


Removal of inflammatory factors and prognosis of patients with septic shock complicated with acute kidney injury by hemodiafiltration combined with HA330-II hemoperfusion

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Abstract

Introduction: To explore the effect of CRRT using CVVHDF + HP on the removal of inflammatory mediators in patients with septic shock complicated with AKI.

Methods: A total of 20 patients between January 1, 2018, and December 31, 2021, were included. The patients were randomly divided into the treatment group (CVVHDF + HP) and the control group (CVVHDF). Changes in inflammatory factors, including IL-1 β , IL-6, IL-8, TNF- α , PCT, and CRP were compared. Other observed measures were also analyzed, for example, Lac, Scr, BUN, SOFA, and norepinephrine (NE) dosage. The clinical outcomes of both groups were followed up for 28 days.

Results: The IL-6 and PCT levels in the treatment group were significantly lower ($p = 0.005, 0.007$). Although the IL-1 β , TNF α , and CRP levels in the treatment group decreased, there were no statistical differences ($p > 0.05$). There were significant differences in Lac, SOFA, and NE dosage levels between both groups ($p = 0.023, 0.01, 0.023$). Survival analysis showed that the 28-day survival rate was significantly higher in the treatment group.

Conclusion: CRRT using CVVHDF+HP can effectively remove inflammatory factors and improve the prognosis of patients.

KEYWORDS

acute kidney injury, hemodiafiltration, hemoperfusion, septic shock

1 | INTRODUCTION

Septic shock is a life-threatening disease that can lead to multiple organ dysfunction syndrome (MODS) and has high clinical mortality and a poor prognosis [1]. Sepsis causes abnormal immune system response and cascade reactions of inflammatory factors [2]. Among them,

endothelial cells over-release serum interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor- α (TNF- α), and other inflammatory factors. This aggravates vascular endothelial cell damage and permeability changes, resulting in micro-circulation disturbance in the body, and MODS are the main cause of death [3]. In recent years, continuous blood purification technology-related equipment has been developed in many fields, such as oXiris, polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP),

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and HA330 hemoperfusion (HP). These blood purification devices can remove excessive inflammatory factors and are gradually increasingly used in clinical practice [4]. Given the significance of inflammatory factors in sepsis, it is important to explore different effective therapeutic methods to clear inflammatory factors and regulate the body's immunity in this group of patients. The purpose of this study was to investigate the therapeutic effects of continuous venovenous hemodiafiltration (CVVHDF) combined with HP on removing inflammatory factors and regulating immunity in patients with septic shock complicated with acute kidney injury (AKI) and to assess its influence on patient prognosis.

2 | MATERIALS AND METHODS

This study was approved by the Ethics Committee. A total of 20 adult patients with septic shock complicated with AKI between January 1, 2018, and December 31, 2021, were included. Patients were randomly divided into the treatment group (CVVHDF + HP) and the control group (CVVHDF) using the random number table method. There were 10 patients (7 male and 3 female) in the treatment group and 10 patients (6 male and 4 female) in the control group. Signed written informed consent was obtained from all the patients.

The inclusion criteria were patients aged 18–85 years diagnosed with septic shock [1] and AKI [5]. The exclusion criteria were patients who died or abandoned treatment within 24 h, with underlying chronic kidney disease or malignant tumor, with immunodeficiency diseases, or taking immunosuppressants. Patients in both groups received comprehensive treatment for septic shock, including early antibiotic use, hemodynamic monitoring, fluid resuscitation and individualized volume management, application of vasoactive drugs, assessment and support of organ function, maintenance of blood glucose of 8–10 mmol/L, maintenance of blood electrolyte within the normal range, and appropriate nutritional support.

After patient enrollment, a blood purification pathway (jugular vein or femoral vein) was immediately established (within 2 h) under bedside ultrasound guidance. In the treatment group, **CVVHDF + HP continuous renal replacement therapy (CRRT) was applied for 4 h/day** (HP was provided using HA330-II HP machine) and CVVHDF for the rest of the time. In addition, **the patients received 3–5 HP treatments**. Patients in the control group were treated with conventional CVVHDF CRRT. Two patients were unable to recover due to renal injury and received RRT as required. The blood flow velocity during CRRT was 180–200 mL/min. The replacement fluid was finished replacement fluid 4 L/bag, and

the replacement volume was maintained at 3000–4000 mL/h. According to the patient's condition, a low-molecular-weight heparin/4% citrate/naphthalthalmoestat mesylate/no anticoagulant scheme was adopted. Blood pressure, heart rate, coagulation function, and blood electrolyte were closely monitored during treatment. Blood samples were collected from each patient before and after the treatment. IL-1 β , IL-6, IL-8, TNF- α , CRP, and PCT serum levels were detected by ELISA. Other observed measures were also collected, for example, Lac, Scr, BUN, and norepinephrine (NE) dosage. The clinical outcomes of both groups were followed up for 28 days.

