Effects of enteral nutrition on pro-inflammatory factors and intestinal barrier function in patients with acute severe pancreatitis

Ying-Jie Chen, Yao-Dong Zhuang, Zhe Cai, You-Ni Zhang and Sen-Ren Guo

Abstract
The main objective of this study was to explore the effect of enteral nutrition on serum pro-inflammatory cytokines, tumor necrosis factor, and intestinal barrier function in patients with acute severe pancreatitis. A total number of 140 patients were recruited and divided randomly into parenteral nutrition (PN) and enteral nutrition (EN) groups. They received parenteral nutrition and enteral nutrition, respectively. The levels of serum total protein (TP) and albumin (ALB) in peripheral blood were detected in the two groups. Interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFα) in the two groups were comparatively analyzed. The levels of pro-inflammatory factors (IL-1β, IL-6, and TNFα) for both groups were same, and there was no significant difference (P < 0.05) between the two groups before treatment. However, after treatment, a significant reduction was found in EN group which were 31.16 ± 1.95, 36.09 ± 4.44, and 29.21 ± 3.85 ng/L, respectively, showing significant lower values as compared to PN group. The levels of TP and ALB in EN group were 64.46 ± 3.77 and 27.19 ± 1.56 g/L, respectively, after treatment, showing significantly (P < 0.05) elevated values than PN group. The incidence rates of pancreatic necrosis and pancreatic abscess in EN group were 28.57% and 11.43%, respectively, which were found to be lower significantly than PN group. Enteral nutrition is found to be more effective than parenteral nutrition in the treatment of severe acute pancreatitis, which can significantly reduce the level of pro-inflammatory factors as well as the degree of systemic inflammatory response and protect the intestinal barrier function; thus, this study is worthy for awareness and application in clinical practice.

Keywords
enteral nutrition, intestinal barrier function, parenteral nutrition

Date received: 31 May 2018; accepted: 8 January 2019

Introduction
Acute pancreatitis (AP) has got numerous diverse aetiologies, although about 80% of all cases are due to either alcohol or gallstones. The frequency of diverse aetiologies fluctuates evidently in different countries. Alcohol is the contributing factor in about 70% of the cases, and the occurrence of AP associates with the amount of alcohol usage in Finland. Since the aetiology of AP is difficult and complex, the two utmost common reasons are biliary region illnesses and extreme alcohol intake.¹ Investigational readings propose that the prognosis
for AP rests on the degree of pancreatic necrosis and the severity of multi-system organ failure caused by the systemic inflammatory reaction. This recommends a convoluted equilibrium among local tissue injury with pro-inflammatory of cytokine and a systemic anti-inflammatory comeback that limits the unsuitable program of pro-inflammatory mediators inside the circulation. The precarious actors of this collaboration comprise the pro-inflammatory cytokines: tumor necrosis factor alpha (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6) and interleukin-8 (IL-8), and platelet-activating factor.2

C-reactive protein is the typical and standard intended for serum marker valuation in prognosis and rigorousness in severe acute pancreatitis (SAP). Other indicators include IL-6, polymorphonuclear elastase, and trypsinogen-activation peptide. Hence, regardless of wide research in the current decade, not any method of cure has been established which could effectively develop the consequence of SAP. IL-6 motivates the production of acute phase proteins, C-reactive protein and procalcitonin, inside the liver. Emergent confirmation has pointed to inflection of the patient’s immune system in tactical therapeutic improvement by justifying the inflammatory response and harshness of AP.2 Formerly, IL-6 was considered as a pro-inflammatory cytokine. Though, few years ago, it was exposed to action mainly as an anti-inflammatory cytokine for instance stops synthesis of IL-1β and TNFα.

