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A simplified protocol for individualized regional citrate anticoagulation for hemodialysis

A single-center, randomized clinical study

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Abstract

Introduction: The lack of individualized treatment protocols and complicated procedures are important factors limiting the use of regional citrate anticoagulation (RCA) technology in hemodialysis. This study aims to validate the safety and efficacy of a simplified individualized RCA protocol for hemodialysis.

Materials and methods: From June 2019 to August 2019, 45 patients with active bleeding or bleeding tendency undergoing maintenance hemodialysis in the Nephrology Department of the First Affiliated Hospital of Nanchang University were randomly divided into a modified conventional RCA protocol group with a low-flux dialyzer, a simplified individualized RCA protocol group with a high-flux dialyzer, and a simplified individualized RCA protocol group with a low-flux dialyzer.

Results: A total of 45 patients were included in this study. The mean age of the patients was 57.38 ± 19.05 years, and 78% were men. Forty-three patients completed 4 hours of hemodialysis, and the median total clotting scores in the 3 groups were 11, 12, and 12. Compared with the modified conventional RCA protocol group with a low-flux dialyzer, the 2 simplified individualized RCA protocol groups had better clotting scores for the dialyzer, arterial bubble trap, and single-pool urea clearance index (spKt/V_{BUN}) and lower costs. Moreover, these parameters did not differ between the 2 simplified individualized RCA protocol groups. No electrolyte or acid–base imbalances or citrate poisoning was observed in any of the 3 groups. Adverse events did not differ significantly among the 3 groups.

Conclusions: The simplified individualized RCA protocol is safe, effective, and easy to implement. Therefore, this protocol can be promoted for clinical practice.

Trial Registration: This study was registered in the Chinese Clinical Study Registry under registration number ChiCTR1900023801.

Abbreviations: ACD-A = acid citrate dextrose solution-A, ANOVA = analysis of variance, LMWH = low-molecular-weight heparin, LSD = least significant difference, PO_2 = pressure of oxygen, RCA = regional citrate anticoagulation, TBIL = total bilirubin.

Keywords: calcium-containing dialysate, hemodialysis, individualized medicine, prospective study, regional citrate anticoagulation

1. Introduction

Anticoagulation is necessary to ensure the smooth progress of hemodialysis. Heparin and low-molecular-weight heparin (LMWH) are currently the main anticoagulation agents used for hemodialysis, but they affect systemic coagulation function and are associated with a risk of bleeding[1]; therefore, they cannot be used in patients with bleeding tendencies or active bleeding. Such patients usually undergo heparin-free hemodialysis. However, clinical studies have found that heparin-free hemodialysis does not improve prognosis[2] and has shortcomings such as inadequate dialysis, an inability to ensure ultrafiltration volume, blood loss, and thromboembolic disease.

In 1961, Morita et al[3] first reported the use of regional citrate anticoagulation (RCA) for hemodialysis. This method does not affect systemic coagulation activity and has a good anticoagulant effect. However, the procedure is complex, and potential adverse reactions such as serious hypocalcemia and electrolyte and acid–base disorders[4–6] prevent wider use of this technique. To minimize the complexity of the procedure and reduce the risk of adverse reactions, various modified RCA protocols have been developed.[7–9] These protocols use a fixed blood flow rate, provide a fixed initial citrate preparation infusion rate according to the blood flow rate, and then allow for adjustment of subsequent citrate preparations by frequently detecting the

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Ethical approval: This study was registered at the Chinese Clinical Study Registry with registration number ChiCTR1900023801.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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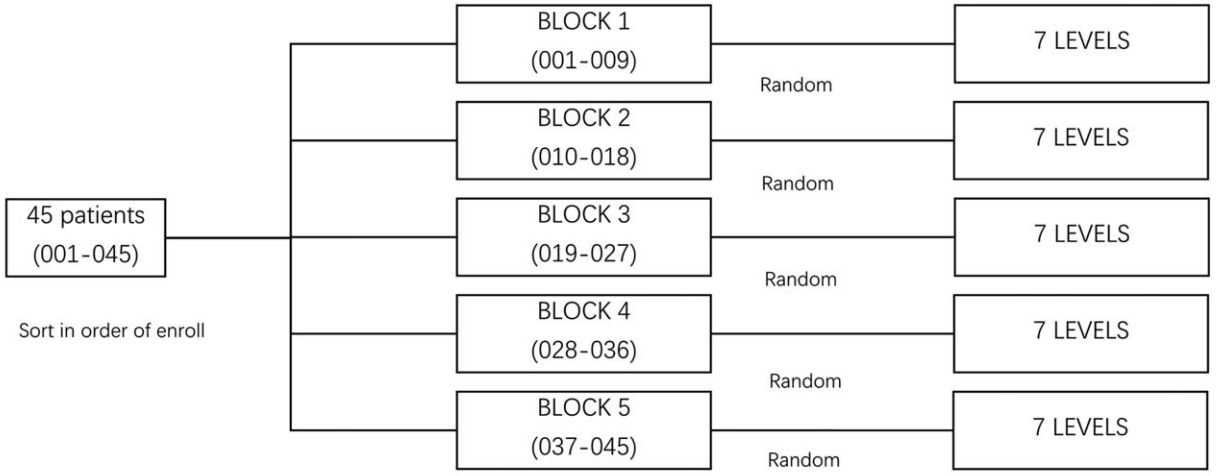
patient's systemic ionized calcium (iCa^{2+}) and predialyzer iCa^{2+} concentrations to ensure safety and efficacy. This method cannot achieve individualized treatment, requires frequent monitoring, is expensive, and is difficult to carry out routinely. During previous treatment using a modified conventional hemodialysis protocol with RCA in our center, the blood flow speed and/or citrate infusion speed were continuously adjusted according to the patient's systemic iCa^{2+} and predialyzer iCa^{2+} during treatment to achieve effective anticoagulation and safety. In addition, analysis of the data revealed that the citrate concentration in the extracorporeal circulation pipeline had a linear correlation with the patient's systemic iCa^{2+}, consistent with the premise of ensuring anticoagulation effectiveness and treatment safety. Moreover, we summarized a formula for calculating the citrate infusion speed based on the patient's systemic iCa^{2+} and blood flow speed, thus enabling a simplified individualized hemodialysis protocol with RCA. This protocol involves calculating the required citrate infusion dose based on the set blood flow rate and determining the patient's systemic iCa^{2+} during hemodialysis. This technique can achieve a better anticoagulant effect than the modified conventional protocol while reducing the nursing burden and cost. To validate the safety and efficacy of this protocol for hemodialysis under different blood flow velocities and different performance dialyzers, we conducted a single-center clinical study.

