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Original Article

Efficacy and prognosis of continuous renal replacement therapy at different times in the treatment of patients with sepsis-induced acute kidney injury

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Abstract: Objective: To investigate the efficacy and prognosis of CRRT at different times in the treatment of sepsis-induced acute kidney injury (SAKI). Methods: A total of 156 patients with SAKI were grouped into two groups in accordance with a random number table, with 78 patients in each group. Patients in the observation group (OG) were treated with early CRRT, and in the control group (CG), patients were treated with delayed CRRT. According to whether the patients died, there were 51 cases in the death group and 105 in the survival group. Renal function and inflammatory factors were compared before and after treatment; univariate and multilateral comparison were conducted to analyze the survival status of the patients. Results: After treatment, the blood urea nitrogen (BUN) and serum creatinine (Scr) in both groups fell below those prior to treatment, while the estimated glomerular filtration rate (eGFR) was elevated ($P<0.01$); the decrease of BUN and Scr in the OG was greater than that of the other group, while increase eGFR was more than that the other group ($P<0.01$). After treatment, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in both groups decreased compared to that prior to treatment ($P<0.001$); the decrease of the three factors in the OG was greater than that in the CG ($P<0.05$). The 60-day survival rate of patients in the OG was 76.92%, which was higher that of 57.69% in the CG ($P<0.05$). The age, acute physiology and chronic health enquiry (APACHE-II) score and proportion of chronic obstructive pulmonary disease (COPD) in the death group was elevated compared to those in the survival group, while the number of patients with early CRRT and eGFR level before treatment were lower than those in the survival group ($P<0.05$). Age was an independent risk factor for the prognosis of SAKI, and early CRRT was a protective factor for the prognosis ($P<0.05$). Conclusion: Early CRRT for SAKI can improve the renal function and inflammatory state effectively, and reduce the mortality of patients. Age is an independent risk factor affecting the prognosis of patients with SAKI, and early CRRT is a protective factor for the prognosis.

Keywords: Continuous renal replacement therapy, sepsis-induced acute kidney injury, efficacy, prognosis, influencing factors

Introduction

Sepsis is a clinically common and high-incidence severe infection. It is also one of the common causes of hospitalization and death in the intensive care unit (ICU) [1, 2]. The main pathogenic factor is infection, and the clinical manifestations are mainly systemic inflammatory reactions [3]. Previous studies have shown that sepsis can induce the occurrence of multiple organ dysfunction and even failure [4]. AKI is a frequent complication in severely ill patients. Studies have shown that about 30% of severely ill patients are associated with complications of AKI [5, 6]. Sepsis is closely related to the occurrence of AKI. Previous studies have indicated that more than 50% of the cases of AKI are closely linked to sepsis [7]. Another study showed that the mortality rate of patients with SAKI can be as high as 50%, which has a negative impact on prognosis [8].

At present, CRRT is clinically advocated for in the treatment of patients with SAKI, which can eliminate inflammatory mediators in the body, regulate the immune system and improve renal

function, with good clinical efficacy [9]. A previous study showed that early CRRT for SAKI is likely to improve the survival rate. However, this study only included SAKI patients undergoing CRRT, those without early CRRT were not involved in the study. Therefore, the evidence of the study cannot fully explain the significance and value of early CRRT in the treatment of patients with SAKI [10]. Another study showed that early CRRT can effectively correct the water-electrolyte imbalance in the body and acid-base metabolism, however, it also points out that early CRRT still has uncontrollable risks, such as thrombosis from vascular access, infection, hemorrhage, low blood pressure and dialysis imbalance in the initial dialysis patients and a risk of long-term renal non-recovery for patients with early CRRT [11].

There is still a controversy as to when to conduct CRRT for patients with SAKI. Based on this, this study compared the efficacy and prognosis of CRRT at different times for the clinical treatment of SAKI to provide more clinical basis for the treatment of SAKI.

