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A retrospective study of ulinastatin for the treatment of severe sepsis

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Abstract

This retrospective study aimed to investigate the efficacy and safety of existing approach of ulinastatin for the treatment of severe sepsis (SS).

A total of 130 eligible patients with SS were included in this study. We divided them into an intervention group (n = 65) and a control group (n = 65). Patients in both groups received conventional therapy. In addition, patients in the intervention group received ulinastatin for 7 days. Outcomes were measured by Acute Physiology and Chronic Health Evaluation II (APACHE II), Multiple Organ Failure (MOF), Glasgow Coma Scale (GCS), $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, and adverse events. We assessed all outcomes before and after treatment.

After treatment, patients in the intervention group showed better improvement in APACHE II ($P < .01$), MOF ($P < .01$), GCS ($P < .01$), $CD3^+$ ($P = .03$), $CD4^+$ ($P = .03$), and $CD4^+/CD8^+$ ($P < .01$), than those of patients in the control group. There are similar safety profiles between both groups.

This study suggests that ulinastatin may be beneficial for SS. Future studies are still needed to warrant the results of this study.

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, GCS = Glasgow Coma Scale, MOF = Multiple Organ Failure, SS = severe sepsis.

Keywords: adverse events, efficacy, severe sepsis, ulinastatin

1. Introduction

Sepsis is a systemic inflammatory response syndrome to infection.[1,2] It is a leading cause of morbidity and mortality in patients with sepsis, particularly in those patients who are elderly and critical ill.[3,4] It manifests as fever, shortness of breath, and increased peripheral blood leukocytes.[5] It is clinically classified as sepsis, severe sepsis (SS), and septic shock in accordance with its severity.[6,7] Of those, SS is often associated with at least 1 organ dysfunction.[8] Its incidence is increasing worldwide annually.[9,10] It has been reported that the incidence rate of SS is about 1/1000 people, and its hospital mortality rate is about 48.7% in China.[11]

Up to present, there is still no ideal approach to prevent and manage SS. Fortunately, ulinastatin, as an urinary trypsin inhibitor, is a very promising candidate to treat patients with SS satisfied.[12–14] It is an important intrinsic broad-spectrum protease inhibitor, and is generally believed to manage a series of proinflammatory mediators and cytokines.[15,16] In addition, it is also reported to have protective effect on many organs against sepsis.[17] Although previous studies have shown a trend towards of decreased mortality and hospital stay in SS,[18,19] there is still insufficient evidence to support ulinastatin for the treatment of SS. Thus, we conduct this retrospective study to assess the efficacy and safety of ulinastatin in patients with SS.

2. Methods

2.1. Design

This retrospective study included 130 eligible patients with SS. We divided them into an intervention group and a control group according to the different treatments they received, 65 patients in each group. Patients in both groups received conventional management. Additionally, patients in the intervention group also underwent ulinastatin for a total of 7 days. All outcome data were collected before and after treatment. This retrospective study did not utilize approach of randomization and blinding to both patients and researchers.

This study was approved by the Medical Ethical Committee of Nanjing First Hospital of Nanjing Medical University. All patient case records were performed from this hospital between January

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2016 and December 2018. All of them were recruited through department of critical care medicine of Nanjing First Hospital of Nanjing Medical University, and they all provided informed written consent.

2.2. Inclusion and exclusion criteria

Patients were included if they were adults (over 18, but less than 70 years old) with confirmed diagnosis of SS according to the Guidelines for the treatment of severe sepsis/septic shock in China,[20] and informed consent were provided. In addition, patients should fulfill any one of the following criteria:[20] hypotension caused by sepsis; level of lactic exceeds its upper limit of the normal level tested in the laboratory; even if sufficient fluid is given for resuscitation, and urine volume is still less than 0.5 ml/kg/hour for at least 2 hours; acute lung injury caused by non-pneumonia and $PaO_2/FiO_2 < 250$ mm Hg; pneumonia caused by acute lung injury and $PaO_2/FiO_2 < 200$ mm Hg; serum creatinine level >176.8 μmol/L (2.0 mg/dl); bilirubin >34.2 μmol/L (2 mg/dl); platelet count $<100 \times 10^9$/L (100, 000 μl); and coagulopathy (INR > 1.5).

