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Original Article

Effects of regional citrate anticoagulation on clinical outcome and complications in continuous renal replacement therapy for acute kidney injury

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Abstract: Objective: To investigate the effect of regional citrate anticoagulation (RCA) on clinical outcome, renal function, and bleeding complications in patients with acute kidney injury (AKI) undergoing continuous renal replacement therapy (CRRT). Methods: This retrospective study reviewed medical records of 180 patients treated at the Second Affiliated Hospital of Hainan Medical University from January 2020 to January 2023. Patients were divided into two groups based on anticoagulation strategy: 85 patients who received systemic heparin anticoagulation (control group, CG) and 95 patients who received RCA (research group, RG). The clinical efficacy, adverse reactions, and incidence of bleeding complications were compared between the groups. Changes in renal function [blood urea nitrogen (BUN) and serum creatinine (Scr)] and coagulation values [prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count (PLT)] before and after treatment were also analyzed. Results: The total effective rate was significantly higher in the RG compared to the CG ($P<0.05$). The incidence of adverse reactions was 12.94% in the CG and 8.42% in the RG, with no statistically significant difference ($P>0.05$). However, the incidence of bleeding complications was significantly lower in the RG ($P<0.05$). After treatment, both groups showed significant reductions in BUN and Scr, with the RG exhibiting lower levels than the CG (both $P<0.05$). In both groups, PT and APTT increased while PLT decreased, but these values were more favorable in the RG (all $P<0.05$). Logistic regression analysis identified age, AKI stage, and treatment method as independent risk factors influencing treatment efficacy (all $P<0.05$). Additionally, post-treatment levels of hypersensitive C-reactive protein (hs-CRP) and interleukin-4 (IL-4) decreased in both groups, with the RG showing significantly lower levels than the CG (all $P<0.05$). Conclusion: RCA is effective for AKI patients undergoing CRRT, improving renal and coagulation function, reducing the risk of adverse reactions and bleeding, and demonstrating a favorable safety profile.

Keywords: Regional citrate anticoagulation, CRRT, acute kidney injury, efficacy, renal function, bleeding complications

Introduction

Acute kidney injury (AKI) is marked by a sudden decline in kidney function, leading to reduced glomerular filtration rate, which results in the accumulation of metabolic waste and toxins in the blood, as well as disturbances in electrolyte and fluid balance [1-3]. AKI is a significant global health issue, affecting people of all ages, but it is more common in the elderly, critically ill patients, and those with pre-existing conditions such as cardiovascular disease, diabetes, and chronic kidney disease (CKD) [4, 5]. The global incidence of AKI is high, with approximately 1.3 million people hospitalized for AKI each year [6]. Data indicate that around 5% of hospitalized patients may develop AKI, with the incidence reaching up to 30% among intensive care unit (ICU) patients. AKI has adverse patient outcome, leading to increased morbidity, mortality, and long-term complications such as progression to CKD [7].

The primary goal in AKI management is to address the underlying cause, support kidney function, and prevent complications. Current

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treatments include fluid management, pharmacotherapy, nutritional support, and renal replacement therapies (RRT) [8]. Continuous renal replacement therapy (CRRT) is a specialized form of RRT used for patients with severe AKI or advanced CKD, characterized by continuous treatment, filtration and ultrafiltration methods, minimal hemodynamic impact, and suitability for specific patient populations [9]. However, CRRT carries the risk of extracorporeal blood clotting and microthrombus formation, necessitating anticoagulation to maintain therapeutic efficiency and safety. Regional citrate anticoagulation (RCA) is commonly used in CRRT, since citric acid chelates calcium ions, inhibits thrombin activity, and prevents thrombosis [10]. Compared to systemic anticoagulation with agents like heparin, RCA reduces systemic bleeding risks, making it especially useful for patients prone to bleeding or with contraindications to heparin.

This study aims to evaluate the clinical efficacy of RCA in CRRT for AKI patients, with a focus on its effects on renal function and bleeding complications. The novelty of this research lies in its comprehensive assessment of RCA's therapeutic potential to optimize CRRT, enhance renal outcome, and improve patient safety by reducing bleeding risks. As the demand for safer and more effective anticoagulation strategies in CRRT grows, this study provides valuable insights to guide clinical decision-making and improve outcomes for AKI patients.

