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Review Article

Ulinastatin combined with dexamethasone can alleviate the conditions of septic patients and reduce inflammatory factor levels

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Abstract: Objective: This study aims to investigate the application and efficacy of ulinastatin combined with dexamethasone in sepsis. Methods: 110 patients with sepsis in Zhuji People's Hospital from April 2017 to July 2018 were enrolled. Among them, Group A included 50 patients who received dexamethasone monotherapy, and Group B included 50 patients who received ulinastatin combined with dexamethasone. The related scores, adverse reactions, and treatment efficacy of the two groups were observed. In addition, ELISA was employed to measure the serum inflammatory factors and related indicators. Results: After the treatment, the related scores of group B decreased vs group A, as did the inflammatory factors and indexes. Group B presented a decreased total adverse reaction rate and an elevated total effective rate compared with group A. Conclusion: Ulinastatin combined with dexamethasone is effective in sepsis.

Keywords: Ulinastatin, dexamethasone, sepsis, inflammatory factors

Introduction

Sepsis is caused by the host's dysfunctional response to infection, thereby leading to organ dysfunction [1]. Even after treatment, patients still have a persistent risk of death and functional defects [2]. There are reports showing that sepsis can stubbornly resist all the new and improved treatments that are successfully developed and deployed from painstaking efforts [3].

Dexamethasone is a glucocorticoid, an important therapeutic tool for the treatment of inflammatory and immunosuppressive diseases [4]. In addition, dexamethasone has been shown to inhibit the synthesis of inducible nitric oxide synthase in the protection of sepsis [5]. Research has shown that a certain dose of dexamethasone can improve the survival rate of patients with sepsis, and autophagy plays a regulatory role in brain function in sepsis-related encephalopathy [6]. Moreover, dexamethasone has certain proven benefits and no harmful effects in invasive meningococcal diseases as adjuvant therapy [7]. Ulinastatin is a urinary trypsin inhibitor [8]. It is formed by the hydrolysis of neutrophil elastase at the site of the inflammation. It is also believed that ulinastatin has the ability to control a range of pro-inflammatory mediators and cytokines [9]. Randomized controlled clinical studies have further demonstrated that ulinastatin can significantly improve organ failure and reduce mortality in patients with sepsis [10]. There is also evidence indicating that in animal models of sepsis, ulinastatin can reduce systemic and regional inflammatory responses, inhibit lymphocyte apoptosis, increase the production of anti-inflammatory cytokines, and improve survival [11].

In this study, ulinastatin combined with dexamethasone was used in the treatment of sepsis, and the combination had a significant effect on inhibiting the inflammatory response.

Materials and methods

Patients with sepsis

110 patients with sepsis in Zhuji People's Hospital from April 2017 to July 2018 were

recruited for this study, among which 50 patients (28 males and 22 females) were divided into group A and treated with dexamethasone. The other 60 patients (35 males and 25 females) were included in group B and treated with ulinastatin combined with dexamethasone.

Exclusion and inclusion criteria

The patients included in the study were diagnosed with sepsis through a blood test [12]. Also, the included patients and their families were informed about the study and written informed consents were obtained. This study was approved by the Medical Ethics Committee of Zhuji people's Hospital.

Patients were excluded if they had mental disorders, malignant tumors, severe functional insufficiency, if they were allergic to the medication used in this study, or if they were minors or over the age of 50.

Methods

The patients in Group A were treated with dexamethasone: 5 mg of dexamethasone given by injection (Hubei Tianyao Pharmaceutical Co., Ltd. of Tianjin King York Group, State Drug Approval No.: H42020019) The drug was injected into 100 ml of 5% glucose injection, and the patients were injected intravenously twice a day. The patients in Group B were treated with the combination therapy: on the basis of group A, 50,000 units of intravenous ulinastatin (Guangdong Techpool Biochemical Pharmaceutical Co., Ltd., State Drug Approval No.: H20040505) were injected into 100 ml of 5% glucose injection, and the patients were injected intravenously twice a day. The treatment was continued for 6 days. Mechanical ventilation was applied throughout the procedure.

