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ORIGINAL ARTICLE

Effects of probiotics combined with enteral nutrition on immune function and inflammatory response in postoperative patients with gastric cancer

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Summary

Purpose: *To explore the therapeutic effect of probiotics combined with enteral nutrition (EN) in postoperative patients with gastric cancer (GC).*

Methods: *140 GC patients were enrolled in this study and randomly assigned into the test group and the control group, with 70 patients in each group. Patients in the test group were treated with probiotics combined with EN, while those in the control group were treated with common EN. Patients' conditions were observed for 8 days. IgG, IgA, IgM, IL-6, IL-8, TNF-a, hemoglobin, albumin, pre-albumin, time to relief of abdominal distension, time to first flatus, length of hospital stay and adverse events were recorded and analyzed.*

Results: *The factors related to immune function in patients of the test group, such as IgG, IgA and IgM, were higher than those of the control group. Moreover, the improvements of inflammatory cytokines including IL-6, IL-8 and TNF-a in patients of the test group were better than those of the control group. However, no obvious difference was found in the nutritional status before and after treatment between the two groups (p>0.05). In the comparison of clinical symptoms, time to relief of abdominal distention and time to first flatus were both earlier in patients of the test group than in those of the control group (p=0.002, p=0.03, respectively). Additionally, the diarrhea caused by EN was also significantly less in the test group compared with the probiotics control (p=0.03).*

Conclusions: *Probiotics combined with EN could improve the immune function and reduce the inflammatory response and the incidence of diarrhea in postoperative patients with gastric cancer.*

Key words: *enteral nutrition, gastric cancer, immune function, inflammatory response, probiotics*

Introduction

Gastric cancer (GC) is the fourth most common type of cancer. Malnutrition is considered to increase the mortality and incidence in the perioperative GC patients [1]. Accumulating studies have been carried out to explore the effect of postoperative EN in GC patients. Research has shown that early postoperative EN may help improve the negative nitrogen balance, promote immune function and reduce the incidence of postoperative complications [2]. Yao et al. [3] have found that early postoperative EN can reduce the insulin resistance, thus controlling blood glucose in postoperative GC patients. However, EN also causes some complications [4,5]. Among them, diarrhea is the most common one and may affect the overall postoperative recovery. In particular, diarrhea leads to loss of fluid and electrolytes in GC patients, thus eventually prolonging the length of hospital stay and even resulting in abnormal immune function [6,7]. Studies have indicated that the incidence of diarrhea is up to 12-68% [8,9]. Therefore, it is of great significance to reduce the incidence of diarrhea caused by early EN in postoperative GC patients.

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Investigations towards improving the immune response and reducing the inflammatory reaction in postoperative GC patients are of importance since the immune function is fragile under GC pathological conditions. Tannock et al. [10] have suggested that probiotics can be applied as active microorganisms to maintain the balance of intestinal microflora. Duc et al. [11] have indicated that the probiotics applied in humans are at least capable of independently forming colonies, enhancing immune functions and resisting pathogenic microorganisms. At present, the majority of the researched probiotics includes Lactobacillus and Bifidobacterium. The probiotics that could have beneficial effect on the host through selective stimulation of the growth and activity of bacteria in a colony or a few colonies are widely studied. Probiotics are capable of maintaining the balance of intestinal flora, reducing intestinal pH value, decreasing lactose intolerance, enhancing intestinal resistance to infection, improving gastrointestinal peristalsis and absorption through a number of microorganisms [12,13]. In this study we designed and conducted this prospective randomized controlled trial (RCT) to further investigate the role of probiotics combined with EN in the treatment of GC patients.