SAP is one of the most common acute and severe cases in clinic. It is very dangerous, develops very rapidly, and always involves multi-organs with a mortality rate of 30% to 40%. Research data showed that the ineffective rate of SAP treatment (excluding cure rate plus death rate) was 43.5%.3 In the development of SAP, the immune system is stimulated by a variety of factors resulting in systemic, specific, and nonspecific inflammation, thereby releasing inflammatory mediators that cause a disequilibrium between pro-inflammatory factors and anti-inflammatory factors in vivo, thus resulting in “Waterfall Pattern” cascade reaction and giving rise to systemic inflammatory response syndrome (SIRS). In the body during SAP, there occur super high metabolic and stress reactions characterized by gluconeogenesis, enhanced lipid mobilization, and protein decomposition. So patients are gradually suffering negative nitrogen balance, malnutrition, and immune function decline with rising rates of infection and mortality. Studies have shown that immune dysfunction plays an important role in the development of multiple organ dysfunction syndrome and other infectious complications in patients with SAP.4 Nutritional support is an important scheme for the treatment of SAP, including enteral nutrition and parenteral nutrition. Proper enteral nutrition and parenteral nutrition are having a certain influence on the nutritional improvement of severe patients, but the two schemes have their own advantages and disadvantages.5 Therefore, this study analyzed the effects of early enteral nutrition and parenteral nutrition on serum pro-inflammatory cytokines of IL-1β, IL-6, and TNFα, and on intestinal barrier function in patients with SAP.

Data and methods

Research objects

A total number of 140 patients with SAP who visited Jinjiang Hospital of Traditional Chinese Medicine (Jinjiang, Fujian, China) from April 2015 to April 2017 were selected as the research objects, including 90 males and 50 females. They aged from 46 to 71, with an average age of 63.6 ± 2.2 years. Among them, there were 80 biliary pancreatitis, 40 alcoholic pancreatitis, and 20 engorgement pancreatitis cases with a body mass index (BMI) of 17 to 23 kg/m² (20.54 ± 1.73 kg/m², on average). The selected objects were divided into enteral nutrition group (EN group) and parenteral nutrition group (PN group) by random number table, with 70 cases in each group.

Inclusion criteria

Patients underwent a comprehensive examination after their admission, and the disease of acute severe pancreatitis turned out to be confirmed with the course under 48 h.

Exclusion criteria

Patients with the following conditions were not included in the study: allergic to enteral or parenteral nutrition or with liver and kidney dysfunction,
pregnancy, lactation, other pancreatic diseases, malignant tumors as well as mental disorders.

**Treatment method**

All patients were fasted and provided treatments as anti-infection, gastrointestinal decompression, trypsin inhibitor, and correction of water electrolytes while receiving symptomatic and supportive therapy. Patients in EN group were treated with enteral nutrition as: they were given enteral nutrition therapy 2 to 3 days after their hospitalization with continuous injection of amino-acid-based enteral nutrition liquid (1.5 g/kg) through jejunostomy under the control of pump followed by a gradual increase of dose to 125.52 kJ (kg/day). Patients in PN group were treated with parenteral nutrition as: they were continuously injected with parenteral nutrient solutions through subclavicular central venous catheters under the control of pump. The nutritious components for two groups were mixed in a bag of 3 L volume by center of nutritious liquid confection and were dropped at constant speed through the infusion pump.

**Observation index**

Patients in both groups were observed for following indexes pre- and post-treatment:

1. The time of blood amylase and urine amylase recovery and the time of hospitalization with the determination of amylase by colorimetric method;
2. The determination of levels of serum total protein (TP) and albumin (ALB) by biuret colorimetric method for nutrition assessment;
3. The determination of serum pro-inflammatory factors, IL-1β, IL-6, and TNFα, by using enzyme linked immunosorbent assay (ELISA) for the assessment of immune inflammation degree;
4. D-lactate level in peripheral blood, diamine oxidase (DAO) as well as the ratio of lactulose to mannitol (L/M) for the assessment of intestinal permeability;
5. Observation of complications including pancreatic necrosis, pancreatic abscess, pancreatic pseudocyst, respiratory failure, and renal failure with the incidence rate of complications calculated.

