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Original Article

The effect and clinical significance of continuous renal replacement therapy on sepsis and liver and kidney functions

Fan Jiang, Lian Zhang, Hong Xie, Juan Zhang, Maojuan Wang

Department of Critical Care Medicine, People's Hospital of Deyang, Sichuan, China

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Abstract: Objective: To determine the effect of continuous renal replacement therapy (CRRT) on sepsis, early liver and kidney functions, and the prognosis of patients with sepsis. Methods: 131 patients were divided into a study group (n = 71) and a control group (n = 60). Patients in the control group were treated with conventional therapy, but the patients in the study group underwent CRRT plus conventional treatment. Liver and renal functions as well as the levels of CRP and IL-6 in the two groups were measured. The total effective rate, the APACHE-II, and the SOFA scores in the two groups were determined. Results: There was no statistical difference in the clinical data between the two groups (P>0.05). The total effective rate after treatment in the control group was significantly lower than the rate in the study group (P = 0.028); After 3 days of treatment, the levels of IL-6 and CRP in the study group were significantly lower than the levels in the control group (P<0.05). After 3 weeks of treatment, the APACHE-II and SOFA scores in the study group were significantly lower than they were in the control group (P<0.05), and the two groups also showed differences in liver function (P>0.05), but not in renal function (P<0.05). The incidence of complications in the control group was significantly higher than it was in the study group (P = 0.003), and the 28-day mortality in the control group was significantly higher than it was in the study group (P = 0.035). Conclusion: CRRT can effectively treat sepsis and reduce the mortality rate, decrease the incidence of complications, improve renal function significantly, and improve the quality of life and survival in patients with sepsis with no effect on kidney function.

Keywords: Sepsis, CRRT, liver function, renal function, quality of life

Introduction

Pyemia, also known as sepsis, is a systemic inflammatory syndrome caused by infections characterized by a high incidence of complications and high mortality [1]. The clinical manifestations of sepsis are mainly fever, increased heart rate, increased respiratory rate, and confusion. Once the disease enters the progressive stage, symptoms of shock and multiple-organ dysfunction may develop in a patient; this stage poses a serious threat to the quality of life and the survival of the patient [2, 3]. Studies performed in hospital settings have shown that [4] the mortality rate of sepsis exceeds 25.0%; furthermore, more than 14,000 patients worldwide die from sepsis every day, and the mortality is still increasing. A survey showed that [5] between 1992 and 2001, there were more than 2.8 million people admitted to hospitals with sepsis-related diseases. However, many of these patients did not recover from the disease due to ineffective treatment; most eventually gave up the treatment, which finally lead to their deaths. The patients gave up because of the high cost of treatment, which many families could not afford. The high incidence and mortality of sepsis is currently a major problem that requires a solution from medical experts.

The conventional treatment of sepsis, which involves the administration of intravenous fluids and antibiotics, is far from satisfactory [6]. Continuous renal replacement therapy (CRRT) can be used to treat sepsis [7] by reconstructing the immune function of the human body by clearing the inflammatory mediators and further controlling the systemic response in patients. CRRT has been shown to have a good

efficacy in the treatment of severe pancreatitis and sepsis, and it can reduce the incidence of complications. Because the liver and the kidney are important sites for metabolism and protein synthesis in the human body, they are prone to develop functional impairment during the early stage of sepsis, which can result in the failure of patients' normal metabolism and the aggravation of the underlying condition [8].

Therefore, this study was performed to explore the effect of CRRT on sepsis, liver and kidney functions, and the prognosis of patients with sepsis so that it would serve as a reference for clinicians.

Materials and methods

Clinical data of patients

This study retrospectively analyzed the clinical data of 131 patients with sepsis who were admitted to our hospital between March 2014 and February 2016. Based on the treatment administered, the patients were divided into a study group and a control group. There were 60 patients in the control group, including 25 male patients and 35 female patients; their ages ranged from 29 to 70 years, and the mean age was 58.64±5.36 years. There were 71 patients in the study group, including 30 male patients and 41 female patients; their ages ranged from 35 to 69 years, and the average age was 57.82±6.12 years. The study was approved by the medical ethics committee of the hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows: age more than 18 years, presence of acute renal failure, availability of all clinical data, and no absence of the diagnosis of a malignant tumor. The diagnosis of sepsis was based on the diagnostic criteria established by the 2001 International Sepsis Definitions Conference [9].

