Chen *et al. Trials (2024) 25:542*
https://doi.org/10.1186/s13063-024-08370-9

Trials

RESEARCH

Open Access

Study on the application of a segmented sodium citrate solution anticoagulation strategy in critically ill patients receiving CRRT: a prospective, randomized controlled study

Yu Chen[1], Fang Feng[2], Hong Guo[1], Lu Zhang[1] and Jian Liu[1,3*]

Abstract

Background To explore the feasibility and effectiveness of a segmented sodium citrate solution anticoagulation strategy in patients receiving CRRT.

Methods A prospective, randomized controlled study was conducted.

Results According to the inclusion and exclusion criteria, 80 patients were included and randomly divided into two groups. Moreover, coagulation indices, liver function indices, renal function indices, and SOFA and APACHE II scores did not significantly differ between the two groups ($P > 0.05$). The coagulation grade of the venous ports in the experimental group was lower than that in the control group and the two groups of filters, but the difference was not statistically significant ($P = 0.337$). Both sodium citrate solution infusion methods maintained a low blood calcium concentration (0.25–0.45 mmol/L) in the peripheral circulation pathway, and no patient developed hypocalcaemia (< 1.0 mmol/L). The lifespans of the extracorporeal circulation tube in the experimental group and the control group were 69.43 ± 1.49 h and 49.39 ± 2.44 h, respectively ($t = 13.316$, $P = 0.001$).

Conclusion The segmented citrate solution anticoagulation strategy could extend the lifespan of the extracorporeal circulation tube and improve CRRT efficacy.

Trial registration The Chinese Clinical Trial Registry number is ChiCTR2200057272. Registered on March 5, 2022.

Keywords Continuous renal replacement therapy, Regional citrate anticoagulation, Acute kidney injury, Critically ill patients, Anticoagulation strategy

Background

Continuous renal replacement therapy (CRRT) is commonly used to treat critically ill and hemodynamically unstable patients with acute kidney injury. In CRRT treatment, providing effective extracorporeal circulation anticoagulation is particularly important for preventing coagulation [1]. The most commonly used anticoagulation method worldwide is systemic heparin anticoagulation (SHA). However, effective heparin anticoagulation increases the risk of bleeding, and bleeding-related complications are increasingly reported in the literature [2].

*Correspondence:
Jian Liu
medecinliu@sina.com
[1] Intensive Care Unit, The 1st School of Clinical Medicine of Lanzhou University, Lanzhou 730000, Gansu, China
[2] Intensive Care Unit, Lanzhou University Second Hospital, Lanzhou 730000, Gansu, China
[3] Intensive Care Unit, Gansu Provincial Central Hospital, Lanzhou 730000, Gansu, China

In recent years, regional citrate anticoagulation (RCA) has been introduced into clinical practice. When using the RCA, the anticoagulation process is limited to the extracorporeal circuit, leaving the patients' coagulation function undisturbed. There is increasing evidence [3–6] that the use of an RCA can reduce the incidence of bleeding and the need for blood transfusions while extending the service life of the filter. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the use of the RCA as the preferred anticoagulation method for CRRT [7]. Currently, RCA is used in some countries, but its general acceptance worldwide remains low. The first description of the RCA dates back to 1990. Mehta [8] applied 4% sodium citrate for anticoagulation during hemodialysis, which extended the lifespan of the filter. However, due to the small sample size, this topic has not received enough attention. With the widespread use of citrate anticoagulation in clinical practice, increasing evidence shows that, compared with heparin, RCA can reduce bleeding complications and blood transfusion requirements while extending the filter lifespan [3, 9, 10].

Citrate metabolism occurs mainly in the Krebs cycle in liver cells. If this metabolic process is impaired, citrate levels increase. Citrate itself is not toxic; however, impaired metabolism may lead to some physiological disorders [11]. First, as citrate metabolism decreases and citrate content increases, ionized calcium (iCa) cannot be released from the calcium citrate complex, and hypocalcaemia may occur. Therefore, hypocalcaemia and an increased need for calcium replacement are the first signs of citrate accumulation. Second, as citrate metabolism decreases, bicarbonate production decreases. Therefore, ongoing or newly developing metabolic acidosis may be another sign of citrate accumulation [12].

