Heparin-Free Prolonged Intermittent Hemodialysis Using Calcium-Free Citrate Dialysate in Critically Ill Patients

Stanislas Faguer, MD, PhD[1,2,3]; Morgane Saint-Cricq, MD[1]; Marie-Béatrice Nogier, MD[1]; Isabelle Labadens, PharmD[4]; Laurence Lavayssiere, MD[1]; Nassim Kamar MD, PhD[1,2]; Olivier Cointault, MD[1]

Objectives: Critically ill patients who have a high risk of bleeding but require prolonged intermittent dialysis need a heparin-free easy-to-use alternative type of anticoagulation within the dialysis circuit. We assessed the safety and efficiency of heparin-free regional citrate anticoagulation of the dialysis circuit using a calcium-free citrate-containing dialysate, with calcium reinjected according to ionic dialysance.

Design: Prospective cohort study.

Setting: Critical care units.

Patients: Critically ill patients who required renal replacement therapy.

Interventions: None.

Measurements and Main Results: A total of 101 dialysis sessions were performed in 35 patients (mechanical ventilation $n = 78$; norepinephrine $n = 13$). Median duration of dialysis was 294 minutes (interquartile range, 240–300), and median ultrafiltration volume was 2.3 L (1–2.8). Urea and β2-microglobulin reduction rates were 64.5% ± 0.4% and 48% ± 0.13%, respectively. Postfilter ionized calcium was 0.35 ± 0.17 and 0.38 ± 0.14 mmol/L at 1 and 3 hours, respectively, within the extracorporeal circuit. A major clotting event that led to premature termination of the session occurred in only three of 101 sessions. In these three cases, major catheter dysfunction occurred before clotting within the circuit. Prefilter ionized calcium remained within narrow ranges (before/after change +0.07 ± 0.006 mmol/L), and total-to-ionized calcium ratio, a surrogate marker for citratemia, was unchanged.

Conclusions: Dialysis anticoagulation with calcium-free citrate-containing dialysate and calcium reinjection according to ionic dialysance is an easy-to-use, efficient, and inexpensive form of heparin-free regional anticoagulation. It allows prolonged hemodialysis sessions in critically ill patients without the need to systemically monitor ionized calcium. Furthermore, sessions can be safely extended according to the hemodynamic tolerance to ensure an adequate dose of dialysis and a negative water balance, a major point in patients with severe acute kidney disease. (*Crit Care Med* 2017; 45:1887–1892)

Key Words: citrate; dialysis; intensive care unit; ionic dialysance; regional anticoagulation

Worldwide, between 10% and 20% of incident patients admitted in ICUs will ultimately receive renal replacement therapy (RRT), which is typically provided as continuous RRT (CRRT) or standard intermittent hemodialysis (IHD) (1, 2).

Hemodialysis membranes and catheters are inherently prone to coagulation. Thus, the use of anticoagulants is mandatory to prevent clotting in the extracorporeal circuit (ECC) (3). During IHD, risk factors for premature clotting in the ECC are inadequate vascular access and specific circuit-related factors, such as low blood flow, blood transfusions, and inflammatory state, conditions that are often encountered in critically ill patients. Various anticoagulation regimens have been developed and mostly result in systemic anticoagulation, precluding their use in patients at high risk of bleeding. Heparin-free

[1]Département de Néphrologie et Transplantation d'organes, Unité de Réanimation, CHU de Toulouse, Hôpital Rangueil, Toulouse, France.

[2]Université Toulouse-3, Toulouse, France.

[3]Institut National de la Santé et de la Recherche Médicale U1048 (équipe 12), Institut des Maladies Métaboliques et Cardiovasculaires (I2MC), Toulouse, France.

[4]Pharmacology department, Unité de Pharmacie clinique, CHU de Toulouse, Toulouse, France.

Drs. Faguer, Saint-Cricq, and Cointault designed the study and analyzed the data; Drs. Faguer, Saint-Cricq, Lavayssiere, Nogier, Kamar, and Cointault followed the patients; Mr. Labadens furnished the dialysate and calcium solution. Faguer and Cointault wrote the article.

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For information regarding this article, E-mail: faguer.s@chu-toulouse.fr

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dialysis is thus mandatory for patients with acute bleeding disorders, recent and planned surgery, or acute heparin-induced thrombocytopenia syndrome.

