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Original Article

Efficacy of ulinastatin combined with alanyl glutamine for patients with sepsis

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Abstract: Objective: To explore the efficacy of ulinastatin combined with alanyl glutamine for patients with sepsis. Methods: According to a random number table, 84 patients with sepsis were equally divided into the control group in which ulinastatin was applied, and the treatment group in which ulinastatin combined with alanyl glutamine was applied. The comparison was made between the two groups for blood gas indexes, acute physiology and chronic health evaluation (APACHE II) score, inflammation markers, immune function, the incidence of multiple organ dysfunction syndrome (MODS), the incidence of adverse reactions, and the 28-day survival rate. Results: Before the treatment, no significant statistical difference was found between the two groups in the blood gas indexes, APACHE II scores, inflammation markers, immune function markers, incidence of adverse reactions during treatment, and 28-day survival rates (all P>0.05). After the treatment, PaO_2 level in the treatment group (92.92±5.18) was higher than that in the control group (80.64±3.43); $PaCO_2$ level in the treatment group (35.81±1.18) was lower than that in the control group (41.98±1.20); and PaO_2/FiO_2 in the treatment group (226.41±23.22) was higher than that in the control group (194.85±29.63). APACHE II score in the treatment group (14.53±1.66 points) was lower than that in the control group (18.96±2.60 points). C-reactive protein (CRP) level (12.11±2.27 mg/L) and the total number of white blood cells ($8.19±3.32*10^9$/L) in the treatment group were lower than those in the control group which had a CRP level of (18.40±2.75 mg/L) and total white blood cells of ($10.16±3.31*10^9$/L). After the treatment, IgM, IgA and IgG in the treatment group were higher than those in the control group. The incidence of MODS in the treatment group (4.76%) was much lower than the control group (19.05%), and all these differences were statistically significant (P<0.05). Conclusion: Ulinastatin combined with alanyl glutamine in the treatment of patients with sepsis is effective and worthy of clinical promotion.

Keywords: Sepsis, ulinastatin, alanyl glutamine, clinical efficacy

Introduction

Sepsis is a severe disease in which the host is not responsive to various infections, leading to organ dysfunction and is life threatening to patients. Featured by rapid disease progression and high mortality, sepsis, once complicated with septic shock, can have a mortality rate as high as 80% [1-3]. According to some studies, the mortality rate of sepsis remains high in spite of the clinical breakthroughs in the treatment of sepsis [4].

Ulinastatin, a urinary trypsin inhibitor that eliminates and inhibits inflammatory factors in the body to block systemic inflammatory response syndrome, can reduce the damage of tissues and organs and inhibit the apoptosis of splenocytes when used for the treatment of sepsis. Studies have found the marked efficacy of ulinastatin for treating severe sepsis, which can reduce the mortality up to 20% and increase the recovery rate to 40% [5]. Clinically, ulinastatin has been proved to deliver a favorable outcome in treating acute pancreatitis, improving patient's shock and postoperative prognosis, and reducing the complications of cardiopulmonary bypass [6-8]. Glutamine (Gln) is a conditionally essential amino acid and can increase the secretion of intestinal secretory immunoglobulin A (SIgA) and the production of immune cells, maintain the supply of antioxidants in the tissue, strengthen the immune function of the intestinal tract and the body, effectively protect the intestinal mucosal barrier and decrease intestinal bacteria and endotoxin translocation, thus reducing or avoiding the release of a large number of inflammatory mediators [9]. Alanyl glutamine is an immune-nutrient commonly used in clinical practice,

which can improve patients' hypermetabolism and immunity [10]. As effective anti-inflammatory drugs, ulinastatin is rarely combined with alanyl glutamine for the treatment of sepsis, and its effect has not been confirmed yet. This study aimed to investigate the clinical significance of the combination of ulinastatin and alanyl glutamine in the treatment of sepsis and its effects on inflammation and immune function.

Materials and methods

General information

A total of 84 sepsis patients admitted to Gansu Provincial Cancer Hospital from May 2016 to April 2018 were collected and divided into two groups based on a random number table: with 42 patients (24 males and 18 females) in the control group with an average age of (65.30±4.03) years; and 42 patients (22 males and 20 females) in the treatment group with an average age of (65.67±4.58) years. This study has been reviewed and approved by the Ethics Committee of Gansu Provincial Cancer Hospital and has received informed consent from the families of all patients. The two groups of patients were comparable since they were not statistically different in terms of age, gender, body mass index (BMI), and other general information (all $P>0.05$).

Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with sepsis in accordance with the third international consensus definition for sepsis in 2016 [11]; no younger than 18 years, and no gender limitation; patients with voluntary participation in the research and active cooperation with the treatment and the follow-up.