2. Materials and methods

This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University under approval number 2019030. Patients' informed consent was obtained before the study. This study was registered at the Chinese Clinical Study Registry with registration number ChiCTR1900023801.

2.1. Research design and subjects

This was a single-center, prospective, randomized, positively controlled study. A total of 45 patients who were hospitalized and treated in the Nephrology Department of the First Hospital of Nanchang University between June 2019 and August 2019 were recruited. Using blocked randomization, the 45 patients were numbered from 001 to 045 and evenly divided into 5 blocks in numerical order. Forty-five random numbers obeying a normal distribution were obtained using SPSS and sequenced from small to large in each block (serial numbers 1–9). Each number in blocks corresponded to a serial number. Then, the blocks were divided into 7 levels according to serial numbers 1–3, serial number 4, serial number 5, serial number 6, serial number 7, serial number 8, and serial number 9, and the corresponding numbers of each level were included in the same group. A total of 3 groups were classified: a modified conventional regional citrate anticoagulation (RCA) protocol group with a low-flux dialyzer (CG group), a simplified individualized RCA protocol group with a high-flux dialyzer (SIG-HIGH group), and a simplified individualized RCA protocol group with a low-flux dialyzer (SIG-LOW group) (Fig. 1). The patients were not aware of their group assignments. Each patient received hemodialysis treatment according to the specified RCA protocol. The inclusion criteria were as follows: male or female patients aged 18 to 75 years; patients with end-stage renal disease requiring maintenance hemodialysis with an arteriovenous fistula for vascular access; patients with active bleeding or obvious bleeding tendencies determined by 2 renal physicians; and patients who signed the informed consent form. The exclusion criteria were as follows: patients with severe liver damage whose total bilirubin (TBIL) was ≥60 μmol/L; patients with uncorrectable hypotension whose blood pressure was <90/60 mmHg; patients with hypoxemia



LEVES 1: a modified conventional RCA protocol group with a low-flux dialyzer, blood flow: 200ml/min(3 patients);
LEVES 2: a simplified individualized RCA protocol group with a high-flux dialyzer, blood flow: 200ml/min(1 patient);
LEVES 3: a simplified individualized RCA protocol group with a high-flux dialyzer, blood flow: 225ml/min(1 patient);
LEVES 4: a simplified individualized RCA protocol group with a high-flux dialyzer, blood flow: 250ml/min(1 patient);
LEVES 5: a simplified individualized RCA protocol group with a low-flux dialyzer, blood flow: 200ml/min(1 patient);
LEVES 6: a simplified individualized RCA protocol group with a low-flux dialyzer, blood flow: 225ml/min(1 patient);
LEVES 7: a simplified individualized RCA protocol group with a low-flux dialyzer, blood flow: 250ml/min(1 patient);

Figure 1. Randomization scheme.