Methods

Patients

A total of 140 GC patients diagnosed by gastroscopy and pathological examinations were included in the present study. The TNM staging and pathological types of GC were evaluated according to the International Union Against Cancer (UICC) standard in 2002 [14]. All the patients underwent distal gastrectomy in our hospital from June 2014 to June 2016, and then were randomly assigned into the probiotics combined with EN group (test group) and the common EN group (control group). Inclusion criteria were as follows: (1) Patients aged from 18 to 75 years; (2) Postoperative TNM pathological stages of GC I, II, IIIa and IIIb; (3) No preoperative endocrine and metabolic diseases and patient organ functions normal; (4) Length of hospital stay over 10 days. Exclusion criteria were as follows: (1) GC patients received preoperative enteral or parenteral nutrition support; (2) EN contraindications; (3) Usage of preoperative broad-spectrum antibiotics. This study was approved by the ethics committee of the First People's Hospital of Changzhou. Signed written informed consents were obtained from all participants before the study.

Treatment

Early EN was applied in postoperative GC patients. Briefly, the nasal-intestinal tube was placed in the jejunum output loop, 20-30 cm away from the most distal anastomosis. Six hrs after operation, 250-500 ml of glucose and sodium chloride were injected into the nutrient tube in patients of the control group, and EN suspension (Peptison, New Zealand Pharmaceutical Co. Ltd. Palmerston North, New Zealand) was slowly infused within 24 hrs. The postoperative EN treatment was maintained for 7-8 days. After the total EN was completed without any discomfort, fluid and semi liquid diet were gradually given. Meanwhile, the amount of EN was gradually reduced until returning to the normal diet. Patients in the test group were given probiotics combined with EN at the same time three times a day.

Observational outcomes

The immune function of patients in the two groups was observed and assessed. The levels of IgG, IgA and IgM were detected by ELISA. Inflammatory indicators, such as IL-6, IL-8, TNF-α, were also compared between the two groups,. Nutritional status including hemoglobin, albumin, and pre-albumin of the two groups was evaluated. The time to relief of abdominal distension, time to first flatus, length of hospital stay and adverse events between the two groups were observed and analyzed.

Statistics

The Statistical Package for Social Sciences (SPSS 22.0, Armonk, NY, USA) software was used for statistical analyses. The quantitative data were represented as mean ± SD. The t-test was used to compare differences between the two groups. The categorical data were presented as numbers and compared by the chi-square test. $p<0.05$ was considered statistically significant (*$p<0.05$, **$p<0.01$).

Results

General characteristics of the GC patients

Among the 140 GC patients included in this study, none of them was excluded because of severe adverse reactions. No significant differences in age, sex, body mass index (BMI), nutritional status and tumor staging were found between the two groups (Table 1).

Comparison of indicators related to immune function

Our results showed that the levels of IgG, IgA and IgM on the 8th postoperative day in the test group were significantly higher than in those of the control group ($p<0.05$). Among the three indicators, the improvements of IgA and IgM were greater compared with IgG (Figure 1A).

Comparison of inflammatory cytokines

In this study, IL-6, IL-8 and TNF-α were selected to evaluate the inflammatory response in GC patients. The results indicated that the decreased

rates of IL-6, IL-8 and TNF-α in the test group were remarkably faster than those of the control group (Figure 1B).

Comparison of nutritional status

Hemoglobin, albumin and pre-albumin were used as indicators to reflect the nutritional status. However, no statistical differences in the above three indicators were found between the two groups (p>0.05; Figure 2).

Comparison of clinical parameters

The results demonstrated that time to relief of abdominal distension and time to first flatus in the test group were significantly earlier than those of the control group (p=0.002, p=0.03, respectively). However, no significant difference in the length of hospital stay between the two groups was found (p>0.05; Figure 3).

Comparison of postoperative adverse events

In the test group, there were 8 cases of diarrhea, 8 cases of vomiting, 0 case of anastomotic fistula, 4 cases of pulmonary infection and 0 case of duodenal stump fistula. However, there were 18 cases of diarrhea, 10 cases of vomiting, 0 case of anastomotic fistula, 6 cases of pulmonary infection and 0 case of duodenal stump fistula in the control group (Table 2). The results showed that diarrhea was significantly lower compared with the control group.

