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The effect of early immune enteral nutrition on the immune function and inflammatory response of patients with severe acute pancreatitis

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ABSTRACT. Aim: *to investigate the effect of early enteral nutrition (EEN) on immune function and inflammatory reaction in patients with severe acute pancreatitis (SPA).* ***Methods:*** *70 patients with SPA were randomly divided into EEN group and DEN group (delayed enteral nutrition). On the basis of routine treatment, EEN group was treated with enteral nutrition support within 72 hours after onset, and DEN group was given enteral nutrition support therapy on the 5th day after onset, and the course of treatment was 2 weeks. The immune indexes, inflammatory cytokines and clinical symptoms were compared between the two groups before and after treatment.****Results:*** *after treatment, CD3 cells, CD4, CD4 / CD8 cells, NK cells, B lymphocytes and IgA, IgG, IgM (immunoglobulin) were increased in both groups (P < 0.05), and EEN group was higher than DEN group (P < 0.05 or P < 0.01). After treatment, the levels of TNF- α, IL-6, endotoxin and amylase in both groups were lower than those before treatment (P < 0.05), and the scores of acute physiology and chronic health in EEN group were lower than those in DEN group (P < 0.01). EEN) after treatment compared with DEN group (P < 0.01). The incidences of sepsis and multiple organ dysfunction syndrome in DEN group were lower than those in DEN group (P < 0 01), and the improvement time and hospitalization time in DEN group were shorter than those in DEN group (P < 0 01).****Conclusion:*** *EEN can improve the immune function of SAP patients and reduce the incidence of infectious complications.*

keywords: *Severe acute pancreatitis; early enteral nutrition; immune function; inflammatory reaction*

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1. Introduction

Acute pancreatitis is an inflammatory reaction of pancreatic enzymes that are activated in the pancreas due to a variety of causes, leading to digestion, edema, bleeding and even necrosis of the pancreas. Clinical features include acute epigastric pain, distaste, vomiting, fever, and elevated pancreatin. Degree of lesion varies, light to pancreatic edema, clinical more often seen, often self-limited disease, excellent prognosis, also known as light acute pancreatitis. A small number of severe pancreatic hemorrhage necrosis, often secondary infection, peritonitis and shock, high mortality, known as severe acute pancreatitis. About one fifth of the patients with pancreatitis are SPA (severe acute pancreatitis), which can be developed into SIRS (generalized systemic inflammatory response) or MODS (generalized multiple organ dysfunction syndrome) in a short term. The fatality rate of acute pancreatitis can be up to one tenth, and that of severe acute pancreatitis can be up to one half or even higher. Is common in severe acute pancreatitis energy metabolic disorders than catabolism and inner environment, and the early onset of significant acute gastrointestinal function disorders and gastric bowel mechanical obstruction, etc, fire kuang place can lead to intestinal mucosal atrophy and intestinal permeability increases, easily lead to excessive bacteria multiply, cause bacterial translocation, peripancreatic infection and MODS. Therefore, in addition to active regulation of SIRS, maintenance of organ functions and fluid resuscitation, reasonable nutrient support is very necessary in SAP treatment. Now, enteral nutrient (EN) has become the consensus of early treatment of SAP, which can better maintain the function of intestinal mucosal barrier and prevent bacterial translocation in the intestine compared with the nutrition support of extrenteral vein. However, there are still many details concerning the use of EN in SAP, and in particular, there is no consistent definition of EN's use opportunity selection. This study analyzed the effects of EEN (pre-enteral nutrients) and DEN (delayed enteral nutrients) on the immune function and inflammatory response of SAP, aiming to provide references for the induction and treatment of early SAP.