whose partial pressure of oxygen (PO_2) was <60 mmHg; patients with lactic acidosis whose lactic acid concentration was >3 mmol/L; and patients who were not cooperative. The CG group underwent treatment according to the modified conventional RCA principles with reference to similar studies[9,10]: at a blood flow rate of 200 mL/min using a Fresenius F6HPS dialyzer, dialysate with an iCa^{2+} concentration of 1.5 mmol/L at a flow rate of 500 mL/min and acid citrate dextrose solution-A (ACD-A) at a flow rate of 290 mL/h were infused through the arterial line and the venous bubble trap of the extracorporeal circulation at a ratio of 4:1 (arterial line: 232 mL/h, venous bubble trap: 58 mL/h). The treatment duration was 4 hours, and the ultrafiltration volume was set according to clinical needs and included the ACD-A infusion dose. The systemic iCa^{2+} concentration and predialyzer iCa^{2+} concentration were monitored at 30, 60, 120, and 180 minutes after starting treatment. By adjusting the blood flow and the input velocity of ACD-A, the systemic iCa^{2+} concentration was maintained between 1.0 and 1.2 mmol/L, and the predialyzer iCa^{2+} concentration was <0.5 mmol/L. In the SIG-HIGH group, high-flux dialyzers were used. The blood flow rate was set to either 200, 225, or 250 mL/min, with 5 patients per blood flow rate. The ACD-A infusion rate was calculated based on the systemic iCa^{2+} concentration and blood flow rate. After 1 hour of treatment, the ACD-A infusion rate was recalculated according to the systemic iCa^{2+} concentration and blood flow rate The calculation formula was as follows: (systemic $iCa^{2+} \times 0.405 + 2.356$) × blood flow rate × 60/113 (based on previous clinical data). ACD-A was infused at a ratio of 4:1 of the calculated infusion volume from the arterial line and the venous bubble trap of the extracorporeal circulation pipeline, respectively. After treatment for 1 hour, coagulation in the filter and arterial and venous bubble traps were observed with the naked eye. If clots were visible in the filter cap and arterial bubble trap, the infusion speed of ACD-A at the end of the arterial pipeline was increased by 10 mL/h. If clots were visible in the venous bubble trap, the infusion speed of ACD-A at the venous bubble trap was increased by 5 mL/h. The predialyzer iCa^{2+} concentration was not monitored. Systemic iCa^{2+} was monitored before hemodialysis and 1 hour after initiation of hemodialysis, and the other settings were the same as in the CG group. In the SIG-LOW group, low-flux dialyzers were used, and the other settings were the same as in the SIG-HIGH group. Dialysate containing 1.5 mmol/L iCa^{2+} was used in all 3 groups, and the calcium agent was supplemented irregularly. During treatment, if the patient presented manifestations of hypocalcemia, such as numbness of the lips and abnormal sensation in the face and limbs, systemic iCa^{2+} was determined immediately. If systemic iCa^{2+} was lower than 0.9 mmol/L, the calcium agent was supplemented intravenously. The primary evaluation indicators were the clotting scores of different sections of the extracorporeal circulation pipeline. The secondary evaluation indicators were changes in serum total calcium, ionized calcium, serum sodium (Na^+), blood pH, and bicarbonate before and after treatment. All patients were treated through an arteriovenous fistula. The Na^+ concentration in the dialysate was set at 136 mmol/L, and the HCO_3^- concentration in the dialysate was set at 28 mmol/L by a hemodialysis monitor.

2.2. Materials

The instruments included a Fresenius 4008S hemodialysis monitor (Fresenius Medical Care, Bad Homburg, Germany), a Hemoflow F6HPS low-flux dialyzer with a membrane area of 1.3 m^2 (Fresenius Medical Care, Frankfurter, Germany), and a Delang B-16H high-flux dialyzer with a membrane area of 1.6 m^2 (Bain Medical Equipment [Guangzhou] Co., Ltd., Guangzhou, China). The parameters of the two dialyzers are shown in Supplemental Digital Content (Table S1, http://links.lww.com/MD/F635). An ABL90 blood gas analyzer (Radiometer, Medical ApS, Copenhagen, Denmark) was also used. The type of dialysate was SXG-Y-A/B, with ion concentrations of 137 mmol/L Na^+, 2.0 mmol/L K^+, 1.5 mmol/L Ca^{2+}, 0.5 mmol/L Mg^{2+}, 108 mmol/L Cl^-, 31 mmol/L HCO_3^-, and 4.0 mmol/L $CH3COO^-$ (Jiangxi Sanxin Medtec Co., Ltd., Nanchang, China). ACD-A solution was purchased from Sichuani NIGALE Biotechnology Co., Ltd. (Chengdu, China).

2.3. Laboratory examination and blood specimen collection methods

Serum creatinine, urea, electrolytes, and blood gas were analyzed in the 3 groups before and after hemodialysis. Systemic iCa^{2+} concentrations were measured in the SIG groups before and after hemodialysis and 60 minutes after starting hemodialysis. The predialyzer iCa^{2+} concentration and systemic iCa^{2+} concentrations were monitored at 30, 60, 120, and 180 minutes after starting hemodialysis in the CG group. Systemic iCa^{2+} concentrations were monitored at 0, 30, 60, 120, 180, and 240 minutes after starting hemodialysis in the CG group.

