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Clinical efficacy and safety of norepinephrine combined with ulinastatin in the treatment of septic shock

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Abstract: To analyze the clinical efficacy and safety of norepinephrine combined with ulinastatin in the treatment of septic shock. 100 patients with septic shock treated in our institution from May 2019 to May 2021 were recruited and randomly assigned to receive either norepinephrine (control group) or norepinephrine plus ulinastatin (experimental group) according to the treatment scheme. The treatment efficacy, time for shock improvement, intensive care unit (ICU) stay, total hospital stay, in-hospital mortality, 30-day survival, and changes in inflammatory factors (plasma C-reactive protein (CRP), serum lactic acid (LAC), serum procalcitonin (PCT), and interleukin-10 (IL-10)) before and after treatment were analyzed, and the sequential organ failure scores of the two groups were compared. The experimental group exhibited superior performance with respect to efficacy, ICU stays, and total hospital stay, in-hospital mortality to the control group (all $P<0.05$). After treatment, the experimental group presented lower levels of CRP, LAC, PCT and IL-10 and higher SOFA scores than the control group ($P<0.05$). Norepinephrine plus ulinastatin achieved remarkable results in the treatment of septic shock, improving the treatment efficiency, shortening the time for shock improvement and hospitalization, reducing hospital mortality, driving down the expression of inflammatory factors and enhancing the survival of patients, with high safety.

Keywords: Clinical efficacy, norepinephrine, septic shock, ulinastatin.

INTRODUCTION

Septic shock is a common critical illness in emergency internal medicine with high mortality. The main inducing factor for sepsis is a systemic inflammatory syndrome caused by the invasion of pathogenic microorganisms such as bacteria (Rizk *et al*., 2018; Zhong *et al*., 2020). According to the epidemiological survey, there are more than 18 million cases of severe sepsis worldwide every year and 750,000 cases in the United States every year which presents a trend of increase at a rate of 1.5%-8.0% annually. Previous studies have confirmed that sepsis has a higher mortality rate than myocardial infarction, which has become the main cause of death for non-cardiac patients in ICUs. Hence, timely and effective treatment is required for the control of the disease and the prolongation of patients' survival (Duclos *et al*., 2019; Kasugai *et al*., 2020).

Norepinephrine, an anti-shock vasoactive drug, has been widely used in shock emergencies caused by acute hypotension and peripheral vasodilation, with certain efficacy (Hajjar *et al*., 2019; Post *et al*., 2018). Ulinastatin, a protease inhibitor, is a glycoprotein extracted from fresh human urine that can restrain activities of multiple proteolytic enzymes, with an inhibitory effect on the pancreatic enzyme activities such as trypsin, thus yielding a satisfactory efficacy in the treatment of acute pancreatitis and chronic relapsing pancreatitis (Elbouhy *et al*., 2019). Research has confirmed that norepinephrine can ameliorate clinical symptoms of septic shock and elevate the treatment rate and ulinastatin can stem the accumulation of inflammatory cells and inhibit the synthesis of inflammatory factors. Better therapeutic results may be derived from the combination of the two drugs (Antal *et al*., 2019). In order to explore the clinical efficacy and safety of norepinephrine combined with ulinastatin in the treatment of septic shock, 100 patients admitted to this hospital from May 2019 to May 2021 were selected as the research subjects. The report results are presented below and evaluated based on different clinical and inflammatory parameters.

MATERIALS AND METHODS

Data and methods

General information

A total of 100 patients who were admitted to Chongqing Hospital of Traditional Chinese Medicine from May 2019 to May 2021 were selected as research subjects. After screening, all patients met the research criteria and were divided into an experimental group and a control group according to the treatment protocol, with 50 cases in each group.

Inclusion criteria

(1) Patients who met the diagnostic criteria for this disease in the 2016 edition of International Guideline for Septic Shock, with clinical manifestations of persistent hypotension, respiratory rate ≥22 times/min, Glasgow coma score ≤13 points, and systolic blood pressure ≤ 100

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mmHg (Elbouhy *et al*., 2019); (2) Patients with complete and authentic medical records; (3) Patients with no allergies to the used therapeutic drugs; (4) The patients and their families were informed of the study and provided informed consent. The study was approved by the Ethics Committee of the hospital. The ethics approval number is 2019-4-28.

