Effects of Brief Citrate Interruption on Regional Citrate Anticoagulation During Continuous Renal Replacement Therapy

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Research

Keywords: anticoagulation, citrate, continuous renal replacement therapy

Posted Date: September 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-69286/v1>

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Abstract

Background: Regional citrate anticoagulation (RCA) has been widely used in continuous renal replacement therapy (CRRT). Having encountered some unexplained and unexpected situations in clinical practice, we speculated if a brief citrate infusion interruption during regular operation would affect anticoagulation. A review of the literature confirmed that no studies to date have explored the effect of short-term citrate interruption on RCA.

Method: In ten patients who received continuous veno-venous hemofiltration treatment with RCA, we measured concentrations of ionized calcium (iCa) in the post-filtered and peripheral blood before and after the citrate interruption due to effluent dumping and at 5, 10, 20, and 60 minutes after the return to normal working conditions.

Results: The citrate suspension time caused by dumping of the effluent liquid was 5.91 ± 0.89 minutes. The post-filter iCa concentration was significantly increased because of the interruption (0.42 ± 0.04 vs. 0.94 ± 0.06 , $p < 0.001$) and positively correlated with the interruption duration ($r = 0.69$, $p = 0.002$), whereas the peripheral blood calcium concentration was not significantly affected (1.09 ± 0.05 vs. 1.07 ± 0.04 , $p = 0.47$).

Conclusion: A brief citrate interruption may affect anticoagulation efficiency, creating a potential hazard. A more reliable RCA protocol or equipment design requires further study.

Introduction

Continuous renal replacement therapy (CRRT), which can continuously and steadily remove excess solute and fluid while barely affecting the circulation, is widely used in patients with acute kidney injury, sepsis, refractory fluid overload, multiple organ failure, and poisoning. Anticoagulation ensures the stable operation of the CRRT circuit. Coagulation that occurs during cardiopulmonary bypass shortens the filter and circuit life, reduces CRRT efficiency, and increases placement cost and workload[1]. Regional citrate anticoagulation (RCA) was first applied to hemodialysis in 1983[2] and to in CRRT in 1990[3]. Since then, the safety and effectiveness of RCA have been broadly evaluated. Several studies have shown that the incidence of RCA in line loss, filter coagulation, bleeding, and heparin-related thrombocytopenia is lower than that in systemic or local heparin-protamine anticoagulation[4–6]. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend CRRT anticoagulation as the first choice for RCA after the exclusion of contraindications[7].

Ionized calcium (iCa) is the cofactor of coagulation IV, the cofactor of the coagulation cascade, and involved in the internal and external coagulation pathways. RCA effectively thins the in-filter circulation without affecting the body's coagulation function. Maintaining the post-filter iCa concentration at a sufficient level virtually guarantees RCA efficacy. Although RCA has many advantages, clinical studies have found that filter clotting occurs at a frequency of 16.9–49.5%[8, 9].

In clinical practice, we encountered cases in which treatment was unexpectedly terminated due to sudden coagulation after removal of the effluent liquid. We observed that the citrate pump stopped when the waste liquid was dumped and the replacement liquid bag was replaced. We speculated that the short period of time in which the effluent liquid is dumped temporarily affected the anticoagulation effect of RCA and shortened the filter life. Thus, this study aimed to explore the potential fluctuation in iCa concentration during the temporary suspension of the citrate infusion.

Method

This study included ten patients with CRRT treated with RCA in the emergency intensive care unit of our hospital from September to December 2019. Each patient underwent CRRT performed in continuous veno-venous hemofiltration (CVVH) using an AN69 HF membrane® (Baxter, Tennessee, USA) with a Prismaflex CRRT system® (Baxter, Tennessee, USA).

Data collection started within 4 hours after the initiation of each CRRT treatment to ensure that each filter was in relatively similar working status and that the post-filter and peripheral blood iCa concentrations were ideal and stable. Since our intensive care unit has no spare effluent bags, the effluent liquid bag must be drained after it becomes full. Therefore, the ordinary working status cannot be resumed until the effluent has been dumped.