Acute pancreatitis (AP) is one of the common clinical acute abdominal diseases, and its incidence continues to rise, especially severe acute pancreatitis (SAP), and the mortality remains high. SAP is often associated with systemic inflammatoryresponse syndrome (SIRS), which is characterized by high metabolism

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and high decomposition. About 30% of the patients will suffer from malnutrition in varying degrees, as well as negative nitrogen balance and immune dysfunction. Malnutrition will increase the incidence of infection and even multiple organ dysfunction syndrome(MODS) and affect the prognosis of patients. Therefore, nutritional support therapy is very important in disease management. Always pancreatitis treatment focuses on "Rest the pancreas" think enteral nutrition (EN) may stimulate pancreatic exocrine function, aggravating illness, total parenteral nutrition (TPN) not only can avoid the pancreas secretion, also can improve the nutritional status of patients, has become the important way of nutritional support in patients with SAP. However, with the deepening of studies and the understanding of intestinal function, it has been proved that enteral nutrition can protect the integrity of intestinal mucosa and limit bacterial translocation, reduce the incidence of enterogenous infection, and avoid the metabolic complications caused by TPN and the incidence of catheter-related infection. Early enteral nutrition in SAP patients has been shown to reduce mortality and associated complications and improve prognosis. Based on the "rest the pancreas" theory, at present, nasojejunal (NJ) tube is mainly used for enteral nutrition in the intestinal nutrition support of SAP at home and abroad. It is believed that nasogastric (NG) tube for enteral nutrition will stimulate the secretion of pancreatic juice and aggravate the condition. In addition, nasogastricenteral nutrition (NGEN) has a greater risk of inducing vomiting, aspiration and gastric retention than nasojejunal enteral nutrition (NJEN). However, some studies have found that the pancreatic exocrine function of SAP patients is impaired. Although NG can stimulate the secretion of pancreatic juice to a certain extent, it has no significant effect on the prognosis of patients. In recent years, clinical trials and systematic evaluation studies at home and abroad have shown that the efficacy and safety of enteral nutrition NG mode and NJ mode are comparable, and NGEN has advantages of simple catheterization, low cost and simple nursing. However, the efficacy of the two enteral nutrition methods is still controversial, and there is still a lack of sufficient theoretical basis and evidence-based medical evidence. In this study, the clinical efficacy of the NGEN pathway and the prognosis and safety of two early enteral nutrition pathways for patients with severe acute pancreatitis were comprehensively evaluated according to the Cochrane systematic evaluation method, providing a basis for clinical selection of early enteral nutrition pathways in SAP patients.

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2. Materials and Methods

72 SAP patients admitted to XXXXXX hospital from October 2018 to December 2018 were selected.

Included in the specification:(1) It conforms to the diagnostic norms in the strategy for diagnosis and treatment of severe acute pancreatitis;(2) Age 20-70;(3) The initial onset was less than 36 hours from onset to admission.

Out of specification(1) Merger of gastrointestinal bleeding and liver and kidney dysfunction; (2) Obstruction of intestinal motility or mechanical ileus without enteral nutrients; (3) Previous history of heart disease or mental illness;(4) A woman who is expecting, pregnant or lactating.

3. The research methods

3.1 Healing way

All patients were given routine intervention, gastrointestinal decompression, intravenous nutrition, pancreatic excretion, and antibiotics for treatment after admission. Active correction of electrolyte and acid-base balance disorder, H+ proton pump treatment, somatostatin treatment. Patients were randomly assigned to the pre-enterotrophic group and the delayed enterotrophic group. The basic materials of patients in the two groups were shown in table 1. EEN group and DEN group were included in 31 patients. After stable vital signs and stable hemodynamics, the nasal jejunal tube was indwelling under the guidance of gastroscope. The feeding tube was placed 40cm below the ligament and positioned by X-ray fluoroscopy. Fix the outer end of the catheter after confirmation. If the patient has no severe intestinal numbness, gastrointestinal bleeding, shock, intestinal fistula or intestinal obstruction, that is, the beginning of enteral nutrition support treatment. XXX was selected as EN preparation, and the osmotic pressure was XX mOsm/L. The goal of a complete nutrient supply is reached in three to five days(30KCal.Kg-1.d-1).During the period, depending on the specific situation of the patient, a small number of rice soup, fish soup and vegetable soup were drip through nasal-jejunal catheter, and gradually transited to oral feeding. Thirty-one patients in the EEN group received enteral nutrition treatment 36 hours after admission. In the DEN group, 31 patients began to

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receive enteral nutrition treatment 5 days after admission.