Materials and methods

General information

This study was conducted in 156 patients with SAKI who were treated in the ICU of Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University) from January 2017 to December 2018, including 89 males and 67 females aged 45-65 years old. The patients were grouped into two groups according to a random number table, with 78 cases in each group. Patients in the OG underwent early CRRT, while those in the CG were treated with delayed CRRT. All patients signed informed the consent forms. This study was approved by the Ethics Committee of Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients met the diagnostic criteria of sepsis [12]; (2) patients met the diagnostic criteria of acute kidney injury [13]; (3) patient's clinical data were intact; (4) patients cooperated and completed the follow-up.

Exclusion criteria: (1) Patients did not have complete clinical data; (2) patients had severe malnutrition, tumors and other diseases; (3) patients had severe cardiopulmonary or cerebrovascular diseases; (4) patients had mental illness and could not cooperate; (5) there were already acute indications for CRRT or AKI that progressed to stage 3 before treatment; (6) patients were difficult or uncooperative with follow-up.

Methods

Based on the treatment plans in the diagnosis and treatment guidelines of sepsis and acute kidney injury in 2012, patients underwent treatments including: electrocardiograph monitoring of vital signs, supplementary nutrition and respiratory support treatment, anti-infection care, fluid replacement, acid-base balance correction and other treatments [12, 13].

Patients in the observation group received CRRT immediately when they were diagnosed with SAKI. A vascular access was established from the patient's right femoral vein or right internal jugular vein. A Fresenius 4008S hemofiltration machine (Beijing Fresenius Kabi Pharmaceutical Co., Ltd., China) was used to treat the patient with venovenous hemofiltration. Unfractionated heparin was used for anticoagulation, which was diluted by batter displacement liquid, and then infused, with an infusion of 10 hours per day and continuous treatment of 7 days. The decision to discontinue CRRT was based on the patient's individual condition.

For the control group, CRRT was adopted when the disease progressed to acute indications or AKI progressed to stage 3. The treatment plan was the same as that of the observation group.

Outcome measures

Before and after CRRT, 5 mL of venous blood was extracted from the patients, and BUN, Scr and eGFR were determined by automatic biochemical analyzer (Beckman, USA). CRP, IL-6 and TNF-α were measured by ELISA using automatic microplate reader (Thermo, USA).

The survival rate of the enrolled patients within 60 days after treatment was observed.

Table 1. Comparison of general information

Items	Observation group (n=78)	Control group (n=78)	χ^2/t	P
Gender (male/female)	47/31	42/36	0.654	0.419
Age (year)	59.7±9.2	60.8±8.4	0.780	0.437
Body mass index (kg/m^2)	24.12±3.21	23.93±2.87	0.390	0.697
Heart rate (beats/min)	118.42±10.24	119.63±10.87	0.716	0.415
Body temperature (°C)	39.45±1.31	39.84±1.27	1.888	0.061
APACE II score	22.14±2.32	22.34±2.45	0.524	0.601
Combined disease				
Hypertension	48	50	0.110	0.740
Type 2 diabetes	33	30	0.240	0.624
Coronary heart disease	41	47	0.939	0.333
Chronic obstructive pulmonary disease	33	37	0.415	0.520
Cerebral infarction	23	21	0.127	0.722
Infection sites			0.548	0.908
Pulmonary infection	61	64		
Urinary tract infection	7	5		
Biliary tract infection	4	3		
Other	6	6		

Note: APACHE-II: acute physiology and chronic health enquiry.

According to the survival status of the patients at 60 days after CRRT, they were grouped, including 51 cases in the death group and 105 cases in the survival group. Univariate and multilateral comparison were conducted.

Statistical analysis

SPSS 22.0 was used to analyze the data. Measurement data conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd). T-test was used for the data that conformed to the homogeneity of variances. Data not conforming to a normal distribution were represented by M (P25, P75). Rank-sum test was used for the data that did not conform to a normal distribution nor homogeneity of variances. Logistic regression was used to analyze the risk factors affecting the prognosis of patients with SAKI. Univariate analysis was selected to analyze the differences of variables; stepwise forwards multiple-factor analysis was used for variable selection with inclusion and exclusion levels of 0.05 and 0.10, separately. The risk of death was expressed by the adjusted odds ratio (OR value). P<0.05 was considered to be statistically significant.