The exclusion criteria were as follows: the presence of a cognitive dysfunction, immunodeficiency or immune disorder; history of congenital liver dysfunction or renal insufficiency; and pregnancy.

Treatment method

The patients in the control group were treated using the conventional regimen as follows: the patients were administered intravenous fluids, provided with body functional support and circulatory support. Patients with severe acute respiratory distress syndrome were administered ventilatory therapy. Based on the results of bacterial cultures and other microbiological tests, anti-infective therapies were administered using specific medications. Electrolyte balance was maintained, and organ functions were supported and protected. If necessary, intensive insulin therapy was used in the treatment of patients (2-4 U for each injection, 3 times in a day).

Patients in the study group underwent CRRT plus conventional therapy as follows: venipuncture was performed in the center of the femoral vein, and a central venous catheter was inserted to establish an extracorporeal circulation. A CRRT machine (Fresenius 4008S, Germany) was used for filtration, and the matching catheter was selected. The filtration mode was continuous veno-venous hemodiafiltration (CVVHDF). The machine parameter settings were as follows: blood flow control: 3-5 mL/ (Kg*h); dialysate amount, 40±10 mL/ (Kg*h); replacement ratio = 1:2; dehydration amount, 0.2 mL/ (Kg*h); preparation method of the replacement solution, filter base solution (4000 mL) + 10% KCl (10 mL) + 5% $NaHCO_3$ (250 mL); osmotic pressure = 280 mOsm/L. The treatment protocol was adjusted according to the corresponding conditions of the patients, and the two groups of patients were both treated for a total of 3 weeks.

Observation indices and evaluation criteria

The primary observation indices were as follows: liver function test results (bilirubin, albumin, and alanine aminotransferase levels) and renal function test results (urea nitrogen and creatinine levels) before and 3 days after the treatment in the two groups; the levels of CRP and IL-6 before and 3 days after the treatment in the two groups; and the total effective rate after the treatment in both groups [total effective rate = (number of the cured patients + number of the improved patients)/total number of patients*100%]. The evaluation criteria: the survival of the patients in the two groups of patients was assessed statistically, and the survival curve was plotted (**Table 1**).

The secondary observation indices were as follows: the APACHE-II and SOFA scores in the two groups before and after the treatment were

Table 1. Evaluation criteria for efficacy

Classification of curative effect	Evaluation criterion
Cure	After treatment, the lesions were basically healed, and the general discomfort was completely eliminated. All the indicators had returned to normal.
Take a turn for the better	After treatment, the primary lesion area of the patient has basically healed, but the local infection and trauma site have not been cured, and there is no obvious serious discomfort in the body.
Of no avail	After treatment, the patient's condition did not improve and there was no obvious change, the more serious patients' conditions had the tendency of aggravation.

determined; the higher the score was, the more serious the condition was. The incidence of complications in the two groups was observed during the treatment.

Laboratory tests

The liver and renal function tests and measurement of the CRP levels in the two groups were performed using the specific protein analyzer (Lifotronic PA-990, China). The IL-6 level was detected using an IL-6 Elisa kit (Beyotime Biotechnology Institute) following the procedures described below: the required plate was removed and placed in a 96-well frame, 50 μl of the sample assay buffer and 50 μl of the sample were added to the corresponding wells, and the plates were sealed and incubated for 2 h at room temperature. The plate was flushed 5 times, 100 μl/well of biotinylated antibody was added, and the plate was sealed and incubated for 1 hour at room temperature. Then, the plate was flushed 5 times, horseradish peroxidase-labeled streptavidin (100 μl/well) was added, and the plate was sealed and incubated in a water bath at 37°C for 20 minutes away from light. Next, the plate was flushed 5 times, 100 μl/well of the developer TMB solution was added, the plate was sealed and incubated for 30 minutes in a 37°C water bath away from light. Then, 50 μl/well of the stop solution was added, and a microplate reader was used to measure the maximum absorbance at 450 nm within 15 min. Three duplicate wells were set, and the experiment was repeated 3 times.

