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Regulation of ω-3 Fish Oil Emulsion on the SIRS during the Initial Stage of Severe Acute Pancreatitis

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Summary：The aim of this study was to explore the effects of parenteral supplementation with ω-3 fish oil emulsion (Omegaven®) on systemic inflammatory response syndrome (SIRS) during the initial stage of severe acute pancreatitis (SAP). In a prospective, randomized and controlled trial, 60 patients with SAP were randomized either to treat with conventional therapy (Con group, *n*=30) or conventional therapy plus intravenous supplementation with ω-3 fish oil emulsion 0.2 g/kg every day (FO group, *n*=30). The effects were analyzed by the SIRS-related indexes. The results showed that APACHE-II scores in FO group were significantly lower, and the gap increased much farther after the 4th day than those in Con group ($P<0.05$). Fluid equilibrium time became shorter markedly in FO group than in Con group (5.1±2.2 days vs 8.4±2.3 days). In FO group, SIRS scores were markedly decreased and the SIRS state vanished after the 4th day; Plasma level of TNF-α was significantly reduced, while IL-10 decreased markedly, most prominently between the 4th and 7th day, and the ratio of IL-10/TNF-α raised as compared with Con group ($P<0.05$). During the initial stage of SAP, parenteral supplementation with ω-3 fish oil emulsion could efficiently lower the magnitude and persistence time of the SIRS, markedly retrieve the unbalance of the pro-/anti-inflammatory cytokines, improve severe condition of illness and may provide a new way to regulate the SIRS.
Key words：severe acute pancreatitis; systemic inflammatory response syndrome; ω-3 fish oil emulsion; pro-/anti-inflammatory cytokines; parenteral supplementation

The balance of the pro-/anti-inflammatory cytokines is destroyed by excessive release of cytokines, which can result in systemic inflammatory response syndrome (SIRS) during the initial stage of severe acute pancreatitis (SAP). Multiple organ dysfunction syndromes (MODS) induced by the SIRS is the main cause of SAP patients' deaths. At present, how to control excessive inflammatory response becomes an important topic of the early management of SAP. Although varieties of therapeutic measures to regulate the different states of inflammation are confirmed in many experiments such as cytokine antagonisms, glucocorticoids and hemofiltration, their clinical effects remain obscure. The results of many studies confirmed that ω-3 unsaturated fatty acid was applied to inhibit inflammation and regulate the immune function in many diseases[1]. Currently, ω-3 fish oil emulsion, a new clinical nutriment, may become an efficient way to regulate the SIRS in SAP patients. The purpose of this study was to evaluate the effects of parenteral supplementation with ω-3 fish oil emulsion on the SIRS during the initial stage of SAP.

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1 MATERIALS AND METHODS

1.1 Patients

From Sep. 2006 to Jan. 2008, a prospective, randomized and controlled trial was performed on 60 patients with SAP, who were recruited from our department of Pancreatic Surgery. The severity of pancreatitis was defined according to the Atlanta classification system for acute pancreatitis[2]. Inclusion criteria were age from 18 to 65 years old, within 72 h after the onset and the SAP diagnosis according to clinical symptoms and physical examination; the APACHE-II score ≥8; Ranson's score ≥3; Balthazar CT severity score >6[3]. And the subjects were excluded if they had any of the following conditions: pregnancy; plasma levels of triglyceride (TG) >3.0 mmol/L; clotting time (CT) prolonged; or immunosuppressive drugs, chemo- and radiotherapy within the previous 8 months.

The management of SAP was performed according to the course of SAP[4]. In the initial phase, patients usually require early and aggressive fluid resuscitation, adequate analgesia and antibiotics. After remission of SIRS phase, nutritional support was given. Surgery was recommended to determine whether necrotic pancreatic tissue has become infected. The patients were at risk of developing MODS and local complications of pancreatitis, so the patients needed close supervision and moni-

toring in the pancreatic intensive care unit (PICU).

