Comparison of Anticoagulant Effect of Low-Molecular-Weight Heparin Sodium and Sodium Citrate on Patients with Severe Acute Kidney Injury Treated by Continuous Renal Replacement Therapy

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Keywords. Acute kidney injury; Low-molecular-weight heparin sodium; Sodium citrate; Continuous renal replacement

Introduction. Continuous renal replacement therapy (CRRT) is effective in treating acute kidney injury (AKI), but it requires anticoagulants. The study was conducted to compare the anticoagulant effect of low-molecular-weight heparin (LMWH) sodium and sodium citrate on AKI patients treated by CRRT.

Methods. The medical records of 150 severe AKI patients treated by CRRT in the Second Affiliated Hospital of Hainan Medical College (China, Hainan) from January 2020 to January 2023 were analyzed retrospectively. LMWH sodium was administered as an anticoagulant for 72 patients in the control group, and the remaining 78 receiving sodium citrate were enrolled into the observation group. Outcomes compared between groups included coagulation indices, inflammatory factors and renal function indices prior and post therapy, filter lifespan and adverse reactions.

Results. Post therapy, in contrast to the control group, the observation group showed notably lower prothrombin time (PT) and activated partial thromboplastin time (APTT) levels and a notably higher platelet (PLT) level ($P < .05$) and presented notably lower C-reactive protein (CRP) and interleukin-6 (IL-6) levels ($P < .05$). In contrast to the control group, the observation group experienced a notably longer filter service life and a notably lower total incidence of adverse reactions ($P < .05$).

Conclusion. Sodium citrate had a better anticoagulant effect than LMWH for severe AKI patients treated by CRRT, improving renal function and filter longevity with fewer adverse effects.

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INTRODUCTION

Acute kidney injury (AKI) refers to the rapid decline in kidney function within several hours or days, which is not considered as a pathological state of single organ failure, but a syndrome, in which the kidney takes a part in the progress of multiple organ dysfunction.1 Currently, AKI shows an increasing incidence, accounting for 8-16% of the inpatient, with a corresponding in-hospital mortality rate of as high as 20%.[2,3] The treatment strategies for AKI primarily involve correcting acid-base and electrolyte disorders, managing fluid level, avoiding nephrotoxic medications, and considering renal replacement therapy.[4] However, the management of electrolyte disorders and other interventions are often individualized, and the effectiveness of these

approaches remains controversial.[5] Continuous renal replacement therapy (CRRT) is the only alternative available for renal diseases, which is crucial for the treatment of AKI.[6]

Although CRRT can restore some important renal functions by correcting fluid imbalance and removing toxins, anticoagulants are required to ensure the patency of circulation during treatment.[7] If extracorporeal circulation coagulation occurs in the process of CRRT, it will compromise the treatment effect on patients, and also endanger life and safety of patients in serious cases, so effective anticoagulation is particularly important.[8] Sodium citrate and low-molecular-weight heparin (LMWH) sodium are clinically available anticoagulants in recent years. At present, LMWH sodium is extensively adopted to prevent thrombosis and treat thrombotic diseases.[9] Increased friction between blood and the inner wall of blood vessels and the activation of coagulation factors can easily trigger thrombosis, and LMWH can prevent thrombosis by inhibiting the activation of coagulation factors and platelet (PLT) aggregation, but it may increase the risk of bleeding.[10] Moreover, prior research has pointed out that LMWH has the risk of binging bleeding.[11] Sodium citrate can achieve complete anticoagulation in vitro while avoiding significant effect on blood coagulation in vivo, and it has stable and lasting anticoagulation effect while having a low risk of causing bleeding.[12] However, more clinical studies are required to verify the application effect of sodium citrate.

This study was to compare the anticoagulant influence of LMWH sodium and sodium citrate on severe AKI patients treated by CRRT, to provide direction and basis for clinical treatment.

