Calcium-containing versus calcium-free replacement solution in regional citrate anticoagulation for continuous renal replacement therapy: a randomized controlled trial

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Abstract

Background: A simplified protocol for regional citrate anticoagulation (RCA) using a commercial calcium-containing replacement solution, without continuous calcium infusion, is more efficient for use in continuous renal replacement therapy (CRRT). We aim to design a randomized clinical trial to compare the safety and efficacy between calcium-free and calcium-containing replacement solutions in CRRT with RCA.

Methods: Of the 64 patients receiving RCA-based postdilution continuous venovenous hemodiafiltration (CVVHDF) enrolled from 2017 to 2019 in West China Hospital of Sichuan University, 35 patients were randomized to the calcium-containing group and 29 to the calcium-free replacement solution group. The primary endpoint was circuit lifespan and Kaplan–Meier survival analysis was performed. Secondary endpoints included hospital mortality, kidney function recovery rate, and complications. The amount of 4% trisodium citrate solution infusion was recorded. Serum and effluent total (tCa) and ionized (iCa) calcium concentrations were measured during CVVHDF.

Results: A total of 149 circuits (82 in the calcium-containing group and 67 in the calcium-free group) and 7609 circuit hours (4335 h *vs.* 3274 h) were included. The mean circuit lifespan was 58.1 h (95% CI 53.8–62.4 h) in the calcium-containing group *vs.* 55.3 h (95% CI 49.7–60.9 h, log rank $P = 0.89$) in the calcium-free group. The serum tCa and iCa concentrations were slightly lower in the calcium-containing group during CRRT, whereas the postfilter iCa concentration was lower in the calcium-free group. Moreover, the mean amounts of 4% trisodium citrate solution infusion were not significantly different between the groups (171.1 ± 15.9 mL/h *vs.* 169.0 ± 15.1 mL/h, $P = 0.49$). The mortality (14/35 [40%] *vs.* 13/29 [45%], $P = 0.70$) and kidney function recovery rates of AKI patients (19/26, 73% *vs.* 14/24, 58%, $P = 0.27$) were comparable between the calcium-containing and calcium-free group during hospitalization, respectively. Six (three in each group) patients showed signs of citrate accumulation in this study.

Conclusions: When compared with calcium-free replacement solution, RCA-based CVVHDF with calcium-containing replacement solution had a similar circuit lifespan, hospital mortality and kidney outcome. Since the calcium-containing solution obviates the need for a separate venous catheter and a large dose of intravenous calcium solution preparation for continuous calcium supplementation, it is more convenient to be applied in RCA-CRRT practice.

Registration: Chinese Clinical Trial Registry (*www.chictr.org.cn*, ChiCTR-IPR-17012629)

Keywords: Anticoagulant agent; Circuit lifespan; Continuous renal replacement therapy; Dialysis solutions; Randomized controlled trial; Sodium citrate

Introduction

Continuous renal replacement therapies (CRRTs) are widely applied in critically ill patients with acute kidney injury (AKI) or chronic kidney disease (CKD).[1] Various anticoagulation strategies are used to prevent extracorporeal circuits from clotting.[2,3] Regional citrate anticoagulation (RCA), which can reduce the risk of circuit loss and bleeding, has been proven to be more effective and safer than systemic or regional heparin anticoagulation for CRRT.[2,4,5]

Citrate acts as an anticoagulant by chelating ionized calcium (iCa) in the extracorporeal circuit and then blocking the coagulation cascade.[6,7] Since traditional RCA usually applies calcium-free solutions, a persistent and large dose of systemic calcium infusion is needed to replace calcium loss in effluent fluid and prevent hypocalcemia.[8-10] However, the shortage of intravenous calcium in some countries and complex protocols of calcium-free solution as well as the increasing workload have limited the use of RCA.[11-13] To make RCA more convenient to apply in CRRT, we developed a simplified RCA-based continuous venovenous hemofiltration

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002369

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Chinese Medical Journal 2022;135(20)

Received: 22-02-2022; **Online:** 09-12-2022 **Edited by:** Yuanyuan Ji

(CVVH) protocol that utilized 4% trisodium citrate solution and a commercial calcium-containing replacement solution.[14] Together with other previous studies, the calcium-containing solution has been confirmed to be safe and effective without a continuous calcium infusion in RCA.[11,15-17]

However, it is unclear whether these two types of solutions have different effects on hemofilters or even the patients' clinical outcome. To address these questions, we conducted a prospective single-center randomized clinical trial (RCT) to observe the efficacy and safety of RCA using calcium-containing solution. This study may provide evidence that simplified RCA using a calcium-containing replacement solution could be a good choice for patients.

Methods

Study design

This was a single-center, randomized, prospective clinical trial and was performed in six intensive care units (ICUs) in West China Hospital of Sichuan University. Randomization was performed by means of a computer-based random number table procedure by staff not involved in the treatment of the patients. Patients and therapists were not masked to the treatment. Patient data collection and analysis were masked to the treatment group allocation staff. The study was approved by the Ethics Committees of West China Hospital of Sichuan University (2017-102) and was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR-IPR-17012629). Informed consent was obtained from patients or patients' legal representatives.

Patients

Sixty-four critically ill patients (49 males and 15 females) with AKI or CKD receiving CRRT during September 2017 and September 2019 were successfully enrolled in this study. All the included participants who agreed with this study were randomly assigned to RCA-based CRRT with calcium-containing replacement solution (calcium-containing group, $n = 35$) or the calcium-free replacement solution (calcium-free group, $n = 29$).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) critically ill patients who needed renal replacement therapy because of AKI or CKD; (2) hemodynamically stable and suitable for CRRT with a continuous venovenous hemodiafiltration (CVVHDF) modality; (3) aged between 18 and 80 years; and (4) informed consent was given after enrollment. Patients were excluded from the study if they fulfilled the following exclusion criteria: (1) patients with citrate anticoagulant contraindications, such as severe liver failure and irreversible hypotension or hypoxemia; (2) organ transplant patients; (3) expected stay in the intensive care unit (ICU) less than 24 h; (4) pregnancy or breastfeeding; and (5) patients who could not cooperate with the study because of mental diseases or other reasons.

