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Effect of ecological immune-enhanced enteral nutrition on patients with gastrointestinal fistulas

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Abstract. – OBJECTIVE: The aim of this study was to determine the effects of early ecological immune-enhanced enteral nutrition on the nutritional status, immune function and intestinal mucosal barrier in patients with gastrointestinal fistulas.

PATIENTS AND METHODS: 54 patients with gastrointestinal fistulas were randomized to either the ecological immune-enhanced enteral nutrition group (EIEN group, 28) or the parenteral nutrition group (PN group, 26). The changes in the immunity, nutrition index and intestinal mucosal barrier indexes before the ecological immune-enhanced enteral nutrition support and at 7 days and 14 days after the ecological immune-enhanced enteral nutrition support were determined.

RESULTS: Compared with the PN group, the indexes of the CD3 and CD4 positive cells, the CD4/CD8 values and the plasma levels of IgA and IgM were significantly higher than those in EIEN group ($p<0.05$). Moreover, with EIEN nutritional support, the nutrition indexes, such as the plasma ALB, PA and TFN, and the intestinal mucosal barrier index (the plasma D-lactate levels and endotoxin levels), also recovered gradually to normal levels and were higher than those of the PN group ($p<0.05$).

CONCLUSIONS: For patients with gastrointestinal fistulas, ecological immune-enhanced enteral nutrition can not only improve the cellular immunity function, humoral immunity, and nutritional status but also enhance the intestinal mucosal barrier.

Key Words:

Ecological immune-enhanced enteral nutrition, Gastrointestinal fistula, Nutrition status, Immunity, Intestinal mucosal barrier.

Abbreviations

GI = gastrointestinal; LOS, length of stay; ALB = serum albumin; EIEN = ecological immune-enhanced enteral nutrition; NPO, nothing by mouth; PICC = peripherally inserted central catheter; PA = proalbumin; GALT, gut associated lymphatic tissue; SFAs = special short-chain fatty acids

Introduction

A gastrointestinal (GI) fistula is an abnormal opening that allows the contents and fluid of the stomach or intestines to leak out of the abdomen[1]. A GI fistula may occur either postoperatively or for other reasons. Approximately 15% to 25% of fistulas have a close relationship with inflammation (such as diverticulitis and inflammatory bowel disease), cancer, or radiation treatment. Other GI fistulas are mainly associated with postoperative surgical procedures (anastomotic dehiscence, erosion by an adjacent drain, or an unrecognized iatrogenic injury)[2]. Additionally, medical factors, such as inadequate blood supply to the anastomotic stoma, malnutrition, sepsis, shock and hypotension contribute greatly to GI fistulas. Besides, steroid application, inflammatory bowel disease (such as Crohn's disease or ulcerative colitis), and trauma may also result in onset and development of GI fistulas. Dehydration and malnutrition are commonly secondary to GI fistulas, which depends on the location of the fistula. Malnutrition often lead to higher rates of infection and also increased hospital stay, morbidity, and mortality[3].

The increased energy requirements because of the disease-associated stress produce a negative energy balance, which also plays a role in malnutrition. Immunonutrition has become closely associated with attempts to improve the clinical course of critically ill and surgical patients, who often require an exogenous supply of nutrients through parenteral or enteral routes. Improving the immune function may reduce the complications due to infection or stress. In patients with GI fistulas, complex variable immune and inflammatory changes occur that are only now being well defined. A biphasic response with an early hyper-inflammatory response followed by an excessive compensatory response associated with

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immunosuppression is observed in many patients. Ecological immunonutrition is based on an immune-enhancing treatment, adding probiotic bacteria to enhance the effects of nutritional support, suppress the overgrowth of pathogenic bacteria of the gut and protect the intestinal microecology and function of the intestinal mucosal barrier[4,5]. In this case, early ecological immune-enhanced enteral nutrition is aimed at decreasing the inflammatory response rather than enhancing it to abrogate the process of hyper-inflammation and prevent the compensatory immunosuppression of these patients. The initiation and maintenance of nutritional support are essential for treating patients with GI fistulas. Bowel rest, by keeping the patient NPO, is recommended for at least 2 to 3 weeks. When indicated, enteral nutrition is preferred to avoid atrophy of the mucosal villi and to allow for normal bowel function, as it is reasonable to assume that the immune-enhanced enteral nutrition will reach sufficient tissue and plasma concentrations to exert their maximum effects.