Materials and methods

Clinical data

The medical records of 193 patients treated at the Second Affiliated Hospital of Hainan Medical University from January 2020 to January 2023 were reviewed retrospectively. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Hainan Medical University.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the diagnostic criteria for AKI [11]; Patients with normal coagulation function before treatment; Patients receiving CRRT; Patients had not undergone long-term dialysis before treatment; Patients were in a normal mental state; Patients had complete clinical data.

Exclusion criteria: Patients with drug allergies or contraindications to treatments in this study; Patients with severe bleeding disorders, poor treatment compatibility or compliance; Patients with malignant tumors, blood disorders or infectious or immune diseases.

Sample screening

A total of 180 patients met the criteria and were included in the retrospective analysis (**Figure 1**). Based on the treatment approach, 85 patients who received systemic heparin anticoagulation for AKI were designated as the control group (CG), while 95 patients who received RCA were designated as the research group (RG).

Therapeutic schemes

Both groups underwent CRRT. A disposable central venous catheter (12 Fr, 2 × 23 cm) was inserted via the femoral vein (Device Registration Approval No. 20163102086). CRRT was performed using a continuous blood purification device (Device Registration Approval No. 20163101912) and a blood filtration tube (Device Registration Approval No. 202031-00205). The displacement settings were 70% pre-filter and 30% post-filter, with a replacement fluid rate of 3,000 ml/h and a blood flow rate of 120-200 ml/h. Treatment was administered continuously for 7 days in both groups.

In the CG, systemic heparin anticoagulation was used. Heparin sodium injection (Hainan Pharmaceutical Co., Ltd., SFDA Approval No. H41025473, specification: 2 ml:12,500 U/branch) was administered intravenously, with an initial dose of 1,000-5,000 IU followed by a maintenance dose of 3-15 IU/(kg·h), totaling 12,500 IU.

In the RG, RCA was employed. A 4% sodium citrate solution (Sichuan Mianzhu Hongji Pharmaceutical Co., Ltd., SFDA Approval No. H20055065, specification: 200 ml:8 g) was infused through the arterial line at a rate of 180-220 ml/h to achieve a citric acid concentration of 4.0 mmol/L. A 10% calcium gluconate solution (Changzhou Lanling Pharmaceutical Co., Ltd., SFDA Approval No. H32021259,