Exclusion criteria

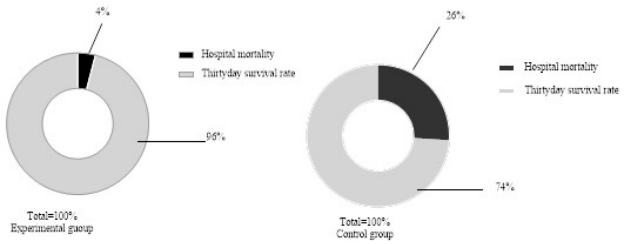
(1) Patients with other infectious diseases; (2) Patients with schizophrenia, incapabilities to communicate and express normally with medical staff, or those who refused to cooperate; (3) Patients with complicated immune function disease, or those who have received similar treatment in other hospitals; (4) Patients who were unable to participate in the whole process due to various uncontrollable reasons.

Ethical approval

The patients and their families knew about the study and had signed the informed consent under the premise of knowing the purpose and content of the study, and the study was approved by the Ethics Committee of Chongqing Hospital of Traditional Chinese Medicine. All the methods were carried out in accordance with the Declaration of Helsinki.

Treatment methods

After admission, patients of both groups were sent to the intensive care unit for emergency treatment. They were observed closely and given oxygen and mechanical ventilation to improve circulation. Fluid resuscitation was conducted, electrolyte balance was maintained, and anti-infection treatment was given if necessary, with gastric acid secretion management and nutritional support. All these treatments were to ensure the stability of the vital signs of the patients.



Note: Black represents the in-hospital mortality rate; Grey represents the 30d survival rate.

in the experimental group, the in-hospital mortality rate was 4%, 2 cases (2/50) and the 30d survival rate was 96%, 48 cases (48/50).

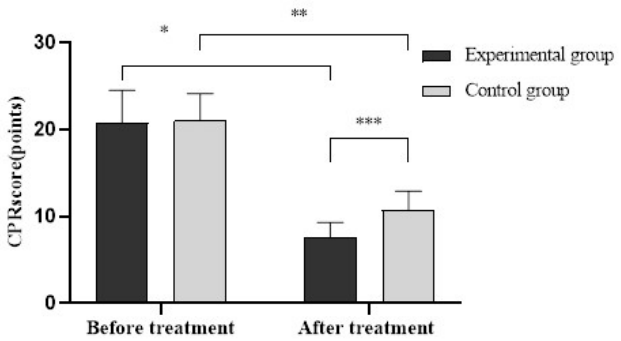
In the control group, the in-hospital mortality rate was 26%, 13 cases (13/50) and the 30d survival rate was 74%, 37 cases (37/50).

There was a significant difference in the in-hospital mortality between the two groups (x^2=9.490, P<0.05).

There was a significant difference in the 30d survival rate between the two groups (x^2=9.490, P<0.05).

Fig. 1: Comparison of inpatient mortality and 30-day survival rates in the two groups [N (%)]

Patients in the control group were treated with single norepinephrine therapy, with prescription of norepinephrine (SFDA Approval No. H12020621; Manufacturer: Tianjin King York Pharmaceutical Co., Ltd.; Specification: 2mL: 10mg). Administration and dosage: intravenous injection; intravenous pumping was performed after 12mg of norepinephrine were mixed with 44ml of glucose injection with a concentration of 5%. The pumping speed was adjusted according to the actual blood pressure of the patient until the blood pressure returned to a normal level. Patients received continuous treatment for 7 days (Dalla *et al*., 2019; Hammond *et al*., 2018).



Note: The CRP levels in the experimental group before and after treatment were (20.82±3.68) mg.L^{-1} and (7.65±1.67) mg.L^{-1}, respectively.

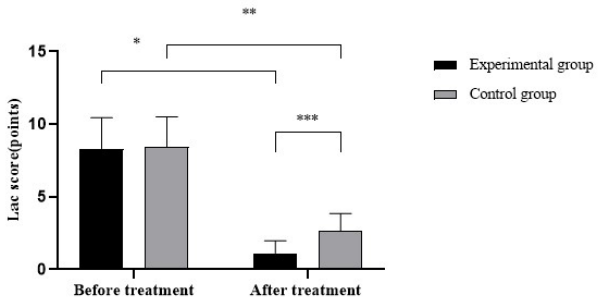
The CRP levels in the control group before and after treatment were (21.01±3.12) mg.L^{-1} and (10.75±2.16) mg.L^{-1}, respectively.

