Int J Clin Exp Med 2020;13(1):118-125
www.ijcem.com /ISSN:1940-5901/IJCEM0100217

Original Article

Efficacy of ω-3 fatty acids combined with ulinastatin in the treatment of ARDS

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Received July 28, 2019; Accepted December 3, 2019; Epub January 15, 2020; Published January 30, 2020

Abstract: *Objective:* This study aims to investigate the efficacy of ω-3 fatty acids with ulinastatin in the treatment of acute respiratory distress syndrome (ARDS). *Methods:* A total of 80 ARDS patients were randomly divided into a control group (n=40) and an observation group (n=40). Patients in the control group were treated with ulinastatin, while those in the observation group were treated with ω-3 polyunsaturated fatty acids combined with ulinastatin. The levels of inflammatory factors, and the oxygenation index, acute physiology and chronic health evaluation (APACHE) II score, and plasma osmotic pressure were analyzed. Moreover, the duration of ventilator therapy, residence time in the Intensive Care Unit (ICU), as well as the complications and outcomes were compared between the two groups. *Results*: The levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), the APACHE II score, the plasma osmotic pressure, the proportions of pneumothorax, pulmonary hemorrhage, digestive tract ulcer, intracranial hemorrhage and the clinical mortality rate in observation group were significantly lower than those in the control group (P<0.05). At 1, 3 and 7 d after treatment, the oxygenation index in the observation group was significantly higher than that in the control group. Moreover, the duration of ventilator therapy, residence time in the ICU and total hospitalization duration in the observation group were all statistically shorter than those in the control group (P<0.05). *Conclusion:* The combined application of nutritional ω-3 fatty acids with ulinastatin in the treatment of ARDS can significantly alleviate the inflammatory response and shorten the duration of ventilator therapy, which provides basis for the improvement of the overall therapeutic effect.

Keywords: ω-3 fatty acids, ARDS, inflammatory response, hospitalization duration, ulinastatin

Introduction

It has been confirmed [1, 2] that when acute respiratory distress syndrome (ARDS) occurs, the levels of inflammatory factors in the body are significantly increased, causing a cascade effect in the immune system. If the inflammatory response in the body is not regulated in time, a large number of inflammatory factors are secreted, resulting in the over production of peroxidation products in the body and impairment of oxygen or hydroxyl free radical scavenging capacity. It thereby accelerates the progression of disease and causes a series of damage to the body [3, 4]. The effective control of the inflammatory response in ARDS patients can relieve the clinical symptoms of patients and presents great value in improving the prognosis of patients. In the past, ulinastatin was often used to interfere with the release of inflammatory factors, but the inflammatory response in patients with ARDS is so severe that the effect on the proinflammation control needs to be improved [5].

ω-3 polyunsaturated fatty acids can increase the neutrophil activity *in vivo*, and the intermediate metabolites also have certain functions of regulating inflammatory cytokines, which can essentially inhibit signal transduction and gene transcription during inflammatory cytokine activation, and thereby reduce the level of inflammation. Cytokines also competitively suppressed the activity of cyclooxygenase and lipoxygenase, and further reduce the level of inflammatory cytokines in the body [6, 7]. Although ω-3 polyunsaturated fatty acids have a certain value in inhibiting the inflammatory

Table 1. Demographic information

	Observation group	Control group
Total number	40	40
Gender (male/female)	29/11	30/10
Age (years old)	18-50	18-50
Average age (years old)	43.4±1.3	43.5±1.3
Duration of disease (h)	2-16	2-16
Average duration	8.2±0.5	8.3±0.5
Multiple injury	19	20
Severe infection	10	10
Severe pancreatitis	5	5
Suppurative cholangitis	3	3
Other causes	3	2

response in the body, there are few studies on the application of ω-3 polyunsaturated fatty acids in the treatment of ARDS at present. In this study, the clinical efficacy of ω-3 fatty acids combined with ulinastatin in ARDS was explored.