Intervention

Prismaflex (Baxter [China] Investment Co., Ltd, Shanghai) CRRT machines and AN69 ST150 hemofilters (Baxter [China] Investment Co., Ltd, Shanghai) were applied for the extracorporeal circuit system. The AN69 ST150 set was replaced every 72 h regularly. Patients in both groups were treated with CVVHDF. Vascular access was provided by the insertion of a double lumen catheter into either the femoral vein (Baxter (China) Investment Co., Ltd, Shanghai, GDHK-1325, 13Fr, 250 mm) or internal jugular vein (Baxter International Inc, GDHK-1215, 12Fr, 150 mm). Postdilution mode was used, and the CRRT dose was 20 to 35 $mL \cdot kg^{-1} \cdot h^{-1}$ (dialysis:replacement fluid = 1:1). The blood flow was set as 150 mL/min and adjusted according to iCa concentration during treatment. Acid–base and electrolyte parameters (Ca^{2+}, Na^{+}, K^{+}) were determined using the Cobas b 123 system (Roche Diagnostics, Basel, Switzerland) at the beginning (0.5 h, prefilter), 2 h and every 6 h (pre- and postfilter) after starting CVVHDF. A 4% trisodium citrate solution (200 mL, Qingshan Likang Pharmaceutical Co. Ltd., Chengdu, China) was pumped into the arterial line of the extracorporeal circuit at an initial rate of 170 mL/h in both groups and titrated at increments or decrements of 10 mL/h to achieve a target postfilter iCa level of 0.25 to 0.35 mmol/L and prefilter iCa level of 0.90 to 1.20 mmol/L.

The commercial calcium-containing replacement solution (Qingshan Likang, Pharmaceutical Co. Ltd.), which contained solution A (glucose 10.6, Cl^{-} 118, Mg^{2+} 0.797, Ca^{2+} 1.60, and Na^{+} 113 mmol/L) and solution B (5% sodium bicarbonate), was adopted in the calcium-containing group. Two liters of solution A combined with 125 mL of solution B had a pH of 7.40 and contained 10.0 glucose, 110 Cl^{-}, 0.75 Mg^{2+}, 1.50 Ca^{2+}, 141 Na^{+}, and 35 mmol/L HCO_3^{-}. During RCA-based CVVHDF, a relatively small dose (solution A/B: 2 L/40 mL) of 5% sodium bicarbonate (solution B) was delivered alone by a pump prefilter; this dose could be adjusted at any time to correct for metabolic acidosis or alkalosis. Ten percent potassium chloride was also infused by another pump prefilter, and the infusion dose as well as net ultrafiltration was adjusted according to the blood gas analysis results and clinical condition of the patient. Ten percent calcium gluconate (Qingshan Likang, Pharmaceutical Co. Ltd.) was infused on an as-needed basis to maintain the target iCa level as an intermittent intravenous bolus. Calcium-free replacement solution (Qingshan Likang, Pharmaceutical Co. Ltd.), which contained solution A (glucose 10.6, Cl^{-} 115, Mg^{2+} 0.797, Ca^{2+} 0, and Na^{+} 113 mmol/L) and solution B (5% sodium bicarbonate), was used in the calcium-free group. To replace calcium losses in blood, intravenous 10% calcium gluconate was administered continuously by a pump via a T-branch pipe in a postfilter at a speed of 18 to 25 mL/h. Other preset parameters were in accordance with the calcium-containing group. The standard scheme for the application of these two replacement solutions in RCA-based postdilution CVVHDF is shown in Figure 1.

The decisions to start or stop CRRT were made by clinicians in both the ICU and Nephrology Department. CRRT was delivered according to the manufacturer's