1.2 Study Protocol

Using SPSS software, version 13 (SPSS Inc., USA), 60 patients with SAP were randomized either to treat with conventional therapy (Con group, n=30) or conventional therapy plus intravenous supplementation with fish oil emulsion 0.2 g/kg every day (FO group, n=30). These patients consisted of 36 males and 24 females with a mean age of 41.6 years. No significant differences in male:female ratio (15.6:16.7) and average age (41.2 and 42.7) were found between the two groups.

The 0.2 g/kg fish oil emulsion was uniformly mixed with 0.9% sodium chloride and 5% or 10% glucose into a 3000 mL intravenous nutrition bag in superclean bench, and then was injected through peripheral or central vein. Liquid resuscitations were carried out with 4.5% hypertonic saline and lactated Ringer's solution, with crystalloid:colloid ratio between 2:1–3:1. Total input volume was adjusted according to the patients' fluid equilibrium. Other managements of SAP had no significant differences between the two groups, including anti-infection, administration of somatostatin, gastrointestinal decompression, catharsis, etc. All patients gave written informed consent, and the study protocol and patient information sheet were approved by the Ethics Committee of Union Hospital, Tongji Medical College, HUST (China).

1.3 Evaluations

1.3.1 Clinical Security The effects of ω-3 fish oil emulsion on digestion, circulation system and body states of SAP patients during management were observed.

1.3.2 APACH Ⅱ Scores After admission, APACH Ⅱ scores were quantified every 24 h to assess the acute phase response. The score was based on the worst states in that day, and were calculated immediately at any times.

1.3.3 Negative Fluid Balance Time Fluid negative balance time, that indirectly represents the magnitude of the SIRS, was recorded. The total capacity of input and output was recorded every day to evaluate the appearance time of negative fluid balance.

1.3.4 SIRS Score The procedures were as follows[5]: temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20 breaths/min or $PaCO_2$ <4.3 kPa, white blood cell count >12 000 cells/mm^3, <4000 cells/mm^3, or >10 immature (band) forms. SIRS score used a combination of simple laboratory and clinical measurements (temperature, heart rate, respiratory rate, and leukocyte count) to give a score of 0–4, with a score of 2 or more declaring the patient in a "SIRS state".

1.3.5 Pro-/Anti-inflammatory Cytokines To evaluate the balance of pro-/anti-inflammatory cytokines, the changes of TNF-α and IL-10 were detected in SAP patients at different time points (before and 4, 7 days after treatment). Peripheral blood was collected at different time points and centrifuged at 2000 r/min for 10 min below 4ºC, and blood plasma was isolated and frozen at –80^o C. After all specimens were collected completely, ELISA was used to detect the levels of plasma TNF-α and IL-10 at different time points in SAP patients (ELISA kit was purchased from Wuhan Boster Co. (China).

1.4 Statistical Analysis

All statistical analyses were performed using SPSS software, version 13 (SPSS Inc., USA). All data were expressed as $\bar{x}\pm s$. Student's t test was used to analyze the difference. A value of P<0.05 was considered statistically significant.

2 RESULTS

2.1 Evaluation of Clinical Security

Only one subject had skin rash and itching of unknown origins in FO group, and the patient became recovery completely after corresponding treatment. And else anyone didn't had abnormal occurrence on digestion, circulation system and body states.

2.2 The Changes of APACHE Ⅱ Score

During observation, APACHE-Ⅱ scores in FO group were significantly lower than in Con group, and the gap increased much farther on the 4th day after treatment (P<0.05, table 1**)**.

Table 1 Changes of APACHE Ⅱ scores in two groups

Groups	1st day	4th day	7th day	10th day	14th day
Con	20.5±2.3	17.8±2.7	13.1±2.3	8.3±1.7	5.9±1.9
FO	19.7±3.7	12.1±2.0*	8.2±1.9*	5.8±1.6*	3.3±1.0*

*P<0.05 as compared with Con group

2.3 The Change of the Negative Fluid Balance Time

The time of negative fluid balance became shorter markedly in FO group than in Con group (5.1±2.2 days vs. 8.4±2.3 days, P<0.05).