However, the current infusion method in which sodium citrate solution is pumped into the arterial end alone often leads to early termination of treatment due to coagulation in the venous port. This results in interruptions in treatment continuity, increased treatment costs, and even additional blood loss. Studies have shown that coagulation and blockage of venous ports are the primary reasons for unplanned removal from the filter. Therefore, this study attempted to infuse sodium citrate solution into intravenous ports at the same time and adopt the segmented citrate anticoagulation (SCA) strategy to explore whether it can prolong CRRT time.

Materials and methods

Patients who were admitted to the department of critical care medicine of the second hospital of Lanzhou University from 2023.6 to 2024.1 were selected

The inclusion criteria were as follows: (1) age > 18 years; (2) received CRRT.

The exclusion criteria were as follows: (1) severe liver dysfunction (TBIL > 2 times the normal value); (2) hypoxemia (arterial partial pressure of oxygen < 60 mmHg) and/or tissue hypoperfusion (blood pressure still lower than 90/60 mmHg after large doses of vasoactive drugs are used); (3) metabolic alkalosis; (4) patients with hyperlactatemia (Lac > 4 mmol/L); (5) hypernatremia; (6) ICU length of stay < 24 h.

All included patients signed informed consent forms.

Methods

The included patients were randomly divided into the experimental group and the control group according to the computer random sequence list (the random sequence was placed in a light-tight sealed envelope). An indwelling double-lumen hemofiltration catheter was used in the femoral vein to establish vascular access in all patients. MultiFiltrate of Fresenius Medical Care was used for CRRT, and the replacement and dialysate fluids made by the commercially manufactured (Chengdu QingshanLiKang Pharmaceutical Co. Ltd.). The treatment mode was continuous veno-venous hemofiltration dialysis (CVVHDF), with a blood flow rate of 150 ml/min. The replacement and dialysate fluid were both with 1.5 mmol/L ionized calcium. The replacement fluid flow is 750 ml/h, and the dialysate solution flow is 750 ml/h. The ultrafiltration rate is 100–500 ml/h and the filtration fraction is less than 30%. We do not use saline flushing to prevent clotting. The anticoagulant was 4% sodium citrate solution. The experimental group was administered a segmented sodium citrate infusion. Specifically, 4% sodium citrate solution was pumped into the prefilter site at 185 ml/h, and at the same time, the solution was pumped into the venous port at 15 ml/h. For the control group, the conventional sodium citrate infusion method was used, and 4% sodium citrate solution was pumped into the prefilter site at a speed of 200 ml/h. A line diagram was showed in Fig. 1. Ten percent calcium gluconate injection is pumped in from postfilter through a micro syringe pump according to the patient's actual condition.

Observation indicators

General information on the patients, including serum creatinine (sCr), total serum bilirubin, glutamic-pyruvic transaminase (ALT), APACHE II score, SOFA score, blood lactate, postfilter iCa concentration, peripheral blood iCa concentration, HCO_3^- concentration, pH, and lifespan of the extracorporeal circulation pathway, was obtained.

The coagulation status of the extracorporeal circulation tube was monitored every 4 h after the start of treatment. After 48 h of treatment, the coagulation status of the