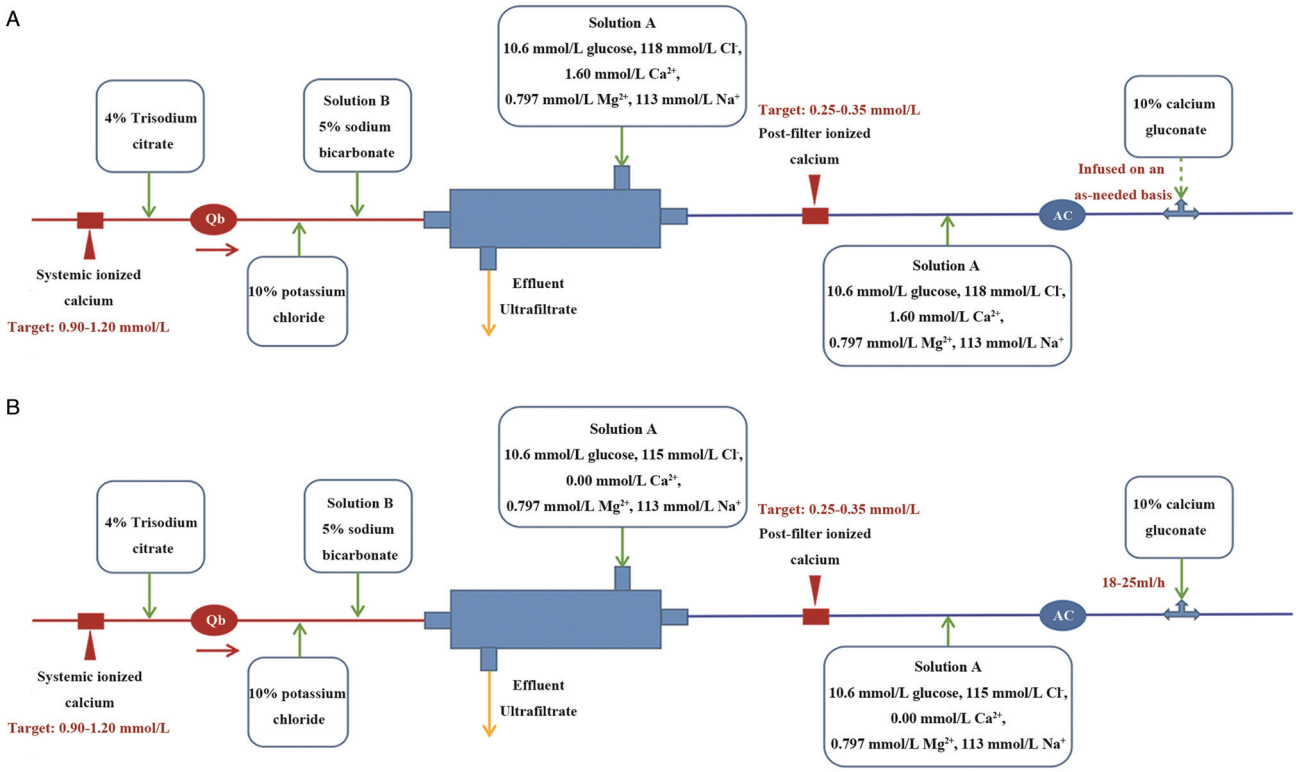

Figure 1: The standard scheme for the application of calcium-containing (A) and calcium-free replacement solutions (B) in RCA-based postdilution CVVHDF. A 4% trisodium citrate solution, 10% potassium chloride and solution B (5% sodium bicarbonate) were infused via the preblood pumps. Calcium-containing and calcium-free replacement solutions were used as both replacement solutions and dialysates (delivered postfilter). Ten percent calcium gluconate was infused on an as-needed basis as an intermittent intravenous bolus in the calcium-containing group (A). In the calcium-free replacement group, intravenous 10% calcium gluconate was administered continuously by a pump via a T-branch pipe in a postfilter (B). AC: Air-trap chamber; CVVHDF: Continuous venovenous hemodiafiltration; Qb: Blood flow rate; RCA: Regional citrate anticoagulation.

specifications, including routine circuit changes after 72 h of use without clotting. CRRT was prescribed by nephrologists and delivered by nursing staff. Patients and treatment information were collected later.

Adverse reactions

One of the most serious complications of patients in both groups during RCA-based CRRT was citrate accumulation. Hypocalcemia, metabolic acidosis, and increased serum lactate levels were noticeable signs. An increased total/iCa (Ca/Ca^{2+}) ratio (>2.5) was recognized as indicative of significant accumulation.[18] When citrate accumulation was suspected, the net citrate load administered to the patient was decreased. RCA would be replaced by alternative circuit anticoagulation if irreversible citrate accumulation occurred. Other adverse potential complications, such as bleeding, hypernatremia or hyponatremia, metabolic alkalosis, paresthesia, twitching movement, and cardiac dysrhythmia, were recorded in both groups.

Study endpoints

The primary outcome was the circuit lifespan (measured in hours). The circuit lifespan started from the extracorporeal circulation of blood and ended when the circuit was clotting. The clotted circuit was characterized by having exceeded transmembrane pressure (TMP) over 250 mmHg and/or visible clotting in the air-trap chamber. CRRT circuits might be stopped without clotting for the following reasons: (1) used for 72 h (without clotting); (2) catheter dysfunction and a new vascular access needed to be established (defined as unclear); (3) stopped for treatment reasons such as operations and hospital transfer (defined as unclear); and (4) patient relinquished CRRT (defined as unclear). Taken together, there were three possible outcomes for the circuits: clotted, without clotting, or unclear. Clotted and "without clotting" circuits were defined as circuits with clear outcomes.

The secondary endpoints included hospital mortality, length of ICU stay, kidney function recovery rate of AKI patients, complication incidence, and serum and effluent citrate and calcium concentrations. Kidney function recovery of AKI patients was defined as normal serum creatinine (<110 mmol/L) and urine output >800 mL/day without diuretic applied according to previous studies.[19,20]

Sample size

Sample size estimation was based on our previous circuit lifespan data of a simplified RCA-based CRRT protocol. One hundred and forty-eight sessions were performed, and the mean hemofilter survival was 61.3 ± 21.6 h.[14] The study was designed to demonstrate a $\leq$20% difference in circuit lifespan with a two-sided type I error of 0.05 and 80% power. According to the formula for calculating the sample size of equivalent clinical trials,[21]

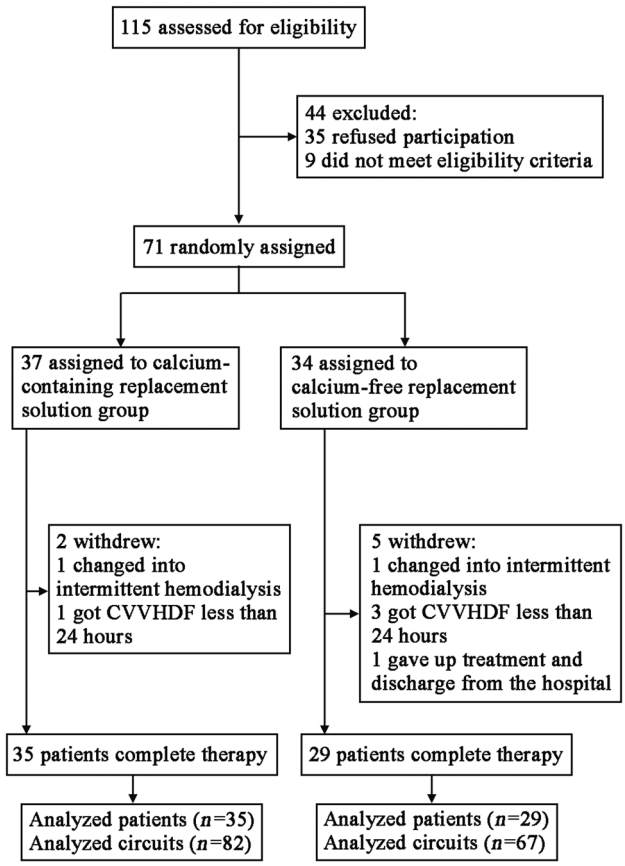

Figure 2: Flow diagram of a participant's involvement. CVVHDF: Continuous venovenous hemodiafiltration.

we set out to enroll 150 circuits (75 assigned to each group) to allow for a dropout rate of 15%. As the study was prematurely discontinued due to slow enrollment of patients, 149 circuits were included at the end of the study [Figure 2].