Statistical analysis was performed using SPSS version 26.0. Normal distribution of measurement data to mean \pm standard deviation ($x \pm s$) said. A comparison of before and after treatment between groups was performed using a matching *t*-test. An independent sample *t*-test was also conducted to compare between both groups. Skewness distribution parameter measurement data description using quarterback spacing, according to the control group and treatment group compared with two independent sample test, before and after treatment comparison using double correlation sample test. The chi-square test was used for the comparison of counting data. The Kaplan–Meier curve was used for survival. A *p*-value of <0.05 was considered statistically significant.

3 | RESULTS

3.1 | General data analysis

There were no significant differences in age, sex, blood urea nitrogen, serum creatinine, Ventilator use time, Acute Physiology and Chronic Health Evaluation II score, and Sequential Organ Failure Assessment (SOFA) score between the two groups at the time of enrollment ($p > 0.05$) (Table 1). In the treatment group, three patients were at AKI stage I, two patients were at AKI stage II and five patients were at AKI stage III. In the control group, four patients were at AKI stage I, three patients were at AKI stage II and three patients were at AKI stage III. In the treatment group, seven patients were infected by potentially pathogenic microorganisms from the digestive system, two from the urinary system, and one from bones and joints. In the control group, one was infected by pathogenic microorganisms from the respiratory system and nine from the digestive system. No serious blood purification-related complications, such as bleeding, hemolysis, severe electrolyte disorder, and in vitro coagulation, occurred in all the enrolled patients during RRT.

TABLE 1 General data of treatment group and control group.

	The treatment group	The control group	<i>t</i> / χ / <i>Z</i>	<i>p</i>
Age (years)	63.20 ± 16.92	71.80 ± 9.09	-1.416	0.174
Gender (Male /%)	7/70%	6/60%	0.220	0.639
APACHE II score	17.00 ± 5.83	16.30 ± 6.22	0.260	0.798
SOPA score	12.10 ± 4.61	14.10 ± 1.91	-1.268	0.229
HB (g/L)	101.50 ± 23.64	101.90 ± 22.07	-0.227	0.820
WBC (10 ⁹ /L)	13.69 ± 9.41	11.72 ± 8.29	0.497	0.625
PLT (10 ⁹ /L)	96.60 ± 70.38	99.40 ± 60.64	-0.302	0.762
BUN (mmol/L)	20.97 ± 10.57	22.18 ± 12.34	-0.236	0.816
Scr (μmol/L)	299.10 ± 157.92	279.70 ± 214.86	0.230	0.821
PT (s)	17.64 ± 4.00	15.74 ± 2.06	1.335	0.198
APTT (s)	45.06 ± 10.04	47.42 ± 10.12	-0.524	0.607
Ventilator use time (d)	20.50 ± 23.99	9.30 ± 3.95	9.486	0.178
Staging of AKI				
Stage I (cases/%)	3/30%	4/40%		
Stage II (cases/%)	2/20%	3/30%		
Stage III (cases/%)	5/50%	3/30%		
Source of infection				
Respiratory system (cases/%)	0	1/10%		
Digestive system (cases/%)	7/70%	9/90%		
Urinary system (cases/%)	2/20%	0		
Bone and joint (cases/%)	1/10%	0		

Abbreviations: APACHE II, acute physiology and chronic health evaluation II score; APTT, activated partial thromboplastin time; AKI, acute kidney injury; BUN, blood urea nitrogen; HB, hemoglobin; PLT, platelet; PT, prothrombin time; Scr, serum creatinine; SOFA, sequential organ failure assessment score; WBC, white blood cell.

3.2 | Levels of inflammatory factors in both groups before and after CRRT treatment

The inflammatory factors in both groups were analyzed, and the changes before and after treatment were calculated. As shown in Table 2, the IL-1 β , IL-6, TNF α , CRP, and PCT serum levels in the treatment group decreased after CRRT treatment, while little changes were observed in the control group. IL-8 levels in both groups increased after treatment (Table 2). There were significant differences in IL-6 and PCT levels between both groups. Although IL-1 β , TNF α , and CRP levels decreased in the treatment group, the difference between both groups was not significant ($p > 0.05$) (Figure 1).