Patients and methods

General data

A total of 80 ARDS patients treated in our hospital from March 2016 to April 2018 were selected. In the diagnosis of ARDS, symptoms, vital signs, chest X-ray, and contrast-enhanced computed tomography, were adopted in the evaluation. The patients enrolled all met the unified diagnostic criteria developed by the European Respiratory Society in Berlin, Germany in 2011. Imaging examination showed that the transmission rates of both lungs were significantly decreased, which could not be explained by simple pleural effusion, atelectasis and nodular lesions. There was no high circulating load of cardiac causes, and the body oxygenation index (OI) was lower than 300 mmHg. Exclusion criteria: 1) patients with malignant tumors, 2) patients with systemic immune dysfunction, 3) patients treated with immunosuppressive therapy, 4) patients complicated with diseases of the blood system, 5) patients complicated with respiratory system infections in the past, 6) patients with other diseases in the lungs, or 7) patients who were allergic to drugs used in this study. Patients enrolled were equally divided into a control group (n=40) and an observation group (n=40) using the random number method. In the observation group, there were 29 males and 11 females, aged 18-50 years old with an average age of (43.4±1.3) years. The duration of disease was 2-16 h with an average of (8.2± 0.5) h. In terms of cause of disease, there were 19 cases of multiple injury, 10 cases of severe infection, 5 cases of severe pancreatitis, 3 cases of suppurative cholangitis and 3 cases of other causes. In the control group, there were 30 males and 10 females aged 18-50 years old with an average age of (43.5±1.3) years. The duration of disease was 2-16 h with an average of (8.3±0.5) h. In terms of cause of disease, there were 20 cases of multiple injury, 10 cases of severe infection, 5 cases of severe pancreatitis, 3 cases of suppurative cholangitis and 2 cases of other causes (**Table 1**). This study was approved by Ethics Committee of Gansu Provincial Maternity and Child-care Hospital and all the enrolled subjects signed informed consent.

Methods

In the control group, artificial airway was established by endotracheal intubation or tracheotomy. First, anti-infective treatment was performed based on experience, and then according to the drug sensitivity test combined with cough phlegm and anti-asthmatic drugs, antibiotics were selected for treatment. At the same time, the nutritional function and water, electrolytes and acid-base balance in the body of patients was observed. 200,000 U ulinastatin (Guangdong Techpool, NMPN H200-40476) added with 100 mL normal saline was used for intravenous injection twice a day at an interval of 12 h. In the observation group, ω-3 polyunsaturated fatty acids (Huarui Pharmaceutical, NMPN H20040723) were delivered via oral feeding or nasal feeding for continuous nutrition at a dose of 20 mL/kg per day (30 Kcal/kg), 6-8 times a day. All patients were treated for 7 consecutive days as a single course of treatment.

Observation indexes

The levels of inflammatory factors, the changes in the OI, APACHE II score and plasma osmotic pressure in both groups during intervention were analyzed. The duration of ventilator therapy, residence time in the Intensive Care Unit (ICU) and total hospitalization duration were compared between the two groups, and the

Table 2. Detection of inflammatory factors, OI, APACHE II score and plasma osmotic pressure before intervention between the two groups ($\bar{x}$ ± s)

	hs-CRP (mg/L)	IL-1 (ng/mL)	TNF-α (ng/mL)	OI (mmHg)	APACHE II score (point)	Plasma osmotic pressure (mOsm/L)
Observation group	25.5±2.4	231.4±23.1	24.9±2.1	214.3±11.7	64.3±2.7	367.2±13.5
Control group	25.6±2.4	231.5±23.0	24.8±2.0	214.4±11.8	64.4±2.7	367.3±13.5
t	0.186	0.019	0.218	0.038	0.166	0.033
P	0.523	0.985	0.828	0.970	0.869	0.974

Table 3. Comparisons of levels of inflammatory factors after intervention between the two groups ($\bar{x}$ ± s)

	hs-CRP (mg/L)	IL-1 (ng/mL)	TNF-α (ng/mL)
Observation group	7.9±0.8	51.7±6.2	8.1±0.7
Control group	15.1±1.1	111.2±9.6	17.4±1.2
t	17.348	32.928	42.338
P	0.000	0.000	0.000

complications and outcomes in both groups during treatment were recorded.

