

Effects of fiber and probiotics on diarrhea associated with enteral nutrition in gastric cancer patients

A prospective randomized and controlled trial

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Abstract

Background and objectives: Diarrhea is a common complication of enteral nutrition (EN), which affects recovery and prolongs the length of hospital stay (LOHS). To investigate the effect of fiber and probiotics in reducing diarrhea associated with EN in postoperative patients with gastric cancer (GC), the authors designed this prospective randomized-controlled trial.

Methods and study design: This study included 120 patients with GC, and the patients were classified into 3 groups via random picking of envelopes: fiber-free nutrition formula (FF group, n=40), fiber-enriched nutrition formula (FE group, n=40), and fiber- and probiotic-enriched nutrition formula (FEP group, n=40). All patients were given EN formulas for 7 consecutive days after surgery.

Results: The number of diarrhea cases was higher in the FF group than in the FE group ($P = .007$). The FEP group had a lower number of diarrhea cases compared with the FE group ($P = .003$). Patients in the FE group had a significantly shorter first flatus time than the FF group ($P = .002$). However, no significant difference was observed between the FE group and FEP group ($P = .30$). Intestinal disorders were similar between the FE group and FF group ($P = .38$). The FEP group had a lower number of intestinal disorder cases than the FF group ($P = .03$). LOHS in the FE and FEP groups was shorter than that in the FF group ($P = .004$; $P < .001$). However, no significant difference was observed between the FE and FEP groups ($P = .28$). In addition, no significant difference was observed between the 3 groups in terms of total lymphocyte count, albumin, prealbumin, and transferrin levels on day 7 of enteral feeding.

Conclusions: The combination of fiber and probiotics was significantly effective in treating diarrhea that is associated with EN in postoperative patients with GC.

Abbreviations: ALB = albumin, BMI = body mass index, EN = enteral nutrition, ERAS = enhanced recovery after surgery, FE = fiber-enriched nutrition formula, FEP = fiber- and probiotic-enriched nutrition formula, FF = fiber-free nutrition formula, GC = gastric cancer, LOHS = length of hospital stay, PA = prealbumin, RCT = randomized-controlled trial, TLC = total lymphocyte count, TRF = transferrin.

Keywords: diarrhea, enteral nutrition, fiber, gastric cancer, probiotics

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1. Introduction

Gastric cancer (GC) is the 4th most common type of cancer worldwide, and more than 50% of cases occur in Eastern Asia.^[1] Malnutrition is prevalent in patients with GC, which can increase the risk of mortality and morbidity in perioperative patients with GC.^[2] Enteral nutrition (EN) is a recommended nutrition support for patients with GC (Grade A) after surgery.^[3] A prospective multicenter randomized-controlled trial (RCT) showed that EN could preserve intestinal structure and function, enhance intestinal-mediated immunity, and shorten the length of hospital stay (LOHS).^[4] However, EN can also cause some complications.^[5,6] Among the complications, diarrhea is common and the most prevalent, and it can affect the overall recovery of postoperative patients with GC, causing fluid and electrolyte loss, which results in intestinal disorders, ultimately prolonging the LOHS, and even increasing mortality and morbidity.^[5,7,8] Numerous studies reported that the prevalence rate of diarrhea in patients who were receiving EN was between 12% and 68%.^[9,10] Therefore, reducing diarrhea that is associated with EN is critical in enhancing recovery and shortening the LOHS in patients with GC after gastrectomy.

Several factors that are involved in the pathogenesis of diarrhea that is associated with EN were observed.^[11-13] One of the risk

factors was intestinal flora imbalance. Previous studies have shown that intestinal flora imbalance occurred in patients with diarrhea that is associated with EN and might be involved in its pathogenesis.^[14] Whelan showed that bifidobacteria, one of the main probiotics in the intestinal flora, can vary by 1000-fold in patients who are receiving EN.^[15] Patients who experience diarrhea during EN had a low level of bifidobacteria in the intestinal flora, and these patients also had a high level of clostridia, which are the pathogenic bacteria that causes diarrhea.^[16] Intestinal flora imbalance can affect intestinal function, resulting in diarrhea, vomiting/nausea, abdominal distension, and abdominal pain.