3.2 Survey parameter

3.2.1 The humoral immune

Before and in the morning after treatment, 2ML of the patient's fasting peripheral venous blood was taken, and the routine centrifugation was performed. The serum was taken as a sample, and IgA, IgG and IgM indicators were measured by ARRAY360 immunodetector.

3.2.2 The Cellular immune

Before and in the morning after treatment, 2ML of the patients' fasting peripheral venous blood was taken, and the blood was treated with edta-k2 anticoagulation skill. The T lymphocyte subsets, NK cells and B lymphocytes were determined by flow cytometry.

3.2.3 The inflammatory factor

ELISA double antibody sandwich method was used to determine IL-6 and TNF-α in patients before and after treatment. Limulus test was used to determine the level of serum endotoxin. Serum amylase (AMS) levels were determined by iodine-starch colorimetry.

4. Statistical treatment

SPSS24.0 software was used for statistical analysis. The measurement data were indicated by mean gauge difference (X S), and t test was performed. The counting material was indicated by percentage, line X,2-test. $P<0.05$ was considered statistically significant.

4. The result

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4.1 Basic information of the two groups of patients

Patients were randomly divided into EEN group and DEN group, with 31 patients in each group. In the EEN group, 17 males and 14 females were aged 21--67 (47.6±3.5) years.Etiology: biliary in 13 cases; Obstruction of sphincter of hepatopancreas: 6 cases; Binge eating and drinking in 2 cases; There were 3 cases of alcoholism and 5 cases of hyperlipidemia. Two other cases. In the DEN group, 15 males and 16 females were aged 25-68 (51.4±2.7). Etiology: biliary in 12 cases; Obstruction of sphincter of hepatopancreas: 7 cases; Binge eating and drinking in 3 cases; Alcoholism in 2 cases; Hyperlipidemia in 6 cases; 1 other case. There was no significant difference between the two groups (P>0.05). See table 1

Table 1 basic data of patients in two groups

Project	EEN group	DEN group
Age	47.6±3.5	51.4±2.7
Gender (male/female)	17/14	15/16
Etiology(Biliary Etc.)	13/6/2/3/5/2	12/7/2/3/6/1
Blood pressure	124.6±13.5/79±8.7	122.5±14.2/81±9.6

4.2 Immune indexes before and after treatment in both groups

CD3+ cells, CD4+, CD4+/CD8+ cells, NK cells, B lymphocytes, IgA, IgG, and IgM were all higher than before treatment (P< 0.05), and EEN group was higher than DEN group (P< 0.05 or P< 0.01). See table 2.

Table 2 immune indexes before and after treatment in two groups

Immune cells	Groups			
	EEN group		DEN group	
	Before the treatment	After treatment	Before the treatment	After treatment
CD3+ cells	54.34±5.36	67.45±6.56	56.32±5.47	65.53±6.32
CD4+ cells	29.53±4.21	45.32±6.53	31.34±4.52	38.45±6.11
CD8+ cells	24.46±5.23	25.56±5.41	25.82±5.16	25.76±5.68

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CD4+/CD8+ cells	1.21±0.26	1.77±0.30	1.21±0.23	1.49±0.29
NK cells	12.46±3.54	15.29±4.25	13.12±2.65	16.14±2.97
B lymphocytes	10.65±3.43	14.65±3.24	11.26±3.48	13.65±3.45
IgA	1.34±0.46	2.62±0.51	1.62±0.39	1.94±0.53
IgG	9.43±2.12	17.31±3.97	9.98±2.42	12.47±2.36
IgM	1.24±0.12	2.46±0.38	1.67±0.43	1.96±0.48

4.3 Inflammatory cytokines, endotoxin and AMS before and after treatment in the two groups

TNF-α, IL-6, endotoxin and amylase were lower in both groups after treatment than before treatment (P< 0.05), and EEN group was lower than DEN group (P< 0.01). As shown in the table 3.