Statistical methods

In this study, the collected data was statistically analyzed using the SPSS 20.0 software package (Guangzhou Bomai), and the images were plotted using GraphPad Prism 7 (Shanghai Beka). Count data are expressed as percentages (%) and were analyzed using a chi-square test; continuous data are expressed as the means ± standard deviations (Means ± SD). All data are in a normal distribution, and the two groups was compared using a *t* test; the Kaplan-Meier estimator was used for the survival analysis, and a log-rank test was used to verify the statistical significance. A $P<0.05$ was considered statistically significant.

Results

No differences in two groups of base clinical data

In a comparison of the clinical data of the two groups of patients, it was observed that there were no statistically significant differences between the two groups with respect to gender, age, BMI, course of disease, smoking history, history of hypertension, and diabetes history ($P>0.05$) (**Table 2**).

The study group showed a higher effective rate than the control group

An assessment of the efficacy in both groups showed that there were 15, 30, and 15 patients that were cured, improved, or did not improve, respectively, in the control group; the corresponding number of patients in the study group was 30, 36, and 5, respectively. This implied that the total effective rate in the control group after the treatment was significantly lower than it was in the study group ($X^2 = 4.835$, $P = 0.028$) (**Table 3**).

The two groups showed significant differences in post-treatment renal function

We measured the liver and the renal functions before and 3 days after the treatment in both groups. The results showed that there were no differences in the liver function indices in the study group and in the control group between the time before and 3 days after the treatment

Table 2. Comparison of the clinical data between the two groups of patients [n (%)]

Factor	Control group (n = 60)	study group (n = 71)	X^2/t	*P* value
Sex			0.005	0.946
Female	25 (41.67)	30 (42.25)		
Male	35 (58.33)	41 (57.75)		
Age (years)	58.64±5.36	57.82±6.12	0.808	0.420
BMI (kg/m^2)	23.54±1.55	22.94±1.99	1.899	0.060
Course (h)	8.94±1.32	8.56±1.42	1.576	0.118
Smoking history			0.153	0.695
Yes	25 (41.67)	32 (45.07)		
No	35 (58.33)	39 (54.93)		
History of hypertension			2.971	0.085
Yes	50 (83.33)	66 (92.96)		
No	10 (16.67)	5 (7.04)		
Diabetes history			0.538	0.463
Yes	36 (60.00)	47 (66.20)		
No	24 (40.00)	24 (33.80)		

(*P*>0.05). The liver function indices were not significantly different between the two groups 3 days after the treatment (P>0.05). There were significant differences in the renal function indices between before and 3 days after the treatment in the study group (P<0.05); the renal function indices before the treatment and 3 days after the treatment were not significantly different in the control group. After 3 days of treatment, the renal function indices were significantly different between the two groups (P<0.05) (**Table 4** and **Figure 1**).

The study group exhibited lower IL-6 and CRP than the control group after treatment

We measured the levels of IL-6 and CRP in the two groups before and 3 days after the treatment and found that there was no statistical difference between the control group and the study group before treatment (P>0.05). After 3 days of treatment, the levels of IL-6 and CRP were significantly lower compared with those before the treatment in both groups (P<0.05), and the IL-6 and CRP levels were significantly lower in the study group than they were in the control group 3 days after the treatment (P<0.05) (**Table 5** and **Figure 2**).

The study group exhibited lower APACHE-II and SOFA than the control group after treatment

We evaluated the APACHE-II and SOFA scores in the two groups after the treatment and found that there was no difference in the APACHE-II and SOFA scores between the two groups before the treatment (P>0.05). After 3 weeks of treatment, the APACHE-II and SOFA scores was significantly lower compared to the scores before the treatment in both groups, and the APACHE-II and SOFA scores in the study group were significantly lower than they were in the control group (P<0.05) (**Table 6**).

The study group exhibited a lower incidence of complications than the control group during treatment

We found that the incidence of complications in the control group was significantly higher than it was in the study group by statistically comparing the incidence of complications in patients during treatment. (X^2 = 8.881, P = 0.003) (**Table 7**).

The study group exhibited a higher 28-day survival rate than the control group after treatment

We performed a 28-day survival analysis of the patients and found that the 28-day mortality in the control group was significantly higher than it was in the study group (P = 0.035) (**Table 8** and **Figure 3**).