Some studies reported that fiber-based enteral formulas could help reduce diarrhea that is associated with EN.^[17–19] However, a systematic review concluded that evidence on this association was insufficient.^[20] Our previous meta-analysis also had the same conclusion.^[21] Meanwhile, over the years, probiotics had been extensively studied, and several beneficial effects had been discovered, such as protection against colonization by pathogenic bacteria, regulation of the immune system, and enhancement of intestinal barrier function.^[22,23] In the recent years, the use of probiotics as a treatment for various kinds of severe diarrhea has been increasing.^[24,25] However, some studies reported that probiotics were not effective in preventing diarrhea.^[26–28] Guidelines on the use of fiber or/and probiotics in the treatment of diarrhea that is associated with EN are conflicting. To investigate the effect of fiber or/and probiotics on diarrhea that is associated with EN in postoperative patients with GC, we designed this prospective RCT.

2. Materials and methods

2.1. Patients

This RCT included 120 patients based on the guidelines and power calculation of previous studies (NCSS-PASS 11). All patients were confirmed to have GC via pathological diagnosis, and they underwent distal gastrectomy between October 2015 and October 2016 in West China Hospital, Sichuan University. All the patients had stage II or III tumors (NCCN Guideline for Gastric Cancer 2016), and this was confirmed via preoperative computed tomography. In addition, these tumors were assessed and completely resected by 2 experienced surgeons. The inclusion criteria were as follows: patients aged 18 to 80 years of either gender and those who did not receive neoadjuvant chemotherapy or whose expected lifetime is longer than 6 months. The exclusion criteria were as follows: patients with diarrhea, hepatic, renal, or cardiac dysfunction, sepsis, or a history of drug abuse; those who were receiving enteral or parenteral nutritional support before surgery; those with contraindications to EN; and those who were taking broad-spectrum antibiotics before surgery. All patients who met the criteria were randomly classified into 3 treatment groups by picking sealed numbered envelopes: fiber-free nutrition formula (FF group, $n=40$), fiber-enriched nutrition formula (FE group, $n=40$), and fiber- and probiotic-enriched nutrition formula (FEP group, $n=40$) for better readability and conciseness. We assessed the baseline characteristics of the patients, including age, sex, body mass index (BMI), and cancer stage, according to the tumor-node-metastasis classification of the International Union against Cancer (7th edition), American Society of Anesthesiologists (ASA) score, and results of total lymphocyte

count (TLC), albumin (ALB), prealbumin (PA), and transferrin (TRF) tests.^[29]

2.2. Study design

For all patients who underwent their respective procedure, an enteral feeding tube was inserted into the first jejunal loop 15 to 20 cm below the lowest intestinal anastomosis by a surgeon and anesthesiologist at the time of operation. Early EN that was based on the ESPEN guideline was initiated on day 1 after surgery using an enteral feeding tube.^[30] Each group received nutritional support with daily EN dose of EN emulsion (Sino-Swed Pharmaceutical Corp. Ltd, Beijing, China) (FF group); EN emulsion and Shen Jia (Beijing Tiantian Yikang Biological Technology Corp. Ltd, Beijing, China) (FE group); EN suspension, Shen Jia, and a combination of live bifidobacterium and lactobacillus in tablets (Inner Mongolia Shuangqi Pharmaceutical Corp. Ltd, Beijing, China) (FEP group). No differences were observed between the FF group and FE group in terms of EN with fiber intake. In addition, a difference was observed between the FE group and FEP group in terms of EN with probiotic intake. After 2 days, all patients only received 500 mL of EN per day. On day 3, patients began to receive 1500 mL of EN until the procedure ended. All patients were given EN support for 7 consecutive days after surgery, and their total caloric intake everyday should reach 125.52 kJ (30 kcal)/kg. If energy intake via EN was insufficient, residual energy will be obtained by the infusion of 10% glucose and normal saline infusion (Fig. 1). Fecal output was monitored by a nursing staff using the King's Stool Chart.^[31] The definition and standard were as follows: Fecal score was assessed according to a score defined by the King's Stool Chart. The chart incorporates descriptors of fecal frequency, weight, and consistency. Each fecal of the patient was scored, and the sum of the scores within 24 h was considered as the fecal score of the patient. Diarrhea is classified by a daily fecal score of 15 or higher.^[31,32] On days 1, 3, 5, and 7 after surgery, TLC, ALB, PA, and TRF tests were carried out, which are the indicators of the nutrition status of the patients. On day 8, that marks the endpoint of the RCT, it was decided whether EN is continued. LOHS and intestinal function recovery, such as abdominal pain, vomiting/nausea, anastomotic fistula, and abdominal distension, were expressed in days, and the duration of the first fecal was recorded.

