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ORIGINAL SCIENTIFIC REPORT

Impact of Preoperative Exclusive Enteral Nutrition on Postoperative Complications and Recurrence After Bowel Resection in Patients with Active Crohn's Disease

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Abstract

Background The impact of preoperative enteral nutrition (EN) on postoperative complications and recurrence in Crohn's disease (CD) has not been investigated to date. The purpose of the present study was to determine the effect of preoperative exclusive EN on postoperative complications and recurrence after bowel resection in patients with active CD.

Methods Patient data were obtained from a prospectively maintained database. 81 patients who received bowel resection for ileal or ileocolonic CD were studied. Before operation, 42 CD patients received exclusive EN for 4 weeks, and the other patients had no nutritional therapy. All patients were followed up regularly for 2 years after surgery, and ileocolonoscopy was performed every 6 months after bowel resection.

Results Patients receiving exclusive EN had a dramatic improvement of nutritional (BMI, albumin, pre-albumin, and Hb) and inflammatory (CRP and CDAI) status compared with baseline after the EN therapy for 4 weeks ($P < 0.05$). Furthermore, significantly lower incidence of both infectious and non-infectious complications was observed in patients receiving exclusive EN compared with those received no nutritional therapy ($P < 0.05$). Exclusive EN therapy for 4 weeks significantly reduced endoscopic recurrence rates after resection for CD 6 months after operation. However, during the 2-year follow-up, incidence of clinical recurrence was similar in both groups ($P > 0.05$).

Conclusions Preoperative exclusive EN therapy for 4 weeks reduced postoperative complications, which may be associated with improvement of nutritional and inflammatory status in patients with active CD.

Introduction

Crohn's disease (CD) is a relapsing inflammatory disease, mainly affecting the gastrointestinal tract, and frequently presents with abdominal pain and clinical signs of bowel obstruction or diarrhea [1]. The patients suffer from different patterns of disease and different complications, which impair the quality of life in the individual patient significantly [2, 3]. A majority of patients with CD require surgery at least once in their life [4]. However, surgery in CD is not a cure, but only a relief of symptoms for a prolonged period of time [5].

Current treatments of CD include 5-aminosalicylates, corticosteroids, antibiotics, immunosuppressives, biological

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agents, and nutritional therapy [6]. Unfortunately, most of these treatment options, though effective, come at a significant cost to the patient in terms of adverse effects [7]. Corticosteroids are limited in their use by risk of infection, osteoporosis, hypertension, poor mucosal healing, and early relapses on cessation of therapy [8, 9]. In addition, prolonged immune suppression with immunomodulators is also concerning owing to the risk of opportunistic infections besides problems with hematologic disorders [10]. Biologic agents such as infliximab are limited by loss of efficacy over time due to the development of antibodies, as well as a risk of local reactions, anaphylaxis, and vasculitis [11, 12]. Moreover, the reported risk of lymphomas especially in young adult males on concomitant azathioprine (AZA) and infliximab, albeit low, further limits their use [11, 13].

Some of the trials showed the enteral nutrition (EN) to be as effective as steroids in achieving short-term remission in patients with CD. In Japan, EN is a preferred therapeutic strategy for induction and maintenance of remission [14]. Malnutrition is very common in hospitalized adult patients with active CD, with an incidence ranging from 25 to 80 %, mainly caused by anorexia, increased intestinal losses, and systemic inflammation [15]. Exclusive EN is the provision of 100 % of a patient's nutritional requirements from a liquid nutrition formula either orally or via a feeding tube [10]. Furthermore, exclusive EN has been shown to have significant nutritional benefits besides inducing mucosal healing and reducing inflammation [10, 14, 16]. Yamamoto et al. [17] demonstrated that long-term EN significantly decreased clinical and endoscopic recurrence after resection for CD. Additionally, it is widely accepted that malnutrition adversely affects the postoperative outcome of surgical patients [18]. In clinical practice at our inflammatory bowel diseases (IBD) center, patients are generally recommended to receive exclusive EN before surgery. However, some patients refused to use exclusive EN because of personal choice or economic issue. The impact of preoperative EN on postoperative complications and recurrence in active CD has not been investigated to date. Therefore, the purpose of this study was to investigate if EN therapy for 4 weeks before surgery is effective in reducing postoperative complications and relapse rates in patients with active CD.

