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Efficacy of Ulinastatin Combined with Continuous Renal Replacement Therapy in the Treatment of Sepsis Acute Kidney Injury and Its Effects on Systemic Inflammation, Immune Function and miRAN Expression

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Abstract

Objective: To research the effectiveness of ulinastatin in combination with continuous renal replacement therapy in treating sepsis acute kidney injury and its effect on systemic inflammation, immune function and miRAN expression. **Methods:** The 84 patients who were diagnosed with sepsis complicated by acute kidney injury in our hospital between May 2020 and June 2022 were chosen and randomly assigned to the study group (n = 42) and the control group (n = 42). Ulinastatin in combination with continuous renal replacement therapy was administered to the study group, whereas the control group was administered with continuous renal replacement therapy alone. Both groups' clinical effects were observed. The levels of blood urea nitrogen (BUN), serum creatinine (SCr), tumor necrosis factor-α (TNF-α), high sensitivity C-reactive protein (hs-CRP), vascular cell adhesion molecule-1 (VCAM-1), IgG, IgA, IgM, expression levels of miR-233 and miR-10a were compared among both the groups, pre-, and post-treatment. **Results:** The study group's overall effectiveness rate was higher that is 95.24%, in comparison to the control group's 78.57%, and this difference was statistically significant ($P < 0.05$). Following the treatment, serum levels of BUN, Scr, TNF-α, hs-CRP, VCAM-1, and miR-233 and miR-10a expression levels in both the study and control groups were decreased, however, the study group had reduced levels in comparison to the control group, with statistically significant differences ($P < 0.05$). Upon treatment, the serum levels of IgG, IgA, and IgM in both the study and control group were elevated, and the levels in the study group were greater in comparison to the control group, with statistically significant dif-

ferences ($P < 0.05$). **Conclusion:** Ulinastatin in combination with continuous renal replacement therapy for treating sepsis acute kidney injury exhibits a positive effect and can significantly improve the systemic inflammation and immune function in patients.

Keywords

Ulinastatin, Immune Function, Continuous Renal Replacement Therapy, Systemic Inflammation, Sepsis Acute Kidney Injury, miRAN

1. Introduction

The prime reason for septic shock and multiple organ dysfunction syndromes is sepsis, a systemic inflammatory response syndrome brought on by an infection or trauma. The disease can cause the death of critically ill patients as depicted by its high rates of mortality and morbidity. Sepsis is currently becoming more common each year, and nearly 40% of patients with sepsis can develop into sepsis acute kidney injury, with a high mortality [1] [2]. Therefore, it is very important to provide effective treatment for patients with sepsis and acute kidney injury. Relevant studies indicate that the incidence and progression of sepsis are directly associated with an inflammatory response. Therefore, the treatment of sepsis can start from the perspective of reducing the body's inflammatory response. Continuous renal replacement therapy (CRRT) is a new type of renal replacement therapy, which has developed from the use of maintenance hemodialysis technology and equipment to the application of CRRT platform for critically ill patients. Its function is not limited to renal replacement and other organ support, but also plays a role in protecting organ function and improving patient prognosis. CRRT is a commonly used technique for the treatment of acute kidney injury caused by sepsis [3]. CRRT can slowly remove inflammatory factors of small and medium molecular weight and reduce inflammatory response. It can effectively remove inflammatory factors and help improve the patient's internal environment through external blood purification [4]. Recent SCC guidelines suggest that continuous or intermittent renal replacement therapy can be used in patients with sepsis and AKI (weak recommendation, moderate quality of evidence) [5]. Ulinastatin is a protease inhibitor, which can stabilize the lysosomal membrane, modulate the inflammatory factor release, and effectively regulate immune function. According to relevant studies, microRNA (miR)-205 and miR-233 are strongly connected to the inflammation levels in the body, which are important components of RNA molecules and has a crucial part in cell growth and differentiation [6]. Based on this, this study applied ulinastatin combined with CRRT in patients having sepsis acute kidney injury to observe its effects on systemic inflammation, immune function, and miRAN expression, to present a resource for treating the sepsis acute kidney injury in clinical practice.

2. Materials and Methods

2.1. General Information

By employing a random number table technique, 84 patients with sepsis complicated by acute kidney injury who were diagnosed in our hospital between May 2020 and June 2022 were chosen, with 42 cases in each of the study group and control group. The study group had a total of 26 men and 16 women, ranging from 51 to 72 years, with an average age of 61.35 ± 5.82 years; the primary disease types were abdominal infection in 6 cases, pulmonary infection in 28 cases, and blood-borne infection in 8 cases. The control group comprised 31 males and 11 females; 50 - 73 years of age, with an average of 62.95 ± 5.45 years; primary disease types: 4, 31, and 7 cases of abdominal infection, pulmonary infection, and blood-borne infection, respectively. No statistical difference could be observed in general data among both the groups ($P > 0.05$), which was comparable. The hospital ethics committee gave their approval for this research.