Outcome measures

The Acute Physiology and Chronic Health Evaluation (APACHE) II score [13], the Sepsis Related Organ Failure Assessment (SOFA) score, [14] and the general clinical efficacy of the two groups were observed and compared.

After extracting 5 ml fasting blood from the patients before and after the treatment, the serum concentrations of TNF-α (tumor necrosis factor), IL-6 (interleukin 6), IL-10 (interleukin 10), Cr (creatinine), BUN (urea nitrogen), and CK (creatine kinase) were quantified using ELISA.

The treatment efficacy of the two groups after the treatment was observed and compared. According to the definition of severe sepsis [15], effective was defined as a marked improvement of the main clinical symptoms and conditions, and an APACHE II score of ≤20 points. Ineffective was defined as an insignificant melioration of the clinical manifestations, disease deterioration, and an APACHE II score of > 20 points.

Statistical analysis

The statistical analysis was performed using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). The measurement data were expressed as (x±sd), and t tests were employed for the inter-group comparisons. The count data were represented as [n (%)], and the data in the two groups were compared using chi-square tests. A difference was considered significant when $P < 0.05$.

Results

General patient information in the two groups

There were no significant differences in the general patient information in group A and group B (**Table 1**).

Difference of scores and general efficacy between two groups

The APACHE II scores in group A and group B were (23.13±8.32) points and (24.34±9.11) points respectively before the treatment, and the corresponding APACHE II scores after the treatment were (16.43±5.23) points and (11.48±2.43) points. Before the treatment, the SOFA scores in group A and group B were (13.46±4.28) points and (14.23±3.98) points respectively; However the SOFA scores after the treatment were (6.78±2.45) points and (4.28±1.33) points respectively. From the above data, it was clear that after the treatment, both the APACHE II and SOFA scores of group B were decreased when compared to group A. The urine volumes in group A and group B were (24.43±5.23) ml/h and (25.23±5.21) ml/h before the treatment respectively, and the urine volume after the treatment was

Table 1. General information (x±sd) [n (%)]

Categories	Group A (n=50)	Group B (n=60)	t/χ^2 value	*P* value
Gender			0.060	0.805
Male	28 (56.00)	35 (58.33)		
Female	22 (44.00)	25 (41.67)		
Age (years)	29.58±9.32	30.37±8.24	0.472	0.637
Weight (kg)	52.68±5.20	53.13±5.34	0.445	0.657
Course of disease (days)	7.23±2.58	8.13±2.43	1.881	0.062
Residence			0.586	0.443
Rural	23 (46.00)	32 (53.33)		
Urban	27 (54.00)	28 (46.67)		
Education			0.085	0.769
Below high school	18 (36.00)	20 (33.33)		
Above high school	32 (64.00)	40 (66.67)		
Ethnicity			1.538	0.214
Han	43 (86.00)	46 (76.67)		
Ethnic minorities	7 (14.00)	14 (23.33)		
Economic level			0.149	0.698
Poor	6 (12.00)	13 (21.67)		
Comparatively well-off	34 (68.00)	32 (53.33)		
Well-off	10 (20.00)	15 (25.00)		
Drinking history			0.262	0.608
Yes	34 (68.00)	38 (63.33)		
No	16 (32.00)	22 (36.67)		
Smoking history			0.078	0.779
Yes	27 (54.00)	34 (56.67)		
No	23 (46.00)	26 (43.33)		
Obesity			0.152	0.695
Yes	19 (38.00)	25 (41.67)		
No	31 (62.00)	35 (58.33)		
Infection site			0.208	0.901
Abdominal infection	14 (28.00)	19 (31.67)		
Intestinal infection	27 (54.00)	30 (50.00)		
Other infections	9 (18.00)	11 (18.33)		
Body temperature			0.078	0.779
Fever (> 38.3°C)	22 (44.00)	28 (46.67)		
Low temperature (< 36°C)	28 (56.00)	32 (53.33)		
Leukocyte change			0.001	0.972
Increased (> 12000 μL)	26 (52.00)	31 (51.67)		
Decrease (< 4000 μL)	24 (48.00)	29 (48.33)		
SOFA score			0.679	0.409
2-3 points	33 (66.00)	35 (58.33)		
3-4 points	17 (34.00)	25 (41.67)		

(82.23±14.45) ml/h and (132.82±17.13) ml/h, respectively, which indicated that the urine volume of group B after the treatment increased more than it did in group A (**Figure 1**). The mechanical ventilation time, the ICU occupancy time, and the antibiotic use time of group A were (14.54±3.49) d, (16.26±4.13) d, and (15.23±2.11) d, respectively, while the corresponding times in group B were (11.25±2.43) d, (12.59±3.35) d, and (12.48±2.45) d. The general efficacy in group B was statistically better than it was in group A (**Figure 2**).