Results

General information

There were no differences between the two groups in gender, body mass index, heart rate, body temperature, APACE II score, combined disease and infection sites (P>0.05). See **Table 1**.

Renal function

It was found that no significant difference in BUN, Scr and eGFR was noted between two groups prior to treatment (P>0.05). After treatment, BUN and Scr in both groups declined compared to that before treatment, while the eGFR increased compared to that before treatment (P<0.01). The decrease in BUN and Scr in the OG was greater than that of the CG, while the increase eGFR was better than that of the CG (P<0.01). See **Table 2**.

Inflammatory factors

There was no significant difference in the inflammatory factors of CRP, TNF-α and IL-6 between the two groups prior to treatment (P>0.05). After treatment, CRP, TNF-α and IL-6

Table 2. Comparison of the renal function before and after treatment

	BUN (mmol/L)	Scr (μmol/L)	eGFR (mL•min^{-1} (1.73 m^2)$^{-1}$)
Observation group before treatment	26.48±11.25	328.47±33.56	41.20±8.45
Control group before treatment	28.68±14.26	338.54±41.74	38.56±9.65
t	1.070	1.661	1.818
P	0.286	0.099	0.071
Observation group after treatment	14.21±3.54$^{###}$	173.46±17.92$^{###}$	51.21±11.52$^{###}$
Control group after treatment	18.42±4.29$^{###}$	198.22±20.35$^{###}$	45.36±10.27$^{##}$
t	6.685	8.065	3.348
P	<0.001	<0.001	0.001

Note: Compared with the same group before and after treatment, $^{###}$P<0.001, $^{##}$P<0.01. BUN: blood urea nitrogen; Scr: serum creatinine; eGFR: estimated glomerular filtration rate.

Table 3. Comparison of the inflammatory factors before and after treatment

	CRP (mg/L)	TNF-α (μg/mL)	IL-6 (μg/mL)
Observation group before treatment	130.24±41.21	325.47±85.32	462.36±50.92
Control group before treatment	134.69±48.54	322.76±84.92	471.27±55.41
t	0.617	0.199	1.046
P	0.538	0.843	0.297
Observation group after treatment	75.41±29.41$^{###}$	211.58±49.56$^{###}$	332.87±30.98$^{###}$
Control group after treatment	84.84±28.21$^{###}$	247.22±53.35$^{###}$	367.92±36.23$^{###}$
t	2.044	4.323	6.494
P	0.043	<0.001	<0.001

Note: Compared with the same group before treatment, $^{###}$P<0.001. CRP: C-reactive protein; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6.

Table 4. Comparison of 60-day survival rate

Items	Observation group (n=78)	Control group (n=78)	χ^2	P
Survival	60 (76.92)	45 (57.69)	6.555	0.010
Death	18 (23.08)	33 (42.31)		

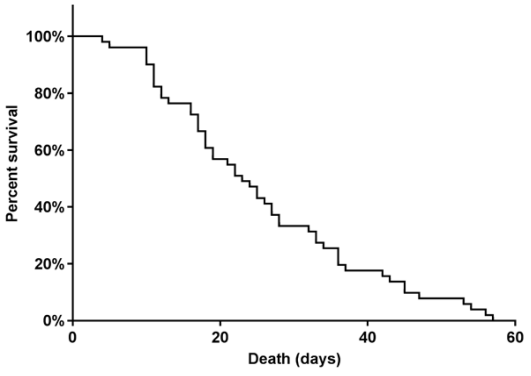

Figure 1. Survival curve of patients who died.

in both groups were significantly lower than those before treatment (P<0.001); the decrease CRP, TNF-α and IL-6 in the OG was greater than that in the CG (P<0.05). See **Table 3**.

