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Therapeutic effect of Bifidobacterium combined with early enteral nutrition in the treatment of severe acute pancreatitis: a pilot study

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Abstract. – OBJECTIVE: To explore the therapeutic effect of Bifidobacterium combined with early enteral nutrition in severe acute pancreatitis.

PATIENTS AND METHODS: A total of 60 patients with severe acute pancreatitis admitted from November 2012 to November 2016 were retrospectively analyzed. According to the different treatment methods, the patients were divided into Bifidobacterium combined with early enteral nutrition group (experiment group) and early enteral nutrition group (control group). Serum ALB (albumin), CRP (C-reactive protein), WBC (white blood cell count) and PCT (procalcitonin) levels in both groups were observed. The pain relief time, diet recovery time, length of stay, and hospitalization costs between the two groups, were compared. The APACHE (acute physiology and chronic health evaluation scoring system) II score and SOFA (sequential organ failure assessment) score before and after nutritional support were compared between the two groups. Adverse events and complications were observed as well.

RESULTS: 58 patients recovered and 2 died after treatment. Improvements in laboratory indicators such as ALB, CRP, WBC and PCT were much better in the experiment group than the control group ($p<0.05$). Both the length of days and hospitalization cost were lower in the experiment group than those of the control group ($p=0.0029$, $p=0.0435$). In the comparison of hospitalization symptoms, shorter pain relief time and diet recovery time were found in the experiment group than those in the control group ($p=0.0003$, $p=0.0218$). After the treatment, APACHE II score and SOFA score of the experiment group were also higher than the control group. No significant differences in adverse events and complications between the two groups were exerted ($p>0.05$).

CONCLUSIONS: Bifidobacterium combined with early enteral nutrition can improve the nutritional status of patients with severe acute pancreatitis in the acute stage, which also enhances the patient's immune capacity and the body's resistance to disease.

Key Words:
Severe acute pancreatitis, Bifidobacterium, Early enteral nutrition, Efficacy.

Introduction

Enzymes in the acinus of the pancreas are activated by a variety of factors, which in turn cause the pancreas to self-digest and spread to adjacent tissues, followed by a series of extensive inflammatory reactions, that is, acute pancreatitis[1,2]. Pathological manifestations of acute pancreatitis include edema, bleeding and even necrosis. Clinically, patients with mild acute pancreatitis are more commonly seen, and have mild self-healing ability, whose symptoms are easier to control[3]. However, a small number of patients have severe pancreatic lesions, which behave as hemorrhage and necrosis of pancreatic tissue. Comparing to mild acute pancreatitis, the condition of SAP (severe acute pancreatitis) is extremely easy to deteriorate, which makes it difficult for clinical treatment. It is also likely to cause secondary infection and lead to shock, and greatly threatens patients' lives[4]. The basic treatment of SAP mainly includes spasmolysis, analgesia, symptomatic treatment, fluid infusion, acid suppression, inhibition of enzyme, gastrointestinal decompression and nutritional supportive therapy.

With the continuous research into SAP, the conventional prohibition of drinking water and TPN (total parenteral nutrition) treatment are gradually replaced by EN (enteral nutrition) support[5]. Long-

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term TPN, however, can lead to intestinal mucosa atrophy and shortened intestinal villi. Therefore, this damages the function of intestinal mucosal barrier altering intestinal flora. These changes eventually result in intestinal bacterial and endotoxin translocation, thereby increasing the prevalence of intestinal infection. Long-term TPN can't effectively reduce mortality in patients with acute pancreatitis[1]. It has been reported that EN support is beneficial for protecting intestinal integrity, the intestinal barrier and immune function, thereby reducing the prevalence of infectious complications[6-9]. Microecological agents are commonly used with intestinal flora regulating drugs, which can be applied for adjuvant treatment of acute pancreatitis to promote intestinal immune function. Therefore, this study aimed at exploring the therapeutic effect of *Bifidobacterium* combined with early EN in treating SAP.