Evaluation criteria

The inflammatory factors tumor necrosis factor-α (TNF-α, 1-10 ηg/mL), interleukin-1 (IL-1, 130-250 ηg/mL) and high-sensitivity C-reactive protein (hs-CRP, <10 mg/L) were detected *in vivo*. OI: OI = arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), and its normal reference value was 400-500 mmHg. If PaO_2 declined and still could not be increased by increasing FiO_2, and the overall OI was lower than 300 mmHg, the respiratory dysfunction was confirmed. The APACHE II score included a total of 12 major items, and patients with the severest conditions within 24 h before treatment in the ICU were included for evaluation. The total score is 0-71 points (0-4 points for each item), and the score was negatively correlated with the severity of disease. The plasma osmotic pressure: 2 [(Na^+) mmol/L + (K^+) mmol/L] + blood glucose/18 + urea nitrogen mg/dL/2.8, its normal reference value was 280-300 mmol/L, and the value >350 mmol/L indicated the hyperosmolar status.

Statistical processing

Statistical Product and Service Solutions (SPSS) 20.0 software was used to analyze the data. Measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± s). *t* test was used for the comparisons of inflammatory factors, OI, APACHE II score and plasma osmotic pressure between the two groups, and chi-square test was adopted for the comparison of rate. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of inflammatory factors, OI, APACHE II score and plasma osmotic pressure before intervention between the two groups

There were no significant differences among the gender, age, duration of disease, cause of disease, inflammatory factors, OI, acute physiology and chronic health evaluation (APACHE) II score and plasma osmotic pressure at admission between the two groups ($P>0.05$) (**Table 2**).

Comparisons of levels of inflammatory factors after intervention between the two groups

After intervention, we found that the levels of hs-CRP, IL-1 and TNF-α in the observation group were significantly lower than those in the control group ($P<0.05$) (**Table 3**).

Analysis of changes in OI during intervention in both groups

Before treatment and at 1, 3 and 7 d after treatment, the OI was (214.3±11.7) mmHg, (276.3±11.9) mmHg, (332.1±12.8) mmHg and (432.6±14.9) mmHg in the observation group, respectively; and (214.4±11.8) mmHg, (232.1±12.3) mmHg, (256.7±13.5) mmHg and (378.9±15.7) mmHg in control group, respectively. At 1, 3 and 7 d after treatment, the OI in observation group was significantly higher than that in control group at the same time point (t=16.334, 25.633 and 15.691, P= 0.000<0.05) (**Figure 1**).

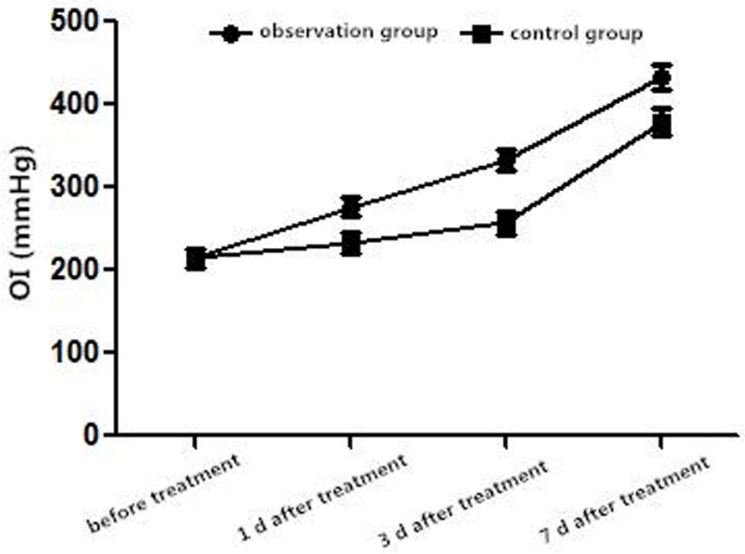

Figure 1. Analysis of changes in OI during intervention in both groups.

