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Original Article

Application of Different Continuous Renal Replacement Therapy Hemofilter in Patients with Septic Shock Complicated with Acute Renal Injury

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Abstract

Background: We aimed to compare the clinical effects of continuous renal replacement therapy (CRRT) with different hemofilters in patients with septic shock and acute kidney injury (AKI).

Methods: Thirty patients with septic shock complicated with AKI admitted to The Fourth Affiliated Hospital of Anhui Medical University from 2018-2020 were selected and divided into the control and observation groups. The control group was treated with CRRT using the conventional ST-100 hemofilter. The observation group was treated with CRRT using the oXiris hemofilter for 48 hours, followed by CRRT with the conventional ST-100 hemofilter. Infection indexes, sepsis-related organ failure assessment (SOFA), changes in corresponding organ function indexes, duration of each treatment, and death were compared between the two groups during CRRT.

Results: The white blood cells (WBC) count, high-sensitivity C-reactive protein (hs-CRP), and procalcitonin (PCT) levels were significantly decreased in the oXiris group 48 hours after CRRT (P= 0.048, 0.036, 0.031, respectively). After 48 hours of CRRT, SOFA score, serum lactic acid, and norepinephrine dose in the oXiris group were significantly lower than those in the control group (P= 0.039, 0.002, 0.021, respectively). The use time of vasoactive drugs and the treatment time of CRRT in the oXiris group was significantly shortened (P= 0.031 and 0.029, respectively). However, there were no significant differences in mechanical ventilation duration, intensive care unit (ICU) hospitalization time, total hospitalization time, ICU mortality, and in-hospital mortality.

Conclusion: For patients with septic shock complicated by AKI, CRRT treatment with the oXiris hemofilter could effectively clear inflammatory cytokine levels and quickly correct hemodynamic disorders, thus accelerating the recovery of organ function.

Keywords: Continuous renal replacement therapy; Septic shock; Acute kidney injury

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by the host's dysfunctional response to infection (1), with relatively complex pathogenesis. It is generally believed that sepsis is related to the large release of endotoxins and inflammatory factors induced by pathogens activating the immune system, causing "inflammation storm" (2).

Acute kidney injury (AKI) is the most common organ dysfunction caused by sepsis and septic shock and the main cause of death in critically ill patients (3). Its incidence rate is about 50%. Continuous renal replacement therapy (CRRT) is considered as a potentially effective treatment for improving the survival rate of patients with septic shock complicated with AKI (4). CRRT can non-selectively remove inflammatory mediators and cytotoxins present in the blood. Over the last decade, various biofilm materials have been developed, thus furthering CRRT technology. For example, a novel oXiris adsorption hemofilter can simultaneously absorb endotoxin and inflammatory factors and significantly reduce the levels of endotoxin and inflammatory factors in blood (5, 6). Yet, so far, there is little clinical study investigated the effectiveness of this treatment (7).

A retrospective case study was conducted to investigate the clinical efficacy of CRRT using oXiris hemofilter in patients with septic shock and AKI, and explore whether it could be effectively used in the clinic, thus, achieving a better prognosis.

Materials and Methods

Research population

In this retrospective case study, 30 patients with septic shock complicated with AKI admitted to the intensive care unit (ICU) of the Fourth Affiliated Hospital of Anhui Medical University between October 2018 and December 2020 were selected and divided into the observation group and the control group (15 cases per each group). Patients meeting the inclusion criteria who were treated with the oXiris hemofilter for 48 hours and then sequentially treated with the conventional ST-100 hemofilter for CRRT were included in the observation group. Patients who used the conventional ST-100 hemofilter for CRRT were included in the control group.

Inclusion and exclusion criteria

Inclusion criteria were: ① age ≥18 years old; ② patients meeting the diagnostic criteria of septic shock (1); ③ patients meeting the diagnostic criteria of grade 2 or 3 AKI proposed by Kidney Disease Improving Global Outcomes (KDIGO) in 2012 (8). Exclusion criteria were ① pregnant or lactating women; ② survival time < 24 hours; ③ those who had received CRRT before admission to ICU.