The blood specimen collection methods were as follows. Blood collection before treatment: in patients with a fistula, blood samples were collected after successful puncture of the fistula using a needle that was not preflushed with saline. Blood collection 60 minutes after starting hemodialysis: Three minutes after stopping the infusion of ACD-A in the arterial line, for the venous bubble trap, a blood sample was collected at the arterial blood collection point to measure the systemic iCa^{2+} concentration. Blood collection after treatment: infusion of ACD-A was stopped 3 minutes before blood collection. Ultrafiltration was stopped at the end of treatment. The blood flow rate was reduced to 100 mL/min, and blood specimens were collected from the arterial blood collection point within 15 to 30 seconds. Predialyzer blood collection: blood samples were collected directly from the blood collection point between the ACD-A infusion point and the blood inlet of the dialyzer.

2.4. Assessment of the effectiveness of anticoagulation

After hemodialysis, the dialyzer and arterial and venous bubble traps were cut. The clotting statuses of the dialyzer and arterial and venous bubble traps were assessed using a semiquantitative method,[9] with a higher score indicating a better anticoagulant effect. The detailed scoring methods were as follows: for the arterial and venous bubble traps, a score of 5 points indicated no visible clotting, a score of 4 points indicated fiber formation, a score of 3 points indicated the presence of small clots (<2 mL), a score of 2 points indicated the presence of large clots (≥2 mL), and a score of 1 point indicated total clotting in the bubble traps. For the dialyzer, a score of 5 points indicated <20 coagulated fibers, a score of 4 points indicated 21 to 50 coagulated fibers, a score of 3 points indicated 51 to 100 coagulated fibers, a score of 2 points indicated >100 coagulated fibers, and a score of 1 point indicated that coagulated fibers accounted for >20% of fibers.

2.5. Statistical analysis

SPSS 24.0 software (IBM Corp., Armonk, NY) was used for the statistical analyses in this study. Normally distributed quantitative data are described as the means and standard deviations and were analyzed with the *t* test between 2 groups or one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) test for comparisons among ≥3 groups. A paired *t* test was used to compare normally distributed quantitative data before and after treatment. Nonnormally distributed quantitative data are described as medians and interquartile ranges and were analyzed with the Mann–Whitney *U* test for comparisons between 2 groups or the Kruskal–Wallis test for comparisons among ≥3 groups. Paired Wilcoxon analysis was used to compare nonnormally distributed quantitative data before and after treatment, and the Friedman test was used for ≥3 related groups with nonnormally distributed quantitative data. Qualitative data are described with frequencies and corresponding percentages, and the chi-square test was used to compare differences between groups. Pearson's linear regression test was adopted to explore the correlation between 2 normally distributed continuous quantitative variables, and Spearman linear test was adopted to explore the correlation between 2 nonnormally distributed continuous quantitative variables. $P < .05$ was considered statistically significant.

3. Results

The primary diseases of the 45 patients included 26 cases of chronic glomerulonephritis, 15 cases of diabetic nephropathy, and 4 cases of obstructive nephropathy. The reasons for RCA included 16 cases of digestive tract bleeding, 5 cases of hemoptysis, 7 cases of hemothorax and ascites, 6 cases of intracranial hemorrhage, 8 cases of recent surgery and invasive operations, and 3 cases of hematuria.

The treatment of 1 patient in the CG group was terminated 15 minutes early due to clotting in the venous bubble trap. The treatment of 1 patient in the SIG-LOW group was terminated 3 minutes early due to clotting in the venous bubble trap. One patient in the CG group developed transient numbness around the corners of the mouth, which resolved spontaneously upon intravenous administration of 10 mL of 10% calcium gluconate. One patient in the SIG-HIGH group had hypoglycemia, and 1 patient in the SIG-LOW group had a hypotensive response. No hemorrhagic complications or increased primary bleeding occurred within 24 hours after treatment. The main data from each group are shown in Tables 1–4.

Our study showed that the treatment duration and ultrafiltration volume did not differ among the groups. The HCO_3^- level was significantly elevated after treatment, and the serum creatinine and urea levels were significantly reduced after treatment. The $spKt/V_{BUN}$ value was higher in the SIG groups than in the CG group (Table 1). This phenomenon was attributable to the higher blood flow rate in the SIG groups than in the CG group and the better performance of the dialyzer used for the SIG-HIGH group than that used for the CG group. The cost in the SIG groups was also significantly lower than that in the CG group, mainly due to the reduction in the number of measurements of systemic and predialyzer iCa^{2+} concentrations. These observations showed that the RCA protocol used in the SIG groups (SIG-HIGH group and SIG-LOW group) could ensure successful completion of hemodialysis within 4 hours, thereby achieving the therapeutic goal of hemodialysis. The SIG groups had significantly higher clotting scores at the dialyzer and arterial bubble trap than the CG group. The clotting score at the venous bubble trap was higher in the SIG-LOW group than in the CG group, and the scores in the SIG-HIGH group and the CG group did not differ significantly (Table 2). Linear regression analysis and curve estimation were carried out using the systemic

Table 1

Data for each group before and after treatment.