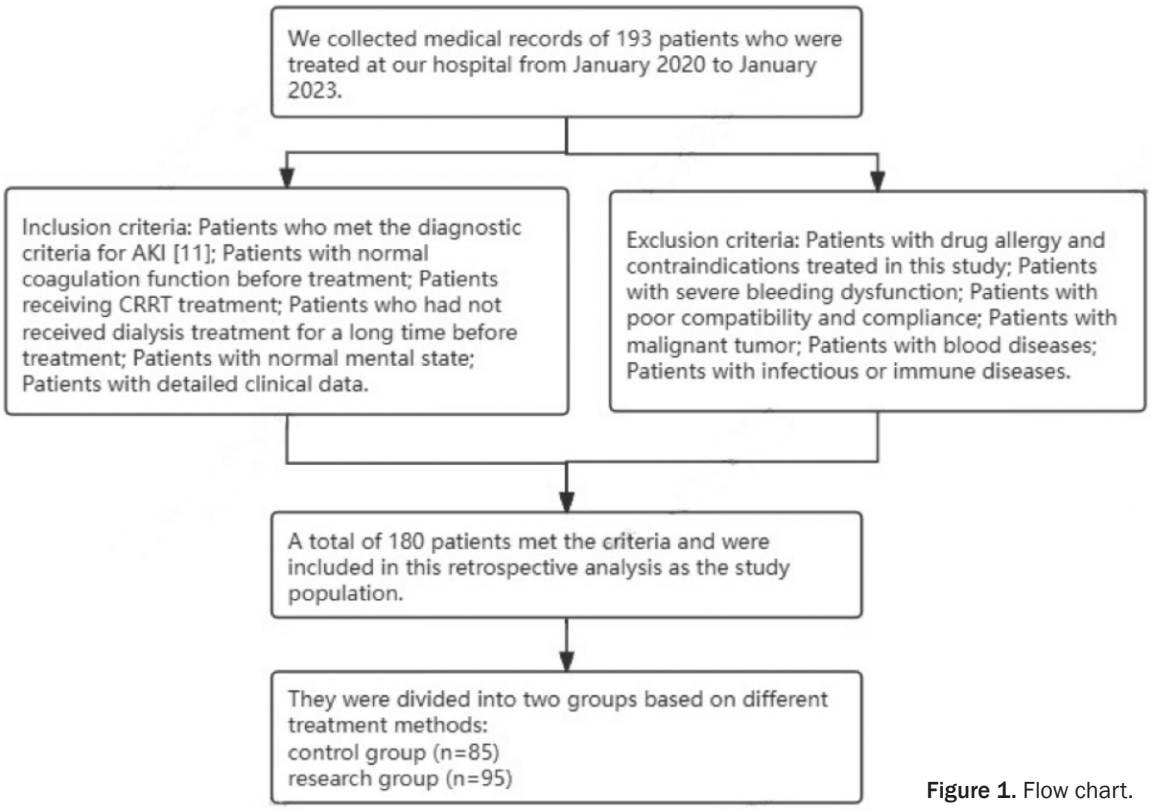

Figure 1. Flow chart.

specification: 10 ml:1 g) was administered via the venous line at an infusion rate of 5.5 mmol/h. The target was to maintain serum free calcium levels above 1.0 mmol/L and post-filter calcium ion concentrations between 0.25 and 0.45 mmol/L.

Index detection

Renal function indicators, including blood urea nitrogen (BUN) and serum creatinine (Scr) levels, were measured using enzymatic methods. The reagents were provided by Zhejiang Yilikang Biotechnology Co., Ltd. Coagulation values, including prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count (PLT), were assessed with the MDC3500 automatic coagulation analyzer. Serum levels of hypersensitive C-reactive protein (hs-CRP) and interleukin-4 (IL-4) were measured before and after treatment.

Data collection

Patient data, such as age, gender, BMI, primary disease, and AKI stage, were obtained from the hospital's medical records system and patient case files. Additionally, levels of BUN, Scr, PT, APTT, and PLT, as well as the incidence of adverse reactions and bleeding complications, were collected for retrospective analysis.

Outcome measures

Primary outcome measures: The therapeutic effects were evaluated and compared between the two groups after treatment. The total effective rate was calculated as follows: (markedly effective + effective) × 100%/total number of patients. The criteria for efficacy evaluation are presented in **Table 1**. Changes in renal function (BUN and Scr) before and after treatment were also compared.

Secondary outcome measures: Coagulation function values (PT, APTT, and PLT) were compared between the two groups before and after treatment. Additionally, the incidence of adverse reactions and bleeding complications was assessed post-treatment.

Statistical analysis

Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, USA). Graphs were generated

Table 1. Evaluation criteria for clinical efficacy [12]

Efficacy grade	Evaluative criteria
Markedly effective	Clinical symptoms (e.g., signs of bleeding complications, renal function abnormalities) have disappeared, and all indicators (e.g., electrolyte balance, blood pressure, and incidence of bleeding events) have returned to normal.
Effective	Clinical symptoms have been relieved, and the degree of improvement in the condition is >50%.
Ineffective	The degree of improvement in the condition is ≤50%, or there is evidence of deterioration.

Table 2. Comparison of baseline data

Factor	Control group (n=85)	Research group (n=95)	χ^2	P
Age (years old)			0.010	0.921
≤60	40	44		
>60	45	51		
Gender			0.040	0.842
Male	46	50		
Female	39	45		
BMI (kg/m^2)			0.047	0.829
≤23	47	51		
>23	38	44		
Primary disease				
Severe pneumonia	52	56	0.093	0.761
Acute and severe pancreatitis	20	25	0.186	0.667
Acute cholangitis	13	14	0.011	0.917
AKI stage				
Stage I	15	20	0.332	0.577
Stage II	59	65	0.021	0.886
Stage III	15	10	1.902	0.168
Educational level			0.005	0.945
Below junior college	55	61		
Junior college and above	30	34		
Place of residence			0.004	0.954
City	46	51		
Rural	39	44		

Note: BMI, body mass index; AKI, acute kidney injury.

with GraphPad Prism 7 (GraphPad Software Inc., San Diego, USA). Categorical data were expressed as percentages and analyzed using the chi-square test. Continuous variables were analyzed with paired t-tests for intra-group comparisons and independent sample t-tests for inter-group comparisons. Statistical significance was set at P<0.05.