*Indicates a difference of CRP level in the experimental group before and after treatment (t=23.044, P<0.001);

**Indicates a difference of CRP level in the control group before and after treatment (t=19.118, P<0.001);

***Indicates a difference in CRP levels after treatment between the two groups (t=26.695, P<0.001).

Fig. 2: **Comparison of CRP levels between the two groups before and after treatment**



Note: The levels of Lac in the experimental group before and after treatment were (8.32±2.13) mmol/L, (1.12±0.86) mmol/L;

The Lac levels in the control group before and after treatment were (8.45±2.06) mmol/L, (2.64±1.21) mmol/L;

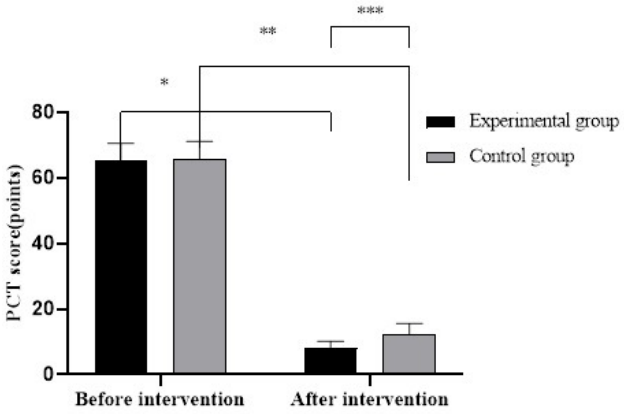
*Indicates a difference of Lac level in the experimental group before and after treatment (t=22.164, P<0.001);

**Indicates a difference in Lac levels in the control group before and after treatment (t=17.196, P<0.001);

***Indicates a difference in Lac levels after treatment between the two groups (t=7.240, P<0.001).

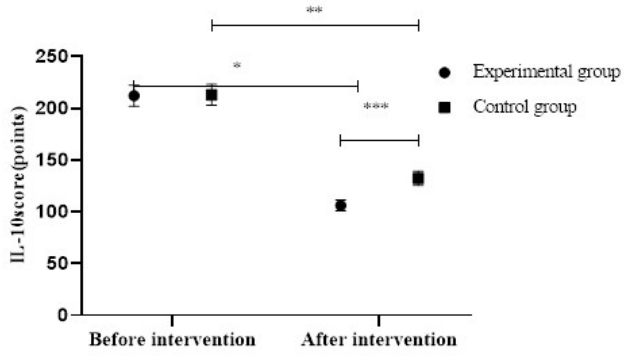
Fig. 3:**Comparison of Lac levels between the two groups before and after treatment**

The experimental group was treated with norepinephrine combined with ulinastatin. The usage and dosage of norepinephrine were the same as the control group. Ulinastatin (SFDA Approval No. H19990131; Manufacturer: Changzhou Tianpu Pharmaceutical Co., Ltd.; Specification: 100,000 IU/branch) was given by intravenous injection. Under the guidance of the doctor, 500,000 IU ulinastatin was diluted into 10,000IU/mL with normal saline, and then 20,000 IU/h intravenous pumps were used. Patients received continuous treatment for 7 days (Bredhold *et al*., 2020; Hamzaoui *et al*., 2018).



Note: PCT levels in the experimental group before and after treatment were (65.24±5.32) ng.mL^{-1}, (8.12±2.07) ng.mL^{-1};
The PCT levels in the control group before and after treatment were (65.72±5.43) ng.mL^{-1}, (12.34±3.26) ng.mL^{-1};
*Indicates a difference of PCT level in the experimental group before and after treatment (t=70.754, P<0.001);
**Indicates a difference in PCT levels in the control group before and after treatment (t=59.597, P<0.001);
***Indicates a difference in PCT levels between the two groups after treatment (t=7.727, P < 0.001).