Several modalities are used for heparin-free dialysis sessions. Iterative saline infusion and heparin-grafted membranes are easy to use and remain the standards-of-care for high-risk bleeding situations. However, their efficiency is low: success rates from hemodialysis sessions range from 50% to 65% and 50% to 75%, respectively (4–10). Furthermore, sessions that last for greater than 240 minutes are rarely achievable and can be problematic when ensuring an adequate dose of dialysis and a negative water balance in patients who cannot tolerate a high ultrafiltration rate. Thus, the development of alternative regional anticoagulation methods is needed urgently to improve IHD in critically ill patients and to avoid systemic anticoagulation in patients with a high risk of bleeding.

The 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines for Acute Kidney Injury and subsequent recommendations from the Canadian and French Societies of Nephrology and Intensive Care recommended that critically ill patients requiring CRRT receive regional citrate anticoagulation (RCA) as the first-line anticoagulation (11–13). Citrate anticoagulation is associated with a lower risk of circuit clotting compared with heparin, it allows prolonged extracorporeal circulation, reduces bioincompatibility-related neutrophil activation, and may improve the outcomes of critically ill patients with sepsis (14–17). Although RCA seems to be more efficient at preventing premature clotting of the circuit and has had a 100% hemodialysis success rate in recent studies (6, 8, 18, 19), several major factors limit the use of RCA for IHD. These include the high volume of citrate trisodium required to obtain ionized calcium (iCa) levels within the target ranges of 0.25–0.45 mmol/L because of hypotonic formulation (anticoagulation citrate dextrose solution, solution A [ACD-A]), the only formulation available in Europe. In addition, there is a subsequent risk of sodium overload and metabolic alkalosis as well as a need for repeat assessment of iCa to avoid the consequent risk of severe hypocalcemia. Despite many validated and simplified protocols that use ACD-A solution and require only minor adaptations to infusion rates of citrate and calcium, RCA remains cumbersome for most dialysis teams.

An easier way to provide citrate inside the filter could be to use diffusive influx from the dialysate. It has been demonstrated recently that the use of citric acid as the acidic component of dialysis can enable a dose reduction of heparin and increase the efficiency of hemodialysis (20–22). However, the amount of citrate (0.8 mmol/L) and calcium (1.25–1.75 mmol/L) contained in this dialysate do not allow the target of iCa to be reached in the ECC (23). In contrast, a citrate dialysate that contains no calcium would provide enough calcium-free transfer to lower iCa below 0.45 mmol/L; however, a problem would be the large amount of calcium loss during the session.

Pivotal studies show that, during dialysis sessions performed with calcium-free dialysate, the rate of calcium reinjection required to compensate for calcium loss in the dialysate can be easily deducted from the ionic dialysance (ID), which is an online measurement of instantaneous small solute clearance, available from most dialysis monitors (24, 25). ID has been also used as a surrogate marker for dialysis dose in ICU patients receiving IHD (26). Thus, the use of calcium-free citrate-containing dialysate with calcium reinjection according to ID could provide enough citrate to prevent coagulation within the filter, and calcium restitution can then be monitored by online ID without the need for systemic measurement of iCa. It may also improve the hemodynamic tolerance of IHD by avoiding acetate in the dialysate.

The objective of our study was to show the efficiency of this approach using RCA for longer sessions of IHD in critically ill patients, based on the success rate of hemodialysis without clotting.

PATIENTS AND METHODS

This single-center observational study included all patients (> 18 yr old) admitted to the ICU of the Department of Nephrology and Transplantation (University Hospital of Toulouse, France). These patients had received IHD with calcium-free citrate dialysate between June 2016 and February 2017. Exclusion criteria were antivitamin K and heparin treatment (anti-Xa activity > 0.15 U/mL). Use of antiplatelet agents was not contraindicated but was recorded. The study was performed according to the Declaration of Helsinki, revised in 2004. Our local Institutional Review Board reviewed the study and waived the need of approval (Comité d'éthique régional n°04-1015).