Exclusion criteria: Patients under 18 years; patients admitted to the hospital within 24 hours before the beginning of this experiment; sepsis patients complicated with refractory hemorrhage, cardiogenic shock, serious disease of the blood system or immune system; patients with recent administration of hormones or immunosuppressants; patients allergic to ulinastatin; patients in gestational period or lactation period; or patients with poor compliance.

Treatment methods

After the diagnosis of sepsis, patient's blood and the secretion or drainage liquid from relevant infected sites were collected for bacterial culture and drug sensitive testing, and attention was paid to the sterility of blood collection and timely follow-up. Carbapenems or cefoperazone sulbactam sodium (sulperazone) was first empirically used for anti-infection therapy according to the third international consensus in 2016. Then the anti-infection treatment regimen was adjusted according to the results of bacterial culture; if necessary or as the condition improved, de-escalation therapy was performed, with a course of 7 to 10 days. Enteral nutrition support was usually adopted, and patients with fasting food and water were given parenteral nutrition support. Patients in the control group received ulinastatin (Techpool Bio-pharma Co., Ltd., China), with an intravenous injection of 0.9% saline containing 200,000 units of ulinastatin every 8 hours for 1 week. Patients in the treatment group were treated with the combination of ulinastatin and alanyl glutamine (Sichuan Kelun Pharmaceutical Co., Ltd., China): in addition to ulinastatin dosed the same as the control group, an intravenous injection of 0.4 g/kg alanyl glutamine was performed once a day for 1 week.

Outcome measures

(1) ABL90 blood gas analyzer produced by Radiometer Medical ApS was applied to analyze the arterial blood which was drawn by the designated medical staff with the matched special arterial blood collection needle. PaO_2, $PaCO_2$, and oxygenation index (PaO_2/FiO_2) were measured as per the instruction of the analyzer. (2) The acute physiology and chronic health evaluation (APACHE II) scores were observed and recorded, including the acute physiological score, the age score, and the chronic health score. (3) BS-600 chemistry analyzer made by Mindray Medical International Limited was used to analyze levels of immunological indicators (IgM, IgA and IgG) before and after treatment in the fasting venous blood. (4) A fully automatic analyzer (Roche cobas8000, Germany) and a hypersensitive C-reactive protein (CRP) reagent with its accompanying standard produced by MedicalSystem Biotechnology Co., Ltd., China were used to separate the serum of patients. Electrical impedance hematology analyzer made by Hlife Brand Management Group Co., Ltd. (China) was used to determine the CRP concentration by the method of latex-enhanced immunoturbidimetry. Counting of white blood cell (WBC) in 2 mL of the collected fasting venous whole blood and blood routine examination were finished by the Sysmex XE-5100

Table 1. Demographic comparison

Observation index	Control group (n=42)	Treatment group (n=42)	Statistical value	P
Gender (male/female)	24/18	22/20	χ^2=0.192	0.661
Age (years old)	65.30±4.03	65.67±4.58	t=0.403	0.688
BMI	23.22±3.12	22.81±4.01	t=0.523	1.989
Admission department (ICU/other departments)	16/26	20/22	χ^2=0.778	0.378
Cause of infection			χ^2=0.741	0.864
Postoperative intestinal obstruction	19	21		
Anastomotic fistula	10	7		
Biliary fistula	4	5		
Others	9	9		

Note: BMI, body mass index; ICU, intensive care unit.

Table 2. Comparison of blood gas indexes between the two groups before and after the treatment

	PaO_2	$PaCO_2$	PaO_2/FiO_2
Before treatment			
Control group	66.64±2.03	60.19±0.94	150.69±23.43
Treatment group	66.54±1.72	60.74±1.59	153.28±25.80
t	0.257	1.929	0.481
P	0.798	0.057	0.631
After treatment			
Control group	80.64±3.43***	41.98±1.20***	194.85±29.63***
Treatment group	92.92±5.18***	35.81±1.18***	226.41±23.22***
t	12.811	23.710	5.434
P	<0.001	<0.001	<0.001

Note: Comparison between before and after treatment, ***P<0.001.

hematology analyzer (Sysmex Corporation, Japan) and related ancillary reagents. (5) MODS refers to a clinical syndrome in which two or more organic or systemic dysfunctions occur in acute diseases such as severe trauma, shock, infection, and major operations, making it difficult for the body to maintain homeostasis. This study observed and recorded the incidence of MODS, the incidence of adverse reactions, and the 28-day survival rate of patients. The incidence of MODS: the percentage of patients with MODS in the whole group; the incidence of adverse reactions: the percentage of patients with adverse reactions such as vomiting, itching, and diarrhea after the treatment in the whole group.

Statistical methods

The data were processed by SPSS 20.0 software. The measurement data were expressed by mean ± standard deviation ($\bar{x}$ ± sd) and compared with the independent sampled t-test; the count data were expressed by case number/percentage (n/%) and compared between groups by χ^2 test. A statistical difference was recognized if P<0.05.