Data collection

Demographic data were collected when CRRT started and treatment group allocation was masked to data collection staff. We gathered clinical information, the need for mechanical ventilation and vasopressors, the sequential organ failure assessment (SOFA) score, and the following laboratory variables when starting CRRT: serum urea, creatinine, estimated glomerular filtration rate, hemoglobin, platelet count, prothrombin time, activated partial thromboplastin time, D-dimer, alanine aminotransferase, aspartate aminotransferase and total bilirubin levels. Other information during CRRT was recorded, such as blood flow rate, the amount of 4% trisodium citrate solution and 10% calcium gluconate administered, filtration fraction, dialysate and replacement solution infusion rates, catheter sites, initial and withdrawn TMP, circuit survival, and causes of circuit replacement and adverse reactions. Other vital signs of the patients were also monitored regularly. The levels of serum and effluent total calcium (tCa) were measured by a Roche Cobas c702 analyzer (Roche Diagnostics, Basel, Switzerland) in both groups and analyzed at the beginning (0.5 h), 6, 12, and then every 24 h after CVVHDF. The follow-up time was hospitalization period, and thus, no patient was lost to the follow-up. By the end of the study, patients' information about the length of ICU stay, kidney function recovery, and causes of death were collected.

Statistical analyses

SPSS (IBM SPSS Statistics 19.0, Chicago, IL, USA) was applied for all statistical analyses. Continuous numeric variables showing normal distributions were compared by *t* test and presented as the mean ± standard deviation (SD); Mann–Whitney *U* test and median (interquartile range [IQR]) were used for nonnormal distribution statistics. Categorical variables were analyzed by Pearson's χ^2 test or Fisher's exact test and presented as the frequency and proportion. Kaplan–Meier survival analysis using the log-rank test (Mantel–Cox test) was implemented to compare hemofilter survival between the two groups. Statistical significance was assigned to *P* values <0.05.

Results

Participants and recruitment

From September 2017 to September 2019, a total of 115 patients were referred to this study, while nine patients did not meet the eligibility criteria, and 35 declined study participation. Seventy-one patients were randomized into two groups, and seven of them withdrew from the study because the treatment modality changed from CRRT to intermittent hemodialysis (IHD, two patients), receiving CVVHDF less than 24 h (four patients) or being discharged from the hospital within 24 h (one patient). Finally, there were 35 patients and 82 circuits that were successfully included in the calcium-containing replacement solution group, 29 patients and 67 circuits in the calcium-free group [Figure 2].

The primary diseases and main diagnoses of these patients were respiratory failure, circulatory failure, septic shock, and postoperative and severe acute pancreatitis. All these patients were diagnosed with AKI or CKD (50/14). Demographic and clinical characteristics at the time of randomization were similar between groups and are listed in Table 1. The severity of critical illness was comparable between the calcium-containing and calcium-free groups by using the ICU scoring systems SOFA score. The groups were well matched at baseline with renal, liver, and other hematological laboratory variables.

Treatment and metabolic parameters during CVVHDF

Treatment parameters during CVVHDF were comparable and are summarized in Table 2. The infusion rate of dialysate solution A was 1.07 ± 0.22 L/h in the calcium-containing group and 1.03 ± 0.13 L/h in the calcium-free group, while the rates of postfilter replacement solution A were 0.98 ± 0.13 and 0.91 ± 0.19 L/h, respectively. The mean filtration fraction was set up to nearly 20%. The blood flow rate (143.0 ± 9.5 mL/min *vs.* 144.7 ± 6.0 mL/min)

Table 1: Demographic and clinical characteristics of the patients with AKI or CKD receiving CRRT.

Variables	Calcium-containing group ($n = 35$)	Calcium-free group ($n = 29$)	$t/z/\chi^2$	*P* value
Age (years)	56.1 ± 16.3	58.7 ± 13.6	−0.67*	0.51
Male	28 (80)	21 (72)	0.51†	0.48
BMI (kg/m^2)	24.87 ± 4.88	23.95 ± 4.42	0.75*	0.46
Main reason for admission to ICU			0.99†	0.91
Respiratory failure	8	9		
Circulatory failure	7	5		
Septic shock	6	5		
Postoperative	6	3		
Severe acute pancreatitis	8	7		
Reasons for CRRT			0.67†	0.41
AKI	26	24		
CKD	9	5		
SOFA score	11 ± 3	12 ± 3	1.03*	0.31
Mechanical ventilation	27 (77)	20 (69)	0.54†	0.46
Vasopressor dependency	11 (31)	11 (38)	0.30†	0.59
Renal variables				
Urea (mmol/L)	17.6 ± 8.4	21.8 ± 8.6	1.50*	0.14
Creatinine (μmol/L)	291.5 ± 88.6	324.5 ± 168.4	0.71*	0.49
eGFR (mL·min^{-1}·1.73 m^{-2})	19.66 (13.05)	16.11 (19.99)	−1.10‡	0.27
Hematologic variables				
Hemoglobin (g/L)	88.0 ± 17.9	92.2 ± 21.7	0.71*	0.48
Platelet count (×10^9/L)	113.5 (82.8)	75.0 (99.0)	−1.73‡	0.08
APTT (s)	38.0 (20.3)	35.1 (12.2)	0.00‡	0.99
PT (s)	13.4 (3.6)	15.7 (4.6)	−1.51‡	0.13
D-dimer (mg/L)	7.41 ± 7.61	9.54 ± 6.13	−1.09*	0.28
Liver variables				
ALT (IU/L)	14 (30)	20 (44)	−0.36‡	0.72
AST (IU/L)	40 (31)	46 (46)	−0.52‡	0.61
Total bilirubin (μmol/L)	15.1 (14.2)	18.7 (15.1)	−1.45‡	0.15

Values were shown as mean ± SD, *n* (%), *n*, or median (IQR). * *t* value. † χ^2 value. ‡ *Z* value. AKI: Acute kidney injury; ALT; alanine aminotransferase; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; BMI: Body mass index; CKD: Chronic kidney disease; CRRT: Continuous renal replacement therapy; eGFR: Estimate glomerular filteration rate; ICU: Intensive care unit; IQR: Interquartile range; PT: Prothrombin time; SD: Standard deviation; SOFA: Sequential organ failure assessment.