Research methods

All patients received routine clinical treatment, mainly including vital signs monitoring, 6h-buddle, vasoactive drugs, anti-shock, anti-infection, respiratory support, nutritional support treatment, etc. At the same time, femoral vein or internal jugular vein hemofiltration catheter was indwelling (ABLE Guangdong Baihe Medical Technology Co., Ltd.). Prismaflex blood purification machine (Baxter Medical Products Trading Co., Ltd.) was used for CRRT. Mode: continuous veno-venous hemofiltration (CVVH) was selected; blood flow rate: 150ml/min, 50% pre-dilution+50% post-dilution; speed of diluted fluid: 2000ml/h, the diluted fluid was finished calcium-containing basic liquid (Huaren Pharmaceutical Co., Ltd.), the ultrafiltration rate was 35ml/kg/h. Anticoagulation method: citric acid local anticoagulation, 4% sodium citrate solution for anticoagulation was used (Sichuan Nangeer Biotechnology Co., Ltd.). Blood gas analysis was monitored before and after hemofiltration. After hemofiltration, *in vitro* iCa was controlled at about 0.2-0.4mmol /L; for *in vivo* experiment, iCa was controlled at about 1.0-1.2 mmol/L. The rate of citric acid was adjusted according to the level of free calcium in blood gas analysis after hemofiltration; the rate of calcium pumping was adjusted according to the level of free calcium ion in blood gas analysis before hemofiltration, and the infusion rate of 5% sodium bicarbonate solution was adjusted according to the concentration of sodium bicarbonate in peripheral arterial blood gas analysis.

All patients started CRRT after the diagnosis was confirmed. The observation group was treated

with the oXiris hemofilter (Baxter, USA) for 48 hours. Then, the conventional ST-100 hemofilter (Baxter, USA) was sequentially used. The control group was treated with the conventional ST-100 hemofilter.

The research protocol was approved by the hospital Ethics Committee (PJ-YX2021-007(F2)), and written informed consent was obtained from all accepted patients or their agents.

Observation indicators

Comparison of systemic inflammation indicators

The observation indicators were white blood cells (WBC) count, high-sensitivity C-reactive protein (hs-CRP), and procalcitonin (PCT). WBC count was detected by BC-6900 automatic blood cell analyzer produced by Shenzhen Mindray Bio-Medical Electronics Co., Ltd., and the hs-CRP level was detected by BC-5390 automatic blood cell analyzer. PCT level was detected by Getein Fluorescence Immunoanalyzer produced by Getein Biotechnology Co., Ltd.

The organ function scores and changes in various indicators

The sepsis-related organ failure assessment (SOFA) score, norepinephrine dose, blood lactic acid value, oxygenation index, platelet count, blood bilirubin, blood creatinine value, and urine volume were compared between two groups. The blood lactic acid and oxygenation index were detected by Renault ABL90 FLEX blood gas analyzer (produced by Shanghai Radiometer Medical Equipment Co., Ltd.), and the platelet count was detected by BC-6900 automatic blood cell analyzer produced by Shenzhen Mindray Biomedical Electronics Co., Ltd. The blood bilirubin and creatinine levels were detected by the BC-5390 automatic blood cell analyzer.

Treatment time and death

The duration of vasoactive drug use, duration of CRRT, duration of mechanical ventilation, ICU hospitalization time, total hospitalization time, ICU mortality and in-hospital mortality were compared between the two groups.

Statistical analysis

SPSS 25.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables conforming to normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm s$). The independent-sample t-test was used to compare the continuous variables between the two groups. Categorical data were expressed as n (%), and χ^2 test was used for comparison between the two groups. $P<0.05$ was considered as statistically significant.

Results

Comparison of basic clinical data between the two groups

Both the observation group and the control group included 15 cases each. The observation group included 9 males and 6 females, aged 65.73±12.66 years. In the control group, there were 8 males and 7 females, aged 62.27±13.72 years. There was no statistical significance in gender and age between the two groups. Before CRRT treatment, there was no significant difference in APACHE II score, SOFA score, site of infection, pH, lactic acid, mean arterial pressure, norepinephrine dose, starting time of CRRT, AKI grade, creatinine, oxygenation index, and other indicators between the two groups ($P>0.05$; Table 1).