**Ethical consideration**

This study was approved from the Institutional Ethical Review Board of Jinjiang Hospital of Traditional Chinese Medicine (Jinjiang, Fujian, China). All the experiments were conducted as per the Helsinki Declaration for Human Volunteers. All subjects gave informed signed consent to participate in the study by themselves (Reference No. 1671/IRB-JHTC/2015).

**Statistical analysis**

The analysis was conducted on SPSS 21 software. Student’s t-test was used for the assessment of the measurement data and the count data (χ² test); P value less than 0.05 (P < 0.05) suggested the significant difference between the values.

**Results**

**Comparison of rates of complications, the times of blood amylase and urine amylase recovery, and time of hospitalization**

In EN group, the time of blood amylase recovery was 5.67 ± 1.12 days, the time of urine amylase recovery was 14.78 ± 1.78 days, while the hospitalization time was 16.09 ± 1.64 days. All these values were significantly low (P < 0.05) than PN group values, as shown in Table 1.

The incidence rates of pancreatic necrosis and pancreatic abscess in EN group were 28.57% and 11.43%, respectively, which were found significantly lesser than those in PN group (P < 0.05). Similarly, there was no significant difference found between the two groups in pancreatic pseudocyst, respiratory failure, renal failure as well as mortality rate, as shown in Table 1.

**Comparison of levels of pro-inflammatory factors**

Before treatment, the pro-inflammatory levels of both the groups were same and no significant difference (P > 0.05) was found between the two groups. After treatment, the values of TNFα, IL-1β, and IL-6 in EN group were greatly reduced
and statistically showed significant reduction than PN group values \((P < 0.05)\), as shown in Table 2.

### Comparison of nutrition indexes

| Group | Blood amylase recovery time (days) | Urine amylase recovery time (days) | Hospitalization time (days) | TP (g/L) Before treatment | TP (g/L) After treatment | ALB (g/L) Before treatment | ALB (g/L) After treatment |
|-------|-----------------------------------|-----------------------------------|----------------------------|---------------------------|--------------------------|---------------------------|---------------------------|
| EN    | 5.67 ± 1.12                       | 14.78 ± 1.78                     | 16.09 ± 1.64               | 40.21 ± 4.2               | 64.46 ± 3.8              | 14.78 ± 1.06             | 27.19 ± 1.56              |
| PN    | 8.82 ± 2.06                       | 19.64 ± 2.13                     | 27.16 ± 4.25               | 40.65 ± 5.0               | 53.78 ± 2.9              | 14.93 ± 1.08             | 22.17 ± 2.01              |
| \(t\) | 0.024                             | 0.016                             | 0.013                      | 0.679                     | 4.653                    | 0.831                     | 5.145                     |
| \(P\) | 0.024                             | 0.016                             | 0.013                      | 0.024                     | 0.032                    | 0.195                     | 0.028                     |

TP: total protein; ALB: albumin; EN: enteral nutrition group; PN: parenteral nutritional group.

### Table 2. Comparison of levels of pro-inflammatory factors between the two groups (n=70 in each group).

| Group | TNFα (ng/L) Before treatment | TNFα (ng/L) After treatment | IL-1β (ng/L) Before treatment | IL-1β (ng/L) After treatment | IL-6 (ng/L) Before treatment | IL-6 (ng/L) After treatment |
|-------|------------------------------|-----------------------------|-------------------------------|------------------------------|-----------------------------|-----------------------------|
| EN    | 378.35 ± 35.23               | 29.21 ± 3.85                | 201.57 ± 25.73               | 31.16 ± 1.95                | 257.94 ± 32.08              | 36.09 ± 9.44                |
| PN    | 377.15 ± 34.96               | 50.16 ± 3.22                | 200.19 ± 24.15               | 53.68 ± 2.04                | 257.06 ± 34.17              | 62.38 ± 9.15                |
| \(t\) | 0.903                        | 5.074                       | 0.663                        | 6.032                       | 0.185                       | 5.792                       |
| \(P\) | 0.176                        | 0.028                       | 0.108                        | 0.024                       | 0.194                       | 0.132                       |

TNFα: tumor necrosis factor alpha; IL-1β: interleukin-1β; IL-6: interleukin-6; EN: enteral nutrition group; PN: parenteral nutritional group.