3.3 | Levels of the other indicators in both groups before and after CRRT treatment

The Lac, Scr, BUN, SOFA, and NE in both groups were also analyzed, and the changes before and after treatment were calculated. As shown in Table 2, the Lac, Scr, SOFA

and NE dosage levels in the treatment group decreased after CRRT treatment, while little changes were observed in the control group. BUN levels in both did not change after treatment. There were significant differences in Lac, SOFA, and NE dosage levels between both groups ($p = 0.023, 0.01, 0.023$) (Figure 2).

3.4 | Survival analysis

Kaplan–Meier curve analysis showed that the 28-day survival rate was significantly higher in the treatment group than in the control group ($p = 0.01$) (Figure 3).

4 | DISCUSSION

Sepsis is a life-threatening condition caused by infection [1]. According to a global survey, approximately 47 million cases of sepsis and 11 million deaths due to sepsis were reported in 2017, accounting for a global death toll of 19.7% [6]. With recent medical advancements,



TABLE 2 Conditions of the treatment group and the control group before and after treatment.

	The control group		Difference value		The treatment group		Difference value	
	Before CRRT treatment	After CRRT treatment	Δd_2	Before CRRT treatment	After CRRT treatment	Δd_1		
IL-1 β (pg/mL)	5.00(5.00,10.40)	5.00(5.00,6.28)	0.00(0.00, 5.40) [#]	15.10 \pm 16.12	12.58 \pm 10.63	0.00(-14.86, 21.15) [#]		
IL-6 (pg/mL)	665.5(311.31000.0) [#]	522.2(141.61000.0) [#]	0.00(-66.8, 231.3) [#]	1000.0(703.0,1000.0) [#]	25.3(17.2,80.3) [#]	900.7(660.4, 976.2) [#]		
IL-8 (pg/mL)	370.76 \pm 427.61	516.37 \pm 490.85	-145.61 \pm 554.87	235.60 \pm 102.64	422.24 \pm 443.50	-186.64 \pm 466.22		
TNF- α (pg/mL)	53.16 \pm 47.47	40.45 \pm 20.64	4.71 \pm 16.92	81.24 \pm 55.06	24.36 \pm 11.47	56.88 \pm 55.93		
CRP (mg/L)	198.45 \pm 72.10	193.94 \pm 65.48	4.50 \pm 30.39	180.72 \pm 94.32	93.53 \pm 54.60	87.18 \pm 115.59		
PCT (ng/mL)	17.37(7.22,43.59) [#]	15.44(3.09,48.70) [#]	4.07(-1.04, 11.39)	100.00(41.94100.00) [#]	8.97(4.93,36.76) [#]	54.27(19.70,90.47) [#]		
Lac (mmol/L)	3.90 \pm 3.34	5.35 \pm 3.82	-0.3(-4.8,0.45) [#]	3.10(1.83,4.85) [#]	1.60(1.48,2.53) [#]	1.3(-0.25,1.73) [#]		
Scr (μ mol/L)	298.80 \pm 214.75 [#]	263.80 \pm 209.25 [#]	35.00 \pm 135.37	285.00 \pm 157.16	185.20 \pm 119.63	99.80 \pm 161.72		
BUN (mmol/L)	19.99 \pm 11.34	18.38 \pm 12.81	1.61 \pm 5.44	21.13 \pm 10.65	21.26 \pm 10.46	-0.13 \pm 10.69		
SOFA	12.10 \pm 4.61	12.20 \pm 5.01	-0.10 \pm 2.99 [#]	14.10 \pm 1.91	10.30 \pm 2.26	3.70 \pm 2.91 [#]		
NE (μ g/kg·min)	0.42(0.19,1.68)	0.98(0.33,2.04)	-0.03(-0.75,0.27) [#]	0.56(0.29,1.22) [#]	0.22(0.17,0.36) [#]	0.28(0.15,0.78) [#]		

