Clinical Kidney Journal, 2021, vol. 14, no. 12, 2534–2538

doi: 10.1093/ckj/sfab087
Advance Access Publication Date: 28 April 2021
Original Article

ORIGINAL ARTICLE

Heparin-free regional anticoagulation of haemodialysis filters with calcium-free dialysate: is citrate mandatory?

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ABSTRACT

Background. There is an unmet need to develop safe and successful heparin-free regional anticoagulation modalities in haemodialysed patients at risk of bleeding. Whether the addition of citrate as a prefilter injection or in the dialysate itself is required to reach anticoagulation objectives when calcium-free dialysate is used as regional anticoagulation remains unclear.

Methods. In this monocentric retrospective study, we report our experience of 908 dialysis sessions performed with a calcium-free citrate-containing dialysate and calcium reinjection according to the ionic dialysance, without additional heparin.

Results. Premature termination for filter clotting occurred in 20 sessions (2.2%) and duration of session was >4.5 h in 135 (15%; maximum duration 6 h). In addition, we could investigate the citrate, calcium and acid–basis status during haemodialysis sessions performed with (citrate group, $n = 20$ sessions) or without (citrate-free group, $n = 19$ sessions) citrate in the dialysate. In 20 sessions performed in patients with underlying liver disorders and using calcium-free citrate-containing dialysate, patients' ionized calcium (iCa) and serum citrate levels were stable and remained within the normal range, respectively. Post-filter iCa was below 0.4 mmol/L in 19/20 sessions and citrate was 0.304 mmol/L (range: 0.011; 0.548). In 19 sessions that used calcium and citrate-free dialysate, post-filter iCa was 0.41 mmol/L (0.34; 0.5) and all sessions extended to 4 h or beyond.

Conclusions. Regional anticoagulation of haemodialysis with a calcium-free dialysate and calcium reinjection according to the ionic dialysance is safe. Adding citrate to the dialysate is not mandatory to prevent dialysis circuit clotting in most patients.

Received: 14.1.2021; Editorial decision: 20.4.2021

Keywords: calcium-free dialysate, citrate, intensive care unit, liver failure

INTRODUCTION

Anticoagulation is the cornerstone of renal replacement therapy (RRT) to prevent circuit clot formation during haemodialysis and is mandatory to obtain adequate blood purification, improve membrane biocompatibility and optimize the volume of ultrafiltration lost during each session [1]. Unfractionated or low-molecular weight heparins are the predominant molecules used to prevent filter coagulation, but they are both associated with systemic anticoagulation [2] and subsequent risk of bleeding. Moreover, heparin may incompletely prevent platelet aggregation and/or neutrophil activation [3, 4], thereby contributing to dialysis-induced systemic inflammation [4]. To decrease systemic anticoagulation administered to patients at risk of bleeding, alternative techniques to reduce dialysis filter coagulation were developed, namely iterative saline flushes, heparin-coated membranes, citrate-based dialysates, online pre-dilution haemodiafiltration or pre-filter citrate infusions with post-filter calcium reinjection [5–8]. The ability of each technique to actually prevent premature termination of dialysis sessions is very heterogeneous, ranging from 50% (iterative saline flushes) [5] to 95% of completed sessions (pre-filter citrate infusion) in patients with chronic RRT [9]. Each technique has different benefits and risks: iterative saline flushes do not allow extension of dialysis sessions beyond 2–3 h, and lead to fluid overload and systemic inflammation [5–7]; citrate-based dialysates only allow reduction of heparin dose in patients receiving chronic RRT, but do not allow heparin-free dialysis [10]; online predilution haemodiafiltration is not available in the majority of intensive care units and leads to the premature termination of session in 25% of patients [11]; premature session termination (<4 h) was observed in 25% of patients when a heparin-coated membrane was used [5]; pre-filter citrate infusion with post-filter calcium reinjection is associated with a risk of fluid overload, severe hypocalcaemia and metabolic alkalosis (especially in patients with liver failure), and requires regular and rapid ionized calcium (iCa) assessment [9]. Critically ill patients are at high risk of bleeding (recent surgery, thrombocytopenia, coagulation disorders) but also of filters clotting (inflammatory state, hyperfibrinogenaemia, extended dialysis sessions to reduce hourly ultrafiltration). In these patients, regional anticoagulation using pre-filter citrate infusion is now recommended as a frontline therapy when continuous RRT is considered [12–14]. A citrate concentration of 3–4 mmol/L should be reached to prevent filter coagulation (i.e. to obtain an iCa <0.45 mmol/L). This approach needs to be used with caution in critically ill patients with severe liver impairment and prothrombin time below 30% to avoid citrate accumulation and subsequent metabolic alkalosis and severe hypocalcaemia [15, 16].