### Table 3. Comparison of rates of complications and mortality between the two groups (n=70 in each group).

| Group | Pancreatic necrosis (%) | Pancreatic abscess (%) | Pancreatic pseudocyst (%) | Respiratory failure (%) | Renal failure (%) | Mortality (%) |
|-------|-------------------------|------------------------|---------------------------|-------------------------|-----------------|---------------|
| EN    | 20                      | 8                      | 20                        | 16                      | 13              | 10            |
| PN    | 58                      | 24                     | 21                        | 17                      | 15              | 12            |
| \(\chi^2\) | 6.642                  | 0.872                  | 0.944                     | 0.832                   | 0.325           |
| \(P\) | 0.016                   | 0.007                  | 0.007                     | 0.065                   | 0.094           |

EN: enteral nutrition group; PN: parenteral nutritional group.

Comparison of nutrition indexes

Before treatment, the levels of TP and ALB of both groups were same and no significant difference \((P > 0.05)\) was found, while after treatment, the levels of TP and ALB in EN group showed significant elevation than PN group \((P < 0.05)\), as shown in Table 3.

Discussion

The patients with SAP are in a high catabolism state at the early stage. It requires a larger amount of energy; the insufficient supply of nutrition may lead to serious metabolic dysfunction. Nutritional support plays an important role in the comprehensive treatment of SAP. According to the developmental stages of the disease, there are different ways of nutritional support.\(^6\) Parenteral nutrition is one of the main nutrition treatments for SAP, but its long duration may easily cause catheter-related infection, intestinal mucosal damage, and systemic metabolic stress syndrome, plus high medical costs, seriously affecting the prognosis in AP patients. As an alternative therapy for parenteral nutrition, enteral nutrition enables to keep the integrity of intestine in SAP patients, improve blood perfusion as well as gastrointestinal motility, and protect immune function as well as intestinal barrier.\(^7,8\)

Recently, prediction of SAP is found to be a clinical assessment at admission and for the period
of the treatment. The detection of the genotypes of critical inflammatory mediators can be valuable for screening population of AP patients at great risk of severe infections in order to enable the administration of early interventions to expand their prognosis.

The results of this study showed that the times of blood amylase, urine amylase recovery, and hospitalization time in EN group were significantly lower than those in PN group, and the levels of TP and ALB were significantly higher in EN group than in PN group, indicating that enteral nutrition therapy is significantly better than parenteral nutrition support in improving the disease condition and nutrition status of SAP patients. The pathogenesis of SAP is very complex, in which over-inflammatory response plays an important role in the progression of the disease. Our findings similar to many other studies have confirmed that the activation and great release of pro-inflammatory cytokines is the initiating factor of severe inflammation in the early stage of SAP, which will aggravate the systemic inflammatory response and becomes the main cause of death in patients with SAP. The pro-inflammatory factors such as IL-1β, IL-6, and TNFα were activated and released into the blood followed by reaching various organs through blood circulation which can further induce inflammatory cells like macrophages to release a large number of inflammation mediators, leading to dysfunction of multiple organs. TNFα is the rapidly increasing pro-inflammatory factor in the earliest stage of SAP development. As the initiating factor of inflammatory response, it can induce production of such pro-inflammatory factors as IL-1β, IL-6, and IL-18, and is also an important factor leading to disorder of pancreas and extra pancreatic organs. In the early stage of SAP, IL-1β induces pancreatic organ dysfunction mainly through activation of neutrophil chemotaxis and migration, and gives rise to release of pro-inflammatory factors such as IL-6, thereby aggravating the degree of inflammatory reaction. It has been revealed that IL-6 is mainly produced by macrophages and endothelial cells, and that it not only induced and secreted by other inflammatory cytokines but also facilitated positive feedback to further secretion of pro-inflammatory factors like TNFα, thus closely related with the progression of the disease. The results of this study showed that after treatment, the levels of TNFα, IL-1β, and IL-6 in EN group were significantly lesser than those in PN group, suggesting that enteral nutrition can help to reduce the extent of systemic inflammatory response in SAP patients.