Changes in the inflammatory factors in two groups

The serum TNF-α levels in group A and group B were (67.43±7.14) μg/L and (68.13±7.32) μg/L before the treatment respectively, but after the treatment, the levels dropped to (36.52±6.46) μg/L and (27.43±4.24) μg/L respectively. The serum IL-6 levels in group A and group B were (205.13±10.42) μg/L and (206.24±10.25) μg/L before the treatment respectively, but they decreased to (158.27±8.20) μg/L and (121.35±7.13) μg/L respectively after the treatment. The serum IL-10 levels in group A and group B were (39.52±12.43) μg/L and (40.11±12.33) μg/L respectively, but the serum IL-10 levels after the treatment were (23.46±10.65) $\mu g \cdot L^{-1}$ and (15.43±9.22) $\mu g \cdot L^{-1}$. The above results revealed that the serum levels of the inflammatory factors in group B were statistically decreased compared to group A after the treatment (**Figure 3**).

Changes in the indicators in the two groups

The serum Cr contents in group A and group B were (126.39±18.22) μmol/L and (127.13±18.26) μmol/L respectively, and the serum Cr

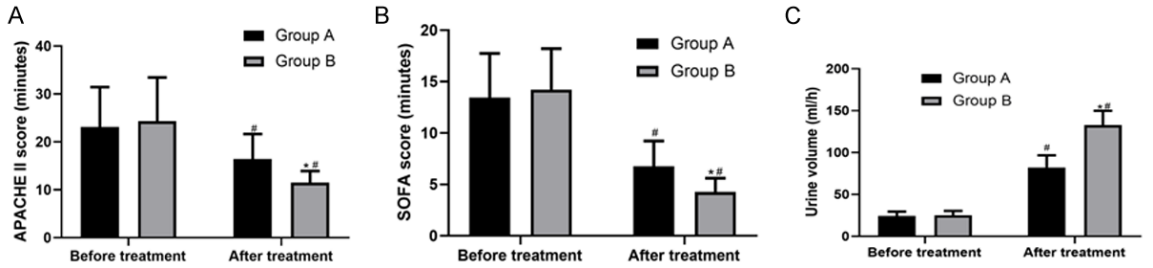

Figure 1. A. The APACHE II scores before and after treatment: No significant differences were observed in the APACHE II scores in the two groups before the treatment ($P > 0.05$), but after the treatment, the APACHE II scores decreased significantly, with those in group B being significantly lower than Group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before the treatment. B. The SOFA scores before and after treatment: Before the treatment, there were no significant differences in the SOFA scores in the two groups ($P > 0.05$). But after the treatment, the SOFA scores dropped notably, with those in group B being significantly lower than group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before treatment. C. Comparison of the urine volumes before and after treatment: There were no significant differences in the urine volume between the two groups before the treatment ($P > 0.05$). However, the urine volume after the treatment increased significantly, and the urine volume of group B was significantly higher than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before treatment.