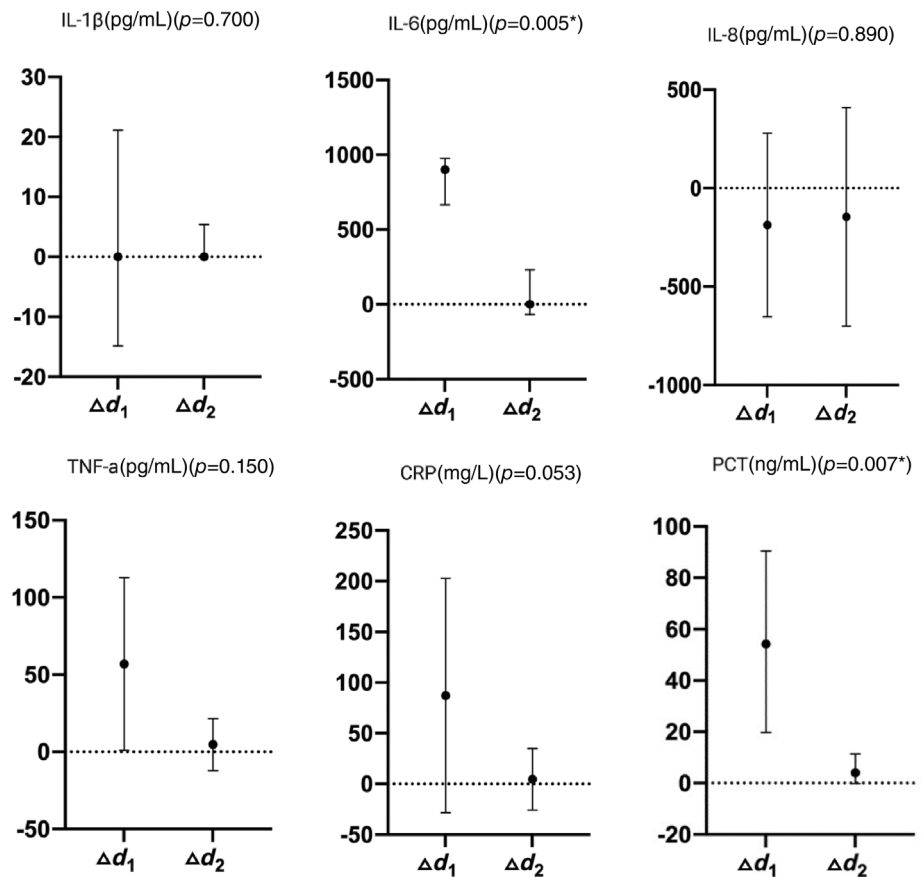
Note: # represents statistical difference. Δd_1 represents the difference value of each index before and after CRRT treatment in the control group. Δd_2 represents the difference value of each index before and after CRRT treatment in the treatment group.

sepsis diagnosis and treatment have improved; however, the case fatality rate for severe sepsis remains high, causing a significant burden on the social economy. At present, patients with sepsis are clinically treated with anti-infection, fluid management, organ support, and other comprehensive treatments. As our understanding of the molecular mechanisms of sepsis has increased, clinical researchers have started to develop a series of new therapeutic directions for sepsis by eliminating inflammatory factors in recent years.

With reported outbreaks of plague [7] and H1N1 virus [8], researchers realized that multiple organ dysfunction in patients with sepsis is not only caused by the pathogen itself but also due to the body's abnormal immune response to the pathogen and the "storm" of inflammatory factors [3]. A study regarding the molecular mechanism of sepsis suggested that the abnormal activation of macrophages, neutrophils, T cells, endothelial cells, and other cells is a result of the joint action of pathogen-related molecular pattern "PAMP" and tissue damage-related molecular pattern "DAMP." Abnormal secretion of cytokines, such as IL-1 β , TNF- α , IL-6, IL-8, and IL-10, can lead to inflammatory storms in severe patients and eventually develop into multiple organ failure or even death [9]. In addition, the study found that special treatments, tumors, autoimmune abnormalities, and infections can lead to inflammatory storms [3]. However, the related inflammatory storm in sepsis; IL-1 β , IL-6, and PCT levels; and markers of endothelial damage were increased more significantly [10]. Reportedly, cytokine storm is also associated with poor prognosis in the recent outbreak of the coronavirus disease 2019 [11, 12], with elevated cytokines including IL-1 β , TNF, IL-6, and IL-10 [13, 14]. Clinically, there are drugs used to neutralize inflammatory factors to achieve therapeutic effects, such as tozilizumab and stuximab, which suppress inflammatory storms by neutralizing IL-6 to achieve therapeutic effects [15]. As an important indicator to distinguish infection from non-infection, PCT also has a certain impact on the prognosis of patients with sepsis. Currently, PCT has been widely used in clinical practice to help clinicians determine when to start and stop antibiotic use [16, 17]. Considering the above findings on the molecular mechanism of sepsis and comprehensive treatment, extracorporeal circulation can remove excessive inflammatory mediators to achieve the stability of hemodynamics and the immune system.