Table 1: Comparison of basic clinical data between the two groups

Characteristics	*Observation group*	*Control group*	*t value/χ^2*	*P-value*
Age (yr)	65.73±12.66	62.27±13.72	0.719	0.478
Gender Male : Female (cases)	9:6	8:7	0.136	0.713
APACHE II score	20.60±3.83	19.27±3.28	1.023	0.315
SOFA score	13.27±2.28	12.00±3.59	1.154	0.258
Site of infection (n,%)	15	15		
Pulmonary	4 (26.67%)	7(46.67%)	1.292	0.256
biliary	3 (20.00%)	1(6.66%)	1.154	0.283
Abdominal	7(46.67%)	4(26.67%)	1.292	0.256
Urinary	1(6.66%)	3(20.00%)	0.154	0.283
PH	7.30±0.04	7.32±0.04	-0.891	0.381
Lactate (mmol/l)	6.32±1.46	5.86±1.42	0.876	0.389
MAP (mmHg)	59.87±2.53	58.93±4.83	0.663	0.513
Noradrenaline dose (ug/kg/min)	0.62±0.25	0.50±0.21	1.423	0.166
Starting time of CRRT(h)	6.07±1.83	5.40±2.75	0.782	0.441
AKI stage at CRRT initiation (n, %)	15	15		
Stage 2	9(60%)	8(53.33%)	0.136	0.713
Stage 3	6(40%)	7(46.67%)		
Creatinine (umol/l)	302.0±83.66	295.5±82.22	0.214	0.833
Oxygenation index (mmHg)	187.8±26.26	190.9±32.69	-0.283	0.779

SOFA: Sequential Organ Failure Assessment; APACHE II: acute physiology and chronic health evaluation II; MAP: mean arterial pressure; AKI: acute kidney injury; CRRT: continuous renal replacement therapy; Oxygenation index: PaO2/FiO2 ratio

Comparison of inflammation indicators between the two groups

There were no significant differences in inflammatory indicators, including WBC, hs-CRP, and PCT levels, between the two groups before CRRT. WBC, hs-CRP, and PCT levels were significantly decreased in the oXiris group 48 hours after CRRT compared with the control group, with statistically significant differences (*P*=were 0.048, 0.036, 0.031, respectively; Fig. 1-3).

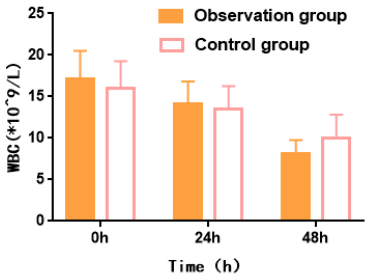

Fig. 1: Comparison of WBC between the two groups. 0h: *P*=0.335,*t*=0.980; 24h: *P*=0.500, *t*=0.683; 48h: *P*=0.048, *t*=-2.071

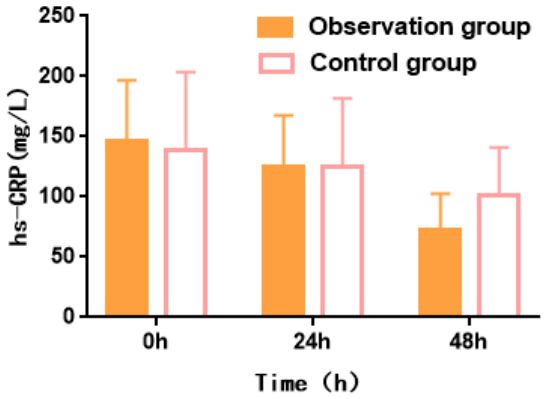

Fig. 2: Comparison of hs-CRP between the two groups. 0h: *P*=0.736, *t*=0.340; 24h: *P*=0.972, *t*=0.035 ; 48h; *P*=0.036, *t*=-2.202