Patients were excluded if they were less than 18 years old; pregnant or breastfeeding females; cancers in other organs; and allergic to study medication. In addition, we also excluded patient case records if they had insufficient information.

2.3. Intervention

All patients in both groups underwent conventional therapy during the whole treatment period. It was performed as symptomatic support treatment based on the recommended treatment guideline,[20] such as antibiotics, nutrition support, non-invasive mechanical ventilation, intravenous fluids, blood transfusion and purification, and supportive care.

In addition, patients in the intervention group also received intravenous ulinastatin with dose of 200,000 IU, thrice daily for 3 days. After that, the following dose of 100,000 IU ulinastatin, trice daily for 4 successive days.

2.4. Outcome measurements

The primary outcomes were measured by Acute Physiology and Chronic Health Evaluation II (APACHE II),[21] Multiple Organ Failure (MOF),[22] and Glasgow Coma Scale (GCS).[23] APACHE II score ranges from 0 to 71, with higher score indicating more severe disease.[24] MOF scale involves 6 organ systems, ranging from 0 (normal function) to 4 (most severe dysfunction), with a maximum score of 24.[22] GCS ranges from 3 to 15, with lower score suggesting more severity of the disease.[23] The secondary outcomes were measured by $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, and adverse events. All outcomes were measured before and after treatment.

2.5. Statistical analysis

SPSS software (SPSSV.19.0, IBM Corp., Armonk, NY, USA) was utilized to analyze all baseline and outcome data. As for continuous values, *t* test or Mann–Whitney *U* test was used to analyze normally distributed or non-normally distributed data, respectively. As for categorical values, χ^2 test or Fisher exact test was utilized to analyze the categorical data. We defined a 2-side $P < .05$ as having statistical significance. Assuming all-cause death rates are 30% and 10% in the control group and intervention group, respectively, we calculated sample size of 65 patients in each group, with $\alpha = 0.05$, $\beta = 0.20$, and an expected dropout rate of 10%.

3. Results

We summarized and presented characteristics of all included patients in both groups in Table 1. There were not significant differences of all patient characteristics between 2 groups (Table 1).

After treatment, patients in the intervention group showed more promising outcomes in APACHE II ($P < .01$, Table 2), MOF ($P < .01$, Table 2), GCS ($P < .01$, Table 2), $CD3^+$ ($P = .03$, Table 3), $CD4^+$ ($P = .03$, Table 3), and $CD4^+/CD8^+$ ($P < .01$, Table 3), than those of patients in the control group.

As for safety, although several adverse events were reported in the patient case records, no significant differences were detected between 2 groups in this study (Table 4).

Table 1

Patient characteristics.

Characteristics	Intervention group (n = 65)	Control group (n = 65)	*P* value
Age (years)	53.2 (8.6)	55.0 (9.1)	.25
Gender			
Male	35 (53.8)	38 (58.5)	.60
Female	30 (46.2)	27 (41.5)	–
Race			
Han ethnicity	43 (66.2)	49 (75.4)	.25
Hui ethnicity	12 (18.5)	9 (13.8)	.48
Man ethnicity	10 (15.3)	7 (10.8)	.44
Factors cause severs sepsis			
Respiratory distress syndrome	17 (26.2)	14 (21.5)	.54
Acute pancreatitis	11 (16.9)	9 (13.8)	.63
Peritonitis	6 (9.2)	5 (7.7)	.75
Neoplasia	5 (7.7)	4 (6.2)	.73
Urinary tract	12 (18.5)	15 (23.1)	.52
Central nervous system	6 (9.2)	8 (12.3)	.57
Acute obstructive suppurative cholangitis	6 (9.2)	7 (10.8)	.77
Others	2 (3.1)	3 (4.6)	.65
Co-morbid diseases			
Diabetes mellitus	15 (23.1)	17 (26.2)	.68
Chronic obstructive pulmonary disease	20 (30.8)	18 (27.7)	.70
Chronic heart failure	10 (15.4)	13 (20.0)	.49
Stroke	8 (12.3)	7 (10.8)	.78
Chronic kidney disease	6 (9.2)	9 (13.8)	.41
Hypertension	14 (21.5)	11 (16.9)	.51
APACHE II score	15.7 (4.3)	16.1 (4.0)	.58
MOF score	14.4 (4.8)	14.9 (4.6)	.54
GCS score	7.5 (3.3)	7.8 (3.0)	.59
$CD3^+$	49.3 (12.6)	51.0 (13.1)	.45
$CD4^+$	23.7 (7.2)	23.5 (6.9)	.87
$CD8^+$	22.9 (6.3)	22.4 (6.0)	.64
$CD4^+/CD8^+$	1.03 (0.4)	1.05 (0.3)	.75

Data are present as mean ± standard deviation or number (%); APACHE II = Acute Physiology and Chronic Health Evaluation, GCS = Glasgow Coma Scale, MOF = Multiple Organ Failure.