Item	CG group (n = 15)	SIG-HIGH group (n = 15)	SIG-LOW group (n = 15)	*P* value (compared in 3 groups)
Sex (male)	9 (60%)	13 (86.67%)	13 (86.67%)/	.017
Age, y	68.40 ± 15.34	50.13 ± 21.91	53.60 ± 14.94	.015
Ultrafiltration volume, kg	2.00 ± 0.66	2.61 ± 1.15	1.53 ± 0.74	.001
ACD-A volume, mL/h	290 (290–300)	328 (294–360)	329 (295–367)	.004
Blood pH before treatment	7.34 ± 0.05	7.40 ± 0.03	7.37 ± 0.06	.001
Blood pH after treatment	7.42 ± 0.04*	7.44 ± 0.06	7.39 ± 0.05	.076
HCO_3^- before treatment, mmol/L	20.75 ± 2.90	22.55 ± 2.87	21.82 ± 3.95	.328
HCO_3^- after treatment, mmol/L	26.51 ± 1.38*	25.47 ± 1.54*	26.45 ± 1.91*	.173
Systemic iCa^{2+} before treatment, mmol/L	1.09 (1.04–1.42)	1.08 (1.01–1.11)	1.13 (1.08–1.17)	.166
Systemic iCa^{2+} 1 h after treatment, mmol/L	1.13 (1.03–1.28)	1.08 (1.04–1.14)	1.11 (1.08–1.15)	.420
Systemic iCa^{2+} after treatment, mmol/L	1.19 (1.10–1.29)	1.10 (1.06–1.17)	1.15 (1.10–1.20)	.183
Systemic total Ca^{2+} before treatment, mmol/L	2.11 ± 0.26	1.96 ± 0.10	2.00 ± 0.19	.107
Systemic total Ca^{2+} after treatment, mmol/L	2.36 ± 0.12*	2.25 ± 0.15*	2.26 ± 0.22*	.151
SCr before treatment, μmol/L	597.73 ± 149.64	601.68 ± 187.67	662.25 ± 326.90	.701
SCr after treatment, μmol/L	235.14 ± 64.72*	255.27 ± 95.27*	278.13 ± 168.65*	.614
BUN before treatment, mmol/L	17.36 ± 6.12	17.29 ± 3.99	18.24 ± 8.40	.904
BUN after treatment, mmol/L	6.15 ± 2.89*	6.82 ± 1.88*	7.61 ± 4.55*	.489
Na^+ before treatment, mmol/L	138.99 ± 3.32	136.12 ± 3.44	137.11 ± 3.36	.073
Na^+ after treatment, mmol/L	137.23 ± 2.36	136.61 ± 2.15	138.61 ± 2.51	.075
Citrate concentration in the extracorporeal circulation, mmol/L	2.73 (2.73–2.88)	2.75 (2.71–2.76)	2.75 (2.71–2.76)	.219
Total Ca^{2+}/iCa^{2+} after treatment	2.00 (1.84–2.08)	2.00 (1.95–2.04)	1.99 (1.84–2.20)	.894
$spKt/V_{BUN}$	1.22 ± 0.15	1.37 ± 0.11	1.32 ± 0.12	.006
Cost per hemodialysis treatment (RMB)	1724.50 ± 1.40	809.80 ± 5.12	810.33 ± 5.49	<.001

* Compared with before treatment, $P \leq .05$ significant.

Table 2

Comparison of clotting scores among the 3 groups.

Group	CG group	SIG-HIGH group	SIG-LOW group	*P* value
Dialyzer clotting score	3 (3–4)	4 (4–5)	4 (4–4)	.009
P value	.008	.012	.364	
Arterial bubble trap clotting score	4 (3–4)	4 (4–4)	4 (4–5)	.008
P value	.035	.003	.299	
Venous bubble trap clotting score	4 (3–4)	4 (4–4)	4 (4–5)	.100
P value	.288	.046	.198	
Total clotting score	11 (10–12)	12 (11–13)	12 (12–14)	.011
P value	.023	.005	.580	
Comparison of coagulation scores in the same part of pipeline between groups	P1 value	P2 value	P3 value	

P1 value: comparison between the CG group and the SIG-HIGH group; P2 value: comparison between the CG group and the SIG-LOW group; P3 value: comparison between the SIG-HIGH group and the SIG-LOW group.
$P \leq .05$ significant.

Table 3

Comparison of the main biochemical indicators in each group before and after treatment.

Group	ΔSerum Na^+, mmol/L	ΔSerum Total Ca^{2+}, mmol/L	ΔSerum iCa^{2+}, mmol/L	ΔBlood pH	ΔBlood HCO_3^-, mmol/L
CG group	−1.76 ± 3.20	0.25 ± 0.22	0.001 ± 0.105	0.09 ± 0.04	5.75 ± 2.64
SIG-HIGH group	0.49 ± 2.03*	0.29 ± 0.17	0.066 ± 0.077	0.03 ± 0.06*	2.59 ± 2.04*
SIG-LOW group	1.11 ± 3.26*	0.24 ± 0.19	0.029 ± 0.074	0.02 ± 0.05*	4.63 ± 2.82
P value	0.025	0.725	0.149	0.001	0.006

ΔSerum Na^+: Serum Na^+ after dialysis − Serum Na^+ before dialysis; ΔTotal Serum Ca^{2+}: total Serum Ca^{2+} after dialysis − total Serum Ca^{2+} before dialysis; ΔSerum iCa^{2+} (mmol/L): Serum iCa^{2+} after dialysis − Serum iCa^{2+} before dialysis; ΔBlood pH: blood pH after dialysis − blood pH before dialysis; ΔBlood HCO_3^-: blood HCO_3^- after dialysis − HCO_3^- before dialysis.
* Compared with the CG group, $P \leq .05$ significant.

iCa^{2+} and the citrate concentration in the extracorporeal circulation pipeline before and 1 hour after treatment in the 2 SIG groups as 2 variables. The linear relationship between the citrate concentration in the extracorporeal circulation and systemic iCa^{2+} concentration in this study is shown in Fig. 2.