Analysis of changes in APACHE II score during intervention in both groups

Also, before treatment and at 1, 3 and 7 d after treatment, the APACHE II score was (64.3±2.7) points, (53.1±2.5) points, (30.2±1.9) points and (25.3±1.2) points, in the observation group, respectively; and (64.4±2.7) points, (60.1±2.6) points, (44.2±2.3) points and (35.2±1.7) points the in control group, respectively. At 1, 3 and 7 d after treatment, the APACHE II score in the observation group was clearly lower than that in control group at the same time point (t=12.274, 29.680 and 30.090, P=0.000<0.05) (**Figure 2**).

Changes in plasma osmotic pressure during intervention in both groups

We then measured the plasma osmotic pressure before treatment and at 1, 3 and 7 d after treatment. The result showed that the plasma osmotic pressure was (367.2±13.5) mOsm/L, (333.1±12.1) mOsm/L, (289.1±11.2) mOsm/L and (256.8±8.8) mOsm/L in observation group, respectively; and (367.3±13.5) mOsm/L, (353.5±12.6) mOsm/L, (319.9±11.7) mOsm/L and (309.8±10.7) mOsm/L in control group, respectively. The combination intervention significantly reduced the plasma osmotic pressure in the observation group compared to single use of ulinastatin in the control group (t=7.386, 12.027 and 24.195, P=0.000<0.05) (**Figure 3**).

Comparisons of duration of ventilator therapy, residence time in the ICU and total hospitalization duration between the two groups

Our data revealed that after the application of ω-3 fatty acids and ulinastatin, the duration of ventilator therapy, residence time in the ICU and total hospitalization duration in the observation group were markedly shorter than those in control group (P<0.05) (**Table 4**).

Comparisons of complications and outcomes during treatment between the two groups

The combined use of ω-3 fatty acids and ulinastatin also present apparent effects on the complications and outcomes. The proportions of pneumothorax, pulmonary hemorrhage, digestive tract ulcers, intracranial hemorrhaging and the clinical mortality rate in the observation group were remarkably lower than those in the control group (P<0.05) (**Table 5**).

Discussion

Predisposing factors for acute respiratory distress syndrome includes infection, poisoning, multiple injuries, shock caused by various causes, harmful gases in the respiratory system, and asphyxia [9]. ARDS is divided into acute lung injury and acute respiratory distress according to its severity, the former of which represents the severe phase of the latter [10]. In terms of pathophysiological changes, the aggravation of pulmonary microvascular permeability, the decline in the alveolar osmotic pressure, and protein-rich substances in the pulmonary interstitium were observed, result in pulmonary edema and formation of pulmonary hyaline membrane. At the same time, pulmonary interstitial fibrosis also appears [11]. The clinical manifestations are mainly decreased lung compliance, abnormal ventilation/perfusion rate caused by pulmonary blood oxygenation, and refractory hypoxemia. Multiple organ failure may occur as the disease progresses, and even endanger the life of the patient [12]. Despite the great progress made in the patho-