60-day survival rate

The 60-day survival rate of patients in the OG was 76.92%, which was higher that of 57.69% in the CG (P<0.05). See **Table 4**.

General information of patients in the death and survival groups

Among the 156 patients, 51 of them died within 60 days, with a mortality rate of 32.69%. The median survival time of the dead patients was 23.000 days (95% CI: 17.002-28.998). Significant differences were noted in age, APACE II score, proportion of chronic obstructive pulmonary disease, CRRT mode and eGFR level before treatment between the death and survival group (P<0.05). See **Figure 1** and **Table 5**.

Multivariate logistic regression analysis of the prognosis of SAKI patients

It was revealed by multivariate regression analysis that age was an independent risk factor for the prognosis of SAKI patients, and early CRRT

Table 5. Comparison of general information of patients in the death and survival groups (n)

Items	Death group (n=51)	Survival group (n=105)	χ^2/t	P
Gender (Male/female)	28/23	61/44	0.143	0.750
Age (year)	65.3±10.3	54.8±8.1	3.631	<0.001
Body mass index (kg/m^2)	24.26±3.25	23.83±2.92	0.831	0.407
Heart rate (beats/min)	120.36±10.85	117.36±10.47	1.659	0.099
Body temperature (°C)	39.56±1.36	39.74±1.23	0.828	0.409
APACE II score	23.48±2.39	21.36±2.12	5.671	<0.001
Combined disease				
Hypertension	30	68	0.518	0.472
Type 2 diabetes	19	44	0.308	0.579
Coronary heart disease	29	69	1.152	0.283
Chronic obstructive pulmonary disease (n, %)	29 (56.86)	41 (39.05)	4.404	0.036
Cerebral infarction	12	32	0.818	0.366
Infection sites			0.865	0.834
Pulmonary infection	43	82		
Urinary tract infection	3	9		
Biliary tract infection	2	5		
Other	3	9		
CRRT mode			6.555	0.010
Early CRRT	18	60		
Delayed CRRT	33	45		
Related indicators before treatment				
BUN (mmol/L)	28.71±14.36	26.41±11.22	1.093	0.276
Scr (μmol/L)	339.36±41.96	327.74±33.32	1.873	0.063
eGFR (mL•min^{-1} (1.73 m^2)$^{-1}$)	37.25±9.47	41.74±8.55	2.969	0.004
CRP (mg/L)	136.73±47.62	129.63±40.25	0.972	0.332
TNF-α (μg/mL)	326.38±85.61	322.25±83.26	0.288	0.774
IL-6 (μg/mL)	473.36±54.36	463.31±52.36	1.111	0.286

Note: APACHE-II score: acute physiology and chronic health enquiry score; CRRT: continuous renal replacement therapy; BUN: blood urea nitrogen; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6.

was a protective factor for the prognosis (P<0.05). See **Tables 6**, **7**.

Discussion

Sepsis is a systemic inflammatory response. The production of a large number of inflammatory mediators leads to renal hemodynamics disorder, and it is also the most important factor resulting in the occurrence of AKI [14]. Previous studies have found that inflammatory factors can cause injury of endothelial cells in the renal tubular capillaries, leading to injury and dysfunction of renal tubules and further to the occurrence of AKI [15, 16]. CRRT plays an important role in the treatment of patients with SAKI. CRRT can effectively eliminate mainly small and medium-sized molecules of inflammatory mediators in patients, improve the immune function and reduce the damage of the inflammatory response to the body [17]. Another study also showed that CRRT used for SAKI can effectively improve the renal function and renal microcirculation state, and has a positive effect on the improvement of the prognosis [18]. This study also showed that CRRT can improve the inflammation state in patients regardless of when CRRT is started, which is consistent with the results of the above studies. There was a study on patients with SAKI undergoing CRRT at different times. In that study, a total of 231 patients who were diagnosed with SAKI were randomly grouped into two groups. Patients in one group received

Table 6. Independent variable assignment of prognostic factors in patients with SAKI