Safety comparisons showed that severe hypocalcemia and other adverse events did not occur in any of the groups. The systemic sodium concentration increased slightly after hemodialysis in the SIG group. This increase in the systemic sodium concentration was higher in the SIG group than in the CG group, and the systemic sodium concentration after hemodialysis did not differ significantly between the SIG and CG groups. After treatment, both the pH and HCO_3^- level were elevated, but no obvious acid–base imbalance was noted. In all 3 groups, serum total calcium levels after treatment were significantly elevated compared with those before treatment but were similar to serum total calcium levels following noncitrate anticoagulation hemodialysis.[10] Systemic iCa^{2+} concentrations before hemodialysis, 1 hour into hemodialysis, and after hemodialysis did not significantly differ among the 3 groups, and no significant differences were found among the 3 groups with respect to changes in systemic total calcium and iCa^{2+} concentrations (Tables 1 and 3). No statistically significant differences were observed among the 3 groups in terms of blood coagulation in the extracorporeal circulation pipelines, symptoms of hypocalcemia, a systemic iCa^{2+} concentration <1.0 mmol/L 1 hour after starting hemodialysis and after hemodialysis, and other adverse events (Table 4). These results showed that the simplified individualized RCA protocol did not cause adverse reactions, such as hypernatremia, hypocalcemia, acid–base imbalance, and citrate poisoning, which can potentially be induced by the classical RCA protocol.[6,11,12]

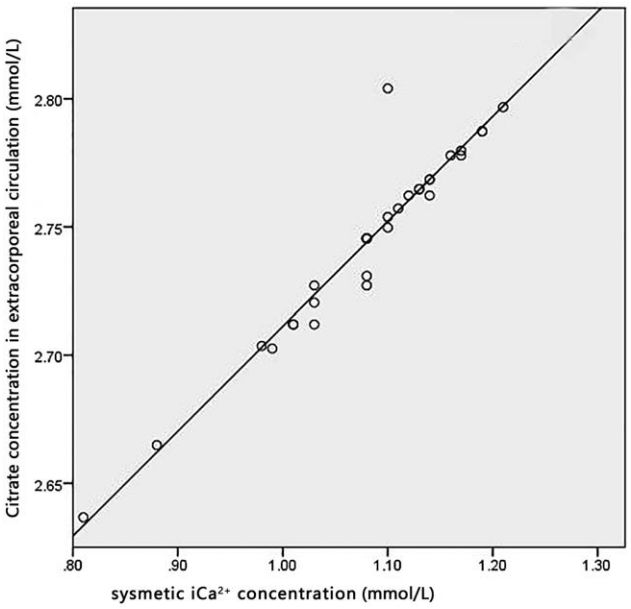


Figure 2. Linear relationship between the citrate concentration in the extracorporeal circulation and systemic iCa^{2+} concentration in this study.

4. Discussion

The original plan for RCA for hemodialysis uses a calcium-free dialysate, and the citrate preparation is infused from the arterial line at a rate proportional to the blood flow rate. Citrate concentrations in different preparations range between 3% and 46.7%, and the ratio between the citrate infusion rate and blood flow rate varies for different preparations.[8,9,13] It is generally believed that an ideal anticoagulant effect can be achieved with a

Table 4

Comparison of adverse events among the 3 groups.

Group	Pipeline coagulation	Symptoms of low calcium	Systemic iCa <1.0 mmoL/L (1 hour after treatment)	Systemic iCa <1.0 mmoL/L (after treatment)	Adverse events
CG group	1	1	2	0	1
SIG-HIGH group	0	0	1	0	1
SIG-LOW group	1	0	1	1	1
P value	.593	.360	.760	.360	1.000