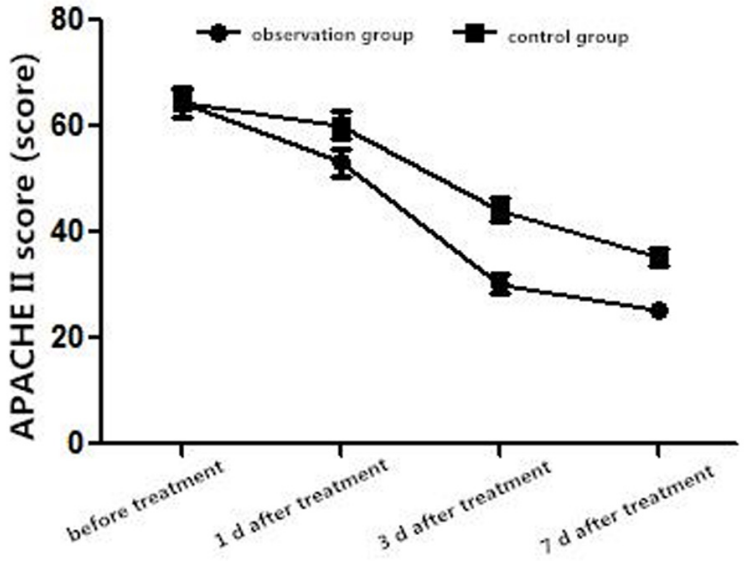

Figure 2. Analysis of changes in APACHE II score during intervention in both groups.

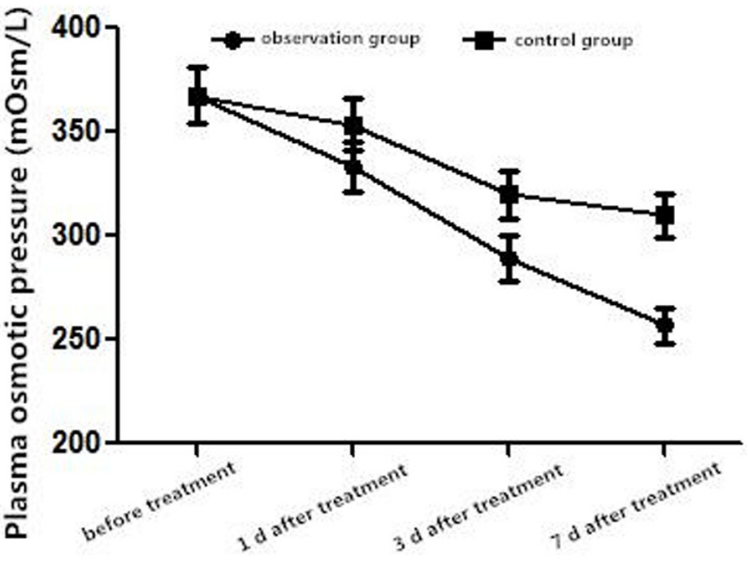

Figure 3. Changes in plasma osmotic pressure during intervention in both groups.

genesis and therapeutic intervention of ARDS, both mortality and disability rates of ARDS are still high. In addition to effective antibiotic treatment, nutritional support, maintenance of vital signs and other symptomatic treatment, the suppression of over-inflammation becomes a primary strategy to improve the therapeutic effect and prognosis of patients.

All subjects in this study received ulinastatin intervention on the basis of conventional antibiotic treatment and other symptom treatment, and the therapy effectively inhibited the activity of various cellular proteolytic enzymes, reduced tissue damage, and stabilized the function of intracellular lysosomes. Strengthening tissue perfusion is a commonly way to reduce the level of inflammatory factors in the body. Considering the severe condition of ARDS patients, excessive inflammatory response in the body, along with cascade effects was clearly found, so that the practical effect of ulinastatin alone is often unsatisfactory. Patients in the observation group underwent the anti-inflammatory therapy using the enteral nutrient ω-3 fatty acids. Comparisons of levels of inflammatory factors after intervention between the two groups showed that the levels of hs-CRP, IL-1 and TNF-α in observation group were significantly attenuated after combined intervention, indicating that the combined application of ω-3 fatty acids can effectively reduce the levels of inflammatory factors in the body. Moreover, it was found in the analysis of changes in OI, APACHE II score and plasma osmotic pressure during intervention in both groups at 1, 3 and 7 d after treatment, the OI in the observation group was significantly higher than that in control group at the same time, with down regulation of the APACHE II score and plasma osmotic, suggesting that the combined application of ω-3 fatty acids with ulinastatin is of great significance in increasing the oxygenation, improving the degree of disease, maintaining the body's osmotic pressure in ARDS patients, as well as alleviating the edema. Our results further indicated that the combined application of ω-3 fatty acids and ulinastatin has important significance in shortening the duration of ventilator therapy and increasing the overall therapeu-