Results

Demographics comparison

According to the basic information of patients at the time of admission, the two groups were comparable since there was no statistically significant difference in gender, age, BMI, admission department, or the cause of infection. See **Table 1** for details.

Comparison of blood gas indexes between the two groups before and after the treatment

Before the treatment, no statistically significant difference was detected between the two groups in terms of PaO_2, $PaCO_2$ and PaO_2/FiO_2 (all P>0.05). After the treatment, the PaO_2, $PaCO_2$ and PaO_2/FiO_2 in the treatment group were all statistically different from those in the control group (both P<0.05). See **Table 2** for details.

Comparison of APACHE II scores

There was no statistically significant difference in the APACHE II scores between the two groups before the treatment. After the treatment, the APACHE II score of the treatment group de-

Table 3. Comparison of APACHE II scores before and after the treatment

Group	Before treatment	After treatment
Control group	24.75±5.67	18.96±2.60***
Treatment group	23.18±6.46	14.53±1.66***
t	1.185	9.316
P	0.239	<0.001

Note: Comparison between before and after treatment, ***P<0.001; APACHE II, acute physiology and chronic health evaluation.

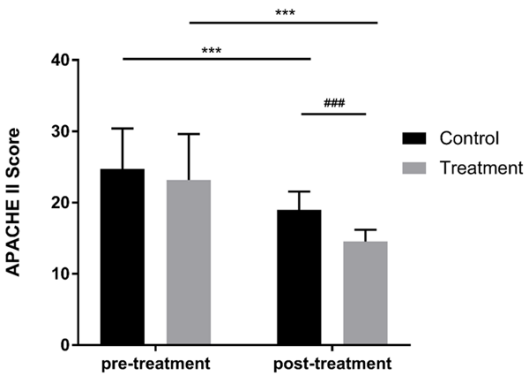

Figure 1. Comparison of APACHE II scores before and after the treatment. Comparison between before and after treatment in the same group, ***P<0.001; comparison between the two groups after treatment, ###P<0.001; APACHE II, acute physiology and chronic health evaluation.

Table 4. Comparison of inflammation indicators

	CRP (mg/L)	WBC (*10^9/L)
Before treatment		
Control group	23.89±5.55	17.06±2.69
Treatment group	24.08±5.14	16.02±2.51
t	0.164	1.823
P	0.870	0.072
After treatment		
Control group	18.40±2.75***	10.16±3.31***
Treatment group	12.11±2.27***	8.19±3.32***
t	11.435	2.717
P	<0.001	0.008

Note: Comparison between before and after treatment, ***P<0.001; CRP, C-reaction protein; WBC, white blood cell.

creased to 14.53±1.66, statistically lower than that of the control group (18.96±2.60) (P<0.05). Check **Table 3** and **Figure 1** for details.

Comparison of inflammation indicators

The two groups were not significantly different in the CRP level and WBC amount before the treatment (both P>0.05). The treatment greatly reduced the CRP level and WBC amount of the two groups. After the treatment, the CRP level in the treatment group (12.11±2.27 mg/L) was statistically lower than that of the control group (18.40±2.75 mg/L), the WBC amount in the treatment group (8.19±3.32*10^9/L) was also statistically lower than that of the control group (10.16±3.31*10^9/L) (both P<0.05). See **Table 4** for more information.

Comparison of immunological indicators levels

There was no statistically significant difference between the two groups before the treatment in terms of IgM, IgA and IgG levels (all P>0.05). After the treatment, IgM, IgA and IgG levels of the treatment group were higher than the control group (all P<0.05). See **Table 5** for more information.

Comparison of adverse reactions and prognosis

The incidence of MODS in the treatment group (4.76%) was significantly lower than that in the control group (19.05%) (P<0.05). During the hospitalization, daily care and monitoring of disease were performed, as well as the recording of adverse reactions such as diarrhea, itching, vomiting, dizziness, etc. The control group had an adverse reaction rate of 9.52%, including 2 cases of diarrhea and 2 cases of itching, the control group had an adverse reaction rate of 4.76%, including 2 cases of vomiting. The difference in adverse reactions between the two groups was not statistically significant (P>0.05). The 28-day survival rates of the control group and the treatment group were 85.71% and 90.48%, respectively, without a statistical difference between the two groups (P>0.05). See **Table 6** for more information.