In intermittent haemodialysis, we and others recently demonstrated that a regional anticoagulation of the dialysis filters using a calcium-free dialysate is highly effective (less than 5% of filter clotting) and well tolerated, including in critically ill patients [17, 18]. As pointed out by Gubensek and Buturovic-Ponikvar [19], the mechanisms that underpin filter anticoagulation using this technique remain elusive. More specifically, it is still unclear whether hypocalcaemia related to the removal of large amounts of calcium when using a calcium-free dialysate is sufficient to anticoagulate the filter, or whether this requires the addition of citrate (0.8 mmol/L) to the dialysate. In recent years, calcium-free dialysates with acetate-based acid component instead of citrate were developed, and may be viewed as a valuable alternative.

The objective of the current retrospective study is to confirm the feasibility and safety of dialysis using a calcium-free dialysate with calcium reinjection according to the ionic dialysance in haemodialysed patients, including critically ill patients with liver disorders, and to assess the role of citrate in dialysate in filter anticoagulation.

MATERIALS AND METHODS

This retrospective observational study included all adult patients who received intermittent haemodialysis with calcium-free (citrate- or acetate-based) dialysates between November 2015 and October 2019. Dialysis was performed as previously described [17]. Briefly, blood and dialysate flow were fixed at 300 and 500 mL/min, respectively. The dialysate contained no calcium, while the concentration of the other electrolytes was the following: potassium (2 or 3 mEq), magnesium 0.5 mmol/L, chloride 103 mmol/L, glucose 1 g/L, acetate 0.3 mmol/L, bicarbonate 37 mmol/L and sodium 140 mmol/L. The dialysate contained citrate 0.8 mmol/L and acetate 0.3 mmol/L ('citrate-containing dialysate') or acetate 2 mmol/L and no citrate ('citrate-free dialysate'). Ionic dialysance was measured each 30 min and calcium was reinjected according to the following formula: $Q_{CaR} = ID \times Ca_{tD}/Ca_R$, where Q_{CaR} is the rate of reinjection of the calcium solution (mL/min), ID the ionic dialysance (mL/min), Ca_{tD} the targeted calcium concentration of the dialysate (i.e. 1.5 mM) and Ca_R the calcium concentration in the calcium solution (i.e. 300 mM).

Citrate concentration was measured at the start of the session (pre-filter), after 30 min of dialysis (pre- and post-filter) and at the end of the session (pre-filter). Citrate (normal values 0.045–0.130 mM) was measured using ionic chromatography according to the manufacturer's recommendations (Biomnis, Paris, France).

Liver functions were estimated by measuring prothrombin time, factor V, conjugated bilirubin, liver enzymes and indocyanine green clearance (Picco Limon®, Pulsion, France). The following parameters were retrospectively collected: age, reason for admission to the intensive care unit, use of vasopressor agents, mechanical ventilation and routine blood tests. Acid–basis status was determined using Stewart's approach [strong ion gap (SIG) and total weak acids].

Data are expressed as numbers and percentages (discontinuous variables), or median and ranges (continuous variables). Continuous variables were compared using the Mann–Whitney non-parametric test or a two-way ANOVA with a post-test Dunnett's correction, where required.