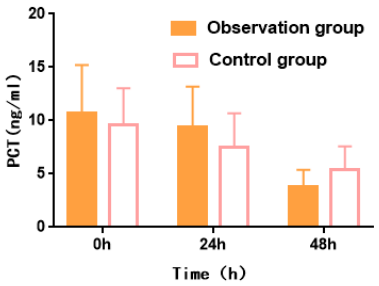

Fig. 3: Comparison of PCT between the two groups. 0h: *P*=0.451, *t*=0.764; 24h: *P*=0.143, *t*=1.509; 48h: *P*=0.031, *t*=-2.274

Organ function score and changes in various indicators of two groups of patients

After 48 hours of CRRT, SOFA score, serum lactic acid value, and norepinephrine dose in the oXiris group were significantly lower than those in the control group, with statistical significance (*P*= 0.039, 0.002, 0.021, respectively). After CRRT, there were no significant differences in oxygenation index, platelet count, blood bilirubin, blood creatinine, and urine volume between the two groups (Table 2).

Table 2: Organ function score and changes in various indicators

Variable	*Observation group*	*Control group*	*t value*	*P value*
SOFA score				
0h	13.27±2.28	12.00±3.59	1.154	0.258
24h	8.80±1.86	9.13±2.97	-0.366	0.717
48h	6.07±1.67	7.67±2.32	-2.169	0.039
Lactate (mmol/l)				
0h	6.32±1.46	5.86±1.42	0.876	0.389
24h	3.21±0.62	3.61±0.75	-1.620	0.116
48h	1.92±0.35	2.52±0.57	-3.504	0.002
Noradrenaline dose (ug/kg/min)				
0h	0.62±0.25	0.50±0.21	1.423	0.166
24h	0.37±0.13	0.35±0.13	0.399	0.693
48h	0.19±0.07	0.29±0.14	-2.450	0.021
Oxygenation index (mmHg)				
0h	187.8±26.26	190.9±32.69	-0.283	0.779
24h	236.8±23.10	239.1±26.34	-0.258	0.798
48h	271.7±12.46	267.3±20.65	0.717	0.479
PLT (*10^9/L)				
0h	121.4±27.80	128.0±33.55	-0.587	0.562
24h	106.4±24.40	114.5±28.61	-0.831	0.413
48h	89.13±21.83	99.27±25.64	-1.165	0.254
Bilirubin (umol/l)				
0h	28.78±8.07	26.31±7.28	0.879	0.387
24h	23.33±5.86	22.79±5.74	0.255	0.801
48h	19.89±4.23	20.71±5.25	-0.475	0.638
Creatinine (umol/l)				
0h	302.0±83.66	295.5±82.22	0.214	0.833
24h	258.9±58.83	255.4±81.13	0.137	0.892
48h	190.6±51.96	200.5±78.95	-0.407	0.687
Urine volume (ml)				
24h	603.7±183.9	706.3±147.6	-1.686	0.103
48h	744.0±180.6	825.3±145.4	-1.359	0.185

The treatment time and death of the two groups of patients

Compared with the control group, the duration of vasoactive drug use and duration of CRRT were significantly decreased in the oXiris group after CRRT (*P* were 0.031 and 0.029, respectively). However, there were no significant differences in mechanical ventilation duration, ICU hospitalization time, total hospitalization time, and clinical mortality between the two groups (Table 3).

Table 3: Comparison of treatment time and death between the two groups

Variable	*Observation group*	*Control group*	*t value/χ^2*	*P value*
Duration of vasoactive drug use (days)	4.78±1.33	5.89±1.35	-2.273	0.031
Duration of CRRT (days)	6.69±1.40	7.88±1.44	-2.295	0.029
Duration of mechanical ventilation (days)	7.98±1.34	8.46±1.28	-1.005	0.324
ICU LOS (days)	9.25±1.20	9.81±1.71	-1.026	0.314
Hospital LOS (days)	17.75±2.92	18.97±3.24	-1.083	0.288
ICU mortality (cases)	1	3	1.154	0.283
Hospital mortality (cases)	2	4	0.833	0.361

CVVH: continuous veno-venous haemofiltration; ICU: intensive care unit; LOS: length of stay; SOFA: Sequential Organ Failure Assessment