Materials and methods

Patients

This study was undertaken at the IBD center of Jinling Hospital, and patients with active CD were identified from the prospectively maintained IBD center database. This study was approved by the Ethics Committee of Jinling Hospital. Eligible patients were selected, and written informed consent was obtained.

Eighty one patients who required resection for ileal or ileocolonic CD were selected from the prospective database at the IBD center of Jinling Hospital between January 2011 and December 2012. Inclusion criteria were as follows: (1) age between 18 and 65 years; (2) patient who had radiologic, endoscopic, and histological diagnosis of CD; (3) those who required resection for ileal and ileocolonic (including ileocaecal) CD, and the main indication for surgery was fibrous stenosis; and (4) does not receive or stop using corticosteroids, 5-aminosalicylates, immunosuppressives, or biological agents in the last 3 months before operation. Exclusion criteria were inflammatory strictures, massive gastrointestinal bleeding, complete intestinal occlusion, nutritional treatment in the last 3 months, or with diffuse small bowel CD. The differentiation between inflammatory and fibrous strictures was performed based on the evidences of radiologic "string sign," thickened bowel wall in CT findings, acute inflammatory variables in hematological examination, and obstructive symptoms which were not responsive to medical treatment. Recurrent attacks of bowel obstruction occurred in these patients. For those with stricture disease, EEN therapy can effectively relieve inflammatory bowel stricture in CD [19].

The database contained all patients with CD and consisted of patients' general information. These patients were divided into the enteral nutrition group (EN group, $n = 42$) and the non-enteral nutrition group (non-EN group, $n = 39$). The main difference was that patients in EN group had been receiving exclusive EN therapy for at least 4 weeks before surgery. Data were collected regarding sex, age, BMI, Hb, serum CRP, CDAI score, smoking history, duration of disease, previous operation times, disease location, and medication history.

Preoperative treatment

In EN group, patients had been receiving exclusive EN for 4 weeks before they underwent enterectomy. The enteral formula used in this study was a commercially available Peptisorb Liquid (Nutricia, Amsterdam, The Netherlands), which is composed of hydrolyzed whey protein peptide, very little fat, vitamins, trace elements, and a major energy source, maltodextrin. A summary of the composition of Peptisorb Liquid is shown in Table 1. The calorie density was 1 kcal/mL with an osmolarity of 400 mosm/L. The enteral formula was infused continuously through a nasogastric tube using a peristaltic pump in patients. The dosage of EN and the infusion speed were gradually increased from one-third to the full strength over 3 days

Table 1 Constituents of Peptisorb Liquid (per 500 mL)

Energy	500 kcal	Se	28.5 μg
Maltodextrin	88 g	Vitamin A	0.41 mg
Hydrolyzed whey protein peptide	20 g	Vitamin B1	0.75 mg
Lipid (vegetable oil)	8.5 g	Vitamin B2	0.8 mg
K	0.75 g	Vitamin B6	0.85 mg
Na	0.5 g	Vitamin B12	1.05 μg
Ca	0.4 g	Vitamin C	50.0 mg
Mg	0.115 g	Vitamin D	3.5 μg
P	0.36 g	Vitamin E	6.5 mg
Cl	0.625 g	Vitamin K	26.5 μg
Fe	8.0 mg	Niacin	9.0 mg
Zn	6.0 mg	Pantothenic acid	2.65 mg
Cu	0.9 mg	Folic acid	0.135 mg
Mn	1.65 mg	Biotin	0.02 mg
F	0.5 mg	Choline	0.185 g
I	0.065 mg	Carotenoids	1.0 mg
Mo	0.05 mg	Taurine	0.05 mg
Cr	33.5 μg		

