

# Effect and analysis of ulinastatin combined with thymosin on cardiopulmonary function and delirium in sepsis patients

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**Abstract:** The aim of this study was to explore the clinical effect of ulinastatin combined with thymosin in patients with sepsis and its influence on cardiopulmonary function and delirium. Sixty-eight sepsis patients were enrolled as study subjects. The patients were randomly divided into a symptomatic treatment group (n=34) and a combined treatment group (n=34) on the basis of random number table. The two groups were first operated and then, the symptomatic treatment group was given symptomatic support treatment, whilst the combined treatment group was treated with ulinastatin and thymosin on the prerequisite of the symptomatic treatment group. After 7 days of treatment, the evaluation of the curative effect was performed, followed by the comparison of the cardiopulmonary function, immune level and safety between the two groups of patients. The cardiac index and oxygenation index of the combined treatment group were higher than those of the symptomatic treatment group 7 days after treatment ( $P<0.05$ ). Whereas, the levels of plasma D-dimer and cTnI were lower than those of the symptomatic treatment group ( $P<0.05$ ). In addition, CD3+, CD4+, CD4+/CD8+ levels of the combined treatment group were higher than those of the symptomatic treatment group 7 days after treatment ( $P<0.05$ ). On the contrary, CD8+ levels of the combined treatment group were lower than those of the symptomatic treatment group 7 days after treatment. There was no significant ( $P>0.05$ ) difference in drug safety between the two groups during treatment.

**Keywords:** Ulinastatin, thymosin, symptomatic support, sepsis, delirium.

## INTRODUCTION

Sepsis is a systemic inflammatory response syndrome caused by infection, and most patients have bacterial or highly suspicious infection foci (Bermejo-Martin *et al.*, 2018). Sepsis is clinically divided into sepsis, severe sepsis and septic shock according to the severity of sepsis, which often occurs in patients with severe burns, multiple injuries, and surgery. The accompanying clinical manifestations are fever, shortness of breath, increased peripheral blood leukocytes and so on, which affects the health and life of patients (Coopersmith and Deutschman, 2016). Delirium has been reported to occur in up to 30-80% of ICU patients. The incidence and duration of delirium have been associated with prolonged hospitalization and increased mortality and morbidity (Zhou *et al.* 2011; Han *et al.*, 2012; Maemondo *et al.*, 2010) and been indicated as a risk factor for the development of later cognitive problems weeks to months after the ICU stay.

Sepsis occurs in one third of ICU patients, and mortality in patients with septic shock is high. Besides carrying a high mortality rate, sepsis is associated with a significant burden of morbidities, such as multiple organ failure (Emily *et al.*, 2018). Ulinastatin belongs to the class of urinary trypsin inhibitors, which can improve local microcirculation and tissue perfusion, scavenge oxygen free radicals in the body, and help to inhibit the release of

inflammatory mediators (Demerle *et al.*, 2017). Thymosin is a polypeptide substance secreted by thymus tissue, which plays an immunomodulatory role, helps promote the generation of cytokines and accomplishes the immune response of B cells (Govindan and Iwashyna, 2016; Keeley *et al.*, 2017). Therefore, a randomized controlled trial was applied in this study to investigate the clinical effects of ulinastatin combined with thymosin in patients with sepsis and its effect on cardiopulmonary function and delirium.

## MATERIALS AND METHODS

### *Clinical data*

Sixty-eight sepsis patients treated from June 2016 to February 2018 were enrolled as subjects. The patients were randomly divided into the symptomatic treatment group (n=34) and the combined treatment group (n=34).

### *Inclusion criteria*

- 1) Patients who confirmed to the diagnostic criteria of sepsis in the New Understanding of Definition and Diagnosis of Sepsis (Moorman *et al.*, 2016).
- 2) Patients who were in accordance with the indications of ulinastatin combined with thymosin.
- 3) All patients who underwent examination and treatment under the doctor's advice.

### *Exclusion criteria*

- 1) Patients who were complicated with primary heart, liver, kidney and malignant tumors.

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- 2) Patients who were complicated with gastrointestinal failure or indwelling gastric tube failure.
- 3) Patients with mental disorders, autoimmune diseases, or coagulopathy.