Dialysis Parameters

All hemodialysis sessions were performed using an Evosys device (Hospal, Lyon, France), which included an online clearance monitor (Diascan; Baxter, Guyancourt, France). The hollow-fiber dialyzer used was the same for all patients (Cordiax Fx100 polysulfone high-flux membrane; Fresenius Medical Care, Fresnes, France). Dialysis priming was performed using 2 L of heparin-free saline. Dialysate flow was fixed at 500 mL/min, blood flow at 300 mL/min, dialysate temperature at 37°C, bicarbonate concentration at 37 mmol/L, and sodium conductivity at 14.0 mS/cm. The final composition of Citrasate 484 dialysate (Hemotech, Ramonville, France) was the following: potassium 3 mmol/L, magnesium 0.5 mmol/L, citrate 0.8 mmol/L, and glucose 1 g/L. Minimal length of each dialysis session was fixed at 210 minutes but could be extended to a maximum of 360 minutes to obtain an adequate dialysis efficiency and to control water balance with optimal hemodynamic tolerance.

Reinjection of Calcium Chloride

We assumed that calcium clearance was equal to ID, taken as a surrogate of effective urea clearance (24, 27). Also, clearance of the calcium-citrate complex was approximately equal to free calcium clearance. The volume of calcium solution that should be infused each minute (Q_{inf}) was determined from ID using the following formula (24) (for further information, see **supplementary text**, Supplemental Digital Content 1, http://links.lww.com/CCM/C850): Q_{inf} (mL/min) = (C_d/C_{inf}) × ID, where ID was the online measurement of ionic dialysance (mL/min), C_{inf} was the final calcium concentration of the reinjected

solution of calcium chloride, and C_d was the calcium concentration of the target dialysate. To obtain the same mass transfer of calcium as a dialysate containing 1.5 mmol/L of calcium, the flow rate (mL/min) of the calcium solution (the concentration was settled at 300 mM in this study) was ID/200.

Reinjection of the calcium chloride solution into the venous catheter was started at a rate of 60 mL/hr for the 30 first minutes (i.e., the rate of infusion was related to a theoretical ID of 200 mL/min). ID was then quantified every 30 minutes by the dialysis monitor, and calcium reinjection was manually adapted according to the ID (supplementary text, Supplemental Digital Content 1, http://links.lww.com/CCM/C850).

Data Collection

The demographic characteristics, the causes of admission within the ICU, and types of artificial organ support at the time of the dialysis session were recorded. Every 30 minutes, dialysis variables were recorded by the attending nurses. Dialyzers were scored according to a global thrombosis index, which ranged from 0 to 3. Identification of a thrombus in the drip chamber was considered as clotting.

Blood tests were performed using arterial devices or by taking a blood sample in the arterial catheter just after catheter/needle insertion. Before dialysis, albumin, fibrinogen, *C*-reactive protein, platelet and WBC counts, and hemoglobin level were measured. Prefilter iCa was measured at 30, 60, and 180 minutes. Postfilter iCa was measured in the venous catheter before catheter/needle insertion and at 60 and 180 minutes. Blood gas, urea, β2-microglobulin, and total/iCa were measured before and at 30 minutes after completing the dialysis session. Small molecule clearance was quantified using the Kt/V_{urea} ratio (where K is the urea clearance, t the length of the dialysis session, and V the urea volume distribution) estimated by the log (predialysis urea/postdialysis urea) formula and the urea-reduction rate; middle-sized molecule clearance was quantified using β2-microglobulin reduction rate.

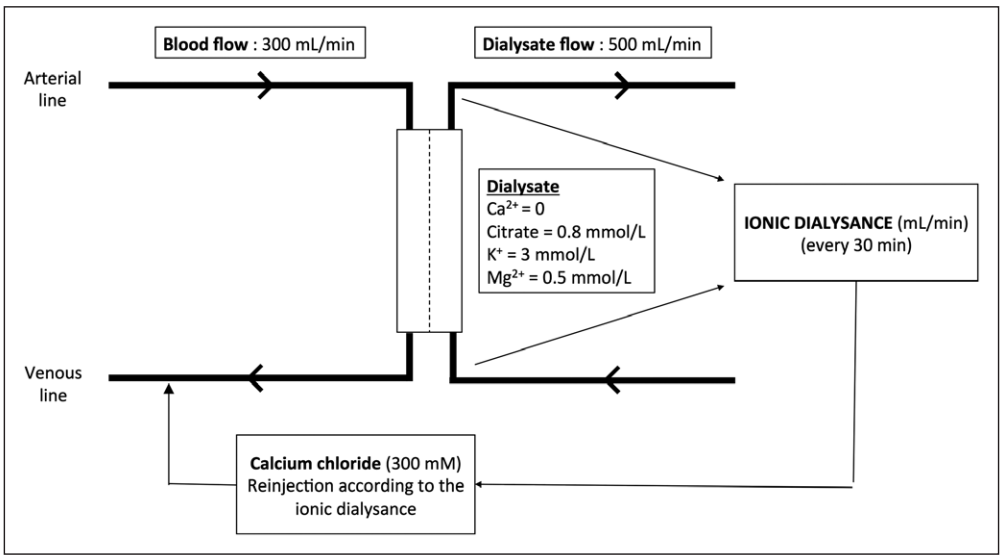

Figure 1. Schematic representation of calcium reinjection according to ionic dialysance.

