Efficacy of Ulinastatin-Assisted Continuous Blood Purification in Managing Severe Sepsis

QIN LI, YIZHU GAO, YIN LIANG AND YIWU ZHOU*

Department of Emergency, West China Hospital, Sichuan University, Sichuan, Chengdu 610017, China

To explore the efficacy of ulinastatin-assisted continuous blood purification in treating severe sepsis. The research included 240 individuals with severe sepsis admitted between June 2022 and June 2023, randomly allocated into an observation group and a control group, with 120 cases in each group. Protective measures such as anti-infection and fluid resuscitation were implemented in both patient groups prior to continuous blood purification, aiming to safeguard organ integrity and maintain the internal physiological equilibrium. Throughout the 1 w duration of continuous treatment, the control group underwent solely continuous blood purification, whereas the observation group was administered ulinastatin *via* injection as an additional intervention. Upon completion of the treatment, a comparison was made between the two groups regarding clinical efficacy, treatment indicators, changes in D-dimer and procalcitonin levels, and improvement rate of clinical symptoms. The observation group exhibited a significantly higher total effective rate of treatment (92.50 %) compared to the control group (80 %). Significant differences were observed between the observation group and the control group ($p<0.05$) in terms of hospitalization time and duration of antibiotic treatment, with the former exhibiting shorter durations. Following the treatment, the observation group displayed significantly lower acute physiology and chronic health evaluation scores in comparison to the control group. With significant reduction, D-dimer and procalcitonin levels in the observation group were lower compared to the control group. Comparative analysis revealed remarkable differences in the improvement rate of clinical symptoms between the observation group (93.33 %) and the control group (82.50 %), with the former exhibiting a higher rate of improvement. To summarize, the application of ulinastatin is worth promoting as it can improve clinical symptoms, reduce inflammatory markers, shorten hospitalization time, reduce antibiotic usage, and enhance the overall physiological status of patients with severe sepsis.

Key words: Ulinastatin, blood purification, severe sepsis, efficacy, brain injury, tumor

Sepsis refers to a Systemic Inflammatory Response Syndrome (SIRS) triggered by infection, causing pathological physiological processes that damage tissues. Posing a serious threat to patient's lives, it is a common and frequently occurring disease in the intensive care unit characterized by a dangerous condition and a high mortality rate[1,2]. Severe sepsis remains a formidable challenge despite the notable progress made in critical care medicine in recent years. Effective in treating sepsis, continuous blood purification techniques, commonly known as Continuous Renal Replacement Therapy (CRRT), offer a viable treatment approach. These techniques utilize blood purification devices to eliminate solutes and toxins from the blood, remove inflammatory factors, alleviate the inflammatory response, and restore acid-base balance[3,4]. Ulinastatin, on the other hand, effectively inhibits various pancreatic enzyme activities, clears oxygen free radicals, suppresses the release of inflammatory mediators, and protects organ function[5,6]. Therefore, there is reason to believe that ulinastatin may play a beneficial role in the treatment of severe sepsis. However, currently, there is a lack of sufficient clinical research supporting the efficacy of ulinastatin-assisted CRRT in treating severe sepsis. Consequently, this research aims to evaluate the effectiveness of ulinastatin-assisted CRRT as a treatment for severe sepsis and investigate its potential role in enhancing patient survival, modifying inflammatory markers, and facilitating