Table 2

Comparison of primary outcome measurements after treatment between 2 groups.

Outcome measurements	Intervention group (n = 65)	Control group (n = 65)	*P* value
APACHE II score	6.4 (2.5)	11.7 (6.0)	<.01
MOF score	4.8 (2.1)	9.2 (4.4)	<.01
GCS score	12.2 (1.6)	9.5 (1.8)	<.01

Data are present as mean ± standard deviation; APACHE II = Acute Physiology and Chronic Health Evaluation, GCS = Glasgow Coma Scale, MOF = Multiple Organ Failure.

Table 4

Comparison of associated adverse events between 2 groups.

Adverse events	Intervention group (n = 65)	Control group (n = 65)	*P* value
Constipation	5 (7.7)	2 (3.1)	.26
Rash	3 (4.6)	0 (0)	.19
Nausea	3 (4.6)	1 (1.5)	.33
Vomiting	2 (3.1)	0 (0)	.29
Diarrhea	4 (6.2)	2 (3.1)	.82

Data are present as number (%).

4. Discussion

SS is a very server condition, and it usually accompanies by immune dysfunction and inflammatory reaction.[25] It results in changes in blood coagulation and immune function, and thus releases a lot of anti-inflammatory factors.[25] During the past few years, ulinastatin is reported to treat patients with SS.[26–32] Although previous studies reported ulinastatin in treating patients with SS,[26–32] most of them involved other similar medication, and very few studies addressed the efficacy and safety of ulnastatin for the treatment of SS. In addition, there are still inconsistent results among those studies.[26–32] Thus, there is still insufficient evidence to support ulnastatin for the treatment of patients with SS. This retrospective study aimed to appraise the efficacy and safety of ulnastatin for SS.

In this retrospective study, we explored and compared the efficacy and safety of conventional therapy and ulnastatin with conventional management alone. For patients in the intervention group, we utilized 200,000 IU intravenous ulinastatin, thrice daily for 3 days. Then, we applied following administration of 100,000 IU ulinastatin, trice daily for 4 successive days. The results of this study showed that patients in the intervention group achieved better outcomes in enhancing APACHE II ($P < .01$), MOF ($P < .01$), GCS ($P < .01$), $CD3^+$ ($P = .03$), $CD4^+$ ($P = .03$), and $CD4^+/CD8^+$ ($P < .01$), than those of patients in the control group. Our results suggest that ulnastatin has promising efficacy for the treatment of patients with SS. As for safety, there are not significant differences of all adverse events between 2 groups. It suggests that ulnastatin may have acceptable safety profile for SS.

This study has several limitations. First, the sample size of this study is still relatively small, which may affect its power. Second, all patient case records were harvested from Nanjing First Hospital of Nanjing Medical University, which may restrict its generalization to other hospitals. Third, this study did not apply randomization and blinding approach to both patients and practitioners, because this retrospective study collected data from previously completed case records. Finally, the outcome measurements may be not comprehensive, thus, more outcome information should be provided in the further studies.

Table 3

Comparison of secondary outcome measurements after treatment between 2 groups.

Outcome measurements	Intervention group (n = 65)	Control group (n = 65)	*P* value
$CD3^+$	65.1 (10.3)	61.4 (9.4)	.03
$CD4^+$	33.6 (8.1)	30.3 (9.0)	.03
$CD8^+$	22.0 (5.5)	21.3 (5.1)	.45
$CD4^+/CD8^+$	1.53 (0.4)	1.42 (0.4)	<.01

Data are present as mean ± standard deviation.

5. Conclusion

The results of this study exert that ulinastatin may benefit for SS. Further studies are still needed to warrant the present findings.

Author contributions

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