Discussion

Sepsis is a complication mainly caused by diseases such as trauma, burns, infections, and ischemia-reperfusion. It is has a high incidence and is characterized by rapid progression, a high rate of complications, and a higher mortality rate [10]. According to statistics of the Centers for Disease Control and Prevention [11], there are more than 750,000 new cases of sepsis in the United States annually, with an annual growth rate of 1.5%. Sepsis has become the disease with the second highest mortality rate in ICU. Most scholars believe that the causes of sepsis are mainly community-acquired infections, nosocomial infections, antibiotic abuse, and invasive surgical operations [12]. Most of the pathogens infected by patients are mainly gram-negative bacilli. A study by Koupetori et al. [13], found that 80% of patients with sepsis were infected during hos-

Table 3. Efficacy of treatment in the two groups of patients [n (%)]

Group	Cure	Take a turn for the better	Of no avail	X^2 value	*P* value
Control group (n = 60)	15 (25.00)	33 (55.00)	12 (20.00)	4.835	0.028
Study group (n = 71)	30 (42.25)	36 (50.70)	5 (7.04)		

Table 4. Liver and kidney functions before and 3 days after treatment

Index	Control group (n = 60)		Study group (n = 71)	
	Pretherapy	3 days after treatment	Pretherapy	3 days after treatment
Bilirubin (μmol/L)	25.32±9.21	22.52±10.36	24.98±8.91	20.36±9.58
Albumin (g/L)	30.52±5.63	27.68±6.84	31.22±5.36	27.32±5.12
ALT (U/L)	52.44±22.98	42.99±20.57	51.83±25.19	40.58±20.37
24-h urine volume (mL)	822.36±45.15	894.56±58.61	843.62±51.36	1189.84±68.62*,#
BUN (mmol/L)	14.25±3.27	15.89±3.88	13.89±3.55	9.15±2.12*,#
Cre (μmol/L)	288.69±70.38	352.84±75.68	279.58±68.94	123.58±65.84*,#

Note: *There was a difference between before and after treatment (P<0.05). #There was a significant difference between the two groups (P<0.05).

pitalization, and *Escherichia coli* was the main pathogen. Owing to its high incidence, mortality, and cost of treatment, sepsis has become an urgent problem that requires a solution from medical experts. The main reason for the development of sepsis is the large number of inflammatory mediators that are released due to the stress reaction at the site of bacterial infection and the trauma that results in an inflammatory reaction [14].

Nowadays, the conventional clinical treatment of sepsis includes the administration of an anti-infective therapy; the control of blood sugar; and the provision of assisted mechanical ventilation, fluid resuscitation, and nutritional support. By adjusting the acid-base balance in patients, the symptom of urine reduction can be improved and homeostasis can be maintained in a patient [15]. However, the above treatment methods have certain disadvantages, including a long treatment duration, a heavy economic burden exerted on the families, and a high mortality rate after treatment. In addition, the abuse of antibiotics has led to the significant increase in the incidence of drug resistance in patients, which has resulted in significant reduction of the therapeutic effect of antibiotics [16]. CRRT is a clinical hemodialysis purification therapy that has emerged with the development of medical technology, and it enables the removal of inflammatory mediators in patients through continuous blood purification. It regulates the immune stress response and reduces the degree of inflammation in the body, which finally restores the homeostasis of the human body [17]. Other studies have shown that [18] CRRT works by regulating the hemodynamic parameters, and it promotes the recovery of various body system functions in humans. Therefore, this study provides the clinicians a reference for the selection of treatment options by retrospectively analyzing the effects of CRRT treatment and the conventional treatment on the improvement of sepsis and the early liver and kidney function as well as the prognosis.

In this study, we performed a 3-week treatment on patients with sepsis, and the results showed that the total effective rate in the control group was significantly different from the rate in the study group. The APACHE-II score was used to evaluate the severity of the acute and critical illness [19]. The SOFA score has also been widely used as an important score for evaluating the condition of patients with sepsis, and the higher the score was, the more serious the condition was. An evaluation of the APACHE-II and SOFA scores showed that the scores in the two groups were significantly decreased after the treatment, and the degree of reduction in the study group was significantly greater than it was in the control group, which indicated that the combination treatment (CRRT and conventional treatment) was significantly superior to the conventional treatment. In addition, the number of cured patients increased significant-