Discussion

Sepsis, manifesting as a “cascade effect” of inflammation aroused by various activated inflammatory factors, can induce serious fatal complications such as MODS and bring poor clinical efficacy due to its complex pathogene-

Table 5. Comparison of immunological indicators levels

	n	IgM (g/L)	IgA (g/L)	IgG (g/L)
Before treatment				
Control group	42	2.37±0.45	1.89±0.28	12.79±3.85
Treatment group	42	2.38±0.50	1.90±0.31	13.04±3.96
t		-0.107	-0.123	-0.309
P		0.914	0.902	0.758
After treatment				
Control group	42	2.45±0.47	1.78±0.28	15.30±2.87
Treatment group	42	2.94±0.43	2.01±0.31	18.23±2.60
t		-4.908	3.555	4.909
P		<0.001	<0.001	<0.001

Table 6. Comparison of adverse reactions (%)

	Incidence of MODS	28-day survival rate	Adverse reaction rate
Control group	19.05	85.71	9.52
Treatment group	4.76	90.48	4.76
χ^2	4.086	0.454	0.718
P	0.043	0.500	0.397

Note: MODS, multiple organ dysfunction syndrome.

sis, unclear disease progression, and diversified inflammatory factors [12, 13]. Ulinastatin, an endogenous anti-inflammatory substance, favors the reduction in inflammatory mediators and the clearance of oxygen free radicals, as well as the decrease of TNF and inflammatory reactions [14]. Glutamine provides nitrogen source for protein synthesis, which promotes protein synthesis, reduces its decomposition and improves nutritional status of patients [15]. This study explored the clinical efficacy of the combination of ulinastatin and alanyl glutamine from the aspects of APACHE II score, inflammation factor, immunological indicators and the incidence of MODS, etc.

The APACHE II score not only quantifies disease severity, but also gives an effective assessment of mortality and prognosis in patients [16, 17]. One study found that an increase in the APACHE II score is accompanied by an increase in mortality and a worsening in prognosis [18]. Dong et al. found that ulinastatin could effectively reduce APACHE II score and significantly improve treatment efficiency for the treatment of sepsis [19]. Such results are similar to this study which discovered a much lower APACHE II score in the treatment group than that of the control group, suggesting that ulinastatin combined with alanyl glutamine could effectively improve the clinical symptoms and prognosis of patients, and reduce the mortality rate.

Patients with sepsis are prone to systemic inflammatory response syndrome and multiple organs impairments due to continuous damage by injury factors. CRP, an important marker of inflammatory responses, refers to a protein secreted under stress conditions such as infection or tissue damage in the body, participating in the local or systemic inflammatory response and increased in the presence of infection [20]. Yang AP and other researchers tested the serum CRP and WBC levels of 60 babies with neonatal septicemia and 60 people without septicemia, and assessed the value of those inflammatory markers for diagnosing sepsis based on the area under the curve (AUC) of the receiver operating characteristic (ROC) and the logistic regression analysis. The results demonstrated good sensitivities of CRP (38.6%) and WBC (52.3%), which can function as biomarkers for diagnosing septicemia when combined with nCD64 and PCT. Wei Guifang and other researchers studied 104 sepsis patients, among whom the observation group was treated with ulinastatin. After treatment, the CRP level of the observation group was 16.8±1.1 mg/L, significantly lower than that of the control group (28.8±1.5 mg/L), implying the effective improvements on infection and great efficacy that ulinastatin can bring for sepsis [21]. This study observed the changes of inflammatory factors before and after treatment and came to the results that the levels of white blood cells and serum CRP were significantly lower after the treatment, and that the combination of alanyl glutamine and ulinastatin resulted in stronger inhibition on the inflammatory response.

Glutamine has an immunoregulatory function, which can promote mitosis, differentiation and proliferation of lymphocytes, accelerate the synthesis of phospholipid mRNA, and maintain normal function of lymphocytes [22]. In the Zhao et al. study of 96 sepsis patients [23], IgM, IgA and IgG levels in the observation group were significantly higher than those in the control group after conventional treatment combined with alanyl glutamine, suggesting that

alanyl glutamine could improve the immune function of sepsis patients, which was beneficial to the prognosis. In this study, IgM, IgA and IgG levels in the serum in the treatment group were significantly higher than those in the control group after treatment ($P<0.05$), indicating that ulinastatin combined with alanyl glutamine could evidently improve the nutritional status and immune function of sepsis patients; the significantly lower incidence of MODS in the treatment group compared with the control group suggested that ulinastatin combined with alanyl glutamine had better clinical efficacy.

In this paper, the efficacy of ulinastatin combined with alanyl glutamine in the treatment of sepsis patients was studied, but the small sample size may lead to bias effect. This study failed to deliver a comprehensive evaluation of the changes in inflammatory response due to the absence of the detection of other inflammatory factors such as PCT, TNF-α, IL-1, and IL-8. In the future study, other relative markers will be included.

In summary, the combination of ulinastatin and alanyl glutamine can bring improved blood gas and immune function, as well as less inflammatory response and lower incidence of MODS, which is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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