Patients and Methods

Patients

60 SAP patients treated in Digestive Department in our hospital from November 2012 to November 2016 were enrolled to our study. They were divided into two groups according to the different treatments, *Bifidobacterium* combined with early EN group (experiment group) and only early EN group (control group), with 30 cases each group. In the experiment group, 19 patients were males and 11 were females, aged 28 to 70 years (46.31 ± 11.23 years). In the control group, 17 patients were males and 13 were females, aged 29 to 68 years (45.38 ± 12.23 years). The disease cause of these patients included biliary disease, alcohol, overeating, hyperlipidemia, etc. This study was approved by the Ethics Committee of The First People's Hospital of Wujiang District Suzhou. Signed written informed consents were obtained from all participants before the study. Exclusion criteria were applied to patients receiving treatment within 2 weeks, patients voluntarily requesting for discharge, severe gastrointestinal dysfunction, severe infection or severe intestinal paralysis caused by surgery, severe immune dysfunction or using immunosuppressive agents for treatment, severe hemorrhage of digestive tract, patients in pregnancy or breast-feeding, patients with unknown medical history or incomplete clinical data.

Methods

The spiral nasogastric tube was inserted into the jejunum, 30 cm under the Treitz ligament, with the assistant of gastroscopy or X-ray. EN through the tranasal jejunum tube given after the successful catheterization was confirmed and the outer part was fixed. At first, 250-500 mL of 5% glucose saline was slowly injected. After patients were adapted (abdominal pain, abdominal distention and other symptoms were not significantly worse than before), short peptide enteral nutrition powder was injected. Then, infusion speed was strictly controlled, meanwhile proper temperature was maintained. Besides, the condition changes and tolerance were closely observed. If there was no significant discomfort, the drip rate and dose could be gradually increased with 100-1500 ml of infusion per day. The dose was adjusted according to patient tolerance. Patients in the experiment group were fed with *Bifidobacterium* daily through the nasal jejunum tube (Bifico, Shanghai Xinyi Pharmaceutical Co., Ltd. Shanghai, China) three times per day. No special treatment was given to patients in the control group. All patients received routine drug therapy for pancreatitis. The main treatment was intravenous drip infusion of octreotide, omeprazole, ceftazidime, ulinastatin and gabexate.

Observed Indicators

General recovery conditions of patients in two groups were observed. Laboratory indicators include ALB (albumin), CRP (C-reactive protein), WBC (white blood cell) and PCT (procalcitonin). The pain relief time, diet recovery time, length of stay and hospitalization costs of the two groups were compared. The APACHE II score and SOFA score before and after nutritional support in the two groups were recorded.

Statistical Analysis

We used statistical product and service solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) for statistical analysis. Measurement data were represented as (EMBED Equation.3 ±s). Two independent samples were compared using *t*-test. Counting data were represented as the number of cases and percentages, and were compared using x^2-test or rank sum test. $p<0.05$ considered the difference as statistically significant.

Results

General Data of Patients

In the experiment group, 19 patients were males and 11 were females, aged 28 to 70 years (46.31 ± 11.23 years). In the control group, 17 patients were

Table I. General data of patients.

	Treatment group (n=30)	Control group (n=30)	p
Age	46.31±11.23	45.38±12.23	0.351
Gender			0.598
Male	19	17	
Female	11	13	
Admission BMI	26.31±3.61	24.52±4.02	0.236
Smoking history			0.371
Yes	21	24	
No	9	6	
Drinking history			0.604
Yes	15	17	
No	15	13	
Aetiological agent			
Biliary tract disease	16	14	0.606
Engorgement	3	2	0.64
Alcohol	6	7	0.754
Hyperlipidemia	4	5	0.718
Other causes	1	2	0.554

Table II. Clinical symptoms of patients.

	Treatment group (n=30)	Control group (n=30)	p
Abdominal pain	30	30	-
Abdominal distension	29	30	>0.999
Fever	5	7	0.519
Emesis	23	20	0.39
Dyspnea	24	22	0.541
Oliguria or anuria	2	2	-

males and 13 were females, aged 29 to 68 years (45.38 ± 12.23 years). There were no significant differences in age, gender, BMI, smoking history, history of alcohol intake and previous related history in patients between the experiment group and control group (Table I). There were no significant differences in the clinical symptoms, such as abdominal pain, abdominal distension, fever, vomiting, dyspnea and oliguria in patients between the two groups (Table II).