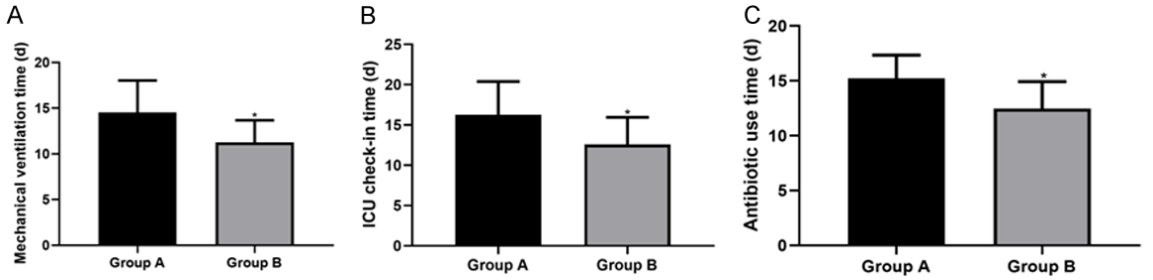

Figure 2. A. Comparison of the mechanical ventilation times in the two groups: The mechanical ventilation time in group B was significantly lower than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A. B. Comparison of the ICU stay durations in the two groups: The ICU occupancy time of group B was significantly lower than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A. C. Comparison of the antibiotic use time in the two groups: The antibiotic use time of group B was significantly less than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A.

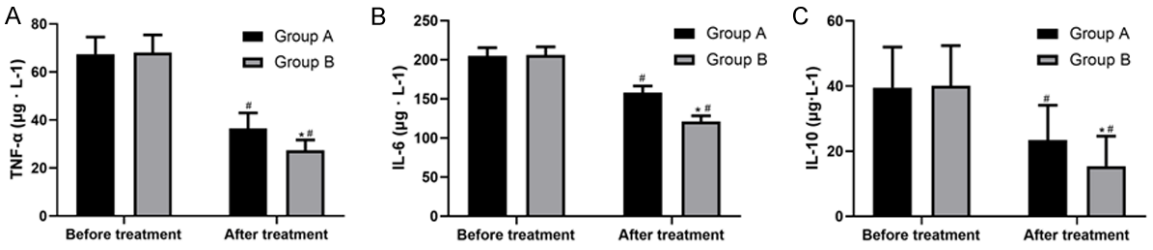

Figure 3. A. The TNF-α levels before and after treatment: There were no significant differences in the serum TNF-α levels in the two groups ($P > 0.05$), but they decreased significantly after treatment, and the level in group B was significantly lower than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before treatment. B. IL-6 levels before and after treatment: No significant differences were found in the serum IL-6 levels in the two groups ($P > 0.05$), but they were reduced significantly after the treatment, and the level in group B was significantly lower than the level in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before the treatment. C. The IL-10 levels before and after treatment in both groups: The serum IL-10 levels did not indicate any significant differences between the two groups ($P > 0.05$), but they dropped significantly after the treatment, and the IL-10 level in group B was markedly lower than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before treatment.

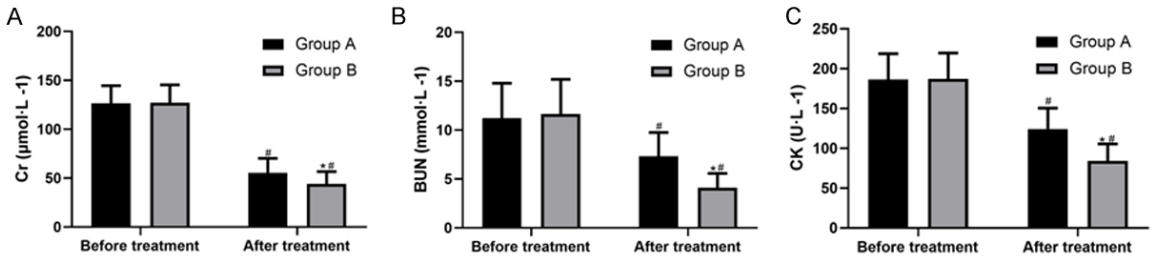

Figure 4. A. The Cr content before and after treatment in the two groups: There were no significant differences in the serum Cr content before the treatment in the two groups ($P > 0.05$), but it dropped significantly after the treatment, and the content in group B was significantly lower than it was in group A ($P < 0.05$). Note: *represents a comparison with group A, and #represents a comparison with the same group before the treatment. B. The BUN content before and after treatment: No significant differences were found in the serum BUN content in the two groups before the treatment ($P > 0.05$), but it declined remarkably after the treatment, and its content in group B was significantly lower than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before treatment. C. The CK content before and after treatment: Before the treatment, there were no significant differences in the serum CK content in the two groups ($P > 0.05$), but it decreased significantly after the treatment, and its content in group B was significantly lower than it was in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before the treatment.

