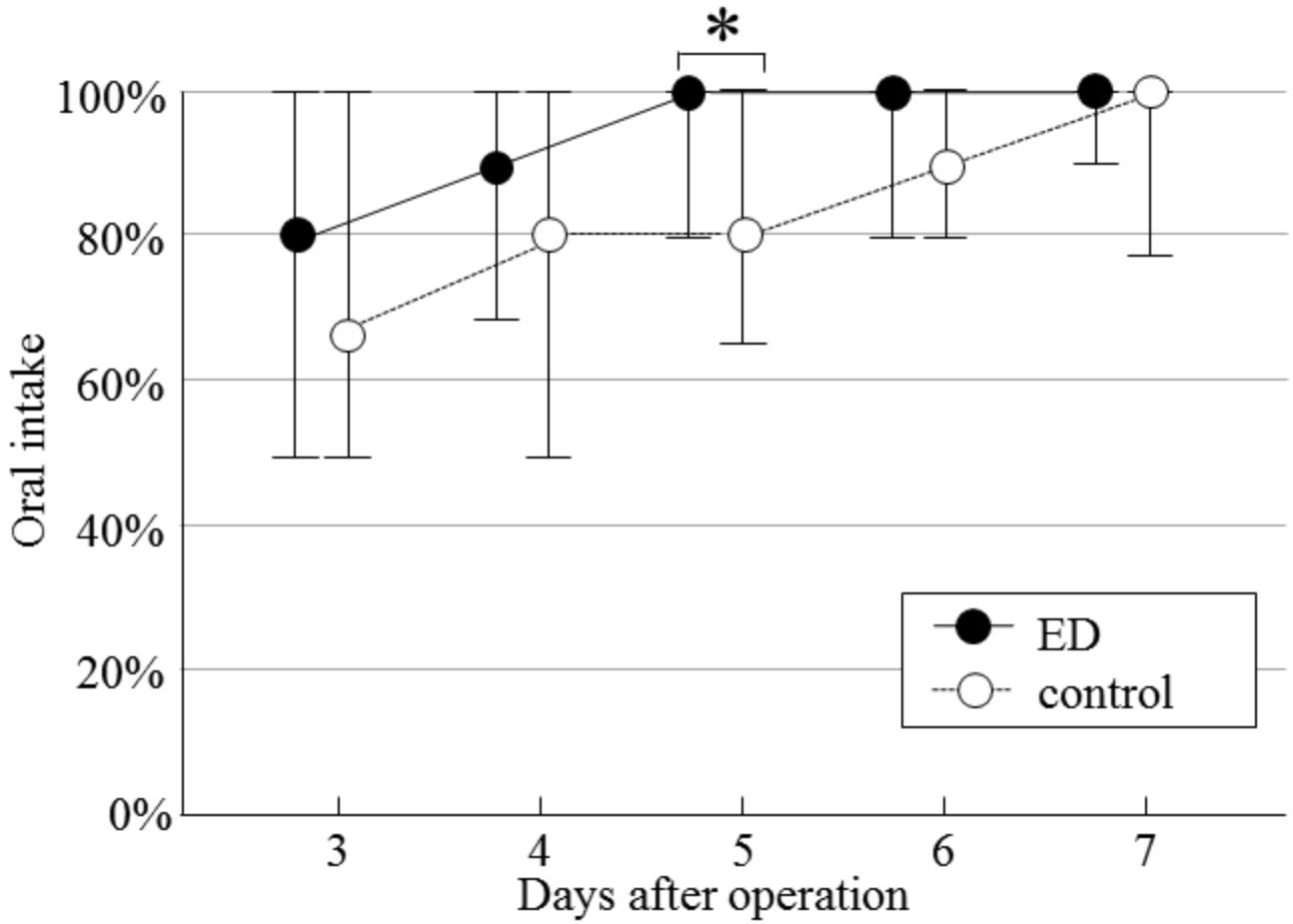

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative relative frequency
ED
control
*
≤4
5
6
7
8
9
10
>10
Days after operation

Fig. 3


*
100%
80%
60%
40%
20%
0%
Oral intake
3
4
5
6
7
Days after operation
ED
control