Factors	Independent variables	Assignment
Age (year)	X1	≥60=1, <60=0
APACE II score	X2	≥22=1, <22=0
Chronic obstructive pulmonary disease	X3	With =1, without =0
CRRT mode	X4	Delayed CRRT =1, early CRRT =0
eGFR (mL•min^{-1} (1.73 m^2)$^{-1}$)	X5	<39=1, ≥39=0

Note: APACHE II score: acute physiology and chronic health enquiry score; CRRT: continuous renal replacement therapy; eGFR: estimated glomerular filtration rate; SAKI: sepsis-induced acute kidney injury.

Table 7. Multivariate logistic regression analysis of prognosis of patients with SAKI

Factors	β	SE	Wald value	OR value (95% CI)	P
Age	2.023	0.849	7.965	7.521 (0.379-10.268)	0.006
CRRT mode	-0.276	0.072	13.283	0.743 (0.634-0.878)	0.035

Note: CRRT: continuous renal replacement therapy; SAKI: sepsis-induced acute kidney injury; OR: odds ratio; CI: confidence interval.

CRRT immediately, while those in another group didn't undergo CRRT until disease indications appeared. The results indicated that the mortality rate of patients on CRRT immediately was 39.3%, which was lower than that of 54.7% in patients who received delayed CRRT, with statistical differences [19]. Another study was conducted on 609 patients with SAKI who were going to receive CRRT (early or delayed) at different times. Among them, 301 cases were in the early CRRT group and 308 were in the delayed CRRT group. A total of 151 patients in the delayed-strategy group did not reach the therapeutic indication of CRRT, hence only 157 patients received CRRT. Moreover, there was no statistical difference in all-cause mortality between the two groups who received CRRT [20]. A study abroad also showed that there was no difference in mortality between delayed CRRT and early CRRT (58% vs 54%) [21]. This study suggested that early CRRT can effectively improve the renal function and the inflammatory state of patients and promote bodily repair, which is conducive to the early recovery of the patients. The all-cause mortality rate after treatment was further analyzed between the two groups. It was found that the mortality rate in the early CRRT group was significantly lower than that in the delayed CRRT group. The reason may be that the improvement of inflammatory state in patients with early CRRT can protect renal tubules from further injury, which is conducive to the recovery of organ function.

In this study, a multivariate logistic regression analysis found that age was an independent risk factor for the prognosis of patients with SAKI, and that early CRRT was a protective factor for the prognosis, suggesting that elderly patients should pay close attention to changes in their disease, actively treat the disease, and undergo early CRRT to improve the prognosis. Previous studies regarding the factors affecting the prognosis of patients with SAKI have found that the mortality rate of patients with SAKI increases with increased age. The reason is that organ function decreases with the increase of age [22, 23]. Another study confirmed that age is an independent risk factor leading to increased mortality in patients with SAKI [24]. APACE II score is a scoring indicator to determine the severity of patients' disease. A higher score indicates a more severe disease and a worse prognosis [25]. Since the main infection site of patients with sepsis is the lungs, patients with chronic obstructive pulmonary disease have a more severe condition after pulmonary infection, leading to an increase in mortality [10]. The worse renal function in patients with SAKI before treatment also indicates a poor prognosis [9]. Early CRRT in patients with SAKI can effectively improve the inflammatory state to avoid further damage to the renal tubules, and thus it is conducive to the recovery of organ function [19]. This result is consistent with that in this study.

There are also shortcomings in this study; multi-center samples were not used, the source was single, the sample size was small and the observation time was short. Further clinical research should be conducted in multiple cen-

ters with larger sample sizes and with a longer follow-up time to observe patients' prognosis.

To sum up, early CRRT in the treatment of patients with SAKI can improve their renal function and inflammatory state effectively, and reduce the mortality. Age is an independent risk factor affecting the prognosis of patients with SAKI, and early CRRT is a protective factor for prognosis.

Disclosure of conflict of interest

None.

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