Table 2: Treatment parameters during CVVHDF of the patients with AKI or CKD receiving CRRT.

Parameters	Calcium-containing group ($n = 35$)	Calcium-free group ($n = 29$)	$t/z/\chi^2$	*P* value
Vascular site			0.38*	0.68
Femoral vein	31 (89)	27 (93)		
Right jugular vein	4 (11)	2 (7)		
Dialysate rate (L/h)	1.07 ± 0.22	1.03 ± 0.13	−1.43†	0.16
Postfilter replacement fluid rate (L/h)	0.98 ± 0.13	0.91 ± 0.19	−1.51†	0.13
Filtration fraction (%)	19.3 ± 2.5	19.7 ± 2.3	0.57†	0.54
Blood flow rate (mL/min)	143.0 ± 9.5	144.7 ± 6.0	1.08†	0.28
4% trisodium citrate infusion rate (mL/h)	171.1 ± 15.9	169.0 ± 15.1	−0.69†	0.49
10% calcium gluconate supplement (mL/h)	1.47 ± 1.34	20.16 ± 3.62	40.11†	<0.01
Initial TMP (mmHg)	53.0 (16.5)	55.0 (30.0)	−0.69‡	0.50
Withdrawn TMP (mmHg)	110.0 (127.5)	127.0 (193.0)	−0.45‡	0.65

Values were shown as mean ± SD, *n* (%), or median (IQR). * χ^2 value. † *t* value. ‡ *Z* value. IQR: Interquartile range; SD: Standard deviation. AKI: Acute kidney injury; CKD: Chronic kidney disease; CVVHDF: Continuous venovenous hemodiafiltration; TMP: Transmembrane pressure.

and 4% trisodium citrate infusion rates (171.1 ± 15.9 mL/h *vs.* 169.0 ± 15.1 mL/h) were adjusted to maintain their postfilter iCa level within 0.25 to 0.35 mmol/L. Total 10% calcium gluconate infusion dose was set up according to the serum iCa concentration (target range 0.90–1.20 mmol/L). In the calcium-containing group, it was infused as an intermittent intravenous bolus when the prefilter ionized serum calcium level was below 0.85 mmol/L and the average infusion dose was 1.47 ± 1.34 mL/h (0.34 ± 0.31 mmol/h). In the calcium-free group, intravenous 10% calcium

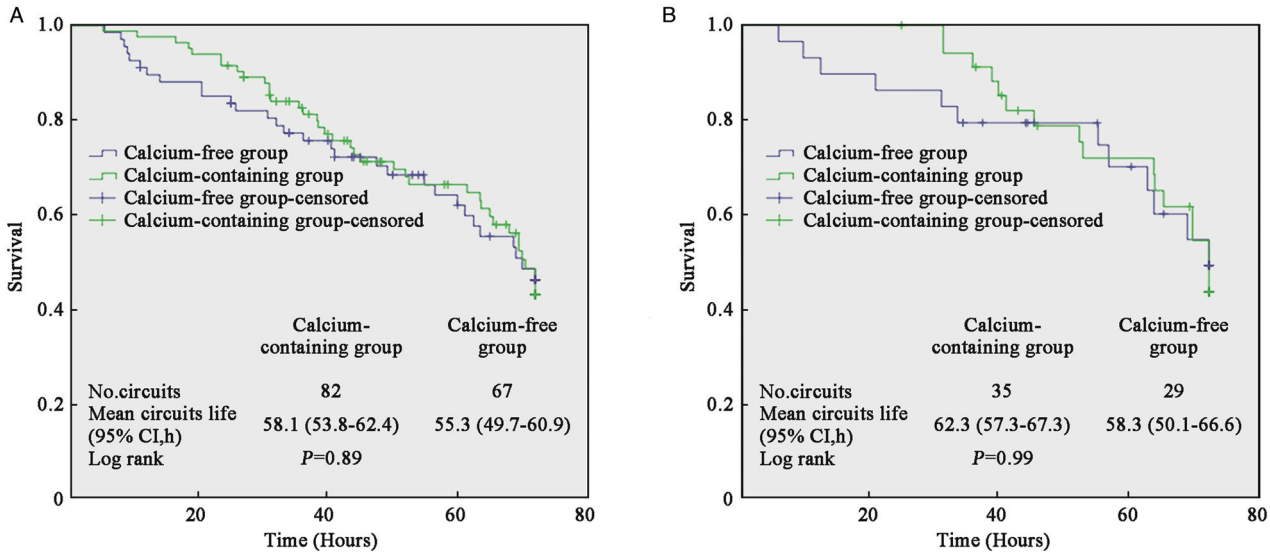

Figure 3: The Kaplan–Meier curve for all hemofilter life spans (A) and the first circuit life span (B). CI: Confidence interval.

gluconate was administered continuously by a pump, and the mean infusion rate was 20.16 ± 3.62 mL/h (4.69 ± 0.84 mmol/h, $P < 0.01$). The median initial TMP was 53.0 and 55.0 mmHg, and the median TMP when withdrawing circuits was 110.0 mmHg *vs.* 127.0 mmHg, respectively.

Circuit lifespan and calcium concentration

A total of 149 circuits (82 in the calcium-containing group and 67 in the calcium-free group) and 7609 circuit hours (4335 h *vs.* 3274 h) were included. The total circuit lifespan was not significantly different between the calcium-containing and calcium-free groups. The mean circuit lifespan was 58.1 h (95% CI 53.8–62.4 h) in the calcium-containing group *vs.* 55.3 h (95% CI 49.7–60.9 h, log rank $P = 0.89$) in the calcium-free group. Kaplan–Meier survival analysis revealed that the circuit lifespan was similar using the calcium-containing replacement solution compared with that in the calcium-free group [Figure 3A]. The total circuit outcomes and reasons for circuit disconnection are summarized in Table 3.