The study was performed in accordance with the 2004 revision of the declaration of Helsinki and complied with French law, which waivers a written informed consent for retrospective studies, and was approved by the Institutional Review Board of the University Hospital of Toulouse (Medical Research and Innovation Department; no. OSB/MEL/IO-2019-1520).

Table 1. Characteristics of the 908 dialysis sessions performed with a calcium-free dialysate and calcium reinjection according to the ionic dialysance

Patients' characteristics	Overall N = 316	Citrate group N = 18	Citrate-free group N = 19
Gender, male [*n* (%)]	205 (65)	15 (83)	13 (68)
Patients receiving chronic RRT [*n* (%)]	209 (66)	16 (89)	16 (84)
Reason for heparin-free dialysis			
Surgery or organ biopsy	188 (60)	5 (28)	8 (42)
Thrombocytopenia	36 (11)	3 (17)	1 (5)
Haemorrhage	48 (15)	0	5 (27)
Other (liver failure, heparin allergy, . . .)	20 (6)	10 (55)	4 (21)
Unknown	26 (8)	0	1 (5)
Dialysis sessions	N = 908	N = 20	N = 19
Intensive care unit setting [*n* (%)]	389 (43)	20 (100)	3 (16)
Session duration (min)			
Median (IQR)	240 (210; 240)	300 (300; 300)	240 (240; 240)
Maximum	360	300	270
Premature termination (filter clotting) [*n* (%)]	20 (2.2)	1 (5)	0

IQR, interquartile range.

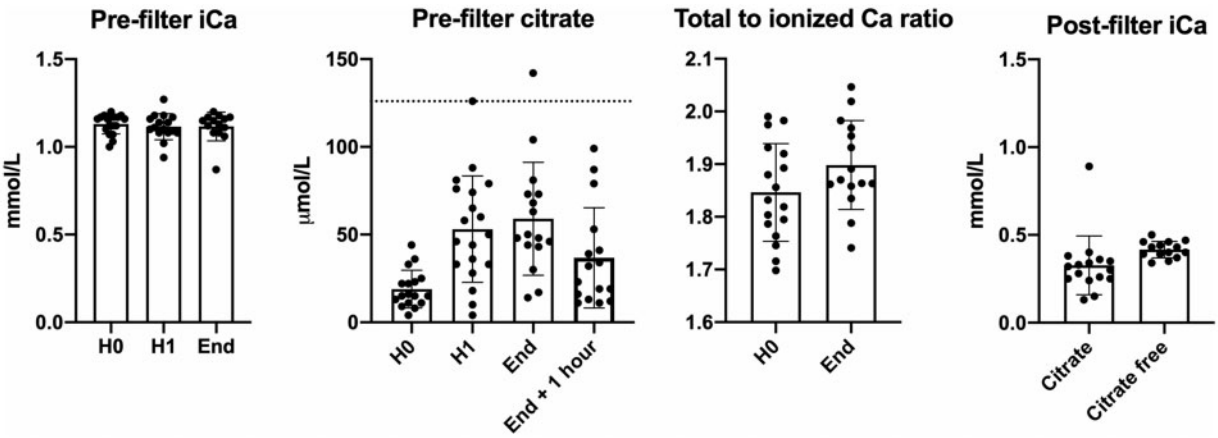

FIGURE 1: Pre-filter (serum) iCa and citrate, total-to-iCa ratio and post-filter iCa. Samples were collected at the start of the dialysis (H0), after 1 h (H1), at the end of the session (End) and 1 h after the end of session (End + 1 hour).

RESULTS

From November 2015 to October 2019, 908 dialysis sessions were performed with a calcium-free citrate-containing dialysate, including 389 within the intensive care unit (Table 1). Premature termination for filter clotting occurred in 20 sessions (2.2%). Duration of session was longer than 4.5 h in 135 (15%), with a maximum duration of 6 h. No patient developed symptomatic hypo- or hypercalcaemia.