2.2. Inclusion Criteria

1) All patients were in accordance with the diagnostic criteria for Sepsis established by the American Society of Critical Care Medicine and the American College of Chest Physicians (SCCM/ACCP) [7]; 2) All were in accordance with the diagnostic criteria in KDIGO Guideline Interpretation: Diagnosis and treatment of acute kidney Injury [8]; 3) Age > 18 years old; 4) Every patient agreed to take part in this study voluntarily.

2.3. Exclusion Criteria

1) Patients with other serious cardiovascular diseases; 2) Patients with chronic kidney disease or history of kidney transplantation; 3) Patients with blood system diseases; 4) Patients with autoimmune diseases; 5) Patients who passed away within 24 hours of getting admitted.

2.4. Methods

CRRT was administered to the control group while ulinastatin and CRRT were administered to the study group. Both groups were treated with primary disease treatment, anti-infection therapy, immunotherapy, nutritional support, fluid resuscitation and other standard anti-sepsis treatments for 6 consecutive days. Then, CRRT was given, and a hemofiltration machine was used to perform continuous venous-venous hemofiltration by inserting a double-lumen dialysis tube in the internal jugular vein or femoral vein. The concentration and content of replacement fluid was adjusted as per the patient's condition. A flow rate of 40 ml/kg/h was set for replacement fluid while the flow of blood was set to 150 - 200 ml/min. The patients with bleeding tendency were given sodium citrate anticoagulation, and the patients without active bleeding were given heparin anticoagulation, 12 h/day, for 6 consecutive days. The study group was also treated with ulinastatin injection (Guangdong Techpool Biochemical Medicine, SFDA

approval number: H20040505), 200,000 U/time [9], 3 times/day, for 14 days.

2.5. Observation Indicators

1) Clinical efficacy. 2) Renal function. The two groups' blood urea nitrogen (BUN) and serum creatinine (SCr) levels were ascertained, both pre and post-treatment. 3) Inflammatory reaction. 5 ml venous blood was drawn in fasting condition both prior to and after the treatment. After that, the blood sample was split into two parts, with one being subjected to centrifugation for 15 minutes at 3000 rpm, and the upper serum was collected and stored at a low temperature until testing. Enzyme-linked immunosorbent assay was utilized for measuring the levels of tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and vascular cell adhesion molecule-1 (VCAM-1). 4) Immune function. The above venous blood was drawn, and the IgG, IgA and IgM levels were determined by immunoturbidimetry. 5) miRNA levels. The above serum was collected, and the relative miR-233 and miR-10a expression levels were determined by RT-PCR.

2.6. Efficacy Evaluation Criteria

Markedly effective: after 7 days of treatment, pulse pressure > 30 mmHg, systolic blood pressure > 90 mmHg, urine volume > 30 ml/d, and the patient's consciousness returned to normal. Effective: systolic blood pressure > 90 mmHg, patients with increased urine volume but needed to take medication to maintain hemodynamic stability, patients with improved consciousness; Ineffective: no improvement or aggravation was observed after treatment [10]. Total effective = markedly effective + effective.

2.7. Statistical Methods

The data were processed and analyzed via SPSS 20.0 statistical software, and mean ± standard deviation ($\overline{x}$ ± s) was utilized for expressing the measurement data. Comparison among the groups was executed via an Independent sample t-test and paired t-test was utilized for drawing comparisons within the groups both before and after the treatment. Frequency and constituent ratios were used to express the count data, and the χ^2 test was employed for comparison. $P < 0.05$ demonstrated statistical significance.

3. Results

3.1. Comparison of the Two Groups' Clinical Efficacy

In the study group, the overall effective rate was 95.24%, compared to 78.57% in the control group, while the difference between both the groups was statistically significant ($P < 0.05$). As shown in **Table 1**.

3.2. Comparison of the Two Groups' Renal Function Index Levels

The BUN and Scr levels among the study and control groups did not differ sig-

nificantly prior to the treatment ($P > 0.05$); however, upon treatment, the BUN and Scr levels in both groups decreased, with the differences being statistically significant ($P < 0.05$). As presented in Table 2.