(adaptation phase) to reduce side effects such as diarrhea, abdominal distension, and colic. The diarrhea sometimes required anti-diarrheal drugs such as loperamide. However, these abdominal symptoms were not serious and could be controlled without an interruption of the treatment. To avoid low-calorie intake and dehydration, intravenous solution including carbohydrates and electrolytes was infused during the adaptation phase. After the adaptation phase, a maintenance dose at the full strength was administered for 4 weeks. The total energy of EN therapy infused per day was determined by indirect calorimetry of each patient. Resting energy expenditure (REE) was measured using indirect calorimetry that measured oxygen consumed and carbon dioxide produced. Measurements were made in the morning after an overnight fast. REE was determined by open circuit indirect calorimetry using a ventilated hood system. The measurement was carried out over 20 min, with the patient in the supine position under standard conditions of rest, immobility, thermoneutrality (22–24 °C), and mental relaxation. The system was calibrated for each patient, and the flow rate of air was adjusted according to the size of the patient. The calorimeter produced a measurement of REE every minute, and the final figure was the average of all measurements. All calorimetry measures were done at steady state. 120–130 % energy of REE was given to patients. Patients were allowed water, but no other food. Patients were evaluated clinically and hematologically to assess the efficacy of the EN treatment when the period of maintenance therapy was completed.

Patients in non-EN group received liquid diet, semi-liquid diet, or intravenous solution including carbohydrates and electrolytes to maintain water–electrolyte balance before surgery.

Postoperative treatment and follow-up

During the postoperative period, all patients were observed for infectious and non-infectious complications using the definitions summarized in Table 2. Although there are still some arguments about the early or tailored prophylaxis to prevent postoperative recurrences of CD, patients in our center were given AZA for prophylaxis within 1 month regularly after surgery. No patients received corticosteroids or infliximab before recurrent symptoms occurred. All patients were reviewed monthly and peripheral venous blood samples were collected for hematological measurements. The disease activity was assessed according to a Crohn's disease activity index (CDAI). Clinical recurrence was defined as the CDAI score of $\geq$150 or with an at least 70 points of increase. Ileocolonoscopy was performed for all patients at 6, 12, 18, and 24 months after operation, and endoscopic recurrence was confirmed by endoscope according to Rutgeerts scores (i2, or higher) [20]. Endoscopic investigators were blind to patient status.

Statistical analysis

Statistical analyses were performed using SPSS software version 17.0 (SPSS, Inc.). Data are expressed as means with their standard errors (SEM). Comparisons of frequencies were analyzed using the Chi square test. Fisher's exact test was used to analyze categorical data when the sample sizes were small. Paired *t* tests were used to compare data in the EN group, and unpaired *t* tests were used to compare data between EN and non-EN groups. The cumulative incidence of recurrence was calculated by the Kaplan–Meier method and was compared between the two groups by the log-rank test, and results were considered statistically significant if *P* values were <0.05.

Results

Characteristics of all patients

As shown in Table 3, all patients in EN and non-EN group were well matched in terms of sex, age, BMI, albumin, prealbumin, Hb, CRP, CDAI, smoking history, duration of CD, previous operation, disease location, indication for resection, and medication history.

Table 2 Definitions of postoperative complications

Complication	Definition
Pneumonia	Abnormal chest X-ray or positive culture of tracheal aspirate associated with the presence of fever (>37.5 °C)
Surgical wound infection	Purulent exudate of a surgical wound with positive bacterial culture
Intra-abdominal abscess	Collection of pus confirmed by percutaneous drainage or at reoperation
Urinary tract infection	Clinical symptoms and bacteriuria ($>10^5$ colony-forming units/mL)
Wound dehiscence	Any dehiscence of the fascia or of skin ≥3 cm
Anastomotic bleeding	Necessity of blood transfusion (2 U)
Anastomotic leakage	Any anastomotic leakage with clinical and/or radiologic evidence
Heart insufficiency	Unstable blood pressure requiring use of extra fluids and cardiac stimulants
Respiratory insufficiency	Presence of dyspnea requiring oxygen support
Renal insufficiency	Abnormal blood urea level and creatinine level
Peripheral veins thrombosis	Clinical symptoms with ultrasonic and/or radiologic evidence

Clinical effects of EN

As shown in Table 4, all patients receiving exclusive EN had significantly higher levels of BMI, albumin, pre-albumin, Hb, lower CRP and CDAI levels compared with those before treatment ($P < 0.05$). A clinical assessment for BMI, pre-albumin levels, CRP, CDAI and other variables in non-EN group and EN group patients are shown in Table 5. Patients in EN group had significantly higher levels of albumin, pre-albumin, lower CRP and CDAI levels compared with those in non-EN group at the time of surgical intervention ($P < 0.05$).