Among these 908 sessions, assessment of the citrate and acid–basis status was available for 20 sessions performed (18 patients; citrate subgroup). Nineteen sessions were also performed without citrate within the dialysate (citrate-free subgroup). The subsequent part of the study focuses on these two subgroups with a special emphasis on the citratre subgroup in which calcium/citrate measurements were available.

Characteristics and outcome of the citrate subgroup

Characteristics of the 18 patients of the citrate subgroup (20 dialysis sessions) are described in Supplementary data, Table S1. Fifteen (75%) and six (30%) dialysis sessions were performed in patients receiving mechanical ventilation or vasopressor drugs (mean norepinephrine dose 0.25 µg/kg/min), respectively. Five patients (28%) were in a post-liver transplant period and 13 patients (72%) had a Child–Pugh score >A6. Median prothrombin time was 69.5% (35; 100). Liver clearance was assessed in seven patients using a Picco Limon® monitoring (Pulsion System, France). Median CR15 and plasma disappearance rate were 33 and 7.4, respectively.

Duration of dialysis sessions was 5 h, except for two sessions (2.5 and 4 h, respectively). The quality of blood purification was confirmed by the ionic dialysance [median 225 (ranges: 130; 240)] and the percentage of urea reduction [median 76% (range: 24; 84)]. None of the patients became haemodynamically unstable.

Median iCa and citrate concentrations after the dialysis filter were 0.31 mmol/L (0.13; 0.89) and 0.304 mmol/L (0.011; 0.548), respectively. In one case, premature filter clotting event was observed, which occurred after severe catheter dysfunction.

iCa remained stable all along the dialysis session (median 1.14 mmol/L at the end of the dialysis) (Figure 1). At the end of the session, no sign of citrate accumulation was observed. The total-to-iCa ratio slightly increased from 1.83 to 1.88, but

remained below 2.2 in all patients. The pH increased from 7.37 (range: 7.19; 7.48) to 7.46 (7.29; 7.53), and the SIG significantly increased from 35.7 to 31.5 ($P < 0.001$) with a concomitant increase of the effective strong ion difference.

The serum citrate concentration (pre-filter) slightly increased from 15 (4; 244) (baseline value) to 49 μmol/L (14; 142) at the end of the session, but remained in the normal value range (i.e. <130 μmol/L) in all except one session (0.142 at the end of the session). One hour after the end of dialysis, serum citrate concentration was normal in all patients [median 27 μmol/L (range: 11; 99)] (Figure 1). In the seven patients with available data, no correlation between indocyanine green clearance (i.e. liver function) and maximal serum citrate concentration could be observed.

Characteristics and outcome of the citrate-free subgroup

Nineteen additional patients had a haemodialysis session with a dialysate containing no calcium and no citrate (dialysate was acidified by 2 mmol/L of acetate; citrate-free subgroup) (Table 1). Duration of dialysis sessions was 240 min (range: 240; 270) and no premature terminations were observed. In all sessions, post-filter iCa at 1 h was below 0.5 mmol/L [median 0.41 (range: 0.34; 0.5)], whereas serum (pre-filter) iCa remained stable, according to the ionic dialysance-guided calcium reinjection.

DISCUSSION

There is an unmet need to develop efficient, safe, low-cost and easy-to-use RRT. Several criteria should be fulfilled, such as efficient blood purification (low and middle molecular weight clearance), a low frequency (<5%) of premature session termination (with sessions lasting for at least 4 h), the risk of bleeding should not be increased, a good haemodynamic and metabolic tolerance and no iterative or complex monitoring.

We recently demonstrated that regional anticoagulation using a calcium-free citrate-containing dialysate allows to extend the haemodialysis time (over 5 h) in critically ill patients, without the need for systemic anticoagulation or citrate infusion [17]. This approach is safe and reproducible [18]. This technique has been routinely performed in our department since 2015. Further technical developments, including automatized ionic dialysance-guided calcium reinjection and a better understanding of calcium-free dialysate anticoagulation mechanisms, may help to refine this technique. In light of the recent development of alternative, better tolerated, techniques of RRT that do not require acidification of the dialysate, such as acetate-free biofiltration, it was mandatory to assess whether including citrate in the dialysate contributes to prevent filter coagulation.