3.3. Comparison of the Two Groups Inflammatory Factor Levels

Prior to treatment, no discernible difference was noticed between the study and control groups in regards to TNF-α, hs-CRP, and VCAM-1 level ($P > 0.05$).The TNF-α, hs-CRP, and VCAM-1 levels were reduced following treatment in both groups, however, the study group had decreased levels as to that of the control group, and these differences were statistically significant ($P < 0.05$). As shown in Table 3.

3.4. Comparison of the Two Groups' Immune Function

The study group's IgG, IgA, and IgM levels were greater than the control group

Table 1. Comparison of the two groups' clinical efficacy [cases (%)].

Group	Marked Effective	Effective	Ineffective	Total effective
Study group ($n = 42$)	29 (69.05)	11 (26.19)	2 (4.76)	40 (95.24)
Control group ($n = 42$)	23 (54.76)	10 (23.81)	9 (21.43)	33 (78.57)
χ^2 value				5.126
P value				0.024

Table 2. Comparison of renal function index levels between the two groups ($\bar{x} \pm s$).

Group	BUN (mmol/l)		Scr (umol/l)	
	Before treatment	After treatment	Before treatment	After treatment
Study group ($n = 42$)	20.53 ± 2.90	10.14 ± 2.42[a]	550.44 ± 44.25	202.61 ± 22.91[a]
Control group ($n = 42$)	20.90 ± 3.50	14.65 ± 2.43[a]	556.34 ± 48.65	217.73 ± 23.01[a]
t value	0.533	8.520	0.581	3.017
P value	0.596	<0.001	0.563	0.003

Note: [a]indicated $P < 0.05$ when compared with before treatment.

Table 3. Changes in the levels of inflammatory factors in the two groups ($\bar{x} \pm s$).

Group	TNF-α (ng/l)		hs-CRP (mg/l)		VCAM-1 (mg/l)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group ($n = 42$)	188.81 ± 19.03	122.37 ± 21.30[a]	128.40 ± 26.23	35.00 ± 6.80[a]	2.95 ± 0.76	1.62 ± 0.45[a]
Control group ($n = 42$)	186.28 ± 19.08	144.21 ± 23.05[a]	132.01 ± 24.08	67.71 ± 5.56[a]	2.84 ± 0.76	2.18 ± 0.49[a]
t value	0.609	4.509	0.656	24.129	0.672	5.474
P value	0.544	<0.001	0.514	<0.001	0.504	<0.001

Note: [a]indicated $P < 0.05$ when compared with before treatment.

following the treatment, with statistically significant differences ($P < 0.05$), in contrast to the pre-treatment levels, which did not significantly differ among the two groups ($P > 0.05$). As demonstrated in Table 4.

3.5. Comparison of miR-233 and miR-205 Levels between the Two Groups

Prior to treatment, no discernible difference among the two groups in miR-233 and miR-10a levels could be observed ($P > 0.05$). The miR-233 and miR-10a levels in both the groups reduced following the treatment, with the study group having lower levels than that of the control group; and the difference was statistically significant ($P < 0.05$). As presented in Table 5.

4. Discussion

Sepsis acute kidney injury can be caused by urethral obstruction, infection, renal blood perfusion insufficiency, cell metabolism disorder and other factors. Patients' lives and health are seriously threatened by its poor prognosis and increased mortality. Therefore, safe and effective treatment should be given to patients [11] [12]. At present, CRRT is one of the main methods for treating sepsis acute kidney injury. However, CRRT still has some shortcomings in treating sepsis acute kidney injury. Therefore, drug-assisted CRRT can be used to treat sepsis acute kidney injury. Ulinastatin is a protease inhibitor, which can keep cells and tissues from being digested by inhibiting serine protease activity and

Table 4. Comparison of the two groups' immune function ($\bar{x} \pm s$).

Group	IgG (g/l)		IgA (g/l)		IgM (g/l)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group ($n = 42$)	9.17 ± 1.09	11.15 ± 1.00[a]	1.85 ± 0.96	3.06 ± 0.90[a]	1.81 ± 0.62	2.87 ± 0.79[a]
Control group ($n = 42$)	9.28 ± 1.04	9.74 ± 0.95[a]	2.33 ± 1.25	2.30 ± 1.09	1.83 ± 0.79	2.09 ± 0.94
t value	0.463	6.594	1.984	3.469	0.102	4.089
P value	0.644	< 0.001	0.051	0.001	0.919	< 0.001

Note: [a]indicated $P < 0.05$ when compared with before treatment.