Results

Comparison of baseline data

An analysis of the baseline clinical characteristics showed no significant differences between the two groups regarding age, gender, BMI, primary disease, AKI stage, educational level, or place of residence (ALL P>0.05) (**Table 2**).

Comparison of efficacy

The therapeutic efficacy was compared between the two groups, revealing that the total effective rate in the CG was significantly lower than that in the RG (P=0.041) (**Table 3**).

Comparison of renal function

Renal function indicators, including BUN and Scr, were compared before and after treat-

Table 3. Comparison of efficacy

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=85)	30 (35.29)	39 (45.88)	16 (18.82)	69 (81.18)
Research group (n=95)	50 (52.63)	37 (38.95)	8 (8.42)	87 (91.58)
χ^2		5.461		4.201
P		0.019		0.041

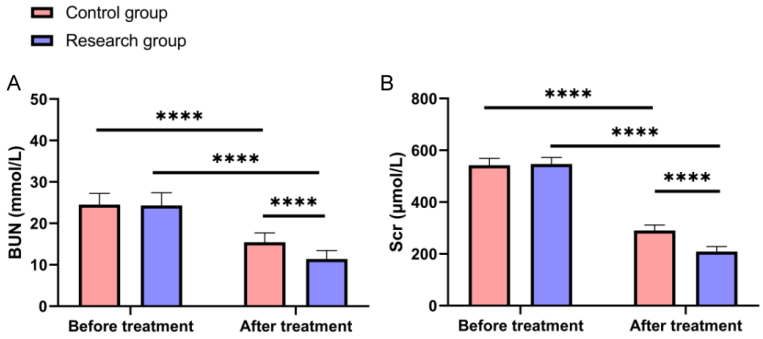

Figure 2. Comparison of renal function. A. Changes in BUN level before and after treatment. B. Changes in Scr level before and after treatment. Note: **** means P<0.0001. BUN, blood urea nitrogen; Scr, blood creatinine.

ment. No significant differences were found between the two groups prior to treatment (both P>0.05). However, post-treatment BUN and Scr levels in the RG were significantly lower than those in the CG (both P<0.05). In both groups, intra-group comparisons showed that BUN and Scr levels were significantly reduced after treatment (both P<0.05) (**Figure 2**).

Comparison of coagulation function

Coagulation values (PT, APTT, and PLT) were compared before and after treatment. No significant differences were observed between the two groups before treatment (all P>0.05). Post-treatment, PT, APTT, and PLT values in the RG were significantly better than those in the CG (all P<0.05). Intra-group comparisons demonstrated that, after treatment, PT and APTT levels significantly increased, while PLT levels significantly decreased in both groups (all P<0.05) (**Figure 3**).

Comparison of adverse reactions and bleeding complications

The incidence of adverse reactions and bleeding complications was compared between the groups. The incidence of adverse reactions was 12.94% in the CG and 8.42% in the RG, with no significant difference (P> 0.05). However, the incidence of bleeding complications was significantly lower in the RG compared to the CG (P=0.002) (**Tables 4** and **5**).

Risk factors affecting efficacy

Univariate analysis: Patients who showed significant improvement or improvement were classified as the good prognosis group (n=156), while those with no improvement were classified as the poor prognosis group (n=24). Univariate analysis identified age, AKI stage, and treatment method as factors associated with treatment efficacy (**Table 6**).

Multivariate analysis: The significant factors identified in univariate analysis were assigned values for multivariate logistic regression analysis, as detailed in **Table 7**. The analysis confirmed that age, AKI stage, and treatment method were independent risk factors influencing treatment efficacy (**Table 8**).

Comparison of inflammatory response

Before treatment, there were no significant differences in inflammatory marker levels between the two groups (both P>0.05). After treatment, levels of hs-CRP and IL-4 decreased in both groups, with the RG showing significantly lower levels compared to the CG (both P<0.05) (**Table 9**).