MATERIALS AND METHODS

Patient data

The medical records of 150 patients with severe AKI treated with CRRT in the Second Affiliated Hospital of Hainan Medical College (China, Hainan) from January 2020 to January 2023 were collected and analyzed retrospectively. LMWH sodium was administered as an anticoagulant in CRRT for 72 participants allocated to the control group, comprising 48 males and 24 females (mean age: (60.8 ± 9.2) years) and the other 78 patients treated with sodium citrate were enrolled into the observation group, comprising 47 males and 31 females (mean age (61.3 ± 9.8) years).

Inclusion and exclusion criteria

Inclusion criteria: Cases diagnosed with severe AKI; patients who were treated with CRRT; aged ≥18 years; patients whose duration of each dialysis was ≥24 h; and cases with required clinicopathological data.

Exclusion criteria: cases with medication allergies, chronic renal insufficiency of various etiologies, autoimmune illnesses, intolerance to the therapeutic techniques used in this investigation, or coagulation malfunction.

Therapeutic regimen

All patients were treated by CRRT. A vascular access was established with a femoral or internal jugular vein, and replacement fluid was infused. The temperature was kept at 37-38°C; the replacement fluid was set to be 2000mL/h, and the blood flow to be 150-200 mL/min. The replacement fluid included 3000 mL 0.9% normal saline, 100mL 5% sodium bicarbonate, 100mL 5% glucose, 1000mL sterile water, 3mL 25% magnesium sulfate and 12-15 mL 10% potassium chloride. The dosage of potassium chloride was adjusted according to the electrolyte level of the patients. The control group patients received LMWH sodium as an anticoagulant. The initial dose was 60-80 U/kg, and then it was added at the dose of 10-20 U/kg. If the patient's glomerular filtration rate was below 30 ml/min, the dosage would be reduced by half. Patients in the observation group received sodium citrate as an anticoagulant. Before hemofiltration, sodium citrate solution for anticoagulation was pumped into arterial vascular access at the pump speed of 160-180 mL/h, and calcium gluconate was infused at the peripheral vein at 10 mL/h. The infusion speed of calcium gluconate and sodium citrate was adjusted according to the body's free calcium concentration to ensure that the free calcium concentration was kept at 1.0-1.2 mmol/L, and the ionic calcium concentration at 0.25-0.40 mmol/L after the filter.

Outcome measures

(1) The coagulation indices in the two groups were compared prior to and post CRRT treatment, involving activated partial thromboplastin time (APTT) prothrombin time (PT), as well as PLT count.

(2) The inflammatory factors in the two groups

were compared prior to and post CRRT treatment, involving C-reactive protein (CRP) and interleukin-6 (IL-6).

(3) The filter lifespan of the two groups was compared.

(4) The levels of renal function indices [creatinine (Cr) and blood urea nitrogen (BUN)] and compared prior to and post CRRT treatment in the two groups.

(5) The adverse reactions including hemorrhage, thrombocytopenia and diarrhea were recorded.

Statistical analyses

In this study SPSS 20.0 (IBM Corp., Armonk, NY, USA) was adopted for statistical analyses of the collected data, and Graphpad Prism 7 (GraphPad Software Co., Ltd., San Diego, USA) for data visualization. Measurement data were described through mean ± standard deviation, and their intergroup and intra-group comparisons were performed through the independent-samples T test and paired t test, respectively. Counting data were presented through cases (%) and compared between groups using the c^2 test which presented a notable difference ($P < .05$).

RESULTS

Baseline data of patients

The patients' baseline data are summarized in Table 1. The two groups were not greatly different regarding age, sex, severe infection, cause of disease, history of smoking, history of alcoholism, blood phosphorus, and blood calcium levels ($P > .05$).

Coagulation function of the two groups

Prior to therapy, the two groups did not differ notably regarding PT, APTT, as well as PLT levels ($P > .05$), whereas after it, PT and APTT in both groups increased conspicuously and PLT count in both groups decreased markedly. Additionally, the observation group presented markedly lower PT and APTT level and a notably higher PLT level in contrast to the control group ($P < .05$, Figure 1).