contents after the treatment were (55.60±14.65) μmol/L and (44.19±12.53) μmol/L respectively. The serum BUN contents in group A and group B were (11.23±3.56) mmol/L and (11.65±3.54) mmol/L before the treatment respectively, but they decreased to (7.33±2.43) mmol/L and (4.13±1.45) mmol/L after the treatment. Before the treatment, the corresponding serum CK content levels in group A and group B were (186.28±32.48) $U{\cdot}L^{-1}$ and (187.12±32.47) $U{\cdot}L^{-1}$, respectively, but after the treatment, they reduced to (124.21±26.31) $U{\cdot}L^{-1}$ and (84.29±21.23) $U{\cdot}L^{-1}$, respectively. After the treatment, the content of the serum indicators in group B statistically decreased compared to group A (**Figure 4**).

Changes in blood pressure and heart rate in two groups

The heart rates of group A and group B before the treatment were (134.57±17.87) beats/min and (135.42±17.57) beats/min, respectively, but the rates of group A and B were (103.49±10.45) beats/min and (86.50±11.38) beats/min after the treatment respectively. After the treatment, the heart rate of group B was slower than that of group A. The systolic blood pressure levels of group A and group B were (72.13±2.13) mmHg and (72.24±2.14) mmHg before the treatment respectively. However, the systolic blood pressure after the treatment were (80.32±3.34) mmHg and (88.32±3.23) mmHg, respectively in groups A and B. The systolic blood pressure of group B was statistically increased compared to group A after the treatment. The diastolic blood pressure levels of group A and group B were (51.48±2.24) mmHg and (51.32±2.42) mmHg before the treatment, respectively, and the diastolic blood pressure levels after the treatment were (56.11±3.74) mmHg and (62.43±3.34) mmHg, respectively. After the treatment, the diastolic blood pressure of group B was higher than it was in group A (**Figure 5**).

Adverse reactions in the two groups

The total incidence of adverse reactions of group B (10%) decreased compared to the total incidence of adverse reactions in group A (32%) (**Table 2**).

Treatment efficacy of the patients in two groups

Group A had a total effective rate of 66%, and group B's total effective rate was 86.67%. It was apparent that the total effective rate of group B increased compared to group A (**Table 3**).

Discussion

Sepsis is a systemic inflammatory response to infection [16], and endothelial injury in sepsis may be caused by persistent and recurrent inflammatory injuries [17]. Sepsis is generally believed to be exacerbated by an inappropriate immune response, sporadically leading to multiple organ failure and shock [18]. TNF-α is a

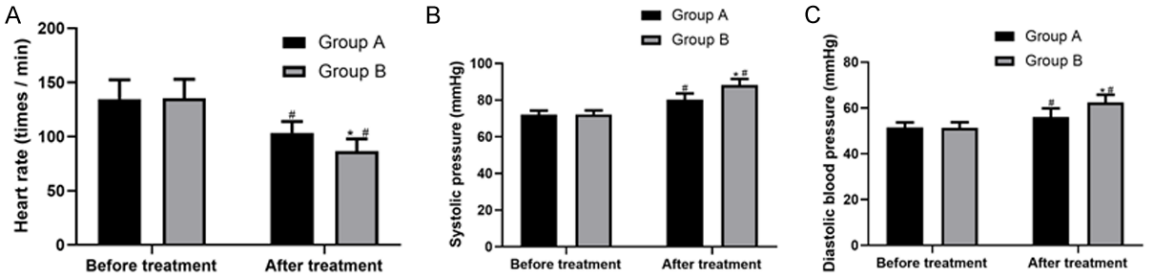

Figure 5. A. Changes in the heart rates before and after treatment: There were no significant differences in the heart rates in the two groups before the treatment ($P > 0.05$), but they decreased significantly after the treatment, with the rates in group B being significantly slower than they were in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before the treatment. B. Changes in the systolic blood pressure before and after treatment: Before the treatment, there were no significant differences in the systolic blood pressure levels in the two groups ($P > 0.05$), but after the treatment, the systolic blood pressure levels in both groups increased significantly, and the systolic blood pressure in group B was significantly higher than it was in group A ($P < 0.05$); Note: *indicates a comparison with group A, and #indicates a comparison with the same group before treatment. C. Changes in the diastolic blood pressure levels before and after treatment: There were no significant differences in the diastolic blood pressure levels in the two groups before the treatment ($P > 0.05$). However, the diastolic blood pressure levels in both groups increased significantly after the treatment, and the diastolic blood pressure levels in group B were significantly higher than they were in group A ($P < 0.05$). Note: *indicates a comparison with group A, and #indicates a comparison with the same group before treatment.