Discussion

Acute kidney injury is the most common complication in patients with septic shock associated with unacceptable morbidity and mortality (9). Despite advances in antibiotic therapy and organ function support, mortality in septic patients remains relatively high (range from 24% to 41%) (10). The pathogenesis of septic AKI is complex and mainly associated with a large content of inflammatory cytokines, which, in turn, lead to the occurrence and development of AKI. This immune reaction is activated through Toll-like receptors, and mannose receptors present on immune cells, endothelial cells, and renal tubular epithelial cells that recognize the pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP) (11). This binding, in turn, releases a large number of inflammatory mediators, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor, etc., forming cytokine storm and leading to continuous activation of the immune system, up-regulation of adhesion molecules, the release of more pro-inflammatory mediators and reactive oxygen species, platelet activation and aggregation, microvascular dysfunction, and hypoxia and tissue inflammation (12).

CRRT can more effectively remove fluid retention and metabolites and maintain internal environment stability, having little effect on hemodynamics (13). At the same time, CRRT can also remove endotoxin or inflammatory mediators, such as interferon-α (IFN-α) and IL-1β, to reduce the kidney damage caused by inflammatory mediators and reduce the mortality of AKI to a certain extent (3, 14), which is considered as an important mean for the treatment of septic AKI.

oXiris is a CRRT hemofilter that has been treated with polyethyleneimine and grafted with heparin on the surface of the basement membrane AN69, which can adsorb endotoxin and cytokines and reduce thrombogenic properties of the membrane (15). *In vitro* studies showed no significant

difference in the adsorption efficiency of inflammatory factors between oXiris and Cytosorb adsorption columns, both of which were higher than polymyxin B adsorption columns (16). In addition, there was no significant difference in the adsorption capacity of endotoxin between oXiris and polymyxin B adsorption columns, both of which were higher than that of Cytosorb adsorption column (16). Moreover, few clinical studies analyzed the treatment efficiency of Oxiris in the patients with sepsis and AKI; after 48 hours of treatment, the SOFA score was significantly reduced when compared with the historical control group (7).

Recently, a large study reviewed 60 patients with sepsis treated with oXiris from 2011 to 2018, showing that oXiris hemofilter treatment can reduce the dosage of vasopressor drugs, reduce the levels of endotoxin and inflammatory factors, and improve the organ function of patients (17). In this retrospective case study we found that WBC, hs-CRP, and PCT levels were significantly decreased after 48 hours of treatment with oXiris hemofilter compared to the control group treated with CRRT with conventional ST-100 treatment, indicating that oXiris hemofilter can quickly adsorb inflammatory factors or endotoxins and improve inflammatory indicators in patients. At the same time, after 48 hours of CRRT, the SOFA score, serum lactic acid value, and norepinephrine dose in the oXiris group were significantly lower than those in the control group(P= 0.039, 0.002, 0.021, respectively), and the duration of vasoactive drug use and duration of CRRT were significantly decreased (P values were 0.031 and 0.029, respectively). These results indicated that CRRT with oXiris hemofilter could reduce inflammatory storms, inhibit the sequential damage of organ function secondary to inflammatory factors, correct hemodynamic disorders more quickly, and facilitate rapid recovery of organ function. These improvements were more pronounced in sepsis patients infected with gram-negative bacilli (18,19). Nevertheless, we found no improvement in ICU hospitalization time or total hospitalization time, ICU mortality, or in-hospital mortality, in the oXiris group comped to the control group, which is consistent with previous studies (7). Interestingly, CRRT with oXiris hemofilter could significantly improve patients' survival rate with severe COVID-19 (20).

Limitation

This study had some limitations. Firstly, this study was a single-center study with small sample size. In addition, a variety of interventions, such as antibiotics, fluid resuscitation, vasopressor drugs, CRRT, etc., were used, which may lead to bias. Moreover, plasma endotoxin levels were not measured. These shortcomings can serve as the direction for future improvement and follow-up research.

Conclusion

CRRT treatment with oXiris hemofilter in patients with septic AKI was more effective in clearing inflammatory levels, correcting hemodynamic disorders more quickly, and improving organ function scores compared to conventional ST-100 hemofilter. However, large-sample, multicenter randomized controlled trials are needed to further evaluate its clinical efficacy.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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No funding was received in this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

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