Statistics

Statistical analyses were performed using GraphPad software. Quantitative variables are shown as medians (interquartile range) or means (SEMs), as appropriate. Qualitative variables are shown as numbers (percentages). Differences in quantitative variables between the groups were tested using the Mann-Whitney *U* test (two groups) or the one-way analysis of variance followed by post hoc correction (for > two groups). Differences between qualitative results were compared using Fisher exact test. All statistical tests were two sided, with a *p* value of less than 0.05 indicating statistical significance.

RESULTS

Patients Characteristics

From June 2016 to January 2017, 101 IHD sessions, using a calcium-free citrate-containing dialysate and calcium reinjection according to ID (**Fig. 1**), were performed in 35 patients (mean age 64 ± 15 yr). Characteristics of the patients are summarized in the **Table 1**. Causes of admission into the ICU were infections in 18 individuals (52%), solid organ transplantation in four (11%), cardiac surgery in four (11%), hemorrhagic shock in four (11%), autoimmune disease in three (9%), and liver failure in two (6%). Ten patients were receiving chronic RRT before admission into the ICU. Nine individuals received antiplatelet agents.

Dialysis was performed using a temporary central femoral venous catheter in 20 patients (57%), an arteriovenous fistula in eight (23%), and tunneled central venous access in seven (20%).

Characteristics of the Dialysis Sessions

Seventy-eight and 13 of the 101 sessions were performed while the patient was on mechanical ventilation or was receiving vasopressive drugs (mean dose of norepinephrine 0.15 ± 0.22 μg/kg/min), respectively.

Median duration of dialysis was 294 minutes (240–300). The objectives for blood flow were obtained in all patients. Seventy-two sessions (72%) were greater than or equal to 270 minutes (maximum 360 min). Median ultrafiltration was 2.3 L (1–2.8). Hemodynamic variables were constant in all sessions (**Supplementary Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/C863). The dose of noradrenaline was slightly increased in 17 of 101 sessions (mean change 0.09 ± 0.1 μg/kg/min). Two patients developed ventricular or supraventricular extrasystoles without hypotension.

Electrolyte variables at baseline and after the dialysis session are shown in **Table 2**. Urea and β2-microglobulin reduction rates were 64.5%

TABLE 1. Characteristics of Patients and Dialysis Sessions

Patients Characteristics	*n* = 35
Gender (male/female)	23/12
Age (yr), median (IQR)	67 (5–75)
Chronic renal replacement therapy, *n* (%)	10 (29)
Antiplatelet agents, *n* (%)	9 (26)
Weight (kg), median (IQR)	
Usual weight	69 (59–78)
Weight change at the time of dialysis[a]	+4.5 (−0.5 to 7.5)
Simplified Acute Physiology Score 2 gravity score at admission, median (IQR)	61 (56–68)
Characteristics of the Dialysis Sessions	*n* = 101
Blood tests before dialysis, median (IQR)	
Hemoglobin (g/dL)	9.7 (8.8–10.4)
Platelets (× 10^3/mm^3)	163 (100–233)
WBC (× 10^3/mm^3)	10.4 (6.5–15.6)
Fibrinogen (g/L)	5 (4.2–6.8)
C-reactive protein (mg/L)	63 (32–109)
Albumin (g/L)	23 (21–25)
Severity of the condition	
Mechanical ventilation, *n* (%)	78 (78)
Vasopressive drugs, *n* (%)	13 (13)
Norepinephrine (μg/kg/mn), mean ± SEM	0.15 ± 0.22

IQR = interquartile range.
[a]Weight change = usual weight − weight on the day of dialysis session.

± 0.4% and 48% ± 0.13%. Kt/V_{urea} was 1.11 ± 0.4. Mean ID was 185 ± 42 mL/min. A significant increase in pH and serum sodium concentration was observed, whereas serum magnesium was slightly decreased. Serum lactate concentration was similar before and after the dialysis sessions.