Inflammatory factors and filter lifespan in the two groups

Before therapy, the levels of CRP and IL-6 in the two groups were not greatly different ($P > .05$), while after it, the levels of them decreased notably, with markedly lower levels in the observation group ($P < .05$). The observation group experienced a notably longer filter lifespan than the control group ($P < .05$, Figure 2).

Renal function of the two groups

Before treatment, the two groups were similar regarding the levels of renal function indices, Cr and BUN ($P > .05$), while post therapy, the levels

Table 1. Baseline data

	Observation group	Control group	t/X^2	*P*
	(n = 78)	(n = 72)	0.322	.748
Age (years)	61.3 ± 9.8	60.8 ± 9.2		
Sex			0.663	.416
Male	47 (60.26)	48 (66.67)		
Female	31 (39.74)	24 (33.33)		
Severe infection			0.709	.400
Yes	22 (28.21)	16 (22.22)		
No	56 (71.79)	56 (77.78)		
Cause of disease				
Prerenal	32 (41.03)	31 (43.05)		
Post-renal	25 (32.05)	19 (26.39)	0.618	.734
Renal parenchymal	21 (26.92)	22 (30.56)		
History of smoking				
Yes	17 (21.79)	13 (18.06)	0.327	.567
No	61 (78.21)	59 (81.94)		
History of alcohol consumption				
Yes	17 (21.79)	18 (25.00)	0.215	.643
No	61 (78.21)	54 (75.00)		
Blood phosphorus (mmoL/L)	1.34 ± 0.32	1.30 ± 0.26	0.836	.405
Blood calcium (mmoL/L)	2.21 ± 0.51	2.30 ± 0.45	1.142	.255

of Cr and BUN in both groups reduced notably, with more significantly lower in the observation group ($P < .05$, Figure 3).

Adverse reactions in patients

Hemorrhage, thrombocytopenia and diarrhea occurred in both groups, and a markedly lower incidence of adverse reactions was found in the

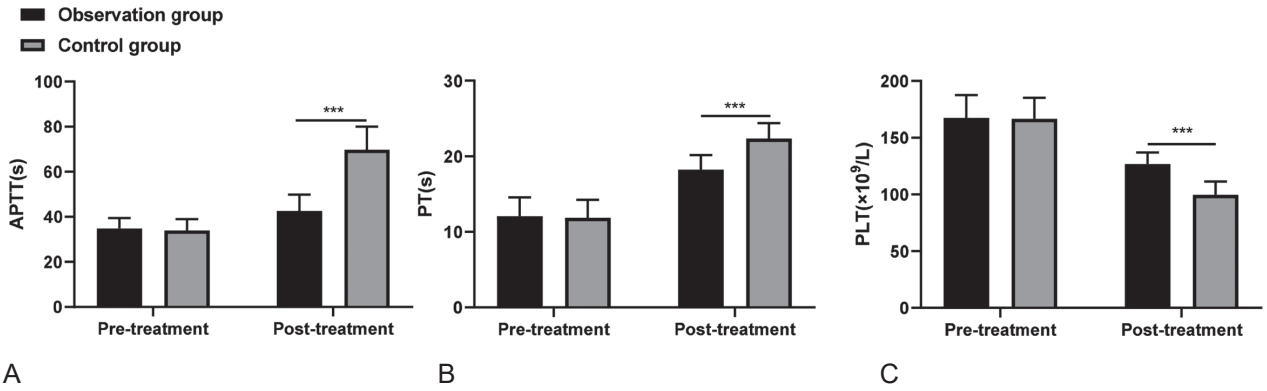

Figure 1. Coagulation function of the two groups before and after treatment. (A) Changes of APTT in patients before and after treatment. (B) Changes of PT in patients before and after treatment. (C) Changes of PLT in patients before and after treatment.