Discussion

Acute kidney injury (AKI) is a complex condition that progresses through stages, including prerenal injury, renal injury, and recovery, with severe cases potentially resulting in permanent kidney damage [13, 14]. The pathogenesis of

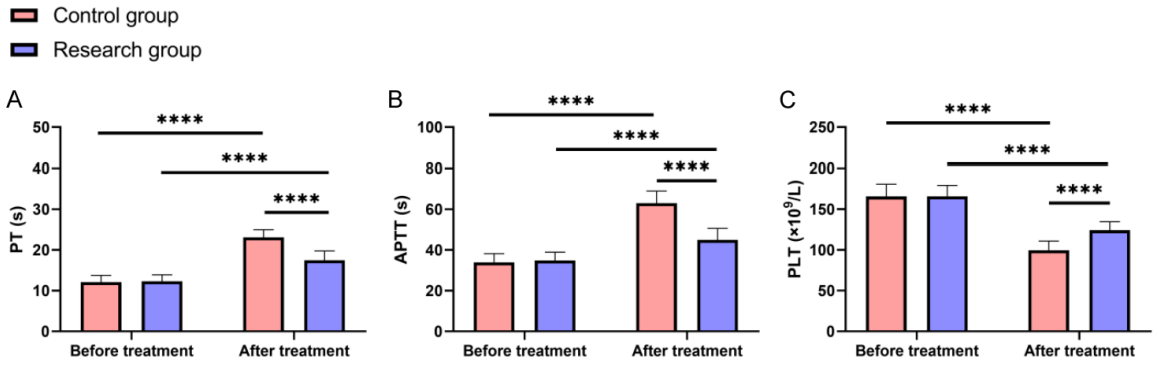

Figure 3. Comparison of coagulation function. A. Changes in PT level before and after treatment. B. Changes in APTT level before and after treatment. C. Changes in PLT level before and after treatment. Note: **** means P<0.0001. PT, prothrombin time; APTT, activated partial thromboplastin time; PLT, platelet count.

Table 4. Comparison of adverse reactions

Group	Thrombocytopenia	Fever	Diarrhea	Total adverse reactions
Control group (n=85)	3 (3.53)	5 (5.88)	3 (3.53)	11 (12.94)
Research group (n=95)	2 (2.11)	4 (4.21)	2 (2.11)	8 (8.42)
χ^2				0.971
P				0.325

Table 5. Comparison of bleeding complications

Group	Bleeding complications
Control group (n=85)	14 (16.47)
Research group (n=95)	3 (3.16)
χ^2	9.296
P	0.002

AKI is multifactorial, involving reduced renal blood flow, tubular obstruction, and triggers such as sepsis and drug toxicity [15-17]. Clinically, AKI is characterized by symptoms like decreased urine output, changes in urine color, fluctuating blood pressure, edema, nausea, vomiting, fatigue, and loss of appetite [18, 19].

Early recognition and timely intervention are crucial for improving outcome, and CRRT is a key treatment for critically ill AKI patients [20]. However, complications like filter clotting can limit CRRT effectiveness, necessitating the use of anticoagulation. Systemic heparin anticoagulation is commonly employed in CRRT to inhibit clot formation and maintain filter patency [21], but it also poses risks, including overall inhibition of coagulation function and an increased risk of bleeding.

RCA is an alternative anticoagulation method used in CRRT. It achieves its effect by adding a citrate-containing solution to the filter, which reduces systemic bleeding risks and minimizes the effect on systemic coagulation [22, 23]. In this study, we compared RCA with systemic heparin anticoagulation in AKI patients undergoing CRRT. Our findings showed that RCA was associated with better clinical outcome and improved renal function, as indicated by significant reductions in BUN and Scr levels compared to the CG.

Both groups showed a reduction in BUN and Scr after treatment, but the decreases were significantly greater in the RG, suggesting that RCA more effectively supports renal function improvement during CRRT. RCA helps maintain filter patency by preventing clot formation, thus ensuring the continuous and effective operation of CRRT. This uninterrupted renal support reduces the kidneys' workload and promotes functional recovery. These results are consistent with the findings of Alvarez et al. [24], who also reported that RCA facilitates renal function recovery in AKI patients. By reducing clot formation in the filter, RCA helps sustain uninterrupted CRRT, alleviating the burden on the kidneys and supporting recovery.