2.3. Ethics statement

The study protocol was approved by the ethics committee of Sichuan University, West China Hospital. A written informed consent was obtained from the patients before the start of the study. The analysis did not involve interaction with human participants or the use of personal identifying information. Patient records/information was anonymized and deidentified prior to analysis, and the methods were performed in accordance with the approved guidelines.

2.4. Statistical analysis

Categorical variables were reported as counts and percentages. Continuous variables were reported as mean and standard deviations. Categorical variables were estimated via chi-squared test and Fisher exact test. Continuous variables were compared across the 3 groups using 1-way analysis of variance. Changes and differences between the 2 groups were assessed via *t* tests. The

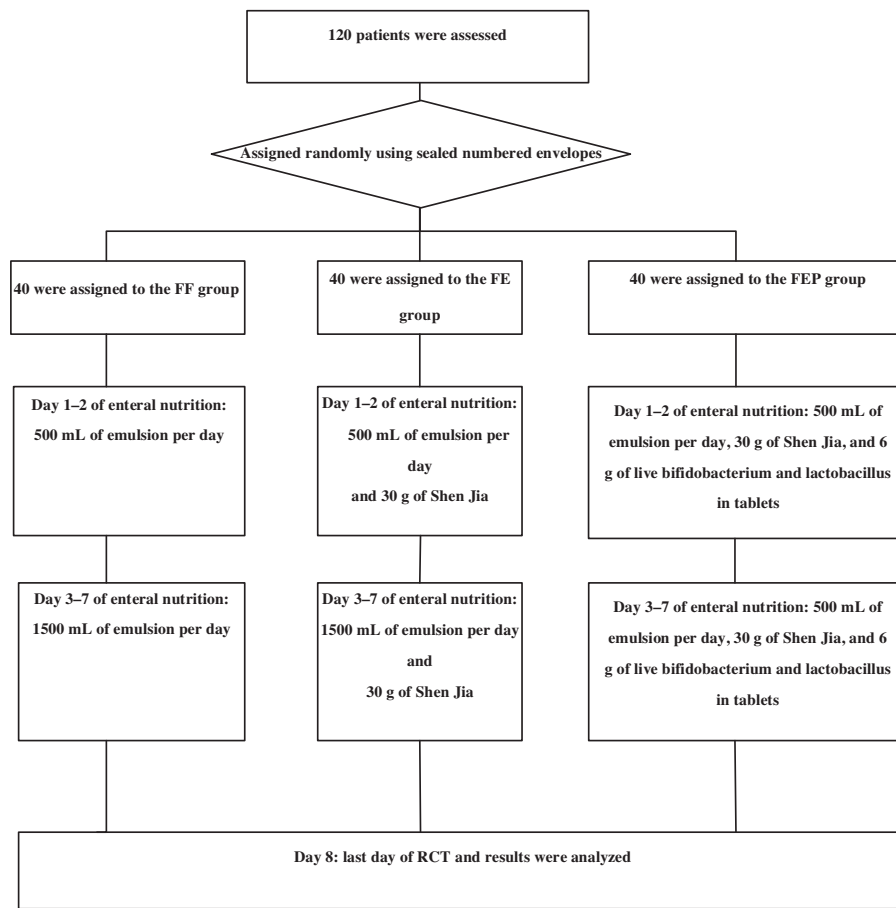


Figure 1. Randomized-controlled trial profile.

statistical package SPSS 20.0 for Windows (IBM) was used for the statistical analysis. A *P* value < .05 was considered statistically significant.

3. Results

A total of 120 patients were included in this RCT. After the initiation of the study, none of the patients were excluded because of severe complications or EN intolerance. No difference was observed between the 3 groups in terms of

age, sex, weight, BMI, ASA score, nutrition status, and cancer stage (Table 1).

When the total number of diarrhea cases was recorded, the same patient cannot be recorded again. In the FF group, 24 patients (60%) had diarrhea for 7 days, whereas 12 (30%) and 2 (5%) patients from the FE and FEP groups had diarrhea, respectively. No significant difference was observed between the 3 groups in terms of the number of diarrhea cases ($\chi^2=28.0$; $P<.001$). The number of diarrhea cases in the FF group was higher than that of the FE group ($\chi^2=7.3$; $P=.007$) (Table 2).

Table 1

Patients' characteristics.