Table 1. Patient characteristics (mean ± SD)

	Test group (n=70)	*Control group (n=70)*	*p value*
Age, years	67.23±10.10	68.36±9.68	0.67
Gender, M/F	29/41	38/32	0.13
BMI, kg/m²	22.37±2.36	23.65±2.01	0.49
Before EN			
Albumin, g/L	27.12±2.74	27.87±2.61	0.78
Prealbumin, g/L	201±8.73	198±7.71	0.65
Hemoglobin, g/L	106.47±4.32	105.68±5.31	0.73
Transferrin, g/L	1.96±0.84	2.12±0.63	0.26
TNM (I & II/III)	51/19	56/14	0.32

EN: enteral nutrition, TNM: tumor node metastasis, M: male, F: female, BMI: body mass index

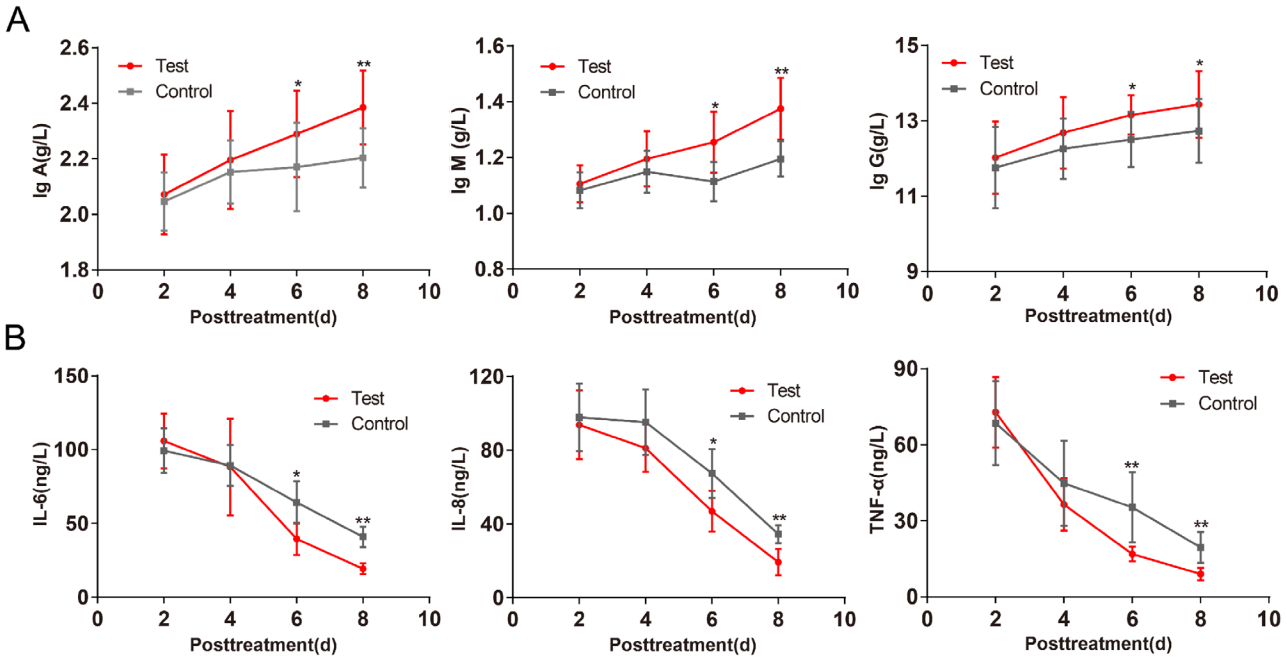

Figure 1. Comparison of immune function and inflammatory indictors between the two groups. **A:** The increased levels of IgG, IgA and IgM in the test group were faster than those of the control group. **B:** The decreased levels of IL-6, IL-8 and TNF-α in the test group were faster than those of the control group. *p<0.05 vs the control group. **p<0.001 vs the control group.