***Address for correspondence**
E-mail: xiaonizi772023@163.com

the recovery of multiple organ functions. The study subjects consisted of 240 individuals with severe sepsis who were admitted to our hospital from June 2022 to June 2023. All patients met the diagnostic criteria for sepsis and were free from severe traumatic brain injury[5], malignant tumors, blood disorders, severe hepatic or renal dysfunction, and immunodeficiency. The patients, who provided informed consent and willingly participated, were divided into an observation group (n=120) and a control group (n=120) using the principles of randomization. Within the observation group, there were 53 males and 67 females, aged 23 y to 77 y, with an average age of (53.38±3.67) y. As for the control group, it comprised 57 males and 63 females, ranging in age from 25 y to 79 y, with an average age of (52.87±3.54) y. No statistically significant differences ($p>0.05$) were observed in general clinical data between the two groups, confirming their comparability. Before undergoing continuous blood purification, protective treatments including antimicrobial therapy and fluid resuscitation were administered to both groups of patients to ensure organ function and maintain internal homeostasis. During continuous blood purification, close attention was paid to vital signs, including heart rate, hemodynamic parameters, and blood flow dynamics of both groups. The patients in the control group received standard continuous blood purification treatment. The blood purification equipment was connected, tubing was established, and venous catheterization was performed to maintain unobstructed catheter patency. Blood flow was controlled (increased gradually) between 170 and 220 ml/min, while replacement fluid flow rate was maintained at 35 ml/kg/h. In addition to the treatment received by the control group, ulinastatin (brand name: Tianpuloan, produced by Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., Approval No. H19990133, Specification: 100 000 U) was administered *via* slow intravenous injection. Two vials of ulinastatin were dissolved in 10 ml of normal saline and administered three times daily in observation group. Both groups received continuous treatment for 1 w. Comparison of clinical efficacy between the two groups of patients including the criteria for assessment are as follows[7]; significant improvement means disappearance of clinical symptoms and systemic discomfort after treatment, with all laboratory test results returning to normal; effective means improvement in clinical symptoms and systemic discomfort after treatment, with laboratory test results showing a positive trend; ineffective means no significant changes in clinical symptoms after treatment, or even worsening of the condition or death. The overall effective rate was calculated as the sum of the significant improvement rate and the effective rate. The comparison of treatment parameters between the two groups encompassed hospitalization duration, duration of antibiotic use, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score[8]. The APACHE II score, which considers age, acute physiological score, and chronic health score, serves as a measure to evaluate the severity of a patient's illness. It is important to emphasize that higher scores on the scale, with a maximum theoretical score of 71 points, correspond to a more severe condition. Both groups were assessed for changes in D-dimer and procalcitonin levels before and after treatment. The comparison of the rate of clinical symptom improvement between the two groups encompassed symptoms such as drowsiness, high or low body temperature, dry mouth, headache and more. Statistical Package for the Social Sciences (SPSS) 25.0 will be utilized to perform the statistical analysis in this research. Continuous variables will be reported as means and standard deviations and analyzed using t-tests. Categorical variables will be expressed as frequencies and percentages (n, %) and analyzed by Chi-square (χ^2) tests. To establish statistical significance, a significance level of $p<0.05$ will be employed. Comparatively, the observation group demonstrated a remarkably higher overall treatment efficacy (92.50 %) than the control group (80 %) ($p<0.05$) as shown in Table 1. The APACHE II scores of individuals in both the observation group (27.76±6.18) and the control group (27.54±6.11) did not differ notably prior to treatment ($p>0.05$). Following treatment, the observation group exhibited remarkably decreased hospitalization duration and antibiotic treatment duration, surpassing the control group in this regard ($p<0.05$). Furthermore, the observation group showed substantially lower post-treatment APACHE II scores compared to the control group ($p<0.05$) as shown in Table 2. No significant disparities were observed in D-dimer and procalcitonin levels between the two groups prior to treatment. Nevertheless, following treatment, both D-dimer and procalcitonin levels showed significant decreases, with significantly lower