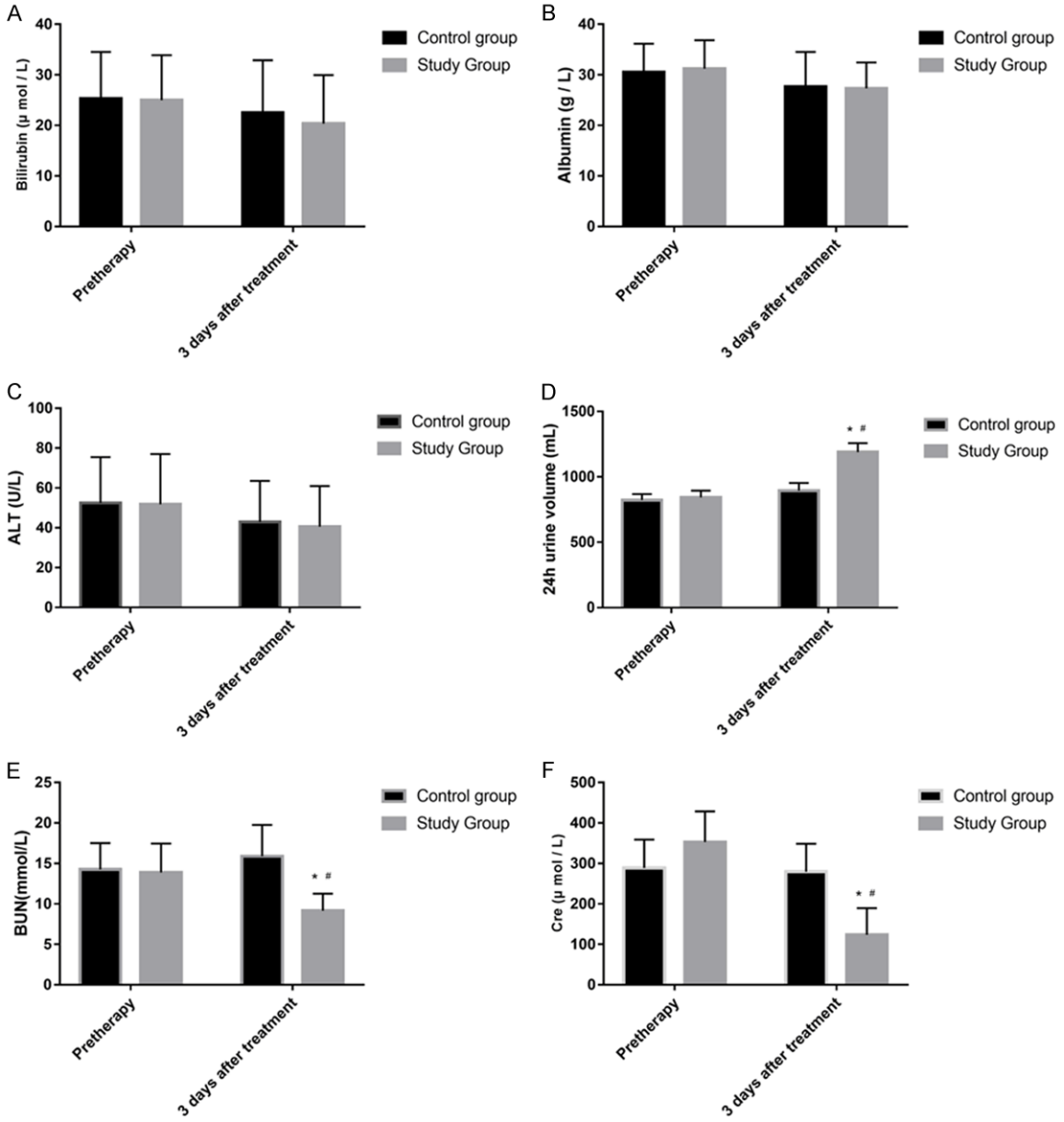

Figure 1. Liver and kidney function before and after treatment. *There was a significant difference between before and after treatment (P>0.05), and there was a significant difference between the study group and control group after treatment (P<0.05).