At present, clinical studies on sepsis and blood purification treatment are mainly focused on purification time, dose, and different filters. Nash et al. found that CRRT did not improve short-term outcomes compared to intermittent hemodialysis [18]. Researchers conducted

FIGURE 1 Comparison of the difference of inflammatory factors between the treatment group and the control group before and after treatment. Δd_1 represents the difference value of each index before and after CRRT treatment in the treatment group. Δd_2 represents the difference value of each index before and after CRRT treatment in the control group.



a clinical study and increased the therapeutic dose of blood purification; the findings showed that there were no differences in the prognosis, ICU stay, SOFA score, vasoactive drug use, and inflammatory factor clearance effect between the increasing therapeutic dose and conventional treatment dose groups [19, 20]. However, a study demonstrated that high-volume hemofiltration can improve patient outcomes at 28 days and enhance hemodynamic stabilization [21]. Therefore, the therapeutic effect of blood purification therapy in sepsis was undefined. With the continuous innovation of medical materials, filters that can absorb and clear inflammatory factors, including oXiris, polymyxin-B, and HA330 HP, have been introduced in clinical practice. The adsorbent of the HA330-II blood perfusion device is a neutral macroporous resin with brown resin granules inside. HA resin belongs to a synthetic polymer adsorbent polymerized from styrene and divinylbenzene, which is a crosslinked polymer with a mesh structure. It has good mechanical strength and is an excellent adsorbent carrier that can effectively clear endotoxins and various inflammatory factors. Sazonov et al. reported that HA330 perfusion is safe and effective when used in pediatric tumor patients complicated with sepsis [22]. Another study also suggested that HA330 can effectively remove inflammatory factors [23].

Based on the above findings, we chose HA330-II HP combined with blood purification therapy and compared it with simple hemodiafiltration (CVVHDF) to observe its therapeutic effect and safety. The results showed that the IL-6 and PCT levels decreased significantly after CRRT treatment in the treatment group compared with the control group. Although there were no significant differences in the IL-1 β , TNF α , CRP, and PCT changes before and after CRRT treatment, the indexes in the treatment group all showed a downward trend. IL-8 levels in both groups increased after the treatment, which may be caused by the disease itself or the poor removal effect of HA330-II hemofiltration. Compared with conventional blood purification therapy, combined blood purification therapy with HA330-II HP can significantly reduce the levels of inflammatory factors, including IL-6 and PCT, and play a better role in regulating immunity. Furthermore, compared with immune-targeted drugs that only block and neutralize a single inflammatory factor, blood purification theoretically has certain advantages owing to the significantly elevated inflammatory factors in patients with septic shock. In addition, no complications including indwelling hemodialysis tube complications, electrolyte disturbances, and arrhythmia were observed in all enrolled patients; hence, its safety is certain but under strict clinical monitoring. Survival analysis was also