Clotting Events

Postfilter iCa was within the target range to block coagulation in all patients (0.35 ± 0.17 and 0.38 ± 0.14 at 1 and 3 hr, respectively) (**Fig. 2*A***). A major clotting event that led to prematurely ending the dialysis occurred in 3% of sessions (3/101 sessions) at, respectively, 30, 60, and 210 minutes. In these three cases, major catheter dysfunction occurred before clotting of the circuit. In addition, clotting score of the dialyzer was higher than 1 in three of 101 sessions (global thrombosis index [GTI] 1.5 and 2 at 240 min and GTI 1.5 at 270 min; see supplementary text, Supplemental Digital Content 1, http://links.lww.com/CCM/C850). No other clotting event without premature termination occurred.

According to the ID, mean reinjection of Ca^{2+} was 78.4 ± 18.7 mmol during the session, and prefilter iCa remained within the narrow ranges (**Fig. 2*B***). During the dialysis sessions, global iCa change was +0.07 ± 0.006 mmol/L. Total-to-ionized calcium ratio, a surrogate marker for systemic citrate accumulation, was unchanged (**Fig. 2*C***). Of note, measurement of ID was performed every 30 minutes, although failed in 10% of measurements.

No bleeding event occurred during the 24 hours following dialysis.

DISCUSSION

Critically ill patients have a high risk of systemic bleeding and, paradoxically, of ECC thrombosis. They also often require prolonged dialysis sessions (> 240 min) to ensure an adequate dose of dialysis and a negative water balance. However, the use of heparin-free techniques to avoid systemic anticoagulation cannot ensure a prolonged session and can result in premature clotting. Hence, uncontrolled but also comparative studies that have tested the anticoagulation effect of iterative saline flushes and heparin-graft membranes report prevalences of premature clotting of 35–50% and 25–50%, respectively (5–8, 28).

Several studies have demonstrated the superiority of RCA over heparin, and RCA has emerged as the gold-standard treatment in CRRT. The advantages of citrate anticoagulation to biocompatibility have only been recently reported (9). As demonstrated in IHD and in vitro, calcium-chelating citrate anticoagulation lowers polymorphonuclear cell degranulation, as occurs with heparin (15, 16).

Previous reports on RCA techniques in IHD have used direct citrate infusion upstream of the filter with either molar trisodium citrate (TSC) or, more recently, hypotonic citrate solution (ACD-A). TSC is no longer available in most countries as it is hypertonic and induces a greater sodium load and, thus, metabolic alkalosis (29, 30). Apart from being cumbersome, TSC and ACD-A may lead to fluid overload, systemic citrate accumulation, and, most importantly, could potentially cause life-threatening systemic calcium disorders. Using this approach, the amount of citrate needed depends on blood-flow rate and should be adjusted to levels of postfilter iCa. Another drawback with prefilter infusion is that citrate accumulation can rapidly appear when citrate clearance is reduced (i.e., a drop in blood flow, pausing of the dialysate flow, partial coagulation of the filter, recirculation).

If a dialysate that contains citrate is used, theoretically, the diffusive flux is proportional to blood-flow rate, thus leading to linear delivery of free citrate into the filter throughout the session. In our study, mean postfilter iCa was kept below 0.45 mmol/L, confirming that the amount of free citrate in the dialysate was sufficient to decrease iCa in the filter to below the coagulation threshold. Indeed, of clinical importance, premature clotting only occurred in 3% of our sessions, a finding similar to previous studies that have used prefilter citrate infusion (6, 8, 18, 19).

This method of delivering citrate into the filter meant that there were no volume infusion and a lower citrate load and accumulation with this method. In unpublished data using a

TABLE 2. Biological Variables at Baseline and at 30 Min After Completing Dialysis