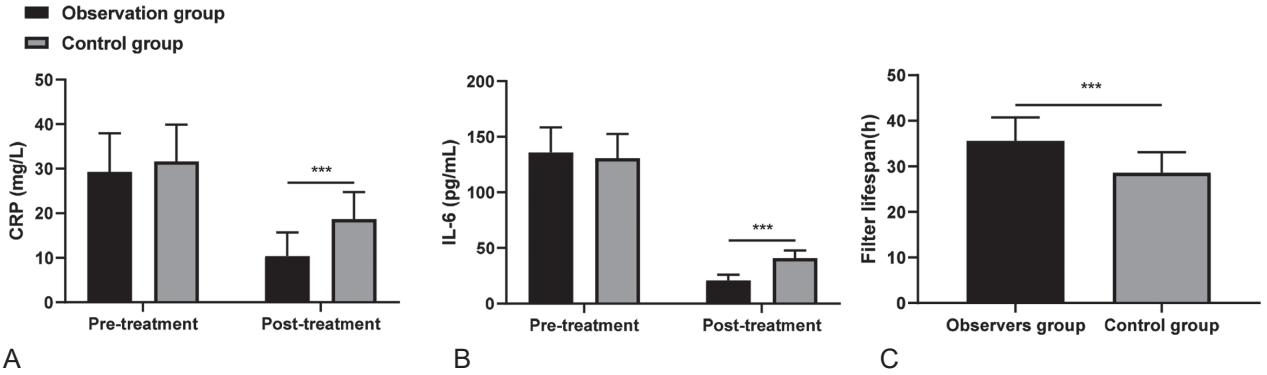

Figure 2. Comparison of inflammatory factors and filter lifespan between the two groups before and after treatment. (A) Changes of CRP in patients before and after treatment. (B) Changes of IL-6 in patients before and after treatment. (C) Comparison of filter usage time between the two groups.

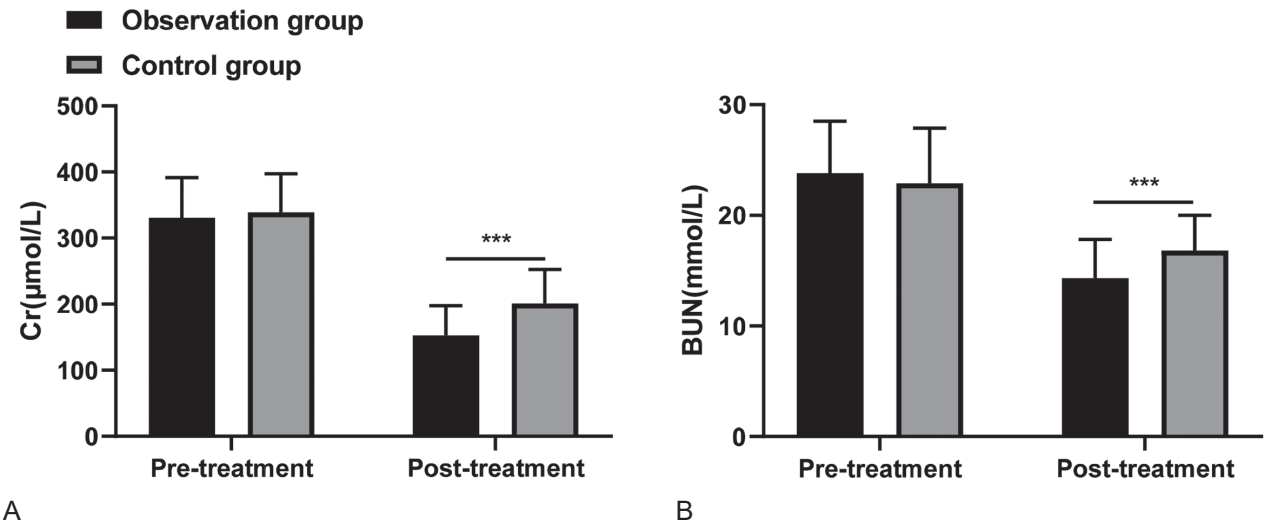

Figure 3. Renal function of the two groups before and after treatment. (A) Changes of Cr in patients before and after treatment. (B) Changes of BUN in patients before and after treatment.