Survival of the first circuit was also comparable between RCA with calcium-containing and calcium-free replacement solution (62.3 h [95% CI 57.3–67.3 h] *vs.* 58.3 h [95% CI 50.1–66.6 h], log rank $P = 0.99$; Figure 3B). Reasons for circuit disconnection of the first circuit are also presented in Table 3. Sixteen of 35 first circuits (46%, two air-trap chamber clotting) in the calcium-containing group were stopped due to clotting, compared with 12 of 29 (41%, two air-trap chamber clotting) in the calcium-free group. There were 22 first circuits (13/35, 37% *vs.* 9/29, 31%, $P = 0.61$) that had normal function within 72 h and were regularly changed. One patient in the calcium-free group had catheter dysfunction, and new vascular access needed to be established together with a new filter change. Other first circuits were disconnected due to relinquishment of CVVHDF (4/82, 11% *vs.* 5/67, 17%) or transport (2/82, 6% *vs.* 2/67, 7%).

To further investigate the lifespans of circuits with clear outcomes, we excluded "unclear" outcomes and analyzed "clotted" or "without clotting" filters. Sixty-two circuits in the calcium-containing group and 50 circuits in the calcium-free group were included. The Kaplan–Meier survival analysis also showed no significant difference in circuit life between groups (mean 55.2 h *vs.* 51.2 h, $P = 0.70$, Supplementary Figure 1, http://links.lww.com/CM9/B251).

During RCA-CVVHDF, the tCa concentration in serum and effluent, as well as serum and postfilter iCa, are summarized in Supplementary Table 1, http://links.lww.com/CM9/B251. Both the systemic serum tCa and iCa concentrations were similar at the initial time and turned slightly lower in the calcium-containing group in the first 48 h during CVVHDF ($P < 0.05$). However, after 72 h of treatment, the systemic serum tCa and iCa levels in the calcium-containing group gradually increased and became comparable with those in the calcium-free group (2.06 ± 0.22 mmol/L *vs.* 2.15 ± 0.22 mmol/L, $P = 0.37$; 0.93 ± 0.07 mmol/L *vs.* 1.00 ± 0.08 mmol/L, $P = 0.002$, respectively). The effluent tCa showed a similar increasing trend with serum tCa. Interestingly, as a postdilution of calcium-containing replacement solution, the postfilter iCa concentration was elevated in the calcium-containing group, and the postdilution of calcium-free replacement solution made the postfilter iCa lower ($P < 0.05$). Both groups achieved the target range of the mean postfilter iCa levels (from 0.25 ± 0.10 to 0.33 ± 0.07 mmol/L, Supplementary Table 1, http://links.lww.com/CM9/B251).

Secondary outcomes and adverse events

Mortality rates were comparable between groups during hospitalization [Table 3]: 14/35 calcium-containing group patients (40%) died *vs.* 13/29 patients (45%) in the calcium-free group died. Furthermore, there was no difference between groups in kidney function recovery rates in AKI patients, with 19/26 (73%) in the calcium-containing group

Table 3: Circuits and clinical outcomes of the patients with AKI or CKD receiving CRRT.

Variables	Calcium-containing group	Calcium-free group	Statistics	*P* value
Total circuits outcomes	*n* = 82	*n* = 67		
Mean circuit lifespan (95% CI, h)	58.1 (53.8–62.4)	55.3 (49.7–60.9)	–	0.89
Median (range, h)	55.3 (5.3, 72.0)	53.0 (5.5, 72.0)		
≥24 h	86%	84%		
≥48 h	56%	55%		
≥72 h	33%	29%		
Reasons for circuits disconnection, *n*/total (%)			2.93*	0.57
Circuit clotting	38 (46)	28 (42)		
Air-trap chamber clotting	8/38	3/28		
Regular filter replacement (72 h)	24 (29)	20 (30)		
Catheter dysfunction	0 (0)	2 (3)		
Relinquishment of CVVHDF	15 (18)	14 (21)		
Transport	5 (6)	3 (5)		
Summarized total circuits outcomes			0.40*	0.82
Clotted	38 (46)	28 (42)		
Without clotting (72 h)	24 (29)	20 (30)		
Unclear	20 (24)	19 (28)		
First circuits outcomes	***n* = 35**	***n* = 29**		
Mean survival time (95% CI, h)	62.3 (57.3–67.3)	58.3 (50.1–66.6)		0.99
Reasons for circuits disconnection			0.18*	0.76
Circuit clotting	16 (46)	12 (41)		
Air-trap chamber clotting	2/16	2/12		
Regular filter replacement (72 h)	13 (37)	9 (31)		
Catheter dysfunction	0 (0)	1 (3)		
Relinquishment of CVVHDF	4 (11)	5 (17)		
Transport	2 (6)	2 (7)		
Patients' outcomes	***n* = 35**	***n* = 29**		
Hospital mortality	14 (40)	13 (45)	0.15*	0.70
Kidney recovery of AKI†	19 (73)	14 (58)	1.21*	0.27
ICU stays (days)	20 (27)	26 (15)	−0.80‡	0.27
Adverse events (%)				
Citrate accumulation	3 (9)	3 (10)	0.06*	0.81
Bleeding	1 (3)	0	0.84*	0.55
Hyponatremia	5 (14)	4 (14)	0.01*	0.96

Values were shown as *n* (%), *n*, or median (IQR). * χ^2 value. † Calcium-containinng group had 26 AKI patients and calcium-free group had 24 AKI patients. ‡ Z value. AKI: Acute kidney injury; CI: Confidence interval; CKD: Chronic kidney disease; CRRT: Continuous renal replacement therapy; ICU: Intensive care unit; IQR: Interquartile range; –: Data not applicable due to log rank test (Mantel–Cox test) was implemented to compare hemofilter survival.

vs. 14/24 (58%) in the calcium-free group having normal kidney function after withdrawing CVVHDF. The length of ICU stay was also similar in the calcium-containing and calcium-free groups (median 20 days *vs.* 26 days).