Patients and Methods

Patients

The data from 54 patients with gastrointestinal fistulas in the Department of General Surgery, Binzhou Hospital of Binzhou Medical University (Binzhou, China) from March 2010 to August 2014 were collected. The inclusion criteria were (1) a fistulography-confirmed intestinal fistula and (2) the ability of the patients to tolerate receiving the enteral nutritional support through adequate drainage and anti-infective therapy. Patients underwent a fistulogram to assist in determining the treatment regimen.

In detail, a soft catheter was inserted into the fistula, and the contrast dye was instilled. We then performed multiple radiographic examinations to identify the location of the fistula in the GI tract, and the patency of the GI tract distal to the fistula and the tract between the GI tract and the skin. In some cases, other tests, such as a barium enema (upper gastrointestinal X-rays with small bowel follow-through), were also needed.

The exclusion criteria were endocrine or metabolic disorders, immune insufficiency, cardiac, hepatic, renal or respiratory dysfunction, a history of radiotherapy or treatment with immunosuppressive drugs and a terminal state. Finally, 54 patients (29 males and 26 females) with a mean age of 48.5 years (range 23-69 years) were included in the study. All of the 54 patients had intestinal fistulas, and there were 19 cases of gastric or esophageal fistulas, 21 cases of pancreatic fistulas, and 14 cases of duodenal fistulas.

Fistulas are usually caused by injury or surgery, but they can also result from an infection or inflammation. Fistulas are generally a disease condition. A GI fistula is a complication that occurs because of an accident, operation or other reasons, resulting in large amounts of digestive liquid flowing from the fistula and the significant loss of fluids and electrolytes, causing an imbalance and systemic pathological changes. Fistula output different from 100ml to 1000 ml because of the causes and patients status and a comprehensive therapy. BMI in this study is not including. Because the nutritional index is observed by the serum albumin (ALB), prealbumin (PA) and transferrin levels. Fistula output before the ecological immune-enhanced enteral nutrition (EIEN) support is more than after trial treatments. But has no different before and during the ecological immune-enhanced enteral nutrition support. Ecological immune-enhanced means which consisted of Nutrition (Intact Protein Enteral Nutrition Powder, Nutrition was made from MilupaGmbH, Dusseldorf, Germany H20130888), according to a 35 kcal/kg.d calculation of the total energy, NPC (kcal):N (g) 130:1. Polymeric diets were also added, particularly those containing glutamine, such as Glutamine Granules and Bifidobiogen, for their immunologic facilitation. With the progress in nutritional support and treatment technology and a combination of somatostatin and growth hormones, the overall mortality has decreased, but the mortality rate is still 20-30% in patients with GI fistulas. The use of Octreotide (Sandostatin) can decrease the fistula's output by inhibiting the release of gastrin and other GI hormones.

Ecological immune-enhanced enteral nutrition can improve the nutritional status, immune function recovery and stimulation of the proliferation and repair of intestinal fistula mucosa cells. The fate of patients after the trial is good than those of PN group patients. No patients condition is worse than those before the EIEN.

In the early-stage intestinal fistulas, a comprehensive therapy was used, such as the continuous intravenous pumping of somatostatin, NPO (nothing by mouth) for 5-18 days, antibiotics and continuous drainage of the intestinal fistula. The patients were randomized into two groups: the ecological immune-enhanced enteral nutri-

tion group (EIEN group, n=28) and the parenteral nutrition group (PN group, n=26), according to a random number table. There were no significant differences between the two groups in terms of age, gender, immunity, and nutrition status and the staging and locations of the fistulas and the severity of the disease (p>0.05).

Nutritional support

Ecological Immune-Enhanced Enteral Nutrition (EIEN) group

Nutritional support was administered using endoscopy distal to the fistula, and a nutritional catheter was inserted to administer the EIEN, which consisted of Nutrition (Intact Protein Enteral Nutrition Powder, Nutrition was made from MilupaGmbH, Dusseldorf, Germany H20130888), according to a 35 kcal/kg.d calculation of the total energy, NPC (kcal): N (g) 130:1. Polymeric diets were also added, particularly those containing glutamine, such as Glutamine Granules and Bifidobiogen, for their immunologic facilitation. A stepwise increase of the intake of calories from the enteral nutrition was scheduled and started. In detail, on the first day, approximately 250 ml of the 5% fluid enteral formula (20-30 ml/hr) was infused. The temperature of the nutrient fluid was set at 38-42 °C, and the speed of input was modulated to 3-4 ml/min using an enteral feeding pump (Foulke 800) to control the speed, time and use. From the second day, the enteral nutrients were administered at a rate of approximately 25 ml/hr, with a gradually increase by approximately 25 ml/hr each day, until the target rate (maximum: 100-120 ml/hr, 20% Nutrition 1500-2000 ml/d, 6225-8300 kJ/d). Energy with a goal of 20-25 kcal/kg per day was achieved. The patient's ability to tolerate this enteral formula feeding was recorded daily, noting symptoms and signs such as cramping, distention, nausea, and diarrhea and other complications. Before and after every infusion of the enteral formula and every 3-4 hr, a syringe filled with 20 ml of normal saline was used to clean the feeding tube to keep it unobstructed.