2.4 The Changes of the SIRS Score

As shown in table 2, the SIRS score was gradually reduced in the two groups during the observation, and the score in FO group significantly become lower than that in Con group (P<0.05). Furthermore, SAP patients in FO group took the lead from the SIRS state after the 4th day. By contrast, patients in control group could not eliminate the SIRS state until the 7th day.

Table 2 The changes of SIRS scores in two groups

Groups	1st day	4th day	7th day	10th day	14th day
Con	3.4±0.5	3.1±0.5	2.5±0.7	1.6±0.7	1.0±0.7
FO	3.3±0.6	2.1±0.6*	1.7±0.5*	1.1±0.5*	0.6±0.5*

*P<0.05 as compared with Con group

2.5 The Changes of Plasma Levels of Pro-/Anti-inflammatory Cytokines

During the observation, plasma levels of TNF-α were gradually reduced in both groups, more significantly in FO group than in Con group (P<0.05). Plasma IL-10 levels were gradually increased, and those in FO group at 4th and 7th day after treatment were significantly higher than in Con group (P<0.05, table 3). The

ratio of IL-10/TNF-α was significantly higher in FO group than in Con group (P<0.05). These results revealed that pro-/anti-inflammatory balancer was restored gradually after ω-3 fish oil emulsion with parenteral supplementation in SAP.

Table 3 The changes of balancing condition of pro-/anti-inflammatory in two groups

Groups	Time	IL-10（g/L）	TNF-α（g/L）	IL-10/TNF-α
Con	1st day	62.8±23.6	495.7±67.5	0.13±0.06
	4th day	70.3±18.7	454.6±79.1	0.16±0.05
	7th day	90.5±27.3	159.6±30.7	0.61±0.30
FO	1st day	65.4±23.0	485.6±61.8	0.14±0.05
	4th day	90.2±18.5*	407.1±56.0	0.23±0.06*
	7th day	121.0±31.4*	93.6±16.3*	1.31±0.34*

*P<0.05 as compared with Con group

3 DISCUSSION

SAP is an acute abdomen that severely threatens human lives and health. It progresses rapidly with a complicated outcome and high mortality up to 20%–30%[6], and the disease incidence is rising year by year. At the present, the management of SAP is still a puzzle to solve unsatisfactorily. Generally speaking, two death peaks occur in the course of SAP. The first peak happens about 1–2 weeks after onset, and its mortality holds 60%–80% of the total deaths[7]. The MODS induced by the over release of cytokines (also called SIRS) is the main cause of patients' deaths in the early stage of SAP. The second occurs after about 2 months, and the main cause of deaths is sepsis and infection-related complications. The SIRS during the early stage of SAP is the critical role to cause the severe outcome as systemic capillary leakage syndrome (SCLS), MODS, abdominal compartment syndrome (ACS)[8]. And the magnitude and persistence time of the SIRS close correlate to severity of illness and prognosis in SAP. Therefore, regulation of SIRS becomes an important role in early management of SAP, and attains close attention in the whole world.

Recently, regulation of SIRS during the initial stage of SAP becomes a hot spot problem on therapy. Wang and partners[9] confirmed that pancreatic trypsin inhibitor (ulinastatin) which could obviously inhibit production of mediators and cytokines of inflammation was benefits for patients with SAP. Previous study suggested that dexamethasone and high concentration of prostaglandin E1 (PGE1) could inhibit the function of TNF-α released from macrophages and other inflammatory factors, maintain the balance of the pro-/anti-inflammatory cytokines in the early stage of SAP, and relieve damage of tissues and organs induced by SIRS, which had some significance for inhibiting SIRS and preventing MODS[10–12]. A study by Gao *et al*[13] showed that calcium antagonist (nitrendipine) which prevented pancreatic cell Ca^{2+} overload could reduce the blood plasma levels of IL-1, IL-6 and TNF-α, and improve the prognosis, lower the magnitude and persistence time of the SIRS, improve condition of MODS and decrease complication incidence. Although the ways to regulate the SIRS during the initial stage of SAP were introduced in mass of experiments and clinical studies, their clinical effects still were observed further.