Three patients (9%) in the calcium-containing group and three (10%) in the calcium-free group developed significant citrate accumulation. These patients showed significant systemic hypocalcemia (<0.8 mmol/L) and an increased total/ iCa (Ca/Ca^{2+}) ratio (>2.5), while metabolic acidosis (pH value <7.20, normal range 7.35–7.45) and increased serum lactate levels (>5.0 mmol/L, normal range 1.0–1.8 mmol/L) were observed. All the abnormal indexes reverted by increasing calcium supplementation and replacement of anticoagulation from RCA into low-molecular-weight heparin (*n* = 4) or no anticoagulation (*n* = 2). Only one patient in the calcium-containing group had bleeding at the femoral vein puncture site. The acid–base and electrolyte parameters were comparable between the two groups during CVVHDF [Supplementary Table 2, http://links.lww.com/CM9/B251]. Hyponatremia (<130 mmol/L) was seen in nine patients (5/35 *vs.* 4/29), and none of the patients had other severe complications, such as hypernatremia, metabolic alkalosis, paresthesia, twitching movement, and cardiac dysrhythmia.

Discussion

Key findings

In the present study, we found that simplified RCA using a calcium-containing replacement solution was safe and efficient compared with calcium-free replacement in postdilution CVVHDF. Compared to the calcium-free replacement solution, patients treated with calcium-containing solution had similar circuit lifespans as well as clinical outcomes in terms of mortality, kidney function recovery, length of ICU stay, and adverse events such as citrate accumulation and hyponatremia rates. Systemic

serum concentrations of tCa and iCa, and postfilter iCa were slightly lower in the calcium-containing group, whereas the calcium levels gradually increased and became comparable between groups after 72 h of treatment.

Relationship to previous studies

CRRT has been frequently applied in critically ill patients with kidney dysfunction, and the choice of extracorporeal anticoagulation is important. Compared to widely used heparin and low-molecular-weight heparin anticoagulation, RCA is more efficacious in prolonging circuit life span and reducing the risk of bleeding.[3,4,10,22]

During RCA-based CRRT, sodium citrate is infused through arterial blood in the extracorporeal circuit. Traditional RCA protocols apply calcium-free replacement solution in CRRT, and calcium chloride or calcium gluconate should be infused at the end of the extracorporeal circuit or directly infused into the patient via a central venous line to maintain a systemic iCa at the physiological range.[9,23] Calcium-containing replacement solutions are not widely used because of a fear that calcium-containing solutions would lead to ineffective anticoagulation or increased citrate requirements.[17] In recent years, the adoption of conventional calcium-containing replacement fluids in RCA-based CRRT represents a further simplification that reduces the need for calcium infusion, as well as labor intensive and the risk of iatrogenic errors when calcium-free solutions are handled.[17,24-26]

Several simplified protocols of RCA were applied during CVVHDF. Cointault *et al*[15-17] used anticoagulant citrate dextrose formula A (ACD-A, Hospal, Lyon, France) solution containing 112.9 mmol/L disodium citrate (3.22%) and reinjection replacement solution and dialysate composed of Hemosol B0 solution combined with Hemosol B0 5.88% HCO_3Na solution (calcium 1.75 mmol/L, Hospal, Lyon, France). The loss of calcium through the dialyser was compensated by infusion of a calcium chloride solution (1.37 mmol/h) to maintain plasma iCa^{2+} >1.1 mmol/L. Gupta *et al*[15] evaluated ACD-A (3% solution: trisodium citrate, 2.2%; and citric acid, 0.8%; 112.9 mmol of citrate/L; Baxter) solution in combination with a commercially available calcium-containing dialysate for regional anticoagulation in CVVHDF. A low-calcium peritoneal dialysis solution (calcium 1.25 mmol/L, Baxter Healthcare, Deerfield, IL) was used as dialysate, and isotonic saline was used as replacement fluid and infused proximal to the hemofilter. Calcium chloride (10% solution, 5.40 ± 4.35 mmol/day) was administered on an as-needed basis as an intermittent intravenous bolus every 6 h to maintain systemic venous iCa levels at 0.88 to 1.00 mmol/L. Rhee *et al*[17] described their experience of RCA with calcium-containing solutions for CVVHDF. They used commercially available PrismaSATE 4/2.5 solution (Baxter Corp), which contains 2.5 mEq/L calcium, as a dialysate. The replacement solution included PrismaSol (32 mmol/L bicarbonate, 3 mEq/L lactate, 2.5 mEq/L iCa; Baxter Corp) or customized bicarbonate solutions composed of sterile water mixed with 150 mEq of bicarbonate, sterile water mixed with 75 mEq of bicarbonate, and 0.45% saline solution mixed with 75 mEq of bicarbonate, 0.45% saline solution, or 0.9% saline solution.

Although all of these protocols used calcium-containing replacement solution or dialysate, a lower bicarbonate concentration fluid was needed to compensate for the buffer overload due to bicarbonate production ensuing from the net citrate load to the patient, therefore preventing metabolic alkalosis during RCA.[27,28] Customized replacement solution or dialysate dedicated for RCA-CRRT were still needed, which made it difficult to change the anticoagulation methods as the conditions of critical patients change rapidly. As a consequence, those protocols were still not "simple" enough. We developed a simplified protocol for RCA using a commercial calcium-containing replacement solution for CVVH in 2012.[14] In our protocol, two liters of solution A combined with 125 mL of solution B had a pH of 7.40 and contained Ca^{2+} 1.50 and HCO_3^- 35 mmol/L. Solution B (5% sodium bicarbonate) was delivered alone by a pump prefilter, which made it able to be adjusted at any time to correct for metabolic acidosis or alkalosis. When the anticoagulation switched from RCA to low-molecular-weight heparin or no anticoagulation, the nurses only needed to withdraw 4% citrate and increased the blood flow and solution B infusion rates. No other solution needed to be replaced or discharged. Therefore, this calcium-containing solution protocol can save medical resources, decrease labor intensity, remarkably shorten the downtime, and simplify anticoagulation in CRRT.