levels detected in the observation group as compared to the control group ($p<0.05$) as shown in Table 3. Comparatively, the observation group displayed a significantly higher rate of clinical symptom improvement (93.33 %) after treatment, in contrast to the control group (82.50 %), as indicated in ($p<0.05$) as shown in Table 4. Sepsis presents with symptoms such as chills, high fever, low body temperature, altered mental status, and even coma. In severe cases, it can lead to multiple organ dysfunction and failure, posing a life-threatening condition to patients[9-11]. Previous studies have reported that continuous dialysis does not significantly reduce the 30 d mortality rate in sepsis patients[12]. Ulinastatin, derived from the liver, contains both pre-Alpha (α)-trypsin inhibitor and inter-α-trypsin inhibitor, which can reduce the release of inflammatory mediators, scavenge free radicals, inhibit various pancreatic enzyme activities, and effectively protect organs[13]. The objective of this research was to assess the effectiveness of ulinastatin-assisted CRRT in managing severe sepsis. The clinical efficacy of the observation group was found to be notably superior when compared to the control group. The observation group exhibited an overall treatment efficacy of 92.50 %, which was remarkably higher than the control group's 80 %. These findings highlight the significant improvement in disease progression and treatment outcomes in individuals with severe sepsis when ulinastatin is used as an adjunctive therapy. Remarkably shorter hospitalization duration and antibiotic usage time were observed in the observation group compared to the control group. This finding suggests that the incorporation of ulinastatin-assisted CRRT treatment has the potential to effectively manage disease progression, decrease hospitalization duration, and optimize antibiotic usage, thereby alleviating the medical burden on patients. In addition, the observation group displayed remarkably lower APACHE II scores than the control group, suggesting that ulinastatin-assisted CRRT treatment has the potential to enhance the overall physiological well-being of patients. The improvement of endothelial function and the anti-inflammatory effects of ulinastatin may contribute to this correlation. Through the inhibition of the inflammatory response and decreased cytokine release, ulinastatin assists in managing disease severity and enhancing the physiological status of patients. Clinical observations have found a correlation between the disease progression of sepsis and the changes in D-dimer levels, where higher D-dimer levels indicate a more severe condition. Reflecting the activity of the inflammatory response, procalcitonin is a protein widely utilized as a significant indicator for assessing the severity of critical illness. Observing the levels of these two markers assists in clinically determining the degree of infection and creates favorable conditions for timely treatment planning[14]. Significantly lower levels of both D-dimer and procalcitonin were observed in the observation group in this research, indicating a notable decrease in comparison to the control group. This suggests that ulinastatin-assisted CRRT treatment can alleviate the inflammatory response, correct coagulation dysfunction, and improve endogenous anticoagulant status. The outcomes of this study are in accordance with prior research, which demonstrates the regulatory effects of ulinastatin on inflammation and the coagulation system[15,16]. The analysis of clinical symptoms revealed a higher rate of improvement in the observation group, reaching 93.33 %, compared to 82.50 % in the control group. This further confirms the positive role of ulinastatin-assisted CRRT treatment in improving the clinical symptoms of patients with severe sepsis. The anti-inflammatory effects of ulinastatin may help alleviate symptoms such as drowsiness, high or low body temperature, dry mouth, and headache, thereby improving patient's life quality. Nevertheless, it is important to acknowledge the limitations of this study. Firstly, the sample size is relatively small, which could potentially compromise the stability and reliability of the statistical outcomes. Secondly, this study solely focused on a single medical institution, thereby raising the possibility of regional and institutional variances. Thus, expanding the research scope is necessary to validate these findings. This research concludes that ulinastatin-assisted CRRT treatment exhibits notable clinical efficacy in the context of severe sepsis. The administration of ulinastatin leads to improved clinical symptoms, reduced inflammatory markers, shortened hospitalization duration, decreased antibiotic usage, and enhanced overall physiological status in patients. Additional clinical research is warranted to validate and gain a deeper understanding of the impacts of ulinastatin-assisted CRRT treatment in severe sepsis, thereby establishing more reliable evidence for its application in clinical practice.

TABLE 1: COMPARISON OF CURATIVE EFFECT

Group (n=120)	Remarkably effective	Effective	Ineffective	Overall effective rate
Observation	62 (51.67)	49 (40.83)	9 (7.50)	111 (92.50)
Control	48 (40.00)	48 (40.00)	24 (20.00)	96 (80.00)
χ^2		-		7.905
p		-		0.005

TABLE 2: COMPARISON OF TREATMENT INDEXES

Group (n=120)	Hospitalization time (d)	Antibiotic use time (d)	APACHE II
Observation	17.94±3.65	15.03±3.22	14.39±3.65
Control	22.68±4.04	18.28±3.33	20.23±4.64
t	9.531	7.662	10.824
p	0.000	0.000	0.000