Comparison of Laboratory Indicators

WBC, PCT and CRP are indicators of the degree of inflammatory infection. WBC in patients from both groups was higher than that before the treatment. As the course of treatment progressed, WBC decreased gradually. WBC on the 12th and 15th day in the experiment group was lower than the control group, and the difference was statistically significant. Improvement of CRP in the experiment group was better than the control group, especially on the 6th day, and the difference was statistically significant. PCT was significantly lower on the 6th and the 9th day in the experiment group than that in the control group. ALB is one of the indicators reflecting the nutritional status of patients, which was significantly higher on the 6th and 15th day in the experiment group than the control group. Detailed results were recorded in Figure 1.

Comparison of Clinical Indicators

The average length of hospitalization stay in the experiment group was 16.13 days, and 18.60 days in the control group. Significant difference in the length of hospitalization stay was exerted between the two groups (p=0.0029, Figure 2A). Higher hospitalization cost was observed in the experiment group than that in the control group (p=0.0435, Figure 2B). Our study found that the improvements of clinical symptoms in the experiment group were also better than that in the control group. The pain relief time in the experiment group was shorter than that of the control group (p=0.0003, Figure 2C). Similar results were observed in the diet recovery time (p=0.0218, Figure 2D). These results demonstrate that the clinical indicators in the experiment group are better than those of the control group.

Comparison of Treatment Scores

APACHE II score reflects severity degree of pancreatitis. Our results revealed pancreatitis condition improved in both groups after treatment. However, it was more remarkable in the experiment group, especially on the 12th day of admission ($p<0.05$, Figure 3A). SOFA score reflects the degree of organ failure in patients. Our study found that the SOFA score in the experiment group was higher than the control group, especially on the 6th and 12th day after admission ($p<0.05$, Figure 3B).

Adverse Events and Complications

In this study, 6 cases appeared pancreatic pseudocyst, 3 appeared pancreatic abscess, 2 appeared pancreatic calcification. There were three cases that were transferred for surgical treatment and one that died in the experiment group. In contrast, 5 cases appeared pancreatic pseudocyst, 5 appeared pancreatic abscess, and 1 appeared pancreatic calcification. There were three cases that were transferred for surgical treatment and one died in the control group. No significant differences in the prevalence of adverse events and complications between the two groups were observed (Table III).

Discussion

The disease course of SAP develops rapidly, which makes the deterioration difficult to control. Secondary infection is easily occurred with many complications and high mortality rate, severely threatens the patient's life[10]. Once SAP occurs, the metabolic balance is disturbed, leading to a poor nutritional status of patients. As a consequence, nutritional support is particularly crucial