This research found that the levels of d-lactate, DAO, and L/M ratio, the permeability of intestinal mucosa as well as the incidence of complications were all significantly reduced in patients with enteral nutrition treatment. In conclusion, enteral nutrition had more significant effects in the treatment of SAP by significantly reducing the degree of immune inflammation and intestinal mucosal permeability, improving the intestinal flora balance, and maintaining intestinal barrier function, thus worthy of clinical application and spreading.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Yao-Dong Zhuang https://orcid.org/0000-0001-7031-2497

References

1. Vege SS, DiMagno MJ, Forsmark CE et al. (2018) Initial medical treatment of acute pancreatitis: American Gastroenterological Association Institute Technical Review. Gastroenterology 154: 1103–1139.
2. Párniczky A, Kui B, Szentesi A et al. (2016) Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis. PLoS ONE 11: e0165309.
3. Cheng J, Huang Z and Huang P (2015) Etiological factors and prognosis of 652 patients with acute pancreatitis in western Guangxi areas. Medical Journal of National Defending Forces in Southwest China 25: 1167–1170.
4. Staubli SM, Oertli D and Nebiker CA (2015) Laboratory markers predicting severity of acute pancreatitis. Critical Reviews in Clinical Laboratory Sciences 52: 273–283.
5. Zhang H, Neuhofer P, Song L et al. (2013) IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality. Journal of Clinical Investigation 123: 1019–1131.
6. Yi F, Ge L, Zhao J et al. (2012) Meta-analysis: Total parenteral nutrition versus total enteral nutrition in...
predicted severe acute pancreatitis. *Internal Medicine* 51: 523–530.

7. Singh N, Sharma B, Sharma M et al. (2012) Evaluation of early enteral feeding through nasogastric and nasojejunal tube in severe acute pancreatitis: A noninferiority randomized controlled trial. *Pancreas* 41: 153–159.

8. Chen P, Wang W, Zhang Y et al. (2016) Decreased MIZ1 expression in severe experimental acute pancreatitis: A rat study. *Digestive Diseases and Sciences* 61: 758–766.

9. Dumnicka P, Kuśnierz-Cabala B, Sporek M et al. (2017) Serum concentrations of angiopoietin-2 and soluble fms-like tyrosine kinase 1 (sFlt-1) are associated with coagulopathy among patients with acute pancreatitis. *International Journal of Molecular Sciences* 18: 753.

10. Li J, Yang WJ, Huang LM et al. (2014) Immunomodulatory therapies for acute pancreatitis. *World Journal of Gastroenterology* 20: 16935–16947.

11. Xia XM, Li BK, Xing SM et al. (2012) Emodin promoted pancreatic claudin-5 and occludin expression in experimental acute pancreatitis rats. *World Journal of Gastroenterology* 18: 2132–2139.

12. Liu Y, Hu SF and Yang J (2013) Advances on the relationship between M1 macrophage activation and inflammatory reaction of severe acute pancreatitis. *Journal of Logistics University of CAPF (Medical Sciences)* 22: 1117–1119.

13. Yang P, Hu H, Liu Y et al. (2018) Dietary stachyose altered the intestinal microbiota profile and improved the intestinal mucosal barrier function of juvenile turbot, *Scophthalmus maximus L. Aquaculture* 486: 98–106.