Fig. 4: **Comparison of PCT levels between the two groups before and after treatment**



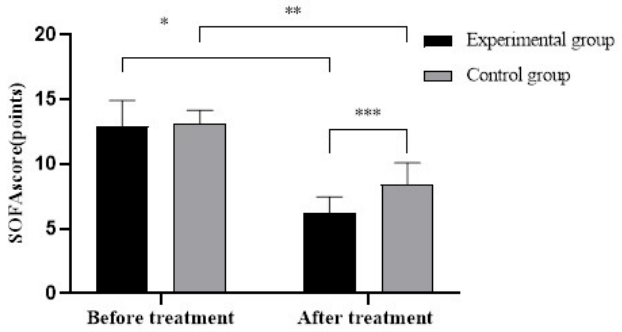
Note: The levels of IL-10 in the experimental group before and after treatment were (212.25±10.24) μg.L^{-1} and (106.24±5.23) μg.L^{-1}, respectively.
The levels of IL-10 in the control group before and after treatment were (213.12±10.02) μg.L^{-1} and (132.33±6.87) μg.L^{-1}, respectively.
*Indicates the difference of IL-10 level in the experimental group before and after treatment (t=65.193, P<0.001);
**Indicates a difference in IL-10 levels in the control group before and after treatment (t=47.022, P<0.001);
***Indicates a difference in IL-10 levels after treatment between the two groups (t=21.367, P<0.001).

Fig. 5: **Comparison of IL-10 levels between the two groups before and after treatment**

Efficacy evaluation

Comparison of the treatment effects between the two groups

According to the criteria of Clinical Efficacy Evaluation (Hammond *et al*., 2018), it is generally divided into groups of cured, markedly effective, improved and ineffective. The two groups of cured and markedly effective would be counted as effective treatment. In addition, for cases whose curative effect could be not obtained from the above criteria, their conditions were reported for further evaluation of the efficacy.



Note: The abscissa indicated before and after treatment and the ordinate indicated SOFA score.
The SOFA scores of the experimental group before and after treatment were (12.93±1.97) and (6.24±1.23), respectively.
The SOF scores of the control group before and after treatment were (13.12±1.02) and (8.42±1.67), respectively.
*Indicates a difference in SOFA score between the experimental group and the control group before and after treatment (t=20.369, P<0.001);
**Indicates a difference in SOFA scores in the control group before and after treatment (t=16.983, P<0.001);
***Indicates a difference in SOFA scores between the two groups after treatment (t=7.432, P<0.001).

Fig. 6: **Comparison of SOFA scores before and after treatment between the two groups**

Comparison of the time for shock amelioration, ICU stay and total hospital stay

The two groups were compared in the time for shock amelioration, ICU stays and total hospitalization according to the treatment situation of patients.

Comparison of the in-hospital mortality and 30-day survival rates of the two groups

The mortality rate and the 30d survival were compared between the two groups.

Table 1: Comparison of general information between the two groups

Item	Number of cases	Experimental group	Control group	t/χ^2	p
Age (years)	50			0.360	0.548
<55		26	23		
≥ 55		24	27		
Average age		41.36±5.24	42.03±4.86	0.663	0.509
Gender	50			0.191	0.663
Male		36	34		
Female		14	16		
Education	50				
Primary school		8	10	0.271	0.603
Junior school		12	10	0.233	0.629
Senior high school		16	17	0.045	0.832
Undergraduate		14	13	0.051	0.822
Place of residence	50			0.040	0.841
Rural		26	27		
Urban		24	23		
Anamnesis	50			0.042	0.838
Hypertension		30	31		
Chronic renal failure		20	19		

Table 2: Comparison of treatment effects between the two groups [N (%)]

Group	Number of cases	Cured	Markedly effective	Improved	Invalid	Total effective rate
Experimental group	50	12	18	19	1	98%(49/50)
Control group	50	3	8	27	12	76%(38/50)
χ^2						10.699
p						0.001

Comparison of the expression changes in inflammatory factors before and after treatment

The levels of plasma C-reactive protein (CRP), lactic acid (Lac), procalcitonin (PCT) and interleukin (IL-10) of the two groups were determined at randomization and after treatment to compare the expression changes in inflammatory factors.

Comparison of the Sequential Organ Failure Assessment (SOFA) scores of the two groups before and after treatment

According to the scoring model proposed by Marshall in 1995, the multiple organ dysfunction scores were used to evaluate the organ failure in both groups before and after treatment.

STATISTICAL ANALYSIS

SPSS version 21.0 software was used for statistical analysis. The count was expressed as the percentage [N (%)], and examined by the X^2 test. The measurement data were expressed as mean number ± standard deviation (x±s), and tested by student t-test. When $P<0.05$, the difference was considered statistically significant.

RESULTS

Comparison of general information between two groups

There was no significant difference in general information such as age, gender, education level, and previous medical records between the two groups ($P>0.05$) (table 1).