Table 4. Comparisons of duration of ventilator therapy, residence time in the ICU and total hospitalization duration between the two groups (d, $\bar{x} \pm s$)

	Duration of ventilator therapy	Residence time in the ICU	Total hospitalization duration
Observation group	4.1±0.3	7.9±1.1	14.2±2.1
Control group	5.6±0.5	8.9±1.4	16.9±2.5
t	16.270	3.552	6.766
P	0.000	0.000	0.000

Table 5. Comparisons of complications and outcomes during treatment between the two groups (n)

	Pneumothorax	Pulmonary hemorrhage	Digestive tract ulcer	Intracranial hemorrhage	Clinical death
Observation group	1	1	1	1	2
Control group	3	5	4	4	14
X^2		8.067			9.453
P		0.005			0.002

tic effect on ARDS patients. Finally, it was found that the proportions of pneumothorax, pulmonary hemorrhage, digestive tract ulcer and intracranial hemorrhage in the observation group were remarkably lower than those in the control group, manifesting an essential role in the reduction of the complications during treatment and improvement of the prognosis of patients.

ω-3 polyunsaturated fatty acids is an essential fatty acid and an important carrier for the metabolism of fat-soluble vitamins. It also provides energy for the human body [13]. Moreover, ω-3 polyunsaturated fatty acids also have influence on cell signal transduction pathways, as well as positive impact on reducing the levels of inflammatory factors in the body, which plays a major role in modulation of body immunity [14]. The inflammatory response in the body can be competitively inhibited through the suppression of the metabolic process of arachidonic acid, reduction of the levels of low-efficiency 5-series leukotrienes and 2/3-series prostaglandin, which exerts certain influences on increasing the phagocytosis of macrophages and improving the immune function in the body [15]. ω-3 fatty acids used in this study can affect the chemotactic movement of inflammatory cells, reduce the release of inflammatory factors and decrease the stability of inflammatory cell membranes, and it thereby further limits the levels of inflammatory factors in the body [16]. Besides, ω-3 fatty acids participate in the regulation of protein, fat, carbohydrate and glucose metabolism [17], and can lower the level of low-density lipoprotein receptor [19] while increase the activity of high-density lipoprotein receptor [18]. ω-3 fatty acids also play an important role in improving the body's glucose uptake utilization rate and stress glucose metabolism disorder and improving the body fat utilization rate [20]. Previous findings indicated that ω-3 fatty acids (FAs) from fish oil can exert potent anti-inflammatory effects through GPR120, a G protein-coupled receptor involved in modulation of metabolism and endocrine and immune function [21]. It has been demonstrated that ω-3 fatty acid contributed to the attenuation of IL-1beta-induced changes in dopamine and metabolites in the shell of the nucleus accumbens [22]. Previous results showed that DHA reduced expressions of tumor necrosis factor-α, interleukin-6, nitric oxide synthase, and cyclo-oxygenase-2, induced by interferon-γ, and induced upregulation of heme oxygenase-1 (HO-1) in BV-2 microglia, which was similar to our finding [23]. However, the limitations in this study still exists that the exact mechanism regarding the inhibitory effect of ω-3 fatty acid on immune response in ARDS patients requires further investigation.

Conclusion

In conclusion, the combined use of ω-3 fatty acids with ulinastatin in the treatment of ARDS can significantly alleviate the inflammatory response in the body, improve the oxygenation, reduce the severity of disease, maintain the body's osmotic pressure and shorten the dura-

tion of ventilator therapy, which provides fundamental leads for the improvement of the overall therapy for ARDS.

Disclosure of conflict of interest

None.

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