Postoperative complications

As shown in Table 6, infectious complications occurred in 9 of 42 patients receiving exclusive EN and in 17 of 39 patients not given exclusive EN, with significant differences ($P = 0.03$). Moreover, incidence of non-infectious

Table 3 Characteristics of the study population

Clinical variable	EN ($n = 42$)	Non-EN ($n = 39$)	P value
Male/female	30/12	27/12	0.83
Age (years)	34.3 ± 1.9	35.9 ± 2.1	0.57
BMI (kg/m^2)	17.9 ± 0.5	18.1 ± 0.5	0.78
Albumin (g/L)	33.5 ± 0.4	32.9 ± 0.5	0.35
Pre-albumin (mg/L)	135.8 ± 4.2	126.9 ± 4.5	0.15
Hb (g/L)	96.7 ± 3.3	97.2 ± 3.7	0.92
CRP (mg/L)	23.5 ± 2.1	24.7 ± 2.3	0.70
CDAI	213.9 ± 4.9	204.7 ± 5.2	0.20
Smoker (n)	4	4	0.91
Duration of Crohn's disease (months)	31.5 ± 3.5	32.7 ± 3.6	0.81
Previous operation (n)	7	6	0.84
Disease location			0.95
Terminal ileum (n)	12	10	
Terminal ileum and colon (n)	23	23	
Ileocolonic anastomosis (n)	7	6	
Indication for resection			0.91
Bowel stenosis (n)	42	39	
Concomitant abscess or fistula (n)	6	6	
Medication history			0.62
Corticosteroids (n)	10	12	
5-Aminosalicylates (n)	35	33	
Immunosuppressive drugs or infliximab (n)	0	0	

Data are expressed as mean ± SEM

EN enteral nutrition, *BMI* body mass index, *HB* hemoglobin, *CRP* C-reactive protein, *CDAI* Crohn's disease activity index

Table 4 Clinical assessment of EN in EN group

Clinical variable	Baseline ($n = 42$)	After EN ($n = 42$)	P value
BMI (kg/m^2)	17.9 ± 0.5	18.5 ± 0.4	<0.01
Albumin (g/L)	33.5 ± 0.4	35.7 ± 0.4	<0.01
Pre-albumin (mg/L)	135.8 ± 4.2	195.3 ± 5.4	<0.01
Hb (g/L)	96.7 ± 3.3	104.5 ± 3.5	<0.01
CRP (mg/L)	23.5 ± 2.1	4.6 ± 0.5	<0.01
CDAI	213.9 ± 4.9	139.8 ± 3.4	<0.01

Data are expressed as mean ± SEM

EN enteral nutrition, *BMI* body mass index, *HB* hemoglobin, *CRP* C-reactive protein, *CDAI* Crohn's disease activity index

complications in patients receiving exclusive EN (11 of 42 patients) was significantly lower than those in non-EN group (20 of 39 patients) ($P = 0.02$).

Postoperative recurrence

As shown in Table 7, 6 months after operation, 3 patients (7.1 %) in the EN group and 10 (25.6 %) in the non-EN group developed endoscopic recurrence ($P = 0.03$). 12 months after operation, endoscopic recurrence was observed in 9 patients (21.4 %) in the EN group and 13 (33.3 %) in the non-EN group ($P = 0.23$). 18 months after operation, endoscopic recurrence was observed in 13 patients (31.0 %) in the EN group and 17 (43.6 %) in the non-EN group ($P = 0.24$). 24 months after operation, endoscopic recurrence was observed in 20 patients (47.6 %) in the EN group and 22 (56.4 %) in the non-EN group ($P = 0.43$). Endoscopic recurrence was observed in the ileum proximal to the anastomosis in all patients. And endoscopic recurrence was defined as Rutgeerts' score ≥i2 (i2, i3, i4), and severity of recurrence (Rutgeerts' score) is shown in Table 7. The mean (median) Rutgeerts score level was 0.52 (0) in EN group and 1.15 (1) in non-EN group, with significantly difference ($P < 0.05$). However, Rutgeerts score levels were similar in two groups at 12, 18, and 24 months ($P > 0.05$).