Comparison of the treatment efficacy between the two groups

The total efficacy in the experimental group was higher than that in the control group ($P<0.05$) (table 2).

Comparison of in-hospital mortality and 30d survival between the two groups

The experimental group saw lower in-hospital mortality rates and higher 30d survival than the control group ($P<0.05$) (fig. 1).

Comparison of CRP levels between the two groups before and after treatment

After treatment, the experimental group saw lower CRP levels than the control group ($P<0.05$) (fig. 2).

Comparison of Lac levels between the two groups before and after treatment

After treatment, the level of Lac in the experimental

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Control group	50	3	8	27	12	76%(38/50)
χ^2						10.699
p						0.001

group was lower than that in the control group (P<0.05) (fig. 3).

Comparison of PCT levels between the two groups before and after treatment

The PCT level in the experimental group after treatment was lower than that in the control group (P<0.05) (fig. 4).

Comparison of IL-10 levels between the two groups before and after treatment

IL-10 level in the experimental group was lower than that in the control group after treatment (P<0.05) (fig. 5).

Comparison of SOFA scores before and after treatment between the two groups

After treatment, the SOFA scores of the experimental group were higher compared with the control group (P< 0.05) (fig. 6).

DISCUSSION

Septic shock is one of the most serious diseases in sepsis, with high mortality, which occurs when pathogenic microorganisms invade the blood system and damage the cells and humoral immune system in the body, thus leading to an inflammatory syndrome in the patients. It damages body organs and poses a serious threat to the life of patients (Hammond *et al*., 2019a; Wu *et al*., 2020). Notwithstanding the progress in anti-infection, improvement of organ function and the application of advanced medical technology for treatment, the mortality of sepsis still exceeds 30%, which poses a huge threat to the physical and mental health of patients (Kang *et al*., 2020; Morelli *et al*., 2019).

In recent years, further clinical research on the pathophysiological mechanisms of sepsis has been conducted. A prior study has found an intensive impact of the body's immune response on septic shock. When the inflammatory factors destroy the invading pathogenic microorganisms, the reaction will damage the immune tissue cells and lead to organ failure, metabolic disorders, and severe dysfunction (Hammond *et al*., 2019c). To date, the key to the treatment of septic shock is anti-inflammation and inhibition of immune system response. Norepinephrine, a neurotransmitter, is mainly synthesized and secreted by sympathetic postganglionic neurons and noradrenergic neurons in the brain. As an anti-shock vasoactive drug, norepinephrine has anti-inflammatory and anti-shock effects. Studies have pointed out that the monotherapy of norepinephrine fails to achieve expected effects and meet the treatment needs (Haiduc *et al*., 2021; Hammond *et al*., 2019b). Ulinastatin, a glycoprotein extracted from fresh human urine, can inhibit the activity

of multiple proteolytic enzymes. It is a protease inhibitor with an inhibitory effect on the release of lysosomal enzymes and myocardial inhibitory factors, which restrain inflammatory factors and regulate the acid-base imbalance of the body. The results of the present study confirmed that the experimental group had a higher total effective rate than the control group (P<0.05), indicating a better effect of the combination treatment. The experimental group showed a lower in-hospital mortality rate than the control group, and a higher 30d survival than the control group (P<0.05), which is consistent with the research results of Musallam *et al*. (Musallam *et al*., 2018). It pointed out that "more patients in NE-DC group 1 were found in SICU (42.9% vs 20.0%; P=0.048)", indicating that norepinephrine combined with ulinastatin in the treatment is associated with anti-inflammation, inhibition of inflammatory response, and anti-shock, and also reduces the mortality in hospitalization, which is of great significance to prolong the life span of patients. The results of this study confirmed that the levels of CRP, Lac, PCT, and IL-10 in the experimental group after treatment were lower than those in the control group (P<0.05), suggesting that the combined medication can effectively drive down the levels of inflammatory factors and facilitate body recovery. The SOFA score of the experimental group was higher than that of the control group (P<0.05). The organ damage was reduced after the treatment, which plays a vital role in accelerating the rehabilitation of the patient.

CONCLUSION

In summary, norepinephrine combined with ulinastatin achieved remarkable results in the treatment of septic shock, improving the treatment efficiency, shortening the time for shock improvement and hospitalization, reducing hospital mortality, driving down the expression of inflammatory factors, and enhancing the survival of patients, with a high safety profile.

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