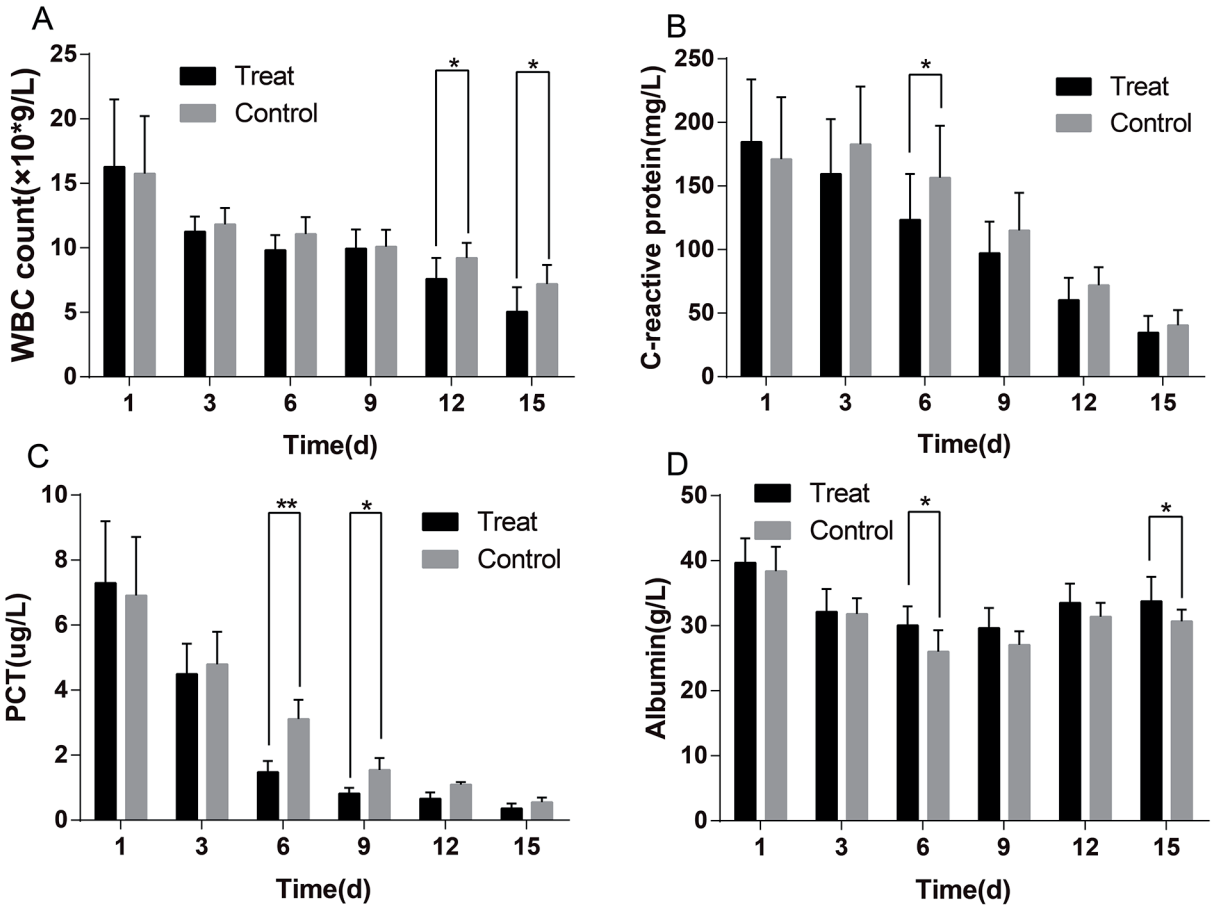

Figure 1. Comparison of laboratory indicators. ***A,*** WBC was decreased in both groups, but the WBC in the experiment group was higher than the control group. ***B,*** The reduction of CRP in the experiment group was greater than that in the control group. ***C,*** The PCT improvement in the experiment group was better than that in the control group. ***D,*** The reduction of ALB in the experiment group was better than the control group.

Table III. Adverse events and complications.

	Treatment group (n=30)	Control group (n=30)	p
Pancreatic pseudocyst	6	5	0.738
Pancreatic abscess	3	5	0.448
Pancreatic calcification	2	1	0.554
Surgery	3	3	-
Death	1	1	-

for the treatment of SAP[11]. On the other hand, gastrointestinal damage and bacterial translocation arose in the early stage of SAP. Studies have shown that the gastrointestinal mucosal barrier function is damaged 2 h after SAP onset and intestinal motility is decreased 3 h after experimental pancreatitis. Another study pointed out that 60-90% of the experimental animals present intestinal bacterial translocation to the abdominal and pancreatic tissue 6 h, 24 h after experimental pancreatitis, respectively[12,13]. An important principle in the treatment of SAP is to minimize pancreatic secretion, keep the pancreas in a quiet state so as to allow the pancreas to have adequate rest[14]. Based on this, PN, especially TPN, has been widely applied in the clinical treatment of SAP and achieved good results. Although PN relieved pancreatic secretion, it inevitably leads to long-term intestinal exclusion, followed by intestinal dysfunction, mucosal ischemia, altered permeability, thus leading to impaired intestinal mucosal barrier function[15,16].