	FF group (n = 40)	FE group (n = 40)	FEP group (n = 40)	<i>P</i>
Age, y	63.53 ± 8.52	65.55 ± 12.91	66.52 ± 7.11	.78
Gender, M/F	16/24	22/18	24/16	.43
Weight, kg	68.52 ± 9.81	67.50 ± 9.48	65.28 ± 10.01	.54
BMI, kg/m ²	21.41 ± 2.20	21.73 ± 2.65	21.83 ± 3.12	.89
TLC, ×10 ⁹ /L	1.25 ± 0.42	1.15 ± 0.34	1.13 ± 0.32	.53
ALB, g/L	37.71 ± 2.72	37.01 ± 2.73	36.30 ± 3.28	.34
PA, mg/L	192 ± 6.72	188 ± 8.41	188 ± 7.43	.16
TRF, g/L	1.83 ± 0.27	1.70 ± 0.31	1.85 ± 0.35	.27
ASA scores (2/3)	21/19	16/24	18/22	.77
Cancer stage (II/III)	23/17	22/18	24/16	.71

ALB=albumin, ASA = American Society of Anesthesiologists, BMI = body mass index, FE = fiber-enriched nutrition formula, FEP = fiber- and probiotic-enriched nutrition formula, FF = fiber-free nutrition formula, PA=prealbumin, TLC=total lymphocyte count, TRF=transferrin.

Table 2
Number of diarrhea cases in the 3 groups.

	Diarrhea	No diarrhea	Total	P
FE group	12	28	40	
FF group	24	16	40	.007
FEP group	2	38	40	.003

FE = fiber-enriched nutrition formula, FEP = fiber- and probiotic-enriched nutrition formula, FF = fiber-free nutrition formula.

The FEP group had a lower number of diarrhea cases compared with the FE group ($\chi^2=8.7$; $P=.003$) (Table 2).

Patients in the FE group had a significantly shorter first flatus time than the FF group ($P=.002$), whereas that of the FE and FEP groups did not differ ($P=.300$). However, intestinal disorders, such as abdominal pain, vomiting/nausea, and abdominal distension, were similar in the 3 groups. However, a lower number of intestinal disorder cases was observed in the FEP group than the FF group ($P=.026$) (Table 3). LOHS in the FE and FEP groups was shorter than that in the FF group ($P=.004$ and $P<.001$). However, no significant difference was observed between the FE group and FEP group ($P=.277$).

The levels of TLC, ALB, PA, and TRF on the 7th day were not significantly different between the 3 groups (Table 3).

4. Discussion

Previous studies reported that adding fiber or probiotics could maintain intestinal microecology that decrease diarrhea that is associated with EN.^[33] However, the effect of the combination of fiber and probiotics on treating diarrhea was inconclusive.^[34–36] This RCT study showed that the combination of fiber and probiotics could be the most effective method in treating diarrhea that is associated with EN in postoperative patients with GC.

The addition of fiber to EN formulas was effective in preventing diarrhea that is associated with EN compared with fiber-free EN formulas.^[37] This RCT study also confirmed this standpoint by comparing the FF and FE groups ($P=.007$) (Table 2). Fiber is a general term for a type of carbohydrates that cannot be used by humans. Numerous kinds of fiber are available based on different characteristics, which play different roles in reducing diarrhea, such as increasing fecal bulk, normalizing intestinal flora, and holding water.^[38–41] Fiber parts can be metabolized by intestinal flora and produce short-chain fatty acids (SCFAs), butyrate, acetate, and propionate, which are the preferred source of energy of colonic cells to improve gut barrier function.^[41,42] The SCFAs can stimulate colonic water absorption and help maintain an environment with a low pH for the colonic flora to prevent enteropathogenic infections, such as those caused by *Clostridium difficile*.^[43,44] Some fibers can be

fermented in the colon and result in the selective growth of beneficial bacteria, such as the stimulation of selective bifidobacterial growth.^[37,45]

The outcome in the FEP group was more favorable than that in the other groups, showing that the combination of fiber and probiotics was effective in the treatment of diarrhea that is associated with EN (Table 2). Several factors are involved in the pathogenesis of diarrhea in which the disruption of intestinal flora can play a key role. Intestinal flora can affect a variety of intestinal functions, such as the maintenance of the integrity of the epithelial barrier and the development of mucosal immunity. Meanwhile, intestinal flora can also produce a variety of substances, ranging from relatively nonspecific fatty acids and peroxides to highly specific bacteriocins, which can inhibit or kill other potentially pathogenic bacteria.^[46,47] Previous studies had shown that the presence of intestinal flora while receiving EN can be a disorder, of which the most remarkable change is the existence of bifidobacteria and lactobacillus.^[15,16] Standard fiber-free EN formulas can cause higher production of aerobes, reduce the number of butyrate-producing bacteria, and decrease colonic flora levels, particularly in the presence of bifidobacteria and lactobacillus.^[48] Lactobacillus can ferment fiber to generate lactic acid, which is the major end product, whereas bifidobacteria are important producers of SCFAs.^[49] Lactobacillus and bifidobacteria can remain as stable elements of the normal intestinal microbiota, and dysbiosis is associated with pathological conditions.^[50] Historically, the most usual application of probiotics was for the treatment of gastrointestinal disorders, particularly diarrhea.^[51] Its application can prevent diarrhea that is associated with EN by competing with enteropathogenic infection and fermenting fiber.