In our current study, we initially confirmed the safety and efficiency of haemodialysis with a calcium-free dialysate, even in critically ill patients with liver disorders, which represent a subset of patients at risk of citrate accumulation when regional citrate anticoagulation is used in continuous RRT [20, 21]. With some 908 haemodialysis sessions (including 389 in the intensive care unit) performed without any additional safety concerns being raised, we now report that more than 97.5% of sessions went to completion.

We subsequently demonstrated that a calcium-free citrate-containing dialysate does not lead to citrate accumulation (median citrate concentration 0.05 mM at the end of the dialysis), even when dialysis sessions are extended (median 5 h) or performed in patients with underlying liver disorders. This was further confirmed by the normal range of total-to-iCa ratio values obtained and by the correction of the SIG. When compared with the target concentration of citrate used in regional anticoagulation of continuous RRT (3 mmol/L), the relatively low citrate concentration detected in the dialysate and in the filter (0.8 and 0.55, respectively) using the technique described here was not associated with an overt risk of citrate accumulation.

We also confirmed that the ionic dialysance was a good predictor of the rate of calcium removal through the filter and the subsequent reinjection rate required to maintain stable serum iCa levels when using calcium-free dialysates. No dyscalcaemia was detected, confirming that adequate calcium supplementation was achieved.

We finally assessed whether the addition of citrate to the dialysate is mandatory to obtain efficient filter anticoagulation. We showed that citrate concentration in the haemodialysis filter (median 0.55 mmol/L) was well below the target concentration of 3–4 mmol/L previously identified as the optimum concentration to keep iCa levels below 0.4 mmol/L in order to prevent filter coagulation [20, 22]. As previously mentioned, this result was expected given the low citrate concentration in the dialysate (i.e. 0.8 mmol/L). The current study nevertheless confirms that most of the decrease in iCa (median post-filter iCa 0.31 mmol/L) observed when using a calcium-free dialysate is due to the removal of calcium through the filter. This observation is consistent with the low post-filter iCa levels (<0.5 mmol/L) observed in the calcium-free citrate-free dialysate haemodialysis sessions performed. Altogether, our results indicate that the addition of citrate to a calcium-free dialysate slightly decreases intra-filter iCa but minimally contributes to prevent filter clotting. This opens up tremendous opportunities to develop intermittent haemodialysis with acid-free dialysates and using calcium-free dialysate as regional anticoagulation.

CONCLUSIONS

Our study confirmed in a large cohort of 908 dialysis sessions that regional anticoagulation of haemodialysis filter with calcium-free citrate-containing dialysates is safe and efficient, even in critically ill patients with underlying liver disorders, and that the citrate component of the calcium-free dialysate is not required to prevent filter coagulation.

DATA AVAILABILITY STATEMENT

Data and materials are available upon request.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of the University Hospital of Toulouse (Direction de la Recherche Clinique et de l'Investigation, no. OSB/MEL/IO-2019-1520), was conducted according to the declaration of Helsinki revised in 2004 and fulfiled the criteria of French law related to retrospective studies.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

FUNDING

Citrate concentrations were measured using a fund obtained from Hemotech (Ramonville, France).

AUTHORS' CONTRIBUTIONS

S.F. performed the statistical analyses and took responsibility for the content of the manuscript, including the data and the analysis. S.F., O.C. and C.M. contributed substantially to the study design. C.M., E.C., L.L., M.-B.N. and N.S. collected the data. S.F., N.K., O.C. and C.M. contributed significantly to the writing of the manuscript. All the authors followed the patients and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Results presented in this paper have not been published previously in whole or part, except in abstract format at the French Society of Nephrology, Dialysis and Transplantation. No conflict of interest to disclose.

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