Table 5. Comparison of miR-233 and miR-205 levels between the two groups ($\bar{x} \pm s$).

Group	miR-233		miR-10a	
	Before treatment	After treatment	Before treatment	After treatment
Study group ($n = 42$)	5.37 ± 0.43	2.71 ± 0.47[a]	4.46 ± 0.57	1.09 ± 0.26[a]
Control group ($n = 42$)	5.31 ± 0.61	4.17 ± 0.57[a]	4.57 ± 0.64	3.41 ± 0.39[a]
*t*value	0.577	12.860	0.872	31.946
*P*value	0.566	< 0.001	0.386	< 0.001

Note: [a]indicated $P < 0.05$ when compared with before treatment.

trypsin activity. According to relevant studies, ulinastatin can also be used as oxygen free radical scavenger to regulate the inflammatory factor release and prevent the further development of inflammatory reactions [13]. In the present research, the patients were sorted in two groups: those receiving ulinastatin and CRRT, and those receiving CRRT alone. Results revealed that ulinastatin in combination with CRRT had a better effect on the treatment of sepsis acute kidney injury, with the study group's total effective rate (95.24%) being greater in comparison to the control group's (78.57%). In addition, the improved BUN and Scr levels in the study group prior to and following the treatment were superior compared to the control group's levels, showing that ulinastatin in combination with CRRT can more effectively improve patients' renal function. The reason may be that ulinastatin can inhibit the activity of protease and other hydrolytic enzymes through IP, which reduces the further damage of hydrolytic enzymes to body tissues and alleviates renal injury. Therefore, after treatment, the study group's efficacy and improved renal function were superior to those of the control group. Multiple previous studies have shown that ulinastatin is effective in treating septic acute kidney injury [14] [15] [16].

In this study, ulinastatin in combination with CRRT can more successfully enhance the inflammatory response and immune function in patients having septic acute kidney injury because the levels of TNF-α, hs-CRP, VCAM-1, and other inflammatory factors as well as the levels of IgG, IgA, and IgM and other immune function indicators were improved more in the study group than the control group, following the treatment. The sudden increase in the levels of TNF-α, hs-CRP, VCAM-1 and other inflammatory factors indicates that the body is in a persistent state of inflammation, which may lead to microcirculation disorders and damage to tissues and organs. IgG, IgA, and IgM can indicate the immune status of the body, and monitoring their levels can reflect towards the body's immune suppression. As a protease inhibitor, ulinastatin can antagonize inflammatory factors, timely remove excess superoxide in the body, and play a therapeutic role. In addition, ulinastatin can also correct humoral immune dysfunction, however its precise mechanism requires more research. Ulinastatin combined with CRRT can improve the inflammatory state and immune response of patients more effectively.

According to relevant studies, miRNA may be highly associated to the occurrence and development of sepsis. The kidney can further modulate the expression of signal proteins by regulating miRNA expression, and participating in the process of cell proliferation and differentiation, which is related to renal injury. There are differences in miR-233 and miR-10a expression levels in patients with different severity of sepsis [17] [18]. High expression of miR-233 may further aggravate renal injury and increase mortality. miR-10a can regulate the level of immune response and has been widely studied in tumors and rheumatic immune diseases. In the present research, the study group's miR-233 and miR-10a levels were relatively low than the control group, implying that the combined therapy can more successfully regulate the miRNA levels in the body, which may

be related to the ulinastatin's ability to relieve inflammation and improving immunological function.

This study is a useful supplement to the data in this field to investigate the clinical efficacy of ulinastatin combined with CRRT in the treatment of septic acute kidney injury and its effect on systemic inflammation, immune function and miRNA expression. However, there are still some shortcomings in this study: 1) the sample size is limited and the number of included patients is small, so it is necessary to further expand the sample size for research; 2) The basic creatinine values of patients with different age groups or different nutritional status are inconsistent, and the changes of more inflammatory indicators in dialysate and blood are not detected in the treatment of sepsis complicated with AKI, so further clinical studies are still needed.