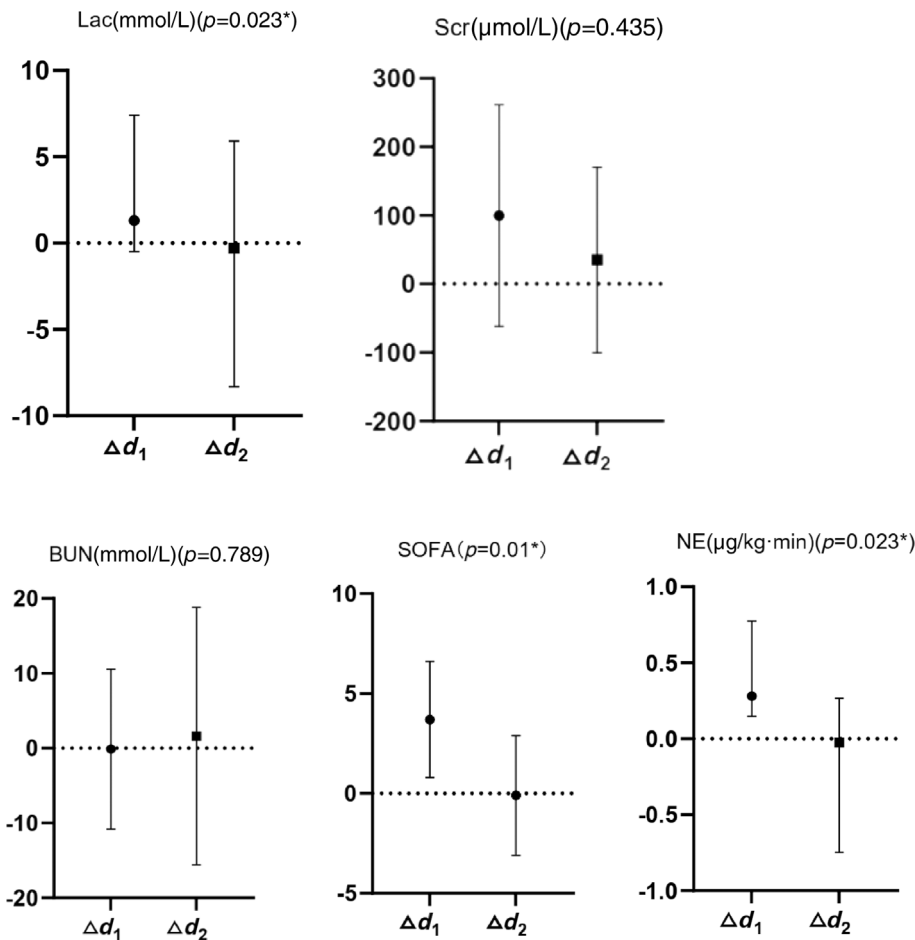


FIGURE 2 Comparison of the Lac, Scr, BUN, SOFA, NE between the treatment group and the control group before and after treatment. Δd_1 represents the difference value of each index before and after CRRT treatment in the treatment group. Δd_2 represents the difference value of each index before and after CRRT treatment in the control group.

Survival analysis of 28-day prognosis between the treatment group and the control group

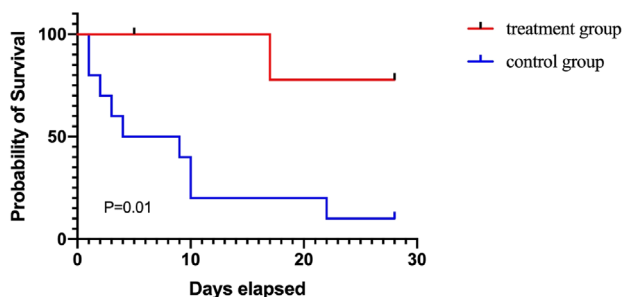


FIGURE 3 Survival analysis of 28-day prognosis between the treatment group and the control group ($p = 0.01$).

performed on 28-day outcomes in both groups, and the results showed that combined blood purification with HA330-II perfusion improved 28-day outcomes in patients with septic shock and acute renal insufficiency compared with hemodiafiltration alone (CVVHDF). This study also analyzed norepinephrine usage, Lac, SOFA scores, and 28-day prognosis between the two groups. The results showed that compared with simple continuous venovenous hemodiafiltration (CVVHDF), the combined

blood purification therapy using the HA330-II blood perfusion device can improve organ function, reduce blood lactic acid levels, decrease norepinephrine usage, and improve the 28-day prognosis in septic shock patients complicated with acute kidney injury. The abnormal immune response and “cytokine storm” of inflammatory factors are the main causes of multiple organ dysfunction in sepsis patients. This study demonstrates that blood purification can reduce abnormally elevated inflammatory factors in patients, thereby reducing the “cytokine storm” damage to various organs and thus improving the prognosis of sepsis patients.

In this study, the clinical use of CRRT not only has a renal replacement effect, which is convenient for clinicians to carry out volume management, but also has the potential effect of improving hemodynamics due to the power pump of the blood purifier [24]. Therefore, conventional CVVHDF treatment in the control group can reduce the specific differences caused by blood purification in both groups. Although this was a prospective, single-blind clinical study with a small sample size, it can provide a basis for future clinical research.

In conclusion, combined blood purification therapy with HA330 HP was effective in removing inflammatory mediators such as IL-6 and improving patient outcomes



at 28 days. Therefore, it may be a potential application for patients with septic shock and AKI.

FUNDING INFORMATION

Clinical study of CRRT to improve outcome in patients with urosepsis and acute kidney injury (NO. ITJ(QN)2010).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PATIENT CONSENT STATEMENT

All patients gave written informed consent before participation in this study.

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