Table 5. Levels of IL-6 and CRP before and after treatment

Group	IL-6 (ng/L)		T value	*P* value	CRP (mg/L)		T value	*P* value
	Pretherapy	3 days after treatment			Pretherapy	3 days after treatment		
Control group (n = 60)	82.54±4.84	34.84±2.95	65.186	<0.001	58.68±12.25	15.66±7.25	23.410	<0.001
Study group (n = 71)	81.32±5.15	19.25±3.68	82.628	<0.001	57.56±11.57	10.84±4.92	31.312	<0.001
T value	1.389	26.413			0.537	4.508		
P value	0.167	<0.001			0.592	<0.001		

ly and the APACHE-II and SOFA scores decreased significantly in the study group. We also measured the levels of IL-6 and CRP in the blood before and 3 days after treatment. IL-6, a

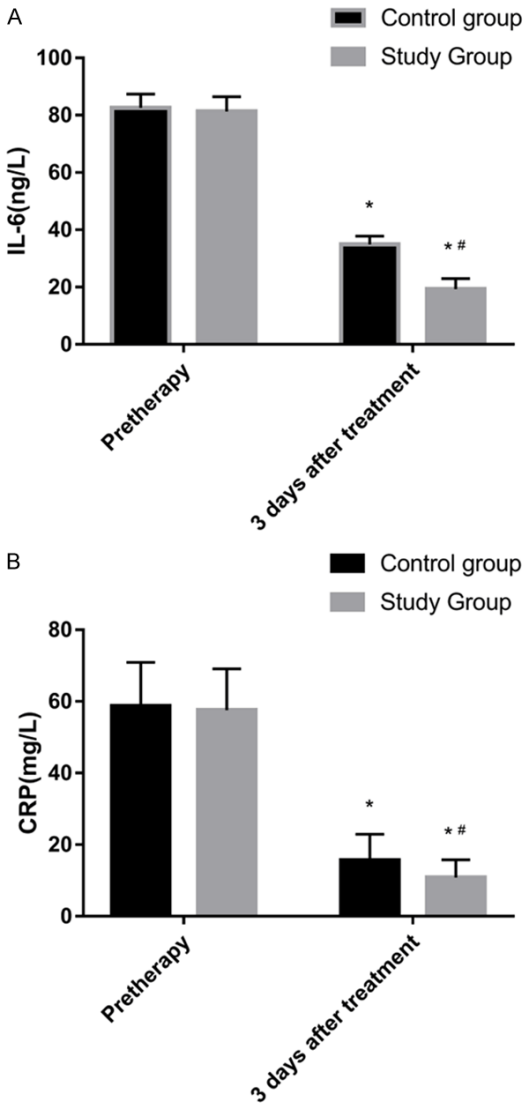

Figure 2. Levels of inflammatory cytokines before and after treatment. The IL-6 level in the study group was significantly lower than it was in the control group after 3 days of treatment (P<0.05). The CRP level in the study group was significantly lower than it was before treatment (P<0.05), and the CRP in the study group was significantly lower than it was in the control group 3 days after treatment (P<0.05). *There was a significant difference between before and after treatment (P<0.05).

pro-inflammatory mediator secreted by mononuclear fibroblasts, macrophages, and T lymphocytes, is involved in a variety of inflammatory reactions; it is stable in healthy bodies and can be used as a marker of various inflammatory and infectious diseases [20]. Studies have shown that the higher the serum IL-6 expression is in patients with sepsis, the worse the prognosis of patients will be. CRP is a type of a protein that is synthesized by the liver and is present in trace amounts in healthy humans. However, when a person develops an infection, the levels of CRP will rise rapidly while the infection is being eliminated; CRP will then significantly decrease [21]. Reports have shown that [22] CRP is of great value in the evaluation of the severity and prognosis of sepsis. We measured the levels of IL-6 and CRP in serum of the two groups and found that the IL-6 and CRP levels in the two groups were significantly decreased after treatment, but the serum IL-6 and CRP levels in the study group decreased by a greater extent than those in the control group, which illustrated well that CRRT enabled the effective removal of inflammatory mediators in patients with sepsis. GaneSan [23] showed that IL-6 combined with CRP is an ideal predictor of neonatal sepsis, and Jiang [24] reported that the IL-6 and CRP levels were significantly decreased in patients with sepsis, which indirectly proved and verified our study result.