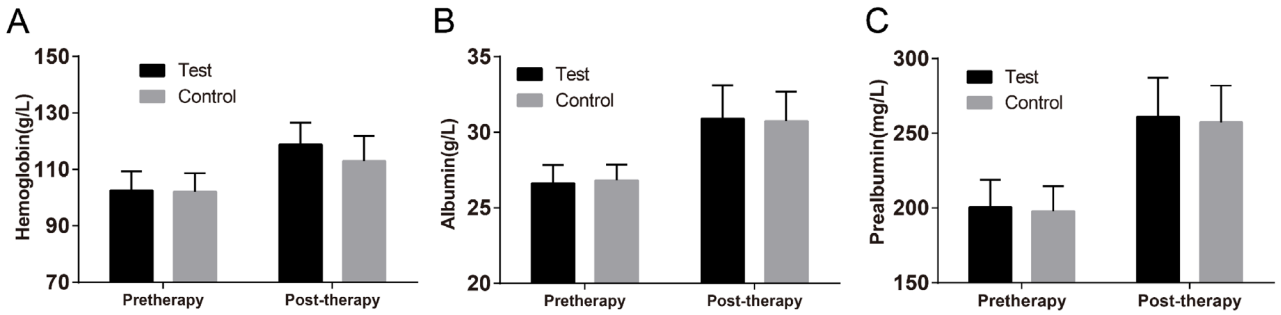

Figure 2. Comparison of nutritional status. **A:** There was no significant difference in hemoglobin between the test group and the control group before and after treatment (p>0.05). **B:** There was no significant difference in albumin between the test group and the control group before and after treatment (p>0.05). **C:** There was no significant difference in pre-albumin between the test group and the control group before and after treatment (p>0.05).

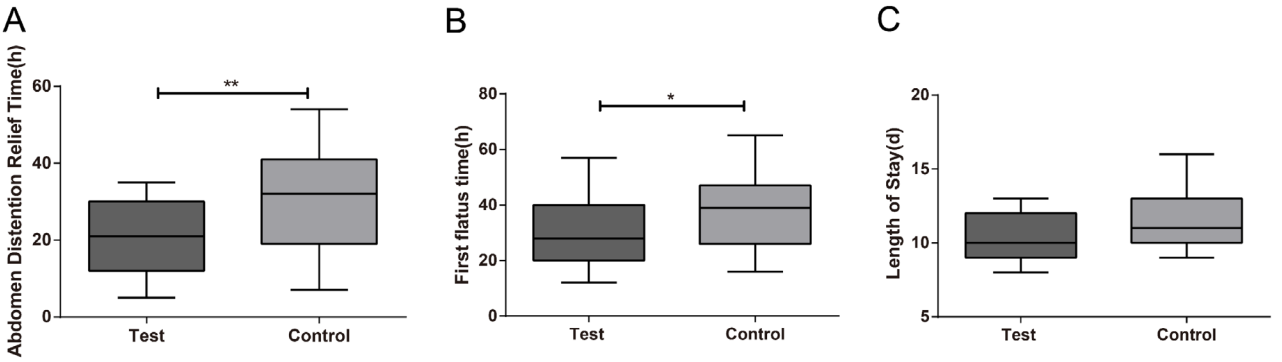

Figure 3. Comparison of clinical parameters. **A:** The time to relief of abdominal distension of the test group was earlier than that of the control group (**p=0.002). **B:** The time to first flatus of the test group was earlier than that of the control group (*p=0.003). **C:** There was no significant difference in the length of hospital stay between the test group and the control group (p>0.05).