#### **Ethical approval**

This study was approved from the institutional ethical review board. All the experiments were conducted as per Helsinki's declaration for human volunteers. All subjects gave informed, signed consent to participate in the study by themselves

#### **Symptomatic treatment group**

The patients were given symptomatic support treatment. After admission, patients were treated with early anti-infection, nutritional support, mechanical ventilation, fluid resuscitation and blood purification, etc. Patients were given the help of correcting water and electrolyte disturbances and maintaining acid-base balance.

#### **Combined treatment group**

The patients were given ulinastatin combined with thymosin treatment on the basis of the symptomatic treatment group. Ulinastatin was taken from "Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., Chinese Pharmaceutical Standard Word: H19990132" 200,000 IU/time, 2 times a day for 1 week (1 course). Each time, 1.6 mg of thymosin (Inner Mongolia Baiyi Pharmaceutical Co., Ltd., Chinese Pharmaceutical Standard Word: H20023389) was injected subcutaneously twice a day for 7 days (1 course), and the therapeutic effect of the patient was evaluated after 7 days of treatment.

#### **Observational index**

##### *Cardio-pulmonary function*

The venous blood and arterial blood were taken 5mL in the fasting state before treatment and 7 days after treatment, centrifuged for 15 min under the centrifugal force of 1251g. After serum separation, the levels of cTnI and plasma D-dimer were measured by automatic biochemical analyzer. The blood oxygen was measured by arterial blood to complete the oxygenation index. Then the cardiac index of the two groups before treatment and 7 days after treatment was recorded and counted (Prescott *et al.*, 2018; Rhodes *et al.*, 2017).

##### *Immune level*

After serum separation, the levels of CD3+, CD4+, CD8+, CD4+/CD8+ were determined by flow cytometry (Wan *et al.*, 2016).

##### *Safety*

The incidence of constipation, rash, abnormal liver and kidney function, fluctuation of blood pressure and drug allergy were recorded.

## **STATISTICAL ANALYSIS**

The data were processed by SPSS 18.0 software, and the count data was analyzed by  $\chi^2$  test, represented by n (%). The detection of measurement data was performed by t test, expressed as ( $\bar{x} \pm s$ ). 5% p values were considered as statistically significant.

## **RESULTS**

### **Comparison of cardiopulmonary function**

There was no significant difference in cardiopulmonary function between the two groups before treatment ( $P>0.05$ ). The cardiac index and oxygenation index of the combined treatment group were higher ( $P<0.05$ ) than the symptomatic treatment group 7 days after treatment. Whereas, the levels of plasma D-dimer and cTnI were lower than those of the symptomatic treatment group ( $P<0.05$ ) as depicted in table 1.

### **Comparison of immune function between two groups**

There was no significant difference in lymphocyte subsets between the two groups before treatment ( $P>0.05$ ). In addition, CD3+, CD4+, CD4+/CD8+ levels of the combined treatment group were higher than those of the symptomatic treatment group 7 days after treatment ( $P<0.05$ ). On the contrary, CD8+ levels of the combined treatment group were lower than those of the symptomatic treatment group 7 days after treatment ( $P<0.05$ ), as demonstrated in table 2.

### **Safety comparison between two groups**

There was no significant difference in the incidence of constipation, rash, abnormal liver and kidney function, fluctuation of blood pressure and drug allergy between the two groups after treatment ( $P>0.05$ ), as shown in table 3.

## **DISCUSSION**

Sepsis usually occurs after surgery, which is often accompanied by oxidative stress, coagulation dysfunction, immune dysfunction and inflammatory reaction (Wang *et al.*, 2016). It has been elucidated in the clinical studies (Wang *et al.*, 2017) that sepsis can engender vascular endothelial damage in the pathogenesis of the disease, leading to changes in blood coagulation and immune function, which is characterized by antagonizing the inflammation and causing the activation of CD4 T lymphocytes, thereby further releasing many anti-inflammatory factors. In recent years, ulinastatin combined with thymosin has been used in patients with sepsis, which has achieved ideal efficacy. The association between sepsis, ICU delirium and prolonged cognitive problems is not fully elucidated, and mechanisms between postulated links are not well understood. In this study, cardiac index and oxygenation index in the combined treatment group were all higher than those in the

**Table 1:** Comparison of Cardiopulmonary Function between the Two Groups ( $\bar{x} \pm s$ )

Groups		Cardiac Index L/ (min.m <sup>2</sup> )	Plasma D-dimer (ug/L)	Oxygenation Index (mmol/L)	cTnI (ug/L)
Combined Treatment	Prior Treatment	3.01±0.46	5.43±0.96	134.52±12.2	5.14±0.63
	7d After Treatment	4.13±0.54	2.10±0.23	215.39±16.8	2.53±0.34
Symptomatic Treatment	Prior Treatment	3.00±0.45	5.42±0.94	135.31±12.2	5.15±0.65
	7d After Treatment	3.21±0.49	4.12±0.46	175.34±14.3	3.98±0.43

Compared with the symptomatic treatment group, <sup>a</sup>P<0.05; compared with before treatment, <sup>b</sup>P<0.05.