Table 3 inflammatory cytokines, endotoxin and AMS in both groups before and after treatment

Immune cells	Groups			
	EEN group		DEN group	
	Before the treatment	After treatment	Before the treatment	After treatment
TNF-α	543.56±196.43	116.45±39.46	521.41±209.47	154.48±67.52
IL-6	34.25±7.16	9.16±2.94	36.14±8.24	15.82±3.12
endotoxin	0.19±0.04	0.06±0.01	0.18±0.08	0.09±0.07
amylase	1248.63±80.65	196.28±39.19	1283.52±88.82	219.53±46.19

4.4 Improvement of clinical symptoms in the two groups

Two weeks after the treatment, EEN with APACHE Ⅱ score below DEN group (P < 0.01), SIRS improvement time and shorter hospitalization time in DEN group (P < 0.01). See table 4 for details.

Table 4 improvement of clinical symptoms in two groups

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Groups	APACHE Ⅱ	SIRS improvement	hospital stays
	Score (points)	time(d)	(d)
EEN group	1.98±0.46	5.18±1.83	21.13±4.26
DEN group	3.54±1.26	7.04±1.98	26.81±6.27

4.5 Complications and deaths occurred in both groups

In the EEN group, 3 patients developed sepsis, 2 developed MODS, and 1 died. In the DEN group, 6 cases developed sepsis, 8 cases developed MODS, and 6 cases died. The incidence of sepsis and MODS was lower in the EEN group than in the DEN group ($P< 0.05$), but there was no significant difference in mortality between the two groups ($P< 0.05$).

5. Discussion

The pathogenesis of SAP is not completely clear, and it is one of the refractory diseases for which treatment and prognosis have not been effectively dealt with, with a high fatality rate. In SAP induction and treatment, nutrient support has a non-substitutable effect. In particular, it is of great significance to select a method that can satisfy the high catabolism of patients and keep the structure of intestinal mucosal barrier intact, so as to avoid disease development and prevent infection. In this study, both EEN group and DEN group had improved nutrient targets after treatment, but EEN group was higher than DEN group, possibly because EEN was more conducive to maintaining the function of intestinal mucosa, balancing nutrients and enhancing immunity. In addition, the rate of sepsis and MOD onset in the EEN group was lower than that in the DEN group, which may be related to the shortened time for systemic improvement, enhanced immune capacity and decreased inflammatory cytokines in the EEN group.

In recent years, there have been many studies on the application of enteral nutrition in severe patients, and the results all show that enteral nutrition can reduce the incidence of infectious complications, contribute to more effective control of blood sugar, reduce or prevent bacterial translocation, so most hospitals regard

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enteral nutrition as the preferred mode of nutritional support at present. Early enteral nutrition is recommended after admission or within 24 hours after surgery to reduce complications and promote the recovery of intestinal function. Enteral nutrients are rich in immune enhancers and nutrients, which can further improve patients' immune function and intestinal barrier function. Therefore, they have attracted much attention. Blood purification is to lead the patient's blood to the outside of the body through specific equipment, and then lead the blood back to the patient's body after the pathogenic substances are removed by the purification device, including hemofiltration, hemodialysis, hemoperfusion, immune adsorption, plasma exchange and so on. Hemofiltration application principle of convection efficient removal of solute, by imitating the nephron filter overweight absorption, drew blood from the patient's body to body, filtered through processing and is outside of the cells and proteins in the plasma solute and water filter, adding liquid composition of electrolyte solution is similar to plasma, fluid replacement, remove excess moisture and metabolites in the blood, so as to purify the blood. This study found that continuous hemofiltration combined with early enteral nutrition support can achieve better efficacy and improve the quality of life of patients.