The effluent was dumped generally without intervention during the study. We recorded the length of time that the regular operation was interrupted accordingly. Samples were taken from the post-filter and peripheral blood to detect the iCa concentrations before versus after the suspension and at 5, 10, 20, and 60 minutes after the return to normal working conditions. The CRRT parameters were not changed during the observation process. The test was performed immediately after the samples were obtained with a blood gas analyzer for rapid bedside testing in our department (Cobas b 123, Roche Diagnostics, Mannheim, Germany). The nurses managing the CRRT sessions were not informed of the purpose of the blood sample collection.

All statistical analyses were performed using R software version 3.5.1. Categorical variables are reported as whole numbers and proportions, while continuous variables are reported as mean $\pm$ standard deviation or median (range) according to normality status, which was assessed using the Shapiro-Wilk W test. Differences in iCa concentration between time points were compared using the paired Student's t-test. A correlation matrix was used to identify variables related to the degree of change in post-filter iCa concentration. The correlation between the length of the suspension and the change in iCa concentration was examined using Pearson correlation analysis. All tests were two-sided, and values of $p < 0.05$ were considered statistically significant.

Results

The baseline characteristics of the ten patients who underwent CRRT treatment in our department and were enrolled in the study are shown in Table 1. Among them, four had sepsis, three had severe acute pancreatitis, two had suffered severe trauma, one had diabetic ketoacidosis, and one had been poisoned. No patient experienced unplanned termination of the CRRT during the observation period.

Table 1
Baseline characteristics

Variables	N = 10
Age, year (range)	62.90 (47–79)
Gender, male (%)	7 (70.0)
Weight, kg (range)	68.60 (52–90)
Height, cm (range)	166.90 (151–179)
Primary disease n (%)	
DKA	1 (10.0)
Intoxication	1 (10.0)
SAP	2 (20.0)
Sepsis	4 (40.0)
Severe trauma	2 (20.0)
Hematocrit (range)	0.30 (0.22–0.39)
Citrate suspension time, min (range)	5.91 (5.0–7.6)
Δ Post-filter [iCa], % (range)	127.11 (30.58)
DKA, diabetic ketoacidosis; SAP, severe acute pancreatitis; Δ Post-filter [iCa], changes in post-filter iCa concentration during suspension of sodium citrate	

All ten patients were treated with CRRT in CVVH modality. The main parameters during the study were as follows: blood flow rate, 180 (150–200) mL/min; 4% sodium citrate, 163 (135–185) mL/h; 10% calcium gluconate, 25 (18–30) mL/h; replacement fluid rate, 2200 (2000–2500) mL/h; net fluid removal rate, 150 (0–300) mL/h; ultrafiltration rate, 35 (26–46) mL/kg/h; and filtration fraction, 14% (10–19%) (Table 2).

Table 2
CRRT parameters

ID	BF	Citrate	CGS	RF	FR	UFR	FF	Suspension time
1	180	165	29	2200	200	34	13	5.1
2	160	145	22	1500	200	29	14	7
3	150	135	29	2300	150	38	16	5.3
4	180	160	24	2200	100	44	19	5.6
5	200	185	30	2000	150	26	10	6.2
6	180	175	26	2000	0	42	18	5
7	160	155	23	1500	0	35	13	5.4
8	150	135	27	2200	300	35	14	6.6
9	180	165	19	2500	100	46	18	7.6
10	180	170	18	2200	250	30	11	5.3
BF, blood flow rate (ml/min); Citrate, 4% sodium citrate solution rate (ml/h); CGS, 10% calcium gluconate solution rate (ml/h); RF, replacement flow rate (ml/h); FR, fluid removal rate (ml/h); UFR, ultrafiltration rate; FF, filtration fraction; Suspension time, the citrate suspension time associated with the dumping of effluent fluid (min)								

While the CRRT machine used by our department is pouring out the effluent liquid, all pumps except the blood pump are suspended, including the pre-blood pump, effluent pump, dialysate pump, and displacement fluid pump. The pre-blood pump infuses the sodium citrate into the blood before the blood is pumped. The citrate suspension time caused by the dumping of the effluent was 5.91 ± 0.89 minutes. The post-filter iCa concentration after the suspension was significantly higher than that before the suspension (0.42 ± 0.04 vs. 0.94 ± 0.06 , $p < 0.001$) for a change of 126.37% (84.09–183.33%)(Table 1), whereas the peripheral blood iCa concentration was not significantly affected (1.09 ± 0.05 vs. 1.07 ± 0.04 , $p = 0.47$) (Fig. 1).