**Table 2:** Comparison of Immune Function between Two Groups ( $\bar{x} \pm s$ )

Groups		CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4+/CD8+
Combined Treatment	Prior Treatment	57.46±2.46	27.43±2.14	24.21±2.44	1.58±1.21
	7d After Treatment	69.57±4.89 <sup>ab</sup>	42.37±4.61 <sup>ab</sup>	21.11±2.09 <sup>ab</sup>	2.08±0.17 <sup>ab</sup>
Symptomatic Treatment	Prior Treatment	57.57±2.49	27.44±2.15	23.98±2.38	1.56±1.20
	7d After Treatment	60.46±3.46 <sup>b</sup>	32.43±3.64 <sup>b</sup>	22.42±2.36 <sup>b</sup>	1.86±0.48 <sup>b</sup>

Compared with the symptomatic treatment group, <sup>a</sup>P<0.05; compared with before treatment, <sup>b</sup>P<0.05.

**Table 3:** Comparison of Safety between Two Groups [N (%)] (n=34)

Groups	Constipation	Rash	Abnormal Liver/Kidney Function	Fluctuation of Blood Pressure	Drug Allergy
Combined Treatment	1 (3.94)	0 (0.00)	0 (0.00)	1 (3.94)	1 (3.94)
Symptomatic Treatment	0 (0.00)	1(3.94)	1(3.94)	0 (0.00)	0 (0.00)
X <sup>2</sup>	1.291	0.496	0.325	0.781	0.336
P	0.592	0.438	0.798	0.121	0.447

symptomatic treatment group 7 days after treatment, while the levels of plasma D-dimer and cTnI were lower than those in the symptomatic treatment group, indicating that ulinastatin combined with thymosin can improve cardiopulmonary function of sepsis patients and help them recover. Ulinastatin is a urinary trypsin inhibitor, which possess two active functional regions. Ulinastatin can inhibit the biological activity of hydrolases of proteins and lipids, improves microcirculation and tissue perfusion, thus eliminating the release of oxygen free radicals and inflammatory mediators (Wei *et al.*, 2017). Modern pharmacological results showed that ulinastatin can inhibit the release of inflammatory mediators in patients with sepsis, which can also increase lymphocyte levels, thereby attributing to the improvement of the immune status of patients (Xiao *et al.*, 2018). Thymosin is a physiologically active group of polypeptides secreted by thymus tissue, which can significantly stimulate lymphocyte proliferation, differentiation and maturation, increases antigen-presenting cell activity and exerts immunomodulatory effects (Zaccone *et al.*, 2017). Clinically, the combination of ulinastatin and thymosin in patients with sepsis can exert the advantages of two therapeutic drugs, which can help improve the patient's immune level. We found a significant correlation between the combined utility of the two drugs which helps to strengthen the tolerance and compliance of patients towards therapy. In the present research, CD3+, CD4+, CD4+/CD8+ levels of the combined treatment group were

higher than the symptomatic treatment group after 7 days treatment. Our findings are in agreement to the results of Dadong *et al.*, who concluded that treatment of ulinastatin combined with thymosin (UTI + Tα1) decreased the short-term mortality rate in septic patients, decreased the duration of mechanical ventilation and levels of IL-6 and tumor necrosis factor α (Dadong *et al.*, 2017). However, due to the different causes and severity of each sepsis patient, the utilization of ulinastatin combined with thymosin should strengthen the monitoring of vital signs of patients, and timely adjust the regimen plan according to the patient's recovery, making the treatment of patients more scientific (Zhu *et al.*, 2017).

## CONCLUSION

Treatment of ulinastatin + thymosin can suppress the production of proinflammatory cytokines, decrease the plasma D-dimer and cTnI, improve the immune level, and improve the survival rate.

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