Table 5 Clinical assessment in two groups at the time of surgical intervention

Clinical variable	EN ($n = 42$)	Non-EN ($n = 39$)	P value
BMI (kg/m^2)	18.5 ± 0.4	18.2 ± 0.5	0.64
Albumin (g/L)	35.7 ± 0.4	33.8 ± 0.6	<0.01
Pre-albumin (mg/L)	195.3 ± 5.4	131.9 ± 4.7	<0.01
Hb (g/L)	104.5 ± 3.5	96.9 ± 3.4	0.12
CRP (mg/L)	4.6 ± 0.5	21.4 ± 2.1	<0.01
CDAI	139.8 ± 3.4	196.5 ± 5.4	<0.01

Data are expressed as mean ± SEM

EN enteral nutrition, *BMI* body mass index, *HB* hemoglobin, *CRP* C-reactive protein, *CDAI* Crohn's disease activity index

During the 1-year follow-up, 4 patients (9.5 %) in the EN group and 4 (10.3 %) in the non-EN group developed clinical recurrence ($P = 0.91$). During the 2-year follow-up, 9 patients (21.4 %) in the EN group and 9 (23.1 %) in the non-EN group developed clinical recurrence ($P = 0.86$). Clinical recurrences were treated with oral corticosteroids (prednisolone, 20–30 mg/day) or biologic therapy (infliximab, 5 mg/kg) for steroid-refractory patients. After treatment, their clinical symptoms were relieved, and all patients achieved clinical remission.

Discussion

The relapsing and diffuse nature of CD indicated that surgery is only a tool to relieve symptoms for a prolonged period of time [21, 22]. Surgical trauma results in significant alteration in metabolic and endocrine function. Even during minor intervention such as laparoscopic cholecystectomy and inguinal hernia repair, these changes have been observed [23, 24]. The classic catecholamine and cortisol release associated with surgical stress has been well described. Surgical trauma is also associated with reduced postoperative insulin sensitivity, immune impairment, and hepatic reprioritization of protein synthesis [18]. These factors are intricately interwoven with the nutrition status of the patient. In surgical practice, great attention is given to the perioperative management of surgical patient with regard to surgical planning, stratification of cardiopulmonary risk, and postoperative management of complications. However, growing evidence supports the beneficial role for implementation of a consistent and literature-based approach to preoperative nutrition therapy, which is designed to prepare the patient metabolically for the insult of surgery, not to make up for several months of deterioration of nutrition status [25]. In the management of CD, nutritional therapy is often required because malnutrition is common, as deterioration of the nutritional status is a key factor affecting the surgical outcome [18, 26]. EN is simpler and has been associated with fewer side effects

Table 6 Postoperative complications

	EN ($n = 42$)	Non-EN ($n = 39$)	P value
Infectious complications (n)	9	17	0.03
Pneumonia	6	10	
Surgical wound infection	3	7	
Intra-abdominal abscess	3	6	
Bacteremia	1	2	
Urinary tract infection	1	1	
Non-infectious complications (n)	11	20	0.02
Wound dehiscence	3	5	
Anastomotic bleeding	4	6	
Anastomotic leakage	3	6	
Heart insufficiency	0	1	
Respiratory insufficiency	1	1	
Renal insufficiency	2	2	
Peripheral veins thrombosis	1	2	

than parenteral nutrition. Accordingly, EN has been used as an adjunctive therapy to treat malnutrition in CD [16]. In addition, EN is a preferred therapeutic strategy for induction and maintenance of remission for patients with active CD in many centers [27–29]. In our present study, we investigated the impact of preoperative exclusive EN on postoperative complications and recurrence after bowel resection in patients with active CD. Patients in EN and non-EN group were well matched in terms of patient demography, BMI, albumin, pre-albumin, Hb, CRP, CDAI, smoking history, duration of CD, previous operation, disease location, indication for resection and medication history. All patients receiving exclusive EN had a dramatic improvement of nutritional (BMI, albumin, pre-albumin, and Hb) and inflammatory (CRP and CDAI) status compared with baseline after the EN therapy for 4 weeks.

Nutritional therapy is a crucial component of medical treatment in all patients undergoing major gastrointestinal surgery [25, 30]. Bozzetti et al. [31] demonstrated that 10 days of total parenteral nutrition significantly reduced postoperative complications rate and mortality in severely malnourished patients with gastrointestinal cancer. Many clinical trials and meta-analyses confirmed that EN significantly reduced the risk of overall and infectious complications compared to parenteral nutritional support in malnourished patients [32]. In the present study, we evaluated the importance of preoperative EN on postoperative complications in CD patients with bowel resection, we found that significantly lower incidence of both infectious and non-infectious complications was observed in patients receiving exclusive EN. These findings may result from modifications of nutritional and inflammatory status after nutritional therapy.