Five minutes after the end of the citrate interruption, the post-filter iCa concentration decreased significantly to close to that before the interruption, but the difference disappeared after only 5 minutes. Meanwhile, the systemic iCa concentration was slightly higher than that at the end of the disruption and then gradually returned to normal (Fig. 1).

A correlation matrix analysis revealed that the change in post-filter iCa concentration was positively associated with the time taken to dump the effluent liquid ($r = 0.69$, $p = 0.002$) (Fig. 2). This finding suggests that the length of citrate interruption time may be related to the post-filter iCa concentration within 5–8 minutes.

Discussion

Ionized calcium is a cofactor of the blood coagulation cascade. Sodium citrate can chelate iCa , producing an anticoagulant effect. Citrate anticoagulation can significantly increase the intensity of anticoagulation in the extracorporeal circulation without affecting blood coagulation in the patient. This anticoagulant effect is reversed by removing most of the calcium citrate complex through the artificial kidney and restoring the plasma iCa concentration to normal levels by calcium infusion. Thus, RCA does not tend to cause systemic bleeding, and at high doses, citrate is more effective than other anticoagulation methods [10–13].

RCA has been shown to have potential benefits over heparin anticoagulation for reducing bleeding risk and extending filter life[14, 15]. Moreover, because calcium ions contribute to coagulation, platelet aggregation, and leukocyte activation, which are important factors in the alternative complement pathway activation[16], RCA has also been found to inhibit the activation of platelets, white blood cells, and complement extracorporeal circulation[4, 17]. Hence, RCA has become the mainstream CRRT anticoagulation method recommended by the KDIGO. However, the commonly used RCA operation process is not ideal. We found that a short-term suspension of RCA, caused by regular operation, may significantly influence the anticoagulant effect and increase with the extension of the suspension time, such as the minutes required to dump the waste liquid.

Our study found that even a 5–8-minute citrate pause during regular operation significantly increased the post-filter iCa concentration, which stabilized after 5–10 minutes. The main problem reported with RCA in previous studies pertains to metabolic complications arising from excessive sodium ions and the citrate calcium complex[18, 19]. Correction hemodiafiltration typically requires a replacement fluid (0.45% NaCl) that removes the excess sodium bicarbonate[20]. Other studies found that when RCA is performed on a dialysis machine without integrated citrate and calcium pumps, the blood pump can stop for any reason, and the citrate and calcium will continue to be directly injected into the patient until the nursing staff restarts the machine, which may stop the infusion[21]. For this study, we used a CRRT machine with an integrated citrate infusion pump, while calcium was infused through a separate peripheral blood vessel. If the blood pump stopped, the citrate pump stopped synchronously, thus preventing the above problem. However, during some operations, such as replacing the fluid bag and dumping the effluent, the machine paused all the mechanical pumps except for the blood pump, resulting in the blood and calcium infusion pumps operating normally in the absence of a citrate infusion. As a result, the anticoagulation effect in the circuit decreased significantly within a short period of time. Meanwhile, calcium was still being infused continuously without the citric acid infusion, which may explain why the peripheral blood iCa concentration increased slightly. Thus, a few minutes after the citrate interruption, the post-filter iCa concentration returned close to the level in the peripheral blood. Nevertheless, calcium supplementation without a simultaneous interruption can lead to an increased peripheral blood iCa concentration. This may risk the routine CRRT operation and contribute to unplanned therapy termination.

By analyzing possible related factors, we found that the degree of change in the post-filter iCa concentration was positively correlated with the length of citrate suspension. The principle of citrate anticoagulation depends on the fact that chelated calcium cannot act as a cofactor in the coagulation cascade, and the anticoagulation occurs instantly. The RCA effect depends on the systemic and post-filter iCa concentrations. The former is affected by the flow of the calcium infusion, while the latter is affected by the flow of citric acid. If the iCa concentration is less than 0.5 mmol/L, the coagulation will be distorted, while if it is less than 0.3 mmol/L, coagulation will be suppressed entirely[22, 23]. Thus, monitoring of the iCa concentration has become a crucial step in RCA, and hemofiltration machine manufacturers recommend measuring the levels of iCa collected after dialysis filtration (filtered samples) and obtained directly from patients (systemic samples)[7]. It should be noted that the post-filter iCa, measured by blood gas analysis, was significantly lower than the normal iCa concentration of an error may occur when. For example, Schwarzer et al. reported that measurements of iCa in post-filter samples might provide misleading information about RCA monitoring and that the iCa level measured in the filtered sample can only prove that the blood in extracorporeal circulation is anticoagulated but cannot control the citrate dose[24]. In our study, the suspension time of the citrate was only 5–8 minutes. In such a short period, the longer the interruption time, the higher the increase in post-filter iCa concentration, which is not a situation that clinicians want to see.