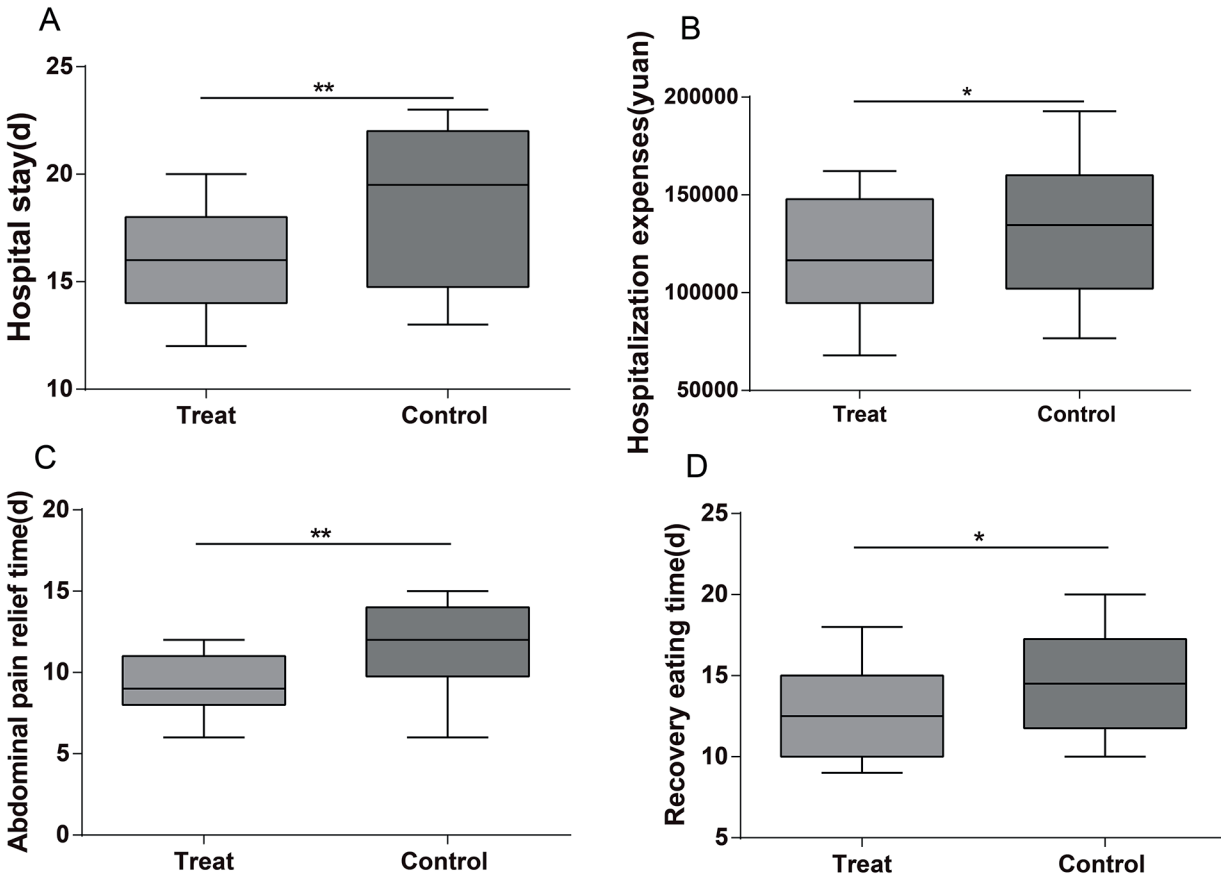

Figure 2. Comparison of clinical indicators. ***A,*** The length of stay in the experiment group was shorter than the control group. ***B,*** The hospitalization cost in the experiment group was less than the control group. ***C,*** The pain relief time in the experiment group was earlier than the control group. ***D,*** The diet recovery time in the experiment group was earlier than the control group.