The present RCT study also found the result on the recovery of patients who were affected by fiber and probiotics as shown in Table 3. Patients in the FE group had a significantly shorter first flatus time than those in the FF group ($P=.002$). Fiber could accelerate intestinal movement and shorten the duration of the first flatus. Fibers could improve fecal passage management by ameliorating small intestinal mucosal atrophy, which would enhance patient recovery after GC surgery.^[52] However, fiber might increase intestinal disorders, even though no significant difference was observed between the FE group and FEP group because of the small sample size (Table 3). GC surgery and antibiotics most likely caused postoperative intestinal flora imbalance, and fiber was not sufficiently fermented, resulting in abdominal pain, vomiting/nausea, and abdominal distension.^[53,54] The LOHS of the FE and FEP groups was shorter than that of the FF group, and this result was also reported by previous researchers,^[55,56] which was in accordance with the current requirements of enhanced recovery after surgery (ERAS).^[31] Based on the results of LOHS and intestinal disorders in the 3

Table 3
Postoperative recovery of patients.

	FF group	FE group	P	FE group	FEP group	P
First flatus time, h	63.03±4.86	58.93±6.52	.002	58.93±6.52	57.35±7.02*	.30
Intestinal disorders, n	9	5	.38	5	2*	.43
Abdominal pain, n	2	1	—	1	1	—
Vomiting/nausea, n	4	2	—	2	0	—
Abdominal distension, n	3	2	—	2	1	—
Length of hospital stay, d	8.05±0.61	7.61±0.72	.004	7.61±0.72	7.42±0.83*	.28

FE = fiber-enriched nutrition formula, FEP = fiber- and probiotic-enriched nutrition formula, FF = fiber-free nutrition formula.

* Significant difference between the FF group and FEP group.

Table 4**Comparison of the nutrition indexes of the 3 groups.**

	FF group	FE group	P	FE group	FEP group	P
TLC, $\times 10^9/L$	1.01 \pm 0.28	0.94 \pm 0.16	.17	0.94 \pm 0.16	0.96 \pm 0.16*	.58
ALB, g/L	33.51 \pm 2.23	32.80 \pm 2.04	.14	32.80 \pm 2.04	33.37 \pm 1.48*	.16
PA, mg/L	137 \pm 15.2	136 \pm 11.8	.74	136 \pm 11.8	135 \pm 15.4*	.75
TRF, g/L	1.15 \pm 0.25	1.13 \pm 0.24	.72	1.13 \pm 0.24	1.16 \pm 0.23*	.57

ALB = albumin, FE = fiber-enriched nutrition formula, FEP = fiber- and probiotic-enriched nutrition formula, FF = fiber-free nutrition formula, PA = prealbumin, TLC = total lymphocyte count, TRF = transferrin.

* No significant difference between the FF group and FEP group.

groups, the combination fiber and probiotics can treat diarrhea that is associated with EN and enhance patient recovery after GC surgery.

No significant difference was observed among the 3 groups in terms of nutritional status (Table 4). Nutritional support of the patients with diarrhea was most likely not interrupted by severe diarrhea. In addition, this RCT study might be conducted for a short period of time, and the change in nutrition status was not clearly shown.

This study has several limitations, considering the interpretation time of the study results. First, although all the patients participated until the end of the trial, its sample size was still small (120 patients), which is considered as the major limitation of the study. Second, the study did not use double blind trial to avoid the loss of samples. Because of ERAS, our observation time was short, which might affect some of the observed indicators, particularly nutritional status.

5. Conclusion

Based on this RCT study, the combination of fiber and probiotics could reduce the incidence of diarrhea, enhance intestinal movement, and decrease the intestinal disorders in postoperative patients with GC who are on EN. In addition, this treatment can shorten the LOHS, which was in accordance with the current requirements of ERAS. Thus, the use of both fiber and probiotics should be considered when initiating EN to avoid diarrhea that is associated with EN, provide comfort for postoperative patients, and enhance patient recovery after surgery.

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