It has been reported that RCA with calcium-containing replacement solution is compatible with an adequate filter lifespan without increasing the risk of venous drip chamber clotting.[24,26,29] However, there are few RCT studies to compare the efficiency and safety between calcium-containing and calcium-free replacement solutions in RCA-based CRRT. A systematic review reported that the mean hemofilter survival time is 55.9 h (IQR 32.8–68.9 h) in RCA-CRRT.[30] Gupta *et al*[15] reported that the mean circuit lifespan was 63.5 ± 27.1 h, and Cointault *et al*[16] found that the mean filter survival was 39 ± 11 h in RCA using calcium-containing replacement and dialysate solutions for CVVHDF. All of these circuit lifespans were comparable to the calcium-containing group in our study (mean 58.1 [95% CI 53.8–62.4] h). Interestingly, in our pilot, a similar circuit lifespan (mean 55.3 [49.7–60.9] h) was observed in RCA with calcium-free replacement solution. Other factors that can affect circuit lifespan independent of anticoagulation, such as CRRT modality, delivery dose, filtration fraction, vascular sites, blood flow rate, and 4% sodium citrate infusion rate, were balanced between groups. Some protocols use a fixed dose of citrate in relation to blood flow according to an algorithm and target such doses at approximately 3 mmol citrate/L blood flow.[27] The infusion rate of 4% trisodium citrate of our protocol was set up as 170 mL/h, and the mean delivery blood flow rate was approximately 144 mL/min, which made the citrate level in the extracorporeal circuit maintain approximately 2.88 mmol citrate/L blood flow. The citrate dose was slightly lower in our study than previously described, but we still obtained an acceptable circuit lifespan. Although the postfilter iCa concentration

was higher in the calcium-containing group during CVVHDF, the circuit lifespan and air-trap chamber clotting rates were not significantly different between the groups. The results of our study demonstrated the efficiency of simplified RCA using a calcium-containing replacement solution in postdilution CVVHDF.

In RCA-based CRRT, the calcium concentration is critical to estimate the safety and efficacy of anticoagulation. According to previous studies, a lower than usual systemic iCa level (0.9–1.0 mmol/L) should be considered a reasonable target when performing RCA CRRT in the clinical scenario.[27,31] The postfilter circuit iCa concentration is usually maintained at <0.3 to 0.5 mmol/L.[27] In our hospital, a target prefilter iCa level of 0.90 to 1.20 mmol/L and a postfilter iCa level of 0.25 to 0.35 mmol/L have been applied. Since the calcium-containing group patients only received 10% calcium gluconate infusion on an as-needed basis by intermittent intravenous bolus when the prefilter iCa level <0.85 mmol/L, the systemic prefilter concentrations of serum tCa, iCa, and effluent tCa were slightly lower than those of the calcium-free group in the first 48 h of CVVHDF. However, the majority of the hypocalcemia could be corrected quickly after calcium gluconate administration (0.34 ± 0.31 mmol/h) in the calcium-containing group. This calcium infusion is lower than that reported by Cointault *et al*[16] (calcium chloride solution, 1.37 mmol/h) but slightly higher than that reported by Gupta *et al*[15] (calcium chloride solution, 5.40 ± 4.35 mmol/d, 0.23 ± 0.18 mmol/h). In the calcium-free group, the mean intravenous 10% calcium gluconate administration rate was 20.16 ± 3.62 mL/h (4.69 ± 0.84 mmol/h), which was comparable to the calcium pump rate in the RCA group of Schilder *et al*.[10] Nevertheless, the appropriate calcium infusion amount still needs to be investigated in our future studies and clinical RCA-based CRRT practice using calcium-containing replacement solution.

In this work, we included 64 patients, and the overall hospital mortality was not significantly different between the calcium-containing (40%) and calcium-free groups (45%). Our findings were in concordance with previous studies, and the mortality was similar to that of citrate group patients (41%, 183/443) in a recent systematic review.[32] Moreover, these two groups in our study had comparable lengths of ICU stay and kidney function recovery rates, which implied that calcium-containing replacement solution will not harm patient-centered outcomes. Regarding adverse reactions, the rates of citrate accumulation that led to RCA withdrawal were comparable between groups (three in each group, total 9%) in our study, and this frequency is similar to the rate reported by Nurmohamed *et al*[25] (9%) and lower than the pooled rate of citrate accumulation (12%) in liver failure patients.[30] Furthermore, the amount of citrate delivered and the blood flow rates were similar between groups, all of which indicated that citrate overload and severe citrate accumulation rate did not differ between calcium-containing and calcium-free replacement solution. Only one patient (1/31) in the calcium-containing group had hemorrhage at the femoral vein puncture site, which might be caused by the high risk of bleeding since the patient had hemorrhagic pancreatitis. No other adverse complications were observed in either group. Patients in our study had rare adverse reactions except minor metabolic complications due to citrate accumulation, which was in concordance with a previous study and could be corrected rapidly by therapy adaptation.[33] Simplified RCA using a calcium-containing replacement solution as well as calcium-free replacement solution are safe protocols for usual clinical practice.

Weaknesses of this trial include that this study is a single-center RCT and the sample size is relatively small; therefore, a larger sample capacity and a multicenter RCT are needed in future research. Subsequently, there was a slight imbalance between groups in filter numbers because six patients in the calcium-containing group had a long CRRT duration time and used more than ten filters per person, but there were no significant differences in patient numbers between admission categories. Moreover, we only used the Prismaflex® Baxter CRRT machine in this trial, and the application of our simplified RCA using a calcium-containing replacement solution CRRT protocol needs to be further confirmed on other devices, such as Fresenius CiCa® and other CRRT modes.

In conclusion, patients who received RCA-based CRRT with calcium-containing or calcium-free replacement solution had similar mortality, kidney outcome, and adverse event rates. Since our simplified RCA using a calcium-containing replacement solution protocol had a similar and acceptable filter lifespan for postdilution CVVHDF and obviated the need for separate venous access for a large dose of continuous intravenous calcium infusion, it is more convenient to use in clinical practice.

Funding

The study was supported by the 1·3·5 project for disciplines of excellence-Clinical Research Incubation Project, West China Hospital, Sichuan University (18HXFH018).

Conflicts of interest

None.

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How to cite this article: Wei T, Tang X, Zhang L, Lin L, Li P, Wang F, Fu P. Calcium-containing versus calcium-free replacement solution in regional citrate anticoagulation for continuous renal replacement therapy: a randomized controlled trial. Chin Med J 2022;135:2478–2487. doi: 10.1097/CM9.0000000000002369