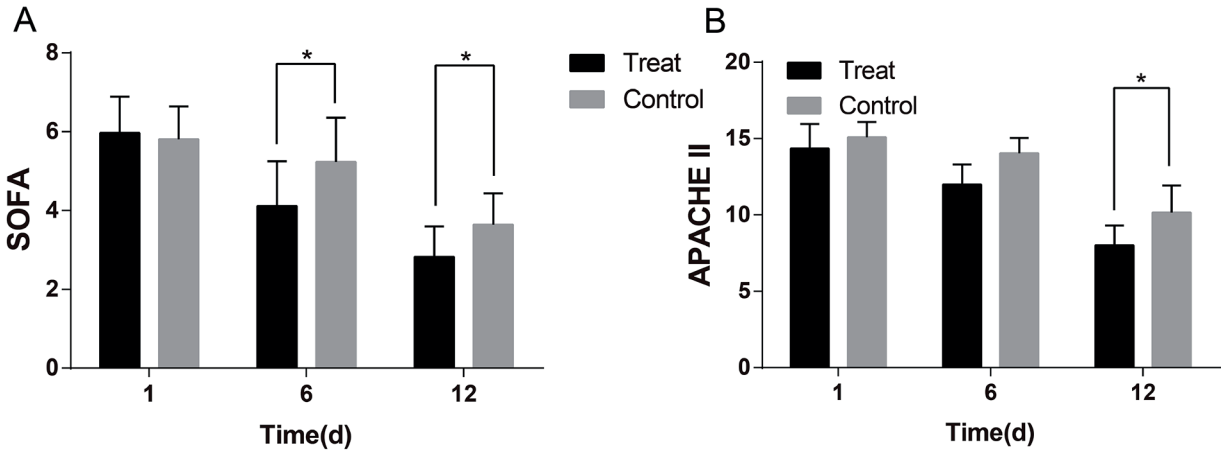

Figure 3. Comparison of treatment scores. ***A,*** SOFA score of the experiment group was better than that of the control group after treatment. ***B,*** APACHE II score of the experiment group was better than that of the control group after treatment.

Therefore, early EN is greatly valued. Windsor et al[17] found that after the SAP patients received EN in clinical trial, prevalence of SIRS (systemic inflammatory response syndrome) sepsis, and intensive care time, were improved, while blood CRP, plasma endotoxin, APACHE II score were decreased significantly. In addition, numerous studies[14,18] have shown that EN can significantly reduce length of stay and the chance of infection and surgery. Petrov et al[19] also found that the application of EN can reduce the mortality of SAP patients, the prevalence of complications and sepsis[20]. Although early EN on the treatment of SAP showed promising outcomes in various trials, at present, there is no definite conclusion on the improvement of gastrointestinal barrier function by combining probiotics with EN support. Therefore, this study aimed at exploring whether probiotics combined with early EN is better than the simple early EN on the diagnosis and treatment of SAP.

In the study, WBC, CPR, PCT are chosen as indicators of the infection and inflammatory response[21,22]. The results showed that patients treated with *Bifidobacterium* combined with early EN experienced a more rapid improvement in inflammation over time. Therefore, we considered that probiotics can improve the resistance to infection, reduce the inflammatory response and reduce the risk of secondary infection. Besides, ALB was found significantly higher in the experiment group than the control group, suggesting that the nutritional status of the experiment group in the acute stage of SAP is better than that of the control group. Further analysis found that the length of stay and hospitalization costs in the experiment group were less than those of the control group, and the differences were statistically significant. For clinical improvement during hospitalization, the pain relief time and diet recovery time in the experiment group were earlier than the control group. According to the APACHE II score and the SOFA score, *Bifidobacterium* can also reduce the risk of multiple organ failure in SAP. However, analysis of adverse events and complications of SAP indicated that *Bifidobacterium* could not reduce the prevalence of adverse events and complications.

In summary, *Bifidobacterium* combined with early EN can improve the nutritional status of SAP in the acute stage, enhance the patient's immune capacity and enhance the body's resistance to disease, the effects of which are better than the simple early EN. Probiotics can be recommended for clinical use in the treatment of SAP. Some of the limitations of this study, however, are noteworthy. For example, this is a retrospective and a single-center study with limited sample size. Prospective studies with large samples are needed for in-depth investigation in the future.

Conclusions

We showed that *Bifidobacterium* combined with early EN can improve the nutritional status of SAP in the acute stage, enhance the patient's immune capacity and enhance the body's resistance to disease.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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