Table 2. Adverse events

	Test group (n=70)	*Control group (n=70)*	*p value*
Diarrhea	8	18	0.03
Vomit	8	10	0.61
Anastomotic leakage	0	0	-
Pulmonary infection	4	6	0.51
Duodenal stump leakage	0	0	-

Discussion

GC is the fifth most common type of malignant tumors and the third major cause of cancer death worldwide [15]. Surgery is still the main treatment method for this malignancy. Studies have shown that 80% of GC patients are associated with different levels of malnutrition [16]. The decreased food intake, inability of diet in the perioperative period of GC, as well as surgical trauma and stress result in severe immunosuppression. In addition, surgical stress produces a systemic inflammatory response that reduces the quality of patient's life, thus influencing the prognosis of postoperative GC. Gabor et al. [17] have proved that postoperative EN treatment is safe and feasible. Postoperative EN can help maintain the integrity of the gastrointestinal mucosa and prevent intestinal microorganisms from translocation into the blood. It is also well recognized that early EN can promote intestinal function recovery, maintain intestinal mucosal barrier function, prevent intestinal bacterial translocation, enhance immune regulation function and adjust intestinal microflora.

Probiotics have been widely applied in various systems. Lim et al. [13] have found that probiotics may reduce intestinal pH, promote the bile acid activity, and further reduce the production and ab-

sorption of intestinal cholesterol. Lactobacillus is also capable of reducing pH, producing metabolites which can inhibit toxins and synthetize bacteriocin with antibacterial activity. Additionally, it can inhibit the growth of pathogenic bacteria or opportunistic pathogens in order to maintain the intestinal microflora, thereby protecting the intestinal biological barrier. Multiple studies have been carried out to explore the role of surface probiotics in the gastrointestinal tract. For example, Medina et al. [18] have confirmed that live bacteria of the Bifidobacterium and Lactobacillus, bacterial structural molecules and genomic DNA all exert immunomodulatory effects. Moreover, Jia et al. [19] have illustrated that probiotics can reduce the nitrogen ammoniacemia in treating mice hepatic encephalopathy. Additionally, Rayes et al. [20] have shown that a variety of probiotics may reduce the incidence of infectious complications after liver transplantation. All this evidence has suggested that probiotics exert a potential role in regulating the immune function.

In the present study, we explored the role of probiotics in early EN of postoperative GC patients. No significant difference was found in the preoperative general condition between the test group and the control group. By comparing the levels of IgG, IgA, IgM between the test group and the control group, we found that probiotics combined with EN were more conducive to improve the immune function in GC patients. Moreover, higher levels of IL-6, IL-8 and TNF-α in the test group suggested that probiotics combined with EN could effectively reduce the inflammatory response. However, no significant difference in the nutritional status was found between the two groups, suggesting that probiotics could not improve the nutrient uptake. Finally, comparison of clinical data demonstrated that time to relief of abdominal distension and time to first flatus in the test group were significantly earlier than those of the control group, control that probiotics could promote the recovery of GC patients.

Furthermore, it was also demonstrated that probiotics could also reduce the incidence of diarrhea in GC patients by comparing postoperative adverse reactions. For instance, Plummer et al. [21] have indicated the amount of Bacillus difficile related toxins in elderly patients was significantly lower than that of the control group. Paton et al. [22] have illustrated that probiotics can effectively treat diarrhea caused by endotoxin. Salazar et al. [23] obtained similar results in a randomized, double-blind, placebo-controlled clinical trial, in which probiotics were used for the treatment of acute watery diarrhea in infants. Therefore, we hypothesized that probiotics could relieve the gastrointestinal dysfunction in postoperative GC patients. However, no significant differences were found in other adverse events such as vomiting, anastomotic fistula, pulmonary infection and duodenal stump fistula between the two groups.

We should acknowledge some limitations in this study. First, this study was conducted in a single center with a small sample size. Second, double-blind trial was not performed to avoid the biases caused by subjective judgments. Multi-center prospective studies with larger sample sizes are still needed to further elucidate the therapeutic effect of probiotics combined with EN on postoperative GC patients.

Conclusions

The combination of probiotics and EN can improve the immune function and reduce the inflammatory response and the occurrence of diarrhea in postoperative GC patients.

Conflict of interests

The authors declare no conflict of interests.

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