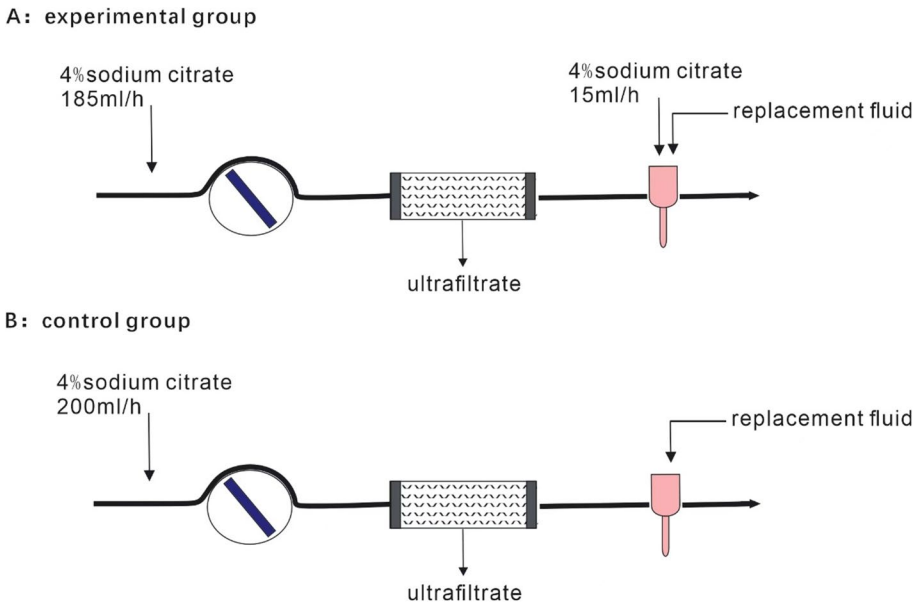

Fig. 1 Diagram of sodium citrate infusion method

filter and venous port was recorded. At level 0, no coagulation in the dialyzer was observed after blood return; at level 1, coagulation of less than 1/3 of the filter was observed after blood return; at level 2, coagulation of 1/3 to 2/3 of the filter was observed after blood return; and at level 3, coagulation of more than 2/3 of the filter was observed after blood return, with significant increases in venous pressure and transmembrane pressure. The grading criteria for venous port coagulation were as follows: level 0: no coagulation; level 1: a few clots in the venous port (< 10% of the volume of the venous port); level 2: clots in the venous port accounting for 10% of the volume of the venous port; and level 3: clots in the venous port accounting for > 50% of venous port volume [8].See Additional file 1.

Statistical analysis

The statistical analysis was performed with SPSS software 21.0 (SPSS, Inc., Chicago, IL, USA). Normally distributed data are expressed as the mean ± standard deviation (x ± s). A *t*-test was used for comparisons between two groups, and a Q–Q normal probability plot was used for normality; if the data were not normally distributed, the median M and interquartile range (Qu, QL) were used. Comparisons between two groups were performed by the Mann–Whitney *U* test or the Spearman nonparametric test; the count data are expressed as *n* (%). The Pearson χ^2 test was used to compare dichotomous data between two groups, and the Mann–Whitney *U* test was used for ordinal multiple classification. All tests were two-sided, and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

According to the inclusion and exclusion criteria, a total of 81 patients were included. One patient was excluded because the length of stay in the ICU was less than 24 h. Finally, 80 patients were included and randomly divided into two groups: 40 in the experimental group and 40 in the control group. See Fig. 2 for detail.

Comparison of general information

There were 22 males and 18 females in the experimental group and 23 males and 17 females in the control group. There was no statistically significant difference ($\chi^2 = 0.52$, $P = 0.63$). The average age was 46.71 ± 12.54 years in the experimental group and 47.08 ± 13.63 years in the control group. There was no significant difference between the two groups ($t = 2.033$, $P = 0.412$). The average weight was 58.71 ± 9.54 kg in the experimental group and 57.91 ± 8.63 kg in the control group. There was no significant difference between the two groups ($t = 3.014$, $P = 0.507$). And there were no significant differences in coagulation indices, liver function indices, renal function indices, SOFA scores, or APACHE II scores between the two groups ($P > 0.05$) (Table 1).