Parenteral Nutrition (PN) Group

The patients in the PN group received a normal infusion, and after their vital signs were stable, PN was administered through a peripherally inserted central catheter (PICC). The parenteral formula selected for use was the standard system nutritional preparation from Huarui Science & Technology Co. LTD. This PN formulation contains amino acids, glucose, and fat emulsion, plus electrolytes, trace elements, vitamins, and additives. The caloric distribution is 50-60% glucose and 40-50% fat. All of the patients in each of two groups received antibiotics for 10-14 days and the same treatments and level of nursing care.

Determining Serum Parameters

The blood parameters of the patients were obtained be using a Hitachi 7080 automatic biochemical analyzer (Hitachi, Tokyo, Japan) to check the serum albumin (ALB), prealbumin (PA) and transferrin levels in the two groups. In addition, we used a flow cytometer to determine the CD3+, CD4+, CD8+ and CD4+/CD8+ levels and the plasma levels of IgA and IgM using immunofluorescent stained mouse anti-human monoclonal antibodies. Spectrophotometry was used to determine the blood lactic acid D level, and the level of the serum endotoxin was determined using the limulus amebocyte lysate test; all the specimens were analyzed in the central laboratory of the hospital.

Statistical Analysis

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. The data are expressed as the mean ±standard deviation (SD). Comparison between groups was done using One-way ANOVA test followed by Post Hoc Test (LSD). p-values < 0.05 were considered statistically significant.

Ethical Considerations

This study received approval from the Ethics Committee of Binzhou Medical University. Informed consent was obtained according to procedures approved by both the University's Research Board and the Human Volunteers Protection Committee. All of the participants gave their written informed consent for participation. All of the participants' information was kept confidential and anonymous.

Results

A total of 54 patients were enrolled in this study. The median age of the subjects was 48.5 years (range 23-69 years). The formulas were well tolerated in all of the patients. The baseline characteristics of the patients in terms of age, gender, biochemical parameters and the staging and location of the fistulas and the severity of the disease was not different between the EIEN

group and the PN group (p>0.05). Regarding the comparison of the immune function, the nutrition index and the index of the intestinal mucosal barrier before the nutritional support (D-1) and at post-nutritional support day 7 (D7) and day 14 (D14), there were significant differences between the 2 groups ($p<0.05$) (Tables I, II, and III). There was no significant difference in the prevalence of complications, including anastomosis leakage and pulmonary infection between the EIEN and the PN groups.

Discussion

The gastrointestinal (GI) tract functions not only to absorb nutrients but also to support important immunological defenses during both health and critical illness. Under certain clinical conditions, gut stimulation attenuates the stress response, limiting the mucosal atrophy and increasing the gut permeability. A GI fistula is a complication that occurs because of an accident, operation or other reasons, resulting in large amounts of digestive liquid flowing from the fistula and the significant loss of fluids and electrolytes, causing an imbalance and systemic pathological changes[6]. Treating patients with a GI fistula requires a comprehensive team approach. These patients will most likely have a prolonged hospitalization, as conservative medical management is generally considered rather than surgery. Medical management of a GI fistula should include maintaining the fluid and electrolyte balance, providing bowel rest and nutritional support, initiating treatment with medication, ensuring skin protection, and containing the fistula effluent[7]. With the progress in nutritional support and treatment technology and a combination of somatostatin and growth hormones, the overall mortality has decreased, but the mortality rate is still 20-30% in patients with GI fistulas. The use of Octreotide (Sandostatin) can decrease the fistula's output by inhibiting the release of gastrin and other GI hormones[8]. This treatment decreases the secretions of bicarbonate, water, and pancreatic enzymes into the intestine, thus decreasing the intestinal volume. Octreotide also relaxes the intestinal smooth muscle, allowing more intestinal capacity, and increases the absorption of intestinal water and electrolytes[9]. Ecological immune-enhanced enteral nutrition can improve the nutritional status, immune function recovery and stimulation of the proliferation and repair of intestinal mucosa cells, avoiding the intestinal mucosa atrophy and thinning caused by the long-term use of PN, thereby enhancing the patients' immunity and their intestinal mucosal barrier function[10]. The plan of care should include treating sepsis, initiating nutritional support, maintaining the fluid and electrolyte balances, and providing patient education and care. This study divided the 54 patients into 2 groups according to the mode of nutritional support. Although the routes of the administration of the diet were different, the patients in each group had a similar total caloric intake, and there were significant differences between the immunological function, nutritional status, and index of the intestinal mucosal barrier analyses between the 2 groups (p<0.05).