5. Conclusion

Ulinastatin in combination with CRRT for treating sepsis acute kidney injury exhibits a positive effect and can significantly improve the systemic inflammation and immune function in patients, which has clinical application value.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Petejova, N., Martinek, A., Zadrazil, J., *et al.* (2020) Acute Kidney Injury in Septic Patients Treated by Selected Nephrotoxic Antibiotic Agents-Pathophysiology and Biomarkers—A Review. *International Journal of Molecular Sciences*, **21**, Article No. 7115. https://doi.org/10.3390/ijms21197115

[2] Montomoli, J., Donati, A. and Ince, C. (2019) Acute Kidney Injury and Fluid Resuscitation in Septic Patients: Are We Protecting the Kidney? *Nephron*, **143**, 170-173. https://doi.org/10.1159/000501748

[3] Chen, L.X., Demirjian, S., Udani, S.M., Trevino, S.A., Murray, P.T. and Koyner, J.L. (2018) Cytokine Clearances in Critically Ill Patients on Continuous Renal Replacement Therapy. *Blood Purification*, **46**, 315-322. https://doi.org/10.1159/000492025

[4] Wen, D. and Li, Z.H. (2021) Timing Selection of Continuous Renal Replacement Therapy for Acute Kidney Injury. *Journal of Pediatric Pharmacy*, **27**, 50-53.

[5] Rhodes, A., Evans, L.E., Alhazzani, W., *et al.* (2017) Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Medicine*, **43**, 304-377. https://doi.org/10.1007/s00134-017-4683-6

[6] Li, Q.Q., Luo, L., Ji, D.D., *et al.* (2020) To Explore the Diagnostic Efficacy of miRNA-494 in Patients with Septic Acute Kidney Injury. *Chinese Journal of Integrated Traditional Chinese and Western Medicine Nephrology*, **21**, 1084-1086.

[7] Singer, M., Deutschman, C.S., Seymour, C.W., *et al.* (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, **8**, 801-810. https://doi.org/10.1001/jama.2016.0287

[8] Tang, X.J. and Mei, C.L. (2012) Interpretation of KDIGO Guidelines: Diagnosis and Treatment of Acute Kidney Injury. *Chinese Journal of Practical Internal Medicine*,

32, 4.

[9] Wang, J. and Zhou, Y.J. (2018) Effect of CRRT Combined with Ulinastatin on Acute Renal Injury in Patients with Severe Rhabdomyolysis Syndrome. *Journal of Guangxi Medical University*, **35**, 522-525.

[10] Gomez, H., Ince, C., De Backer, D., *et al.* (2014) A Unified Theory of Sepsis-Induced Acute Kidney Injury: Inflammation, Microcirculatory Dysfunction, Bioenergetics, and the Tubular Cell Adaptation to Injury. *Shock*, **41**, 3-11. https://doi.org/10.1097/SHK.0000000000000052

[11] Liu, Z., Tang, C., He, L., *et al.* (2020) The Negative Feedback Loop of NF-κB/miR-376b/NFKBIZ in Septic Acute Kidney Injury. *JCI Insight*, **5**, e142272. https://doi.org/10.1172/jci.insight.142272

[12] Nakano, D. (2020) Septic Acute Kidney Injury: A Review of Basic Research. *Clinical and Experimental Nephrology*, **24**, 1091-1102. https://doi.org/10.1007/s10157-020-01951-3

[13] Li, B., Lu, H.J. and Cui, N.Q. (2020) Clinical Study of Continuous Blood Purification Combined with Ulinastatin in the Treatment of Severe Sepsis. *China Journal of Integrative Medicine*, **26**, 42-46.

[14] Zheng, N., Cheng, Y.N. and Yang, H.Y. (2020) Effects of Ulinastatin Combined with Intermittent Hemodialysis on the Levels of Urinary IGFBP-7 and HMGB1 in Patients with Sepsis with Acute Kidney Injury. *Journal of Internal Medicine*, **26**, 134-137.

[15] Wang, J. and Zhu, H.L. (2021) Effects of Continuous Hemofiltration Combined with Ulinastatin on the Condition, Serum miR-155, miR-21 Levels and Short-Term Prognosis of Patients with Acute Kidney Injury. *Hainan Medicine*, **32**, 4.

[16] Sun, W., Li, D.Y., Wang, D.W., *et al.* (2019) Improvement Effect of Different Doses of Ulinastatin on Renal Function, Inflammation and Oxidative Stress Indexes in Patients with Acute Kidney Injury. *Guangxi Medicine*, **41**, 5.

[17] Li, D.Y., Liu, G.L. and Yuan, X.K. (2018) Expression Levels and Clinical Significance of Serum miR-21, miR-233 and miR-107 in Patients with Sepsis Complicated with Acute Kidney Injury. *Journal of Tropical Medicine*, **18**, 1580-1584.

[18] Yan, X.C., Wu, Z.G., Liu, J.W., *et al.* (2021) miR-10a, miR-21 Combined to Predict the Mortality of Elderly Patients with Severe Sepsis. *Chinese Journal of Immunology*, **37**, 6.