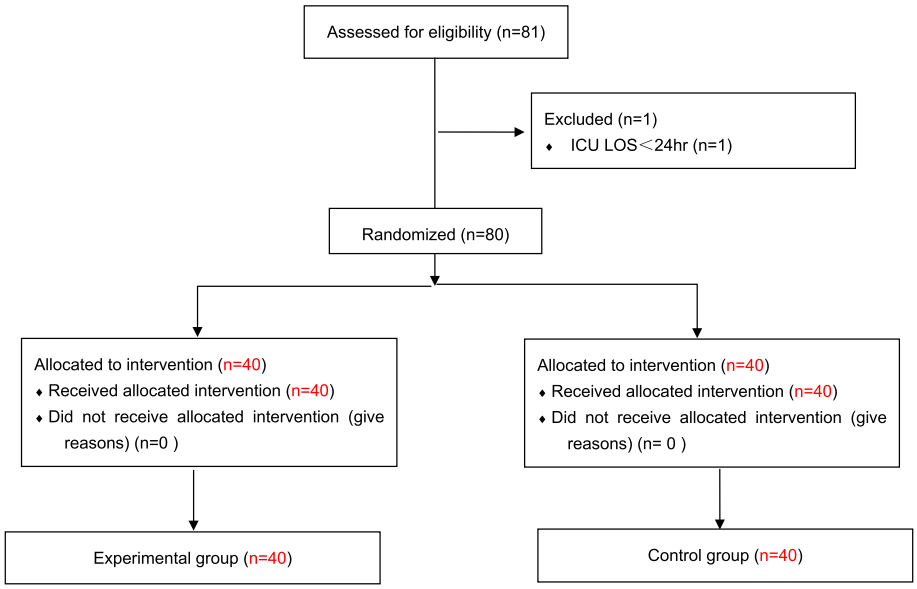

Fig. 2 Flow diagram

Table 1 Basic information

	Experimental group ($n=40$)	Control group ($n=40$)
Characteristic		
Age (years)	46.71 ± 12.54	47.08 ± 13.63
Sex (male)	12	13
Weight (kg)	58.71 ± 9.54	57.91 ± 8.63
Baseline characteristics		
APACHE II score	14.07 ± 3.37	14.48 ± 2.94
SOFA score	12.74 ± 2.73	13.16 ± 1.75
Tbil (mmol/L)	33.8 ± 4.72	32.58 ± 6.03
PTA (%)	69.79 ± 9.43	68.93 ± 7.03
Fib (g/L)	3.86 ± 0.21	3.75 ± 0.18
ALT (U)	116.43 (40.5, 132.5)	104.88 (40.5, 101)
sCr (ummol/L)	349.02 (303, 446)	351.17 (296, 439)
Lac (mmol/L)	1.24 (1.1, 1.3)	1.31 (1.1, 1.3)
Comorbidities		
Hypertension	7 (35%)	9 (45%)
Diabetes	4 (20%)	3 (15%)
COPD	5 (25%)	5 (25%)
Time for randomization to initiation of CRRT	1.4 h (1.1–1.7)	1.5 h (1.2–1.9)

Comparison of coagulation conditions between filters and venous ports

The results of this study showed that the coagulation grade of the venous ports in the experimental group was significantly lower than that in the control group ($P=0.022$). A comparison of the coagulation conditions of the two groups of filters revealed that the difference was not statistically significant ($P=0.337$) (Table 2).

Monitoring indicators

The results of this study showed that both sodium citrate solution infusion methods could maintain a low blood calcium concentration (0.25–0.45 mmol/L) in the peripheral circulation pathway, and no patient developed hypocalcaemia (< 1.0 mmol/L). The average calcium infusion rates were 3.9 ± 0.5 ml/h in the experimental group and 4.1 ± 0.4 ml/h in the control group.

Table 2 Comparison of coagulation conditions between filters and venous ports

	Experimental group ($n=40$)	Control group ($n=40$)	*P* value
Coagulation grade of the venous ports			0.022
Level 0–1	19	13	
Level 2	1	5	
Level 3	0	2	
Coagulation grade of the filter			0.337
Level 0–1	18	16	
Level 2	2	4	
Level 3	0	0	

Table 3 Monitoring indicators

	Experimental group ($n=40$)	Control group ($n=40$)
pH	7.42 ± 0.03	7.41 ± 0.01
HCO_3^- (mmol/L)	23.74 ± 1.47	23.31 ± 0.98
Prefilter iCa (mmol/L)	1.18 ± 0.02	1.19 ± 0.01
Postfilter iCa (mmol/L)	0.28 ± 0.03	0.33 ± 0.01
Calcium infusion rates (ml/h)	3.9 ± 0.5	4.1 ± 0.4

Moreover, the difference was not statistically significant ($P > 0.05$) (Table 3).

Comparison of the lifespan of the extracorporeal circulation tube

The results of this study showed that the lifespans of the extracorporeal circulation tube in the experimental group and the control group were 69.43 ± 1.49 h and 49.39 ± 2.44 h, respectively. The difference between the two groups was statistically significant ($t=13.316$, $P=0.001$) (Table 4).