Table I. Comparison of the index of the immune function before the nutritional support (D-1) and at post nutritional support day 7 (D7) and day 14 (D14) between the two groups ($\bar{x}\pm$ s).

Index	EIEN group	PN group	*p*-value
CD3+			
D-1	60.63±5.48	60.17±5.66	>0.05
D7	68.73±4.76	64.85±7.28 *	<0.05
D14	69.34±5.38	65.24±8.27*	<0.05
CD4+			
D-1	34.76±5.65	35.07±6.37	>0.05
D7	44.65±6.39	40.94±7.76*	<0.05
D14	47.49±5.48	42.66±6.25*	<0.05
CD8+			
D-1	24.16±6.95	23.92±6.85	>0.05
D7	27.59±6.72	24.37±7.48*	<0.05
D14	31.37±5.84	27.89±6.25*	<0.05
CD4+/CD8			
D-1	1.24±0.79	1.26±0.75	>0.05
D7	1.61±0.67	1.32±0.59*	<0.05
D14	1.87±0.53	1.42±0.67*	<0.05
Ig M (g/L)			
D-1	0.61±0.29	0.65±0.25	>0.05
D7	1.53±0.63	1.07±0.59*	<0.05
D14	1.78±0.83	1.32±0.97*	<0.05
Ig G (g/L)			
D-1	10.24±3.79	10.26±3.75	>0.05
D7	15.69±4.64	12.37±4.59*	<0.05
D14	18.87±3.58	15.42±5.61*	<0.05

*p<0.05 when comparing the serum CD3+, CD4+, CD8+and CD4+/CD8+ and the plasma levels of IgA and IgM between the EIEN group and the PN group on D-1 and D7 and D14.

Table II. Comparison of the nutrition index before the nutritional support (D-1) and at post nutritional support day 7 (D7) and day 14 (D14) between the two groups ($\bar{x}\pm$ s).

Index	EIEN group	PN group	*p*-value
ALB (g/L)			
D-1	22.91±1.71	22.87±1.23	>0.05
D7	27.29±2.57	24.53±3.36*	<0.05
D14	31.65±2.39	28.49±2.77*	<0.05
PA (mg/L)			
D-1	204.79±2.58	204.76±2 .77	>0.05
D7	212.56±3.75	207.86±4.73*	<0.05
D14	215.89±4.72	210.29±5.81*	<0.05
TFN (g/L)			
D-1	1.67±0.57	1.76±0.49	>0.05
D7	2.35±1.42	2.06±1.73*	<0.05
D14	2.74±1.91	2.49±1.48*	<0.05

*$p<0.05$ when comparing the plasma ALB, PA and TFN between the EIEN and PN groups on D-1 and at D7 and D14.

Immunological Function of the Gastrointestinal Fistula Patients

In the analyses of the immunological functions of the fistula patients, there were significant differences in the parameters indicating cellular immunity, i.e., the T cell subpopulation and serum immunoglobulins, which play important roles in the humoral immunity ($p<0.05$). Although the serum levels of IgA and IgM dropped remarkably in all the patients after the nutritional support, they recovered more quickly in the EIEN group and were significantly higher than in the PN group ($p<0.05$). However, because of the small number of patients in the present study, it is unclear whether this finding suggests an improvement in the GI fistula patients' immunological status. However, it is becoming increasingly clear that the gut plays a central role in maintaining nutritional status and regulating the immune system[11]. As Table I shows, in the comparison of the post-EIEN nutritional support compared with before the EIEN, the plasma's positive cell counts of the CD3, CD4, and CD4/CD8 ratios gradually returned to a normal level and were higher than in the PN group ($p<0.05$). EIEN nutritional support can enhance the immune function and reduce the excessive inflammatory response. The gastrointestinal tract is the largest immune organ; it is primarily composed of gut-associated lymphatic tissue (GALT), which is the overall component of approximately 80% of the human body's immunity and 50% of the cellular immunity. Glutamine (Gln), as a necessary substance for the synthesis of arginine, purine, pyrimidine and glutathione, is essential for rapid cell proliferation[12,13]. It not only protects the intestinal mucosal barrier but also prevents intestinal mucosal from atrophy and flora shift. In addition, EIEN promotes IgA secretion, enhances the intestinal lymphoid tissue (GALT) function and improves the immune function. Moreover, it reduces intestinal mucosal permeability and intestinal bacteria and endotoxins. A micro-ecological preparation (Jin Shuangqi), which was composed with *Bifidobacterium*, *Lactobacillus bulgaricus,* and *Streptococcus thermophiles*, can improve the intestinal microflora and the intestinal function and is often combined with immune nutrition, which is called ecological immunonutrition[14]. Immunonutrition can make use of the biological antagonism of probiotics, inhibiting pathogenic bacterial overgrowth and improving the immune function of the organism-immune nutrients.