Table 2. Adverse reactions in the two groups [n (%)]

Total adverse reaction rate	Group A (n=50)	Group B (n=60)	X^2	P
Hemorrhage	2 (4.00)	1 (1.67)	-	-
Fever	1 (2.00)	2 (3.33)	-	-
Abdominal discomfort	3 (6.00)	1 (1.67)	-	-
Convulsions	1 (2.00)	0 (0.00)	-	-
Diarrhea	2 (4.00)	1 (1.67)	-	-
Nausea	3 (6.00)	1 (1.67)	-	-
Muscle weakness	4 (8.00)	0 (0.00)	-	-
Total incidence rate	16 (32.00)	6 (10.00)	8.250	0.004

Table 3. Treatment effect of the patients in the two groups [n (%)]

Efficacy	Group A (n=50)	Group B (n=60)	X^2	P
Effective	33 (66.00)	52 (86.67)	-	-
Ineffective	17 (34.00)	8 (13.33)	-	-
Total effective rate	33 (66.00)	52 (86.67)	6.633	0.010

cytokine produced by a variety of cell types. Among cytokines implicated in sepsis, TNF-α is secreted immediately after infection and triggers the pathological process of septic shock [19]. IL-6 is a potent inflammatory mediator with a high sensitivity and specificity for the identification of sepsis [20]. Some studies have shown that the rapid decline of IL-6 concentration to or below the baseline value after 48 hours is evidence of successful empirical antibiotic treatment and is a predictor of survival [21]. As to IL-10, it is an anti-inflammatory cytokine [22] and a key component of the immune system that regulates and inhibits the expression of pro-inflammatory cytokines during the recovery phase of infection, thereby mitigating the damage caused by inflammatory cytokines. On the other hand, its excessive elevation may lead to kidney failure [23]. In this study, the serum levels of inflammatory cytokines in the patients who supplemented with ulinastatin were significantly lower than they were in the patients without ulinastatin administration. This may be due to the fact that ulinastatin inhibits the release of ZTE granulocytic protease, reduces the release of oxygen free radicals and the consumption of superoxide dismutase, thus reducing an excessive inflammatory response [24]. Serum Cr is commonly used to monitor renal insufficiency [25]. When sepsis is accompanied by renal injury, the risk of death is significantly increased, and the poor prognosis is often closely related to a small increase in serum Cr [26]. CK is a dimeric globular protein that is an indicator of muscle necrosis, and its concentration rises with an increasing degree of necrosis [27]. Some studies have also sug-

gested that a disorder of the CK system may be closely related to muscle, brain, heart, and kidney diseases [28]. Thus, the determination of serum BUN is also of great value in the clinical determination of renal function [29]. Cr, CK, and BUN can be used to detect any damage to relevant tissues and organs. In this study, the Cr, CK, and BUN levels were higher in the serum of patients with sepsis, but after the treatment, their levels dropped significantly in both groups, and their serum expression levels in the patients with ulinastatin were significantly lower than in those without. This may indicate that ulinastatin also has an effect on the damage of tissues and organs. Studies have found that the mechanism involved in the protection of ulinastatin on tissues and organs and endothelial cells depends on the inhibition of polymorphonuclear leukocyte-derived elastase, as well as the activation of macrophages and platelets [30].

In this study, we also observed some relevant scores, general clinical efficacy, adverse reactions and efficacy before and after the treatment in both groups. The results showed that the score and efficacy in group B were better than they were in group A, with fewer adverse reactions. All these results indicated that ulinastatin combined with dexamethasone has a good therapeutic effect on sepsis. In conclusion, ulinastatin combined with dexamethasone has a good therapeutic effect on sepsis and significantly reduces the inflammatory factor levels.

Disclosure of conflict of interest

None.

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