Discussion

The venous port is the last line of defense. It is equipped with a filter structure inside to prevent tiny thrombi generated by the extracorporeal circulation path from entering the patient's body. The blood flow in venous ports is relatively slow, and gas–blood contact planes and fibrin rings easily form in the upper venous space. From a hemodynamic perspective, turbulent flow occurs at the blood input port, and mural thrombi easily form on the wall of venous ports. As the time outside the body increases, the viscosity of the blood increases, facilitating coagulation. The particularity of the location and structure of the venous port makes it prone to thrombosis during CBP. Baldwin et al. proposed that the site at which anticoagulants are delivered affects the coagulation condition of the extracorporeal circulation tube and noted that adding anticoagulants to intravenous ports can alleviate coagulation conditions. However, comparative experiments using heparin as an anticoagulant did not reveal this difference. This may be related to whether the anticoagulant is cleared by the filter. Heparin, as a macromolecular substance, cannot be cleared by filtration [13]. Citric acid and calcium citrate complexes are small molecular substances that can be removed by filtration. More than 60% of citrate radicals are removed when passing through the filter [14]. Combined with the chemical formula for the complexation of citric acid and free calcium, it can be calculated that the addition of free calcium to the neutralization unit time replacement solution requires 9 ml of 4% sodium citrate solution, but in clinical practice, 9 ml of 4% sodium citrate solution is not enough to improve the coagulation status of venous ports. Repeated clinical verification has shown that a pump volume of at least 15 ml/h of 4% sodium citrate solution has a significant improvement effect. This difference may be related to the sufficient mixing degree of citrate and blood. The filters removed sodium citrate, calcium citrate, and free calcium to different degrees. One study [15] showed that when 30 ml of sodium citrate was directly added to the replacement fluid, the anticoagulant effect of the intravenous mixture was satisfactory, but the literature did not mention the impact of the addition of sodium citrate on the pH or electrolyte concentration of the replacement fluid. Yang et al. [16] proposed a two-stage sodium citrate pump anticoagulation strategy in which 4% sodium citrate solution was pumped from the prefilter at a rate of 120 to 170 ml/h and from the venous port at a rate of 60 to 170 ml/h. However, sodium citrate is used as a local anticoagulant. This strategy may be associated with an increased risk of multiple electrolyte and acid–base disorders, and excessive infusion can easily cause systemic hypocalcaemia, hypernatremia, metabolic alkalosis, and high anion gap metabolic acidosis, as well as increase treatment costs. In this study, 15 ml of 4% sodium citrate solution was added to the intravenous port, accounting for only 7% of the total

Table 4 Comparison of the lifespans of the extracorporeal circulation tubes

	Experimental group ($n=40$)	Control group ($n=40$)
Lifespan of the extracorporeal circulation tube (h)	69.43 ± 1.49	49.39 ± 2.44

sodium citrate infusion. The concentration of ionized calcium was maintained above 0.9 mmol/L. According to the literature [17], the ionized calcium concentration is 0.9–1.2 mmol/L, which is safe for most critically ill patients. The addition of citric acid dilutes the blood in the venous port and interferes with the gas–blood barrier, which is also one of the reasons for delayed coagulation. If the venous port coagulates to level 2 or above, nurses need to frequently flush the pipeline with normal saline to delay the coagulation process. The effect is poor, and the operation is cumbersome. Nurses also need to calculate the amount of saline used to calculate the human ultrafiltration volume, and the efficiency of CRRT decreases. The improved sodium citrate infusion method effectively delays the coagulation of the extracorporeal circulation tube. Nurses no longer need to flush the circuit with physiological saline, reducing their workload. The cost of the filter accounts for more than half of the entire CRRT treatment consumable. When the filter does not suffer from severe coagulation and can still be used, treatment is forced to cease merely because of clogged coagulation in the venous port, resulting in a waste of medical resources. Of course, a new treatment option always has its own complications. Using this anticoagulation strategy may increase the input of citrate solution, but according to our trial, no patient in the trial group developed metabolic acidosis, metabolic alkalosis, or hypernatremia, which shows that this strategy is safe.

Conclusion

The segmented citrate solution anticoagulation strategy could extend the lifespan of the extracorporeal circulation tube and improve CRRT treatment efficacy.

Abbreviations

CRRT	Continuous renal replacement therapy
SHA	Systemic heparin anticoagulation
RCA	Regional citrate anticoagulation
SCA	Segmented citrate anticoagulation
CVVHDF	Continuous veno-venous hemofiltration dialysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08370-9.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Acknowledgements

We would like to thank AJE (www.aje.cn) for English language editing.

Authors' contributions

Conducted the study: YC, JL. Collected all data: FF, LZ. Performed the statistical analysis: HG, FF.