Variables	T0	End + 30'	*p*
Urea (mmol/L)	23.5 (16–31.8)	7 (4.8–9.7)	< 0.0001
Creatinine (mmol/L)	260 (186–364)	118 (91–152)	< 0.0001
β2-microglobulin (mg/L)	21.7 (16.3–27.2)	11.6 (6.8–14.9)	< 0.0001
pH	7.38 (7.35–7.41)	7.45 (7.42–7.48)	< 0.0001
Sodium (mmol/L)	136 (134–139)	139 (138–141)	< 0.0001
Potassium (mmol/L)	4.3 (3.9–4.8)	3.9 (3.6–4.1)	< 0.0001
Bicarbonates (mmol/L)	25 (21–26)	28 (26–29)	< 0.0001
Calcium			
Ionized calcium (mmol/L)	1.16 (1.06–1.23)	1.21 (1.13–1.29)	0.014
Total-to-ionized calcium ratio	2.2 (2.08–2.31)	1.91 (1.83–1.98)	0.42
Magnesium (mmol/L)	0.77 (0.67–0.97)	0.70 (0.65–0.77)	0.0002
Lactates (mmol/L)	1.1 (0.8–1.6)	1.2 (0.9–1.5)	0.77

Results are shown as medians and interquartile ranges.

similar dialysate (Lebourg and Petitclerc, https://dumas.ccsd.cnrs.fr/dumas-00836041), the mean number of cases of citratemia was reduced by 20% compared with an older report by Janssen et al (31). Also, a previous study reported that a total-to-iCa ratio of greater than 2.5 was predictive of citratemia greater than 1 mmol/L and subsequent citrate toxicity (32). In our study, this ratio never exceeded 2.5, confirming the safety of this anticoagulation approach.

To avoid symptomatic hypocalcemia, iterative measurements of iCa are usually required to accurately adapt calcium infusion when using RCA (8). However, with this approach, the calcium influx was not indexed to the real calcium loss. A more accurate approach would be measurement of calcium clearance through the filter throughout the session. Online determination of ID has been used to measure the clearance of small solutes, such as urea or calcium. Our method was derived from an older method of dialysis, DuoCart biofiltration (DCB). This acetate-free hemodialysis used dialysate containing only sodium chloride and bicarbonate but with infusion into the venous catheter of a solution containing the ionic complement. Because the dialysate is calcium free, the infusion rate of the solution containing the divalent cation was automatically determined according to the online measured value of ID. Citrate anticoagulation during DCB was considered effective and suitable for routine use because the rate of calcium infusion was automatically adjusted without needing to monitor iCa levels (24).

Notwithstanding the single-center status of our study, our results show that this method of RCA overcame the usual limitations of heparin-free dialysis and enabled a prolonged session with subsequent better control of water balance and dialysis dose without needing to monitor iCa. Similar results were obtained with other dialyzer (Faguer S, unpublished data, 2017). The

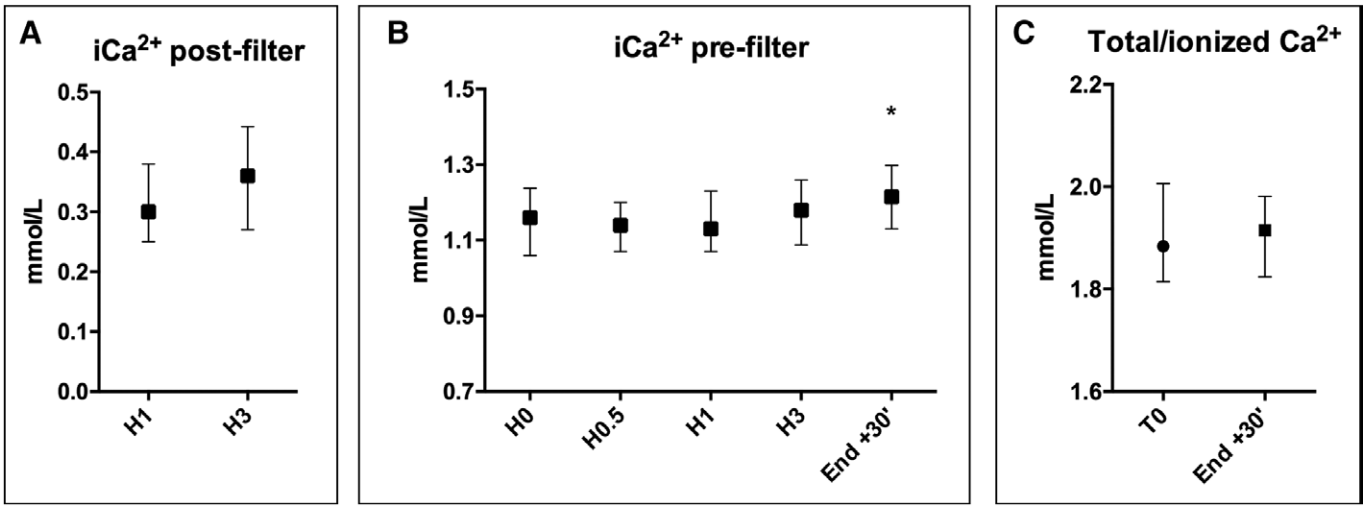

Figure 2. Changes of post- and prefilter (**A** and **B**) ionized calcium (iCa^{2+}) and total/iCa^{2+} (**C**) during 101 dialysis sessions using calcium-free dialysate that contained citrate.