Table 6. Univariate analysis

Factor	Poor prognosis group (n=24)	Good prognosis group (n=156)	χ^2	P
Age (years old)			5.223	0.022
≤60	6	78		
>60	18	78		
Gender			0.008	0.930
Male	13	83		
Female	11	73		
BMI (kg/m^2)			0.725	0.395
≤23	15	83		
>23	9	73		
Primary disease				
Severe pneumonia	18	90	2.596	0.107
Acute and severe pancreatitis	4	41	1.026	0.311
Acute cholangitis	2	25	0.965	0.326
AKI stage			5.404	0.020
Stage I-II	17	138		
Stage III	7	18		
Educational level			0.451	0.502
Below junior college	14	102		
Junior college and above	10	54		
Place of residence			0.220	0.639
City	14	83		
Rural	10	73		
Treatment mode			4.201	0.040
CRRT + systemic heparin anticoagulation therapy	16	69		
CRRT + anticoagulant therapy with RCA	8	87		

Note: BMI, body mass index; AKI, acute kidney injury.

Table 7. Assignment

Factor	Assignment
Age	≤60 =0, >60 =1
AKI stage	Stage I-II =0, Stage III =1
Treatment mode	CRRT + anticoagulant therapy with RCA =0, CRRT + systemic heparin anticoagulation therapy =1
Prognosis	Good =0, Poor =1

Note: AKI, acute kidney injury.

Table 8. Multivariate analysis

	B	S.E.	Wals	Sig.	Exp (B)	EXP (B) for 95% C.I.
Age	1.234	0.518	5.668	0.017	3.435	1.244-9.487
AKI stage	1.085	0.540	4.035	0.045	2.960	1.027-8.533
Treatment mode	1.142	0.485	5.537	0.019	3.132	1.210-8.108

Note: AKI, acute kidney injury.

Moreover, our study found that RCA significantly reduced the inflammatory response, as evidenced by lower levels of hs-CRP and IL-4. This reduction in inflammation may be due to the localized anticoagulation effect of RCA, which minimizes systemic anticoagulant exposure

Table 9. Comparison of inflammatory response

	hs-CRP (mmol/L)		IL-4 (mg/L)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=85)	37.75±5.11	15.34±3.10*	75.63±8.79	37.91±5.92*
Research group (n=95)	38.53±4.85	11.97±2.67*	75.28±9.72	31.62±4.84*
t	1.056	7.830	0.251	7.851
P	0.293	<0.001	0.802	<0.001

Note: Compared to pre-treatment levels in the same group, *P<0.05. hs-CRP, hypersensitive C-reactive protein; IL-4, interleukin-4.

and lowers the risk of systemic inflammatory reactions. These findings support the role of RCA not only in maintaining filter patency but also in reducing inflammatory damage, thereby contributing to better overall outcome.

A key finding of this study was that RCA had a lesser impact on coagulation function compared to systemic heparin. In the RG, PT and APTT were better preserved, and PLT counts were less affected. These results align with the findings of Chang et al. [25], who also reported improved coagulation profiles in patients treated with RCA. The underlying mechanism is that RCA exerts its anticoagulant effect within the CRRT circuit, limiting systemic exposure to anticoagulants and making it safer for patients with bleeding risks or coagulation disorders. Therefore, RCA is a safer option for patients with abnormal coagulation function, a high risk of bleeding, or contraindications to heparin.

At the end of the study, the incidence of adverse reactions and bleeding complications was compared between the groups. Our results showed a significantly lower incidence of bleeding complications in the RG group, with no significant increase in adverse reactions. This is consistent with the study by Kindgen-Milles et al. [26], which also reported a lower risk of bleeding with RCA. Based on these findings, RCA represents a safer alternative to systemic heparin, especially for patients with higher bleeding risk.

Despite these promising results, the study has some limitations. For example, we were unable to conduct long-term follow-up, so the durability of RCA's effects on renal function and patient outcomes over time could not be evaluated. Future studies should include longer follow-up periods to strengthen our conclusions.

In conclusion, RCA has demonstrated significant efficacy in AKI patients undergoing CRRT, effectively improving renal and coagulation function, reducing the risk of adverse reactions and bleeding, and offering a higher safety profile. These findings support the use of RCA for wider application in clinical practice.

Disclosure of conflict of interest

None.

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