Nutritional Status of the Gastrointestinal Fistula Patients

As Table II shows, at post-EIEN nutritional support day 7 (D7), the levels of ALB and PA were slowly recovering. At 14 days (D14), the levels of PA and TNF had recovered to normal in the EIEN group and were significantly higher than those in the PN group ($p<0.05$). The plasma levels of ALB, PA, and TNF reflected the nutritional status and demonstrated that the visceral protein synthesis was an effective and objective index. The primary causes of malnutrition in the GI fistula patients are likely the large amounts of digestive

Table III. Comparison of the index of the intestinal mucosal barrier before the nutritional support (D-1) and at post-nutritional support day 7 (D7) and day 14 (D14) between the two groups ($\bar{x}\pm$ s).

Index	EIEN group	PN group	*p*-value
Endotoxin (pg/ml)			
D-1	27.97±0.78	27.86±0.72	>0.05
D7	21.23±0.92	24.54±0.96*	<0.05
D14	9.63±4.38	12.45±4.57*	<0.05
D-lactic acid (μg/ml)			
D-1	16.71±1.59	16.76±1 .51	>0.05
D7	11.59±3.24	13.85±4.73*	<0.05
D14	8.54±3.75	10.25±5.46*	<0.05

**$p<0.05$ when comparing the serum levels of the endotoxin and D-lactic acid between the EIEN and PN groups on D-1 and at D7 and D14.

fluids lost, with its loss of nutrients. The failure of the intestinal integrity, the infection and the stress status caused by the fistula can lead to catabolism and hyperthyroidism[15]. Whether to choose enteral or parenteral nutrition depends on the location of the fistula. For low-output fistulas and those located in the most proximal portion of the small bowel, Enteral nutrition is a proper choice. For GI fistula patients, EIEN has a lot of advantages. For example, it can directly supply energy and nutrients to the intestine, maintain the structure and intact function of the intestinal mucosa cells. Besides, it can also improve immune function, reduce inflammatory responses and shorten the duration of the systemic inflammatory response syndrome. Furthermore, EIEN also decreases the body's protein consumption, and increase the rate of protein synthesis.

Function of the Intestinal Mucosal Barrier in Patients with Gastrointestinal Fistulas

As Table III shows, in the comparison of the post-EIEN nutritional support group with the PN group, the levels of the endotoxins and D-lactic acid are lower ($p<0.05$). The increase in endotoxins, intestinal mucosal atrophy, and intestinal permeability was closely related to each other. Reducing the intestinal mucosal barrier function can lead to the translocation of bacteria and endotoxins, finally resulting in the presence of bacteria and endotoxins in the blood circulation and enterogenous infection[16]. In recent years, a combined therapy of Nutrition (a kind of whole-protein enteral nutrition with An Kaishu achieved good clinical effects. It can maintain and improve the structure and function of the intestinal mucosa[17]. Because this compound contains glutamine (Gin), and a micro-ecological preparation (Jin Shuangqi), which has a protective effect on the intestinal mucosal barrier, especially under the stress condition of intestinal mucosal growth and differentiation of conditionally essential amino acid cells. Nutritional factors target specific tissue in the small intestinal mucosa, specifically glutamine in the intestinal mucosal immune tissue, and there are special short-chain fatty acids (SFAs) in the colonic mucosa. Improving the nutritional status of patients prevents the translocation of the intestinal bacteria and contributes to the prevention of enterogenic infection and multiple organ dysfunction syndromes.

Conclusions

The immune-enhanced EN can improve the nutritional status and immune function for patients with GI fistulas and enable the recovery of the bowel, immune function, and synthesis of proteins. It is safe and clinically feasible and is recommended for use in GI fistula patients[18]. The management of GI fistulas can be very challenging for the health care team and the patients. The treatment goals are to provide bowel rest, prevent fluid and electrolyte imbalances, protect the perifistula skin, contain the effluent and provide nutritional support. Thus, this study yielded useful information and provided a method for using EIEN in GI fistula patients.

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Conflict of interest

The authors declare no conflicts of interest.

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