Moreover, we tested the liver and renal functions of the patients and found that there was no significant changes in the liver function 3 days after the treatment when it was compared with the liver function before the treatment in both groups. The renal functions in the patients in the control group did not change significantly 3 days after the treatment when it was compared to the renal functions before the treatment, but the renal function after the treatment in the study group was significantly different from the renal function before the treatment, which indicated that CRRT promoted improvement in the renal impairment in patients with sepsis and was renoprotective. In a study by Han [25], it was shown that the renal function was significantly improved in patients with sepsis after CRRT, and the liver function was not significantly changed; these findings are consistent with our results. An analysis of the incidence of complications during the treatment in the two groups showed that the rate of complications in the control group was significantly higher than it was in the study group, which showed that CRRT treatment was effective in reducing the rate of complications during the treatment of patients, decreasing the suffering of the patients, and decreasing the cost of managing the complications. At the end of the study, we performed a 28-day survival analysis

Table 6. APACHE-II scores after treatment

Group	APACHE-II		T value	*P* value	SOFA		T value	*P* value
	Pretherapy	Post-treatment			Pretherapy	Post-treatment		
Control group (n = 60)	18.25±1.52	15.89±1.36	8.963	<0.001	16.11±1.58	13.22±2.02	8.729	<0.001
Research group (n = 71)	18.05±1.49	12.87±1.42	21.206	<0.001	16.39±1.83	7.66±1.59	30.343	<0.001
T value	0.758	12.364			0.928	17.620		
P value	0.450	<0.001			0.355	<0.001		

Table 7. Incidence of complications in patients with [n (%)]

Group	Shock	Acute respiratory distress syndrome	Deep venous thrombosis	Stress ulcer	Disseminated intravascular coagulation	X^2 value	*P* value
Control group (n = 60)	3 (5.00)	5 (8.33)	2 (3.33)	3 (5.00)	4 (6.67)	8.881	0.003
Study group (n = 71)	1 (1.41)	1 (1.41)	0 (0.00)	2 (2.82)	2 (2.82)		

Table 8. Survival of the two groups of patients [n (%)]

Group	7 d	28 d	P
Control group (n = 60)	7 (11.67)	14 (23.33)	0.035
Study group (n = 71)	3 (4.23)	7 (9.86)	

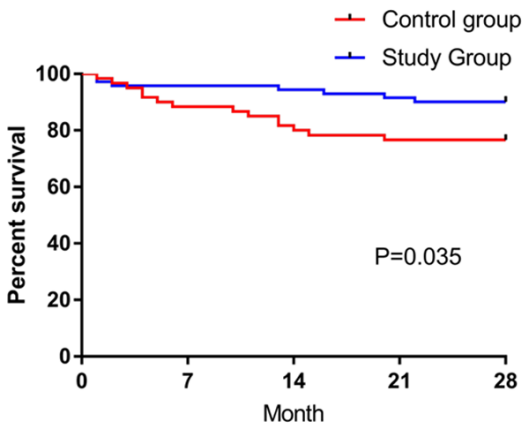

Figure 3. The survival of patients in the control group was significantly lower than it was in the study group (P<0.035), and the survival of the patients in the control group was significantly lower than it was in the study group (P = 0.035).

in the two groups of patients. We found that patients who received the conventional treatment in the control group had a lower 28-survival rate than patients who underwent CRRT treatment in the study group. In a study by Oh et al. [26], it was shown that the 28-day-survival rate of patients with sepsis after CRRT treatment was significantly improved, which was consistent with our study results; these results indicated that the CRRT improves the 28-day-survival rate.

There are some shortcomings in this study. We only performed a short-term follow-up rather than a long term follow-up, the sample size was small, and it is not clear whether there was a bias during the study, and it was a retrospective study. In addition, a study on the generation of sepsis was not further or specifically carried out. Therefore, we expect to perform a study with a longer follow-up and a larger sample size to further explore the pathogenesis of sepsis and to validate the results to this study.

Conclusions

In conclusion, CRRT is effective in the treatment of sepsis; it can reduce mortality, decrease the incidence of complications, significantly improve renal function, and improve the quality of life and survival of patients with sepsis. It hardly affects the kidney function of the patient and is worthy of further promotion into widespread use in clinical practice.

Disclosure of conflict of interest

None.

Address correspondence to: Maojuan Wang, Department of Critical Care Medicine, People's Hospital of Deyang, Deyang 618000, Sichuan, China. Tel: +86-13778280032; E-mail: miuniuj@163.com

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