In patients with CD, postoperative recurrence is common. Despite the growing knowledge regarding the pathogenesis of CD, no treatments are currently available in order to avoid the postoperative recurrence of CD after bowel resection. Therefore, in patients with CD, several medications have been introduced for the suppression of postoperative recurrence. Currently, no definite effective medical strategy was recommended for the prevention of the relapse of CD. Medical prophylaxis such as use of metronidazole, mesalamine, AZA, 6-mercaptopurine, and infliximab and EN were all confirmed to be effective [7, 10, 13, 15]. Although not a controlled trial, a recent prospective, observational long-term study in 56 Spanish patients suggested that early postoperative AZA use delayed endoscopic postoperative recurrence [33]. Even with the limited available data, the European Crohn's and Colitis Organization (ECCO) recommends AZA as first-line therapy for high-risk postoperative CD patients [34]. All patients in our center consequently received prophylactic administration of AZA (1.5–2 mg/kg/day) within 1 month regularly to prevent the postoperative recurrence after surgery. No patients received prophylactic administration of corticosteroids or infliximab before recurrent symptoms

Table 7 Endoscopic and clinical recurrence rates after operation

Clinical variable	EN ($n = 42$)	Non-EN ($n = 39$)	P value
Cumulative endoscopic recurrence (Rutgeerts' score, 0:i1:i2:i3:i4)			
6 months after operation	3 (24:15:2:1:0)	10 (14:15:2:6:2)	0.03
12 months after operation	9 (17:16:3:5:1)	13 (11:15:2:8:3)	0.23
18 months after operation	13(12:17:4:7:2)	17 (8:14:4:9:4)	0.24
24 months after operation	20 (7:15:6:11:3)	22 (5:12:5:12:5)	0.43
Cumulative clinical recurrence			
During 1-year follow-up	4	4	0.91
During 2-year follow-up	9	9	0.86

Endoscopic recurrence was defined as Rutgeerts' score $\geq$ i2 (i2, i3, i4)

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occurred. We assessed both clinical and endoscopic disease activities as clinical symptoms were not always related to recurrent CD. Yamamoto et al. [14] demonstrated that clinical remission was achieved in 71 % of patients with active CD treated with the EN therapy for 4 weeks. In our study, we curatively resected macroscopic disease at surgery. Both endoscopic and clinical recurrence increased with time in two groups. Interestingly, reduced endoscopic recurrence rates after resection at 6 months were found in CD patients receiving preoperative exclusive EN therapy for 4 weeks, which may be caused by high rates of mucosal healing and remission with preoperative EN treatment. However, during the 2-year follow-up, incidence of clinical recurrence was similar in both groups. Although the detailed mechanism of action of EN remains unclear, the efficacy of EN includes improvement in intestinal permeability, decreased mucosa inflammation, and altered bowel microbiota.

There are several limitations to our study. First, this was a single-center, retrospective study and it is possible that those patients without preoperative exclusive EN regimen are sicker patients who are intolerant to exclusive EN therapy and are more likely to have postoperative complications. However, we think this is less likely considering matched cohort analysis nature, and no difference was observed in respect to disease characters or operative information between two groups. Second, because of its retrospective nature and no sample size calculation has been done, this study may result in a potential selection bias. However, the data were extracted from the prospectively maintained IBD database, in which all variables were prospectively collected. In addition, no data on pre- and post-operatively microbiome of the patients to make clear the association between EN and fewer recurrences at 6 months in EN group. Therefore, microbiome of the patients pre- and post-operatively are needed to be studied to clarify the mechanism of fewer recurrences at 6 months in EN group.

Conclusions

In conclusion, reduced postoperative complications were found in active CD patients receiving exclusive EN therapy for 4 weeks, which may be associated with improvement of nutritional and inflammatory status, while the postoperative recurrence rate was not decreased. However, this is a small sample study, and a prospective and multi-center study with a larger number of patients is necessary to strengthen our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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