TNF-α is an important cytokine involved in severe acute pancreatitis. By activating neutrophils, TNF-α can promote the release of superoxide groups and elastase, promote the adhesion of leukocytes to blood vessels, increase the permeability of vascular endothelial cells, and promote the synthesis and release of interleukin. IL-6 is a time phase factor induced by TNF-α, which promotes the differentiation and maturation of B cells and the generation of acute phase reactive protein, and plays an important role in the multi-organ injury caused by severe pancreatitis. Serum IL-6 level is significantly increased within 24 hours after the occurrence of severe acute pancreatitis. CRP plays a role in promoting phagocytosis and regulating immunity, and can activate complement, which is a sensitive indicator for the diagnosis of acute pancreatitis. In this study, the total effective rate of treatment in the observation group was 92%, significantly higher than that in the control group (78%). After treatment, IL-6, TNF-α and CRP levels in the two groups were significantly reduced, and the levels in the observation group were lower than those in the control group ($P < 0.05$), suggesting that the addition of early enteral nutrition is conducive to the control of inflammatory cytokines and the improvement of clinical efficacy. Blood purification treatment can not selectively remove the

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inflammatory mediators in the blood and reduce the concentration of inflammatory mediators, so the levels of inflammatory factors in both groups were significantly reduced after treatment. In addition, long-term fasting will damage the intestinal barrier function, leading to metabolic disorders and increased inflammation. Early enteral nutrition is conducive to the recovery of intestinal function and the protection of intestinal mucosal integrity. Therefore, the intestinal mucosal function indicators in the observation group in this study were significantly improved and better than those in the control group ($P < 0.05$). The intestinal mucosal function is protected, and the microecological agents in the nutrient solution can maintain the intestinal microecological balance, reduce the risk of intestinal bacterial translocation, and further reduce the release of inflammatory factors. Therefore, the level of inflammatory factors in the observation group is lower than that in the control group after treatment.

Currently, it is not possible to directly measure intestinal function. Lactulose/mannitol ratio, procalcitonin and plasma diamine oxidase are often used to determine the function of intestinal mucosal barrier. The higher lactulose/mannitol ratio indicates the more severe intestinal mucosal injury, and the higher level of procalcitonin and diamine oxidase also indicates the more severe intestinal mucosal barrier function injury after the functional injury of intestinal mucosal barrier. CD4/CD8, IgA and IgM are commonly used clinical indicators of immune function. Under the condition of malnutrition and intestinal immune function injury, patients' immune function is impaired, with significant changes in CD4 and CD8, and the CD4/CD8 ratio reduced or even inverted in some patients, at which time patients' immune function is severely inhibited. In this study, glutamine added into the nutritional preparations of the observation group was the energy source of neutrophils, macrophages, lymphocytes and other immune cells. Arginine is an essential amino acid for stress, trauma and hunger. In severe pancreatitis, glutamine can improve the immune function of patients after immune tissue utilization, so in this study, the immune function indicators of the observation group were significantly improved after treatment and were better than those of the control group ($P < 0.05$). In addition, after early enteral nutrition improves the immune system and intestinal mucosal barrier function of patients, it is beneficial to improve the condition and quality of life. Therefore, all scores of QLO-C30 scale in the observation group after treatment in this study were higher than those in the control

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group ($P < 0.05$).

To sum up, the SAP patients with significant disorder of immune system and systemic high metabolism, early (within 72 h) shall be the nasal - jejunum tube enteral nutrition safe and reliable, the DEN can better improve the nutrient status and immunity function, strengthen the body resistance, then drop attack dangerous infectious complications, improve clinical outcomes.

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