Funding

This work was supported by the Natural Science Foundation of Gansu Province (No. 23JRRA0965) and the Cuiying Scientific and Technological Innovation Program of Lanzhou University Second Hospital (CY2021-BJ-A10).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Second Hospital of Lanzhou University approved this study, and the number was 2023A-454. Written informed consent was obtained from the individuals or guardians of the participants.

Consent for publication

Consent for publication was obtained from the individuals or guardians of the participants.

Competing interests

All authors declare that they have no competing interests.

Received: 16 April 2024 Accepted: 5 August 2024
Published: 16 August 2024

References

1. Li L, Bai M, Zhang W, et al. Regional citrate anticoagulation versus low molecular weight heparin for CRRT in hyperlactatemia patients: a retrospective case-control study. Int J Artif Organs. 2022;45(4):343–50.
2. MacEwen C, Watkinson P, Winearls C. Circuit life versus bleeding risk: the impact of achieved activated partial thromboplastin time versus achieved filtration fraction. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. Jun2015;19(3):259–66.
3. Bianchi NA, Altarelli M, Eckert P, et al. Complications of regional citrate anticoagulation for continuous renal replacement therapy: an observational study. Blood Purif. 2020;49(5):567–75.
4. Li L, Bai M, Yu Y, Li Y, Zhao L, Sun S. Regional citrate anticoagulation vs no-anticoagulation for CRRT in hyperlactatemia patients with increased bleeding risk: A retrospective cohort study. Semin Dial. 2021;34:209–17.
5. Kośka A, Kirwan CJ, Kowalik MM, et al. Filter life span in postoperative cardiovascular surgery patients requiring continuous renal replacement therapy, using a postdilution regional citrate anticoagulation continuous hemofiltration circuit. Cardiol J. 2022;29(1):53–61.
6. Dimski T, Brandenburger T, Slowinski T, et al. Feasibility and safety of combined cytokine adsorption and continuous veno-venous hemodialysis with regional citrate anticoagulation in patients with septic shock. Int J Artif Organs. Jan2020;43(1):10–6.
7. Rovin, B. H., Adler, S. G., Barratt, J., et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. Kidney int. 100, 4 (Oct 2021), 753–779.
8. John T. Daugirdas, Peter G. Blake, Todd S. Ing: Handbook of dialysis 5th edition (2015), ISBN: 978–1–4511–4429–1, Wolters Kluwer Health.
9. Zarbock A, Küllmar M, Kindgen-Milles D, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically Ill patients with acute kidney injury: A randomized clinical trial. JAMA. 2020;324(16):1629–39.
10. Ng CJH, Poh CB, Koduri S, et al. Regional citrate anti-coagulation dose titration: impact on dose of continuous renal replacement therapy. Clin Exp Nephrol. Sep2021;25(9):963–9.
11. Köglberger P, Klein SJ, Lehner GF, Bellmann R, Peer A, Schwärzler D, Joannidis M. Low bicarbonate replacement fluid normalizes metabolic alkalosis during continuous veno-venous hemofiltration with regional citrate anticoagulation. Ann Intensive Care. 2021;11(1):62.

12. Schmitz M, Joannidis M, Czock D, et al. Regional citrate anticoagulation in renal replacement therapy in the intensive care station: recommendations from the renal section of the DGIIN, ÖGIAIN and DIVI. Medizinische Klinik, Intensivmedizin und Notfallmedizin. Jun2018;113(5):377–83.
13. Gould DW, Doidge J, Sadique MZ, et al. Heparin versus citrate anticoagulation for continuous renal replacement therapy in intensive care: the RRAM observational study. Health technology assessment (Winchester, England). Feb2022;26(13):1–58.
14. Buturovic-Ponikvar J. Is regional citrate anticoagulation the future of hemodialysis? Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. Jun2016;20(3):234–9.
15. Weng Y, Zhou F, Fu Y, et al. Citrate-based self-circulation anticoagulation protocol for discontinuity of continuous renal replacement therapy. Blood Purif. 2020;49(4):394–9.
16. Yang ST, Zhao N, Hu J, et al. Clinical study of regional citrate anticoagulation in hemodialysis with routine dialysate containing calcium[J]. Chin J Blood Purif. 2017;16(7):474-476.487.
17. Zhang W, Wang JG. Discussion on the clinical value of local citrate anticoagulation in continuous renal replacement therapy for critically ill patients[J]. Guide Chin Medi. 2018;16(10):77–8.

Publisher's Note