only pitfall is the theoretical risk of coagulation of the arterial catheter, where no anticoagulation is applied. A minimal blood flow (e.g., > 200 mL/min) may reduce these unwanted clotting events. In our study, circuit clotting occurred after severe catheter dysfunction and subsequent reduced blood flow below 150 mL/min, started indeed in the arterial catheter. Further enhancements could be proposed, to produce a more secure and easy-to-use method. Implementation of another pump for calcium infusion, directly controlled by both the blood and dialysate pump, could be a first step to secure this approach. We can also theorize that the use of a dialysate free of divalent cations means that acidification is no longer mandatory to prevent carbonation. By replacing citric acid with TSC, an alkali dialysate could be obtained with no production of dissolved dioxide carbon. Because an alkali dialysate reduces bradykinin release after a contact phase reaction with the membrane (a known cause of hypersensitivity reaction and nitric-oxide secretion) (33), a better hemodynamic tolerance approach could be obtained.

In summary, we show herein that regional anticoagulation of ECCs using calcium-free citrate-containing dialysate with calcium reinjection according to the online measurement of ID is an efficient, easy-to-use, and inexpensive method that reduced the barriers faced by IHD patients in ICU.

REFERENCES

1. Bagshaw SM, Darmon M, Ostermann M, et al: Current state of the art for renal replacement therapy in critically ill patients with acute kidney injury. *Intensive Care Med* 2017; 43:841–854
2. Mehta RL, Burdmann EA, Cerdá J, et al: Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: A multinational cross-sectional study. *Lancet* 2016; 387:2017–2025
3. Davenport A: What are the anticoagulation options for intermittent hemodialysis? *Nat Rev Nephrol* 2011; 7:499–508
4. Zimbudzi E: Intermittent saline flushes or continuous saline infusion: What works better when heparin-free dialysis is recommended? *Int J Nephrol Renovasc Dis* 2013; 6:65–69
5. Guéry B, Alberti C, Servais A, et al: Hemodialysis without systemic anticoagulation: A prospective randomized trial to evaluate 3 strategies in patients at risk of bleeding. *PLoS One* 2014; 9:e97187
6. Richtrova P, Rulcova K, Mares J, et al: Evaluation of three different methods to prevent dialyzer clotting without causing systemic anticoagulation effect. *Artif Organs* 2011; 35:83–88
7. Laville M, Dorval M, Fort Ros J, et al: Results of the HepZero study comparing heparin-grafted membrane and standard care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis. *Kidney Int* 2014; 86:1260–1267
8. Evenepoel P, Dejagere T, Verhamme P, et al: Heparin-coated polyacrylonitrile membrane versus regional citrate anticoagulation: A prospective randomized study of 2 anticoagulation strategies in patients at risk of bleeding. *Am J Kidney Dis* 2007; 49:642–649
9. François K, Wissing KM, Jacobs R, et al: Avoidance of systemic anticoagulation during intermittent haemodialysis with heparin-grafted polyacrilonitrile membrane and citrate-enriched dialysate: A retrospective cohort study. *BMC Nephrol* 2014; 15:104
10. Frascà GM, Sagripanti S, D'Arezzo M, et al: Post-dilution hemodiafiltration with a heparin-grafted polyacrylonitrile membrane. *Ther Apher Dial* 2015; 19:154–161
11. Fiaccadori E, Pistolesi V, Mariano F, et al: Regional citrate anticoagulation for renal replacement therapies in patients with acute kidney injury: A position statement of the Work Group "Renal Replacement Therapies in Critically Ill Patients" of the Italian Society of Nephrology. *J Nephrol* 2015; 28:151–164
12. James M, Bouchard J, Ho J, et al: Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 2013; 61:673–685
13. Boussekey N, Chiche A, Faure K, et al: Section 5: Dialysis interventions for treatment of AKI. *Kidney Int Suppl* 2012; 2:89–115