The findings of the present observation suggest that RCA still has room for improvement to increase filter life and reduce risk. Improving the citrate infusion method is the primary solution to the problem of citrate interruption. Expert consensus on the best approach is still lacking[25] as is dialysis equipment tailored for safer RCA delivery. Many scholars believe that a continuously improving RCA scheme and more clinical experience are needed increase the safety of RCA[26, 27]. However, even the most reliable system may be prone to equipment failure (e.g., those not recognized by the calcium infusion pump) or human error (e.g., the operator connecting pre-filters for calcium infusion and post-citrate filters) and rapidly lead to life-threatening complications. As previous experience has suggested that infusion of citrate alone is not a solution[21], automated RCA can improve the integration of citrate pumps, calcium infusion pumps, and blood pumps to achieve synchronized starts and stops, and thus may fundamentally solve the problems identified here.

However, machine improvement takes time, and clinicians cannot solve it. The following measures may reduce the risk as much as possible without altering the current situation. First, clinicians should shorten the citrate interruption time. Changing the replacement or dialysis fluid bag and dumping the waste liquid should be improved to minimize the interruption time. In particular, when dumping the effluent, it is best to use two pockets alternately to mitigate the interruption time. Second, efforts should be directed toward strengthening the management of CRRT by the nursing staff. During the citrate interruption period, more attention should be paid to the operation of the machine, especially in case of patients at high coagulation risk. Third, the post-filter iCa concentration value should not be trusted blindly. In the event of a sudden unexplained significant increase in post-filter iCa concentration, one should check for any sudden disruption in citrate infusion, such as while changing the fluid bag or dumping effluent. Our study found that after returning to normal working conditions for 5–10 minutes, the post-filter iCa concentration

returned to a level close to before interruption. Therefore, the iCa concentration should be re-tested at 10 minutes after return to the standard working condition.

Conclusion

A brief interruption of a citrate infusion will affect RCA anticoagulant efficiency, even without a violation of any operating procedures, and impact the circuit patency of CRRT. Although none of the patients in our study experienced unexpected CRRT termination, our findings suggest that a short RCA suspension period may increase the risk of clotting. The development of a safer and more reliable RCA operation scheme or machine design is required in further studies.

Key Messages

- The brief interruption of a citrate infusion will affect RCA anticoagulant efficiency, even without a violation of any operating procedures.
- The citrate infusion interruption duration may be related to the post-filter iCa concentration within a short period.
- A safer and more reliable RCA operation scheme or machine design is required in further studies.

Declarations

Ethics approval and consent to participate

Since this observational study did not involve intervention in routine treatment strategies, the need for informed consent was waived.

Consent for publication

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Science and Technology Project of Nantong City (Grant No. MS12018048).

Authors' contributions

DJ, ZZ, and ZH came up with the study concept. All authors developed the study design and protocol. XY, WJ, SL, TW, and collected the study data. YS and QC were involved in the analysis and interpretation of the data. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank all the clinicians and staff in the EICU for their assistance in screening the patients.

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Figures

Figure 1

Ionized Calcium (iCa) concentration in peripheral blood and post-filter blood. Post-filter iCa concentration (red circles) increased significantly after the interruption of citrate, while there was no significant change in the peripheral blood iCa concentration (blue squares). 5 minutes after the end of the interruption, the post-filter iCa concentration decreased significantly and approached the level before the interruption, while the peripheral blood iCa concentration increased slightly.

Figure 2

Correlation analysis of variation degree of post-filter iCa concentration. A Correlation matrix diagram of the patient's basic condition and CRRT parameters and the variation degree of post-filter iCa concentration. B Scatter plot and fitting curve of correlation between variation degree of post-filter iCa concentration and interruption time of citrate.