Table 2. Adverse reactions

	Observation group (n = 78)	Control group (n = 72)	X^2	*P*
Hemorrhage	1 (1.28)	5 (6.94)		
Thrombocytopenia	2 (2.56)	6 (8.33)		
Diarrhea	2 (2.56)	3 (4.17)		
Total adverse reactions	5 (6.41)	14 (19.44)	5.609	.018

observation group in contrast to the control group ($P < .05$, Table 2)

DISCUSSION

Patients with AKI experience a sudden or progressive decline in renal function within a short period, causing the rapid accumulation of metabolic waste and harmful substances in the body.[13] Continuous renal replacement therapy (CRRT) employs principles such as convection, diffusion, and adsorption to continuously eliminating toxins, metabolites, and pathogenic biomolecules from the body, making it the preferred treatment for severe AKI patients.[14] Anticoagulation is a critical component of CRRT. An effective anticoagulation protocol can substantially decrease the risk of blood clot formation within the filter, extend the filter's lifespan, and prevent bleeding complications without increasing the risk of embolism.[15]

This study revealed that after CRRT treatment, both groups experienced an elevation in PT and APTT, along with a reduction in PLT count. Particularly, the group receiving sodium citrate exhibited significantly lower PT and APTT values and a significantly higher PLT compared to patients who received LMWH. The results suggest that sodium citrate is safer than LMWH, with little effect on the coagulation function of patients treated with CRRT. The possible reason is as follows: As an anticoagulant in hemodialysis, sodium citrate may decrease PT and APTT values due to inhibition of thrombin, and the level of PLT may be relatively high because it acts for a short time and has relatively little effect on PLTs.[16,17] In addition, in the present study, CRP and IL-6 in both groups decreased notably after therapy and patients treated with sodium citrate showed notably lower levels of these inflammatory factors than the patients treated with LMWH. These results imply that sodium citrate has a better anti-inflammatory effect and can effectively extend the lifespan of the filter. Panichi *et al.* also revealed that sodium citrate is more beneficial in improving the level of inflammation and biocompatibility in chronic dialysis patients.[18]

This study also determined the renal function indices, Cr and BUN, in the two groups and found that sodium citrate could decrease Cr and BUN levels more effectively than LMWH after treatment. The combination of calcium ions and citrate ions in the blood can form soluble calcium citrate, which is more difficult to dissociate, further reducing the concentration of calcium ions in the blood, promoting the discharge of harmful substances such as serum Cr and BUN, slowly and continuously removing harmful substances, alleviating kidney damage, thereby improving kidney function.[19,20] Finally, this study found a markedly lower incidence of adverse reactions among patients treated with sodium citrate than those treated with LMWH. Szymczak *et al.* have also revealed that sodium citrate can substantially reduce the probability of bleeding and infection as an anticoagulant in hemodialysis treatment,[21] which supports the results of the present study. Compared with LMWH, sodium citrate has a shorter duration of action and can be quickly removed by liver metabolism after dialysis. Compared with sodium citrate, LMWH has a longer duration of action and needs a longer time to be removed after dialysis. Therefore, sodium citrate can exert an effective anticoagulant effect while simultaneously being safer.[22]

To sum up, for severe AKI patients treated by CRRT, sodium citrate has a better anticoagulant effect than LMWH, can improve renal function effectively, and prolongs the filter lifespan with fewer adverse reactions.

LIMITATIONS

The case number of the study was small, so it is difficult to comprehensively reflect the comparison results of LMWH sodium and sodium citrate. Secondly, due to the limitation of research time, the long-term prognosis of patients is not completely

clear. Finally, because this is a retrospective study, there may be some unavoidable bias.

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ETHICAL CONSIDERATIONS

This study was approved by This study was approved by the Ethic Committee of the Second Affiliated Hospital of Hainan Medical College (ethnical approval number: TZ901453).

CONFLICT OF INTERESTS

All authors declare no conflicts of interest for this article.

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