citrate concentration of 3 to 5 mmol/L of blood in the extracorporeal circulation.[14,15] Calcium is supplemented through the venous line. Treatment safety and efficacy are ensured by frequently measuring the systemic iCa^{2+} concentration and predialyzer iCa^{2+} concentration and adjusting the infusion rates of the citrate preparation and calcium supplementation accordingly. In many countries and regions, calcium-free dialysate is not commercially available, which limits wider use of this protocol. With the successful implementation of the modified hemodialysis protocol with RCA using calcium-containing dialysate,[9,16] this conventional protocol has become the most widely used option. However, clinical application of this modified conventional protocol still remains limited because the systemic iCa^{2+} concentration and predialyzer iCa^{2+} concentration must be monitored even though calcium supplementation is not required. Initially, our center also used this type of modified conventional RCA protocol, which included the following steps. First, dialysate with an iCa^{2+} concentration of 1.5 mmol/L at a flow rate of 500 mL/min and ACD-A at an initial flow rate of 240 mL/h were infused through a 3-way connection into the arterial line at a blood flow rate of 200 mL/min using a low-flux dialyzer with a membrane area of 1.6 m^2. During hemodialysis, the systemic iCa^{2+} concentration (desired range: >1.0 mmol/L) and predialyzer iCa^{2+} concentration (desired range: <0.4 mmol/L) were monitored every hour. If the systemic iCa^{2+} concentration was below 1.0 mmol/L and the predialyzer iCa^{2+} concentration was below 0.4 mmol/L, the flow rate of ACD-A should be reduced, and calcium could be injected intravenously when necessary. If the systemic iCa^{2+} concentration was below 1.0 mmol/L and the predialyzer iCa^{2+} concentration was >0.4 mmol/L, the blood and ACD-A flow rates should be reduced, and the proportion of the reduction in the blood flow rate should be greater than the proportion of the reduction in the flow rate of ACD-A. If the systemic iCa^{2+} concentration was greater than 1.0 mmol/L and the predialyzer iCa^{2+} concentration was below 0.4 mmol/L, no adjustment was required. If the systemic iCa^{2+} concentration was >1.0 mmol/L and the predialyzer iCa^{2+} concentration was >0.4 mmol/L, the flow rate of ACD-A should be increased. This protocol ensured the safety and effectiveness of treatment. In 30 patients undergoing this modified conventional RCA protocol, only 1 patient experienced early termination of treatment due to clotting in the venous bubble trap, and none of these patients had severe hypocalcemia. We found that flow rates were usually adjusted in the first hour of hemodialysis. The citrate concentration in the extracorporeal circulation pipeline is linearly correlated with the systemic iCa^{2+} concentration based on the statistical analysis of the citrate and systemic iCa^{2+} concentrations of these patients after the blood and ACD-A flow rates stabilized. The applicable formula was citrate concentration in the extracorporeal circulation (mmol/L) = $X \times 0.113 \times 1000/Y \times 60$ = systemic iCa^{2+} concentration (mmol/L) $\times 0.405 + 2.306$ ($R^2 = 0.88$, $F = 200.92$, $P < .001$), where X is the ACD-A infusion rate (mL/L), Y is the blood flow rate (mL/min), and 0.113 is the quantity of citrate per 1 mL of ACD-A (mmol). The following formula was derived from the preceding formula: ACD-A infusion rate (mL/h) = (systemic iCa^{2+} concentration (mmol/L) $\times 0.405 + 2.306$) $\times$ blood flow rate (mL/min) $\times 60/113$. The systemic iCa^{2+} concentration remained extremely stable during the entire hemodialysis procedure. Therefore, we believe that the amount of citrate infused can be calculated based on the systemic iCa^{2+} concentration, with no need to frequently monitor the predialyzer iCa^{2+} concentration.

The clotting score was higher in the SIG groups than in the CG group. These results were attributable to the fact that the citrate anticoagulant effect was associated with the blood flow rate, systemic iCa^{2+} concentration, and iCa^{2+} concentration in the dialysate. When the iCa^{2+} concentration in the dialysate was fixed, the blood flow rate and systemic iCa^{2+} concentration were the main factors affecting the anticoagulant effect. For the anticoagulation protocol in the CG group, only the blood flow rate at the beginning of the citrate infusion was considered. There may not have been an adequate quantity of citrate infused if the systemic iCa^{2+} concentration was high. Under these circumstances, anticoagulation of the extracorporeal circulation was not sufficient, possibly resulting in coagulation. Alternatively, the citrate infusion rate was increased only when the predialyzer iCa^{2+} concentration was higher than the target value. If the citrate infusion rate was increased too late, clotting may have occurred in the extracorporeal circulation. By contrast, in the SIG groups, the blood flow rate and the systemic iCa^{2+} concentration were considered at the beginning of citrate infusion; as a result, the anticoagulant effect was better. Therefore, the clotting scores at both the arterial bubble trap and the dialyzer were higher in the SIG groups than in the CG group. Furthermore, the clotting score at the venous bubble trap was higher in the SIG-LOW group than in the CG group since low-flux dialyzers are less capable of removing citrate, leading to more citrate at the venous bubble trap. The high-flux dialyzer had a strong ability to clear citric acid, leading to a lower amount of citrate at the venous bubble trap. As a result, the venous bubble trap clotting score in the SIG-HIGH group was not better than that in the CG group. Additionally, since the dialysate contained calcium, the calcium in the dialysate entered the blood when the blood passed through the dialyzer, leading to an increased iCa^{2+} concentration, and the blood entering the venous bubble trap was more prone to coagulation. This phenomenon was also responsible for the infusion of citrate at 2 segments. A linear formula was obtained via curve estimation of the citrate concentration in the extracorporeal circulation and the systemic iCa^{2+} concentration in the SIG group: ACD-A infusion rate = (systemic iCa^{2+} concentration [mmol/L] $\times 0.409 + 2.302$) $\times$ blood flow rate [mL/min] $\times 60/113$ ($R^2 = 0.918$, $F = 315.10$, $P < .001$). This formula is similar to the original linear formula but had a better correlation coefficient (Fig. 2).