TABLE 3: COMPARISON OF INFECTION INDEXES

Group (n=120)	D-dimer		Procalcitonin	
	Before	After	Before	After
Observation	4.74±0.72	0.84±0.39*	54.02±5.86	1.56±0.61*
Control	4.58±0.76	2.59±0.73*	53.46±5.57	6.37±0.98*
t	-1.677	23.179	-0.761	45.544
p	0.095	0.000	0.447	0.000

Note: *p<0.05

TABLE 4: CLINICAL SYMPTOMS (n %)

Group (n=120)	Lethargy	High fever or hypothermia	Dry mouth	Headache	Improvement rate
Observation	1 (0.83)	2 (1.67)	2 (1.67)	3 (2.50)	112 (93.33)
Control	6 (5.00)	4 (3.33)	6 (5.00)	5 (4.17)	99 (82.50)
χ^2		-			6.629
p		-			0.010

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Zhang Y, Chen T, Liu P. Application of continuous blood purification in the treatment of sepsis. Mod Pract Med 2009;21(2):2.
2. Wang S. The value of continuous blood purification in the treatment of severe sepsis. Henan Med Res 2015;24(4):2.
3. Wei G. Evaluation of efficacy and safety of ulinastatin in the treatment of severe sepsis. China Med Guide 2017;15(4):2.
4. Lu X, Wu Q, Xiao Z. Clinical study of continuous hemofiltration in the treatment of severe hand-foot-mouth disease with cardiopulmonary failure. China Pediatr Emerg Med 2015;22(3):14.
5. Jin X, Cheng X, Lin M. Clinical effect of ulinastatin combined with continuous blood purification on acute respiratory distress syndrome. Chin Gen Med 2016;14(10):3.
6. Ding Y, Chen G, Li J. Application of continuous blood purification in the treatment of severe sepsis. Chin Med Innov 2012.
7. Severe medicine branch of Chinese medical association. Chinese guidelines for the treatment of severe sepsis/septic shock (2014). Chin J Int Med 2015;6:25.
8. Li X, Zhang C, Li Q. Correlation and clinical significance of serum lactic acid, soluble myeloid cell trigger receptor-1, procalcitonin and acute physiological chronic health score in elderly patients with severe pneumonia. Chin J Clin Health 2023;26(1):105-8.
9. Zhang L. Prognostic value of serum procalcitonin and D-dimer in patients with sepsis. Chin Exp Diagnost 2018;22(4):3.
10. Tang W. Analysis of the prognostic value of serum procalcitonin and D-dimer in patients with sepsis. Mod Health Med 2017;2:1.
11. Luo Y, Hu W, Geng X. Application of ulinastatin combined with continuous blood purification in patients with severe sepsis. Contin Med Educ China 2016;8(31):2.

12. Wang Y, Ji X, Zhan LB. Observation on the efficacy of continuous blood purification in the treatment of 29 cases of severe sepsis. Chin Gen Med 2016;14(4):580-2.
13. Chen W, Hu Z, Yang Y. Effects of ulinastatin assisted high volume hemofiltration on serum cell adhesion molecule-1, cholinesterase and blood coagulation in severe sepsis. Chin J Mod Med 2016;26(11):5.
14. Ma S. Effects of continuous blood purification combined with ulinastatin on D-dimer and procalcitonin in patients with severe sepsis. Northern Pharm 2019;16(2):20-1.
15. Yang Y, Xue J, Liu J. Effects of ulinastatin on inflammatory factors and blood coagulation in patients with severe multiple injury. Chin J Med 2020;34(4):3.
16. Zhu Y, Shi J, Gao L. Effect of ulinastatin reduning injection on blood coagulation and inflammatory reaction in patients with heat ejection disease of summer heat syndrome. China Med Forum 2021;25(2):3.

This article was originally published in a special issue, "Exploring the Role of Biomedicine in Pharmaceutical Sciences" Indian J Pharm Sci 2024:86(1) Spl Issue "159-163"