In recent years, the new ω-3 fish oil emulsion not only supplied energy, but also had some important biological effects such as immune regulation and organs protection[14,15]. The main mechanisms of action were as follows: on the one hand, ω-3 fatty acids could enter the phospholipid pool of cell membrane to replace ω-6 fatty acids, and adjust to appropriate level of ω-3/ω-6 ratio (1:2 to 1:4). And it could competitively combine with cyclooxygenase and lipoxygenase to inhibit production of inflammatory mediators from ω-6 fatty acids which had a strong pro-inflammatory and immune regulation. On the other hand, through reducing the expression of surface receptor and molecule of immune cells membrane, ω-3 fatty acids could participate in the process of immune response, reduce the activity of immune cells and production of cytokine, and inhibit inflammatory response[1,16,17].

APACHE Ⅱ score has now been recognized as the best indicator and independent prognostic factor to assess the condition of patients with SAP[18]. In this study, the decline rate of APACHE Ⅱ score in FO group was markedly increased as compared with Con group, and the difference enlarged significantly from 4th day in the study. In the up-regulation stage of the SIRS in SAP patients, positive fluid balance following abnormal distribution of body fluids caused by serious SCLS is one of the important factors for occurrence and aggravation of multiple organ dysfunction and various complications in the early stage of SAP. The difficulty of the early treatment of SAP was to shift reasonably positive liquid balance to negative liquid balance as soon as possible. The emergence of negative fluid balance was an important symbol of the end of the SIRS. The results of this study showed that negative fluid balance of patients treated with ω-3 fish oil emulsion appeared significantly earlier than that in Con group. Correspondingly, the SIRS score is a direct reflection of the seriousness of the disease in patients with SAP. The score in the both groups was gradually reduced, and the patients in FO group took the lead from the SIRS state on the 4th day after treatment.

To some extent, the ratio of IL-10/TNF-α can represent the power of pro-/anti-inflammatory response. The closer was the stable pro-/anti-inflammatory balance, the more conducive resumption in patients with SAP[19]. The results of this study showed that plasma levels of TNF-α were gradually reduced in both groups, more significantly in FO group than in Con group (P<0.05). Plasma IL-10 levels were gradually increased, and those in FO group at 4th and 7th day after treatment were significantly higher than in Con group (P<0.05). The ratio of IL-10/TNF-α was significantly higher in FO group than in Con group (P<0.05). These results showed that ω-3 fish oil emulsion provided a reliable basis of experiment and theory on clinical treatment of SAP. Similarly, there was evidence that parenteral nutrition with ω-3 fatty acid could improve clinical prognosis in major surgery or critically ill patients[16], which was consistent with the results of this study.

Recently, multi-center clinical trials confirmed that intravenous administration of ω-3 fish oil emulsion on

the treatment of patients with intra-abdominal sepsis received significant clinical effects. It could reduce the dosage of antibiotics, significantly decreased the rate of re-operation, shorten the time of ICU and the length of stay, and lower mortality[16, 20]. In addition, in a single center retrospective study on patients with abdominal major surgery, Tsekos and his partners[21] found that patients receiving ω-3 fish oil emulsion in operation significantly decline the time of the respirator, shorten the hospital stay and lower mortality. We applied ω-3 fish oil emulsion into the early treatment of SAP patients, and through biological effects of inflammatory regulation and immune suppression, it effectively reduced SAP early intensity and duration of the SIRS, correct the imbalance of pro-/anti-inflammatory factors, obviously improve the state of serious diseases, and provided a new means to control the SIRS response during the early stages of SAP.

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