No severe complications occurred in the SIG groups, suggesting that the treatment was very safe. The major reason for this finding is that the ACD-A used for the individualized RCA protocol provided the same quantity of citrate as trisodium citrate but contained less sodium. Moreover, the sodium concentration of the dialysate was reduced by hemodialysis monitoring, and the powerful ability of hemodialysis to remove small-molecule solutes guaranteed that no significant hypernatremia would occur. The use of dialysate containing 1.5 mmol/L calcium effectively supplemented blood iCa^{2+} levels, which were reduced due to chelation by the citrate. In particular, for the individualized RCA protocol, the citrate infusion rate was established according to the systemic iCa^{2+} concentration, thereby preventing the high citrate dose associated with the classical protocol for patients with low systemic iCa^{2+} concentrations. As a result, hypocalcemia was effectively avoided while ensuring that an appropriate anticoagulant effect was achieved. Additionally, although the citrate infusion rate was significantly higher in the SIG groups than in the CG group, the citrate concentration in the extracorporeal circulation was not significantly higher in the SIG groups than in the CG group. Importantly, the serum total Ca^{2+}/iCa^{2+} value, an indicator of citrate poisoning,[17] did not differ significantly among the groups (Table 1), suggesting that the safety of the individualized RCA protocol is excellent. Additionally, as a result of reducing the detection frequency for the patient's systemic iCa^{2+} and predialyzer iCa^{2+}, the medical cost was greatly reduced.

Our study confirms that the individualized RCA protocol is feasible with both high- and low-flux dialyzers when the blood flow rate is within the range of 200 to 250 mL/min. Individualized infusion rates for the citrate preparation can be established based on each patient's blood flow rate and systemic iCa^{2+} concentration. This protocol is convenient for administration and does not require additional calcium supplementation, monitoring of the predialyzer iCa^{2+} concentration or frequent evaluation of the systemic iCa^{2+} concentration. The individualized RCA protocol is simpler and less costly than both the classical RCA protocol that uses a calcium-free dialysate and the modified RCA protocol that uses a calcium-containing dialysate; moreover, with the novel protocol, the systemic iCa^{2+} concentration only needs to be measured before dialysis and 1 hour into dialysis. We measured the systemic iCa^{2+} concentration 1 hour into hemodialysis because there are 2 main components of citrate clearance during hemodialysis using the RCA protocol: metabolism in the body and clearance by the dialyzer. A previous study reported that the citrate clearance rate in critically ill patients with normal liver function was 710 mL/min, with an apparent volume of distribution of 29 L and a citrate half-life of approximately 30 minutes, and that citrate metabolism reached a steady state at approximately 2 hours.[18] The patients included in our study were not critically ill and had no contraindications for the use of citrate. In theory, our patients had higher citrate clearance rates than critically ill patients. Additionally, the citrate clearance rate in the dialyzer was approximately 180 mL/min.[19] The sum of the 2 citrate clearance rates was approximately 1000 mL/min; therefore, citrate entering the body could be rapidly cleared. We thus speculate that citrate in the body reached a steady state approximately 1 hour into dialysis, when the systemic iCa^{2+} concentration and systemic citrate concentration were essentially stable. Therefore, the safety and efficacy of the entire hemodialysis procedure could be ensured by recalculating the infusion rate of the citrate preparation based on the systemic iCa^{2+} concentration at that time. As an anticoagulant, the RCA protocol is better than the currently used heparin or LMWH strategies in many ways and has become the preferred anticoagulation method for continuous renal replacement therapy.[20] Can the citrate preparation become a routine anticoagulation method in hemodialysis? Some hemodialysis centers have tried this method and achieved good results.[21,22] We believe that citrate anticoagulation may become a routine anticoagulation method if it is individualized, has a simplified procedure, and causes only manageable complications. Before the submission of this manuscript, we completed individualized RCA for hemodialysis treatment in 200 patients using this protocol and achieved excellent outcomes. The results will be published separately in the near future. This is a single-center study with a small number of patients. We have not validated the feasibility of this protocol for blood flow rates above 250 mL/min or with more dialyzers, and we have not determined the pharmacokinetics of citrate during treatment. These are limitations of this study. In the future, we will conduct a multicenter clinical study with a larger sample size to further verify the feasibility of this protocol and observe the pharmacokinetic indicators of citrate to improve the RCA protocol for hemodialysis.

5. Conclusions

Our protocol uses a calcium-containing dialysate, does not supplement calcium routinely, and only requires monitoring of the systemic iCa^{2+} concentration of the patient twice. The present study confirmed the good anticoagulant effect, high safety, simplified operation process, and lower nursing burden and medical costs of this protocol. To the best of our knowledge, this simplified individualized citrate anticoagulation protocol has not been reported previously.

Author contributions

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