14. Oudemans-van Straaten HM, Bosman RJ, Koopmans M, et al: Citrate anticoagulation for continuous venovenous hemofiltration. *Crit Care Med* 2009; 37:545–552
15. Gritters M, Grooteman MP, Schoorl M, et al: Citrate anticoagulation abolishes degranulation of polymorphonuclear cells and platelets and reduces oxidative stress during haemodialysis. *Nephrol Dial Transplant* 2006; 21:153–159
16. Böhler J, Schollmeyer P, Dressel B, et al: Reduction of granulocyte activation during hemodialysis with regional citrate anticoagulation: Dissociation of complement activation and neutropenia from neutrophil degranulation. *J Am Soc Nephrol* 1996; 7:234–241
17. Gritters M, Borgdorff P, Grooteman MP, et al: Platelet activation in clinical haemodialysis: LMWH as a major contributor to bio-incompatibility? *Nephrol Dial Transplant* 2008; 23:2911–2917
18. Wright S, Steinwandel U, Ferrari P: Citrate anticoagulation using ACD solution A during long-term haemodialysis. *Nephrology (Carlton)* 2011; 16:396–402
19. Singer RF, Williams O, Mercado C, et al: Regional citrate anticoagulation in hemodialysis: An observational study of safety, efficacy, and effect on calcium balance during routine care. *Can J Kidney Health Dis* 2016; 3:22
20. Sands JJ, Kotanko P, Segal JH, et al: Effects of citrate acid concentrate (citrasate®) on heparin N requirements and hemodialysis adequacy: A multicenter, prospective noninferiority trial. *Blood Purif* 2012; 33:199–204
21. Rocha AD, Padua VC, Oliveira E, et al: Effects of citrate-enriched bicarbonate based dialysate on anticoagulation and dialyzer reuse in maintenance hemodialysis patients. *Hemodial Int* 2014; 18:467–472
22. Kossmann RJ, Gonzales A, Callan R, et al: Increased efficiency of hemodialysis with citrate dialysate: A prospective controlled study. *Clin J Am Soc Nephrol* 2009; 4:1459–1464
23. Stegmayr BG, Jonsson P, Mahmood D: A significant proportion of patients treated with citrate containing dialysate need additional anticoagulation. *Int J Artif Organs* 2013; 36:1–6
24. Ridel C, Mercadal L, Béné B, et al: Regional citrate anticoagulation during hemodialysis: A simplified procedure using Duocart biofiltration. *Blood Purif* 2005; 23:473–480
25. Petitclerc T: Estimation of mass transfer through a hemodialyzer: Theoretical approach and clinical applications. *Artif Organs* 1998; 22:601–607
26. Ridel C, Osman D, Mercadal L, et al: Ionic dialysance: A new valid parameter for quantification of dialysis efficiency in acute renal failure? *Intensive Care Med* 2007; 33:460–465
27. Lindsay RM, Bene B, Goux N, et al: Relationship between effective ionic dialysance and in vivo urea clearance during hemodialysis. *Am J Kidney Dis* 2001; 38:565–574
28. Richtrova P, Opatrny K Jr, Vit L, et al: The AN69 ST haemodialysis membrane under conditions of two different extracorporeal circuit rinse protocols a comparison of thrombogenicity parameters. *Nephrol Dial Transplant* 2007; 22:2978–2984
29. Kelleher SP, Schulman G: Severe metabolic alkalosis complicating regional citrate hemodialysis. *Am J Kidney Dis* 1987; 9:235–236
30. Flanigan MJ, Pillsbury L, Sadewasser G, et al: Regional hemodialysis anticoagulation: Hypertonic tri-sodium citrate or anticoagulant citrate dextrose-A. *Am J Kidney Dis* 1996; 27:519–524
31. Janssen MJ, Deegens JK, Kapinga TH, et al: Citrate compared to low molecular weight heparin anticoagulation in chronic hemodialysis patients. *Kidney Int* 1996; 49:806–813
32. Hetzel GR, Taskaya G, Sucker C, et al: Citrate plasma levels in patients under regional anticoagulation in continuous venovenous hemofiltration. *Am J Kidney Dis* 2006; 48:806–811
33. Amore A, Cirina P, Bonaudo R, et al: Bicarbonate dialysis, unlike acetate-free biofiltration, triggers mediators of inflammation and apoptosis in endothelial and smooth muscle cells. *J Nephrol* 2006; 19:57–64