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Original Article

ORIGINAL ARTICLE

Toward acid- and heparin-free dialysis: the regional anticoagulation approach

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ABSTRACT

Background. In chronic intermittent hemodialysis, heparin is the standard anticoagulant as is the use of acid-containing dialysate. Regional anticoagulation (RA) with a calcium-free, citrate-containing dialysate has been developed. We compared RA using a calcium-free, citrate-free dialysate, routinely used in our center, versus systemic heparinization.

Methods. In a retrospective, observational, single-center, crossover study, we examined 15 patients undergoing chronic hemodialysis who were at high risk of bleeding and temporarily unable to use heparin. These patients received temporary treatment with RA involving calcium-free and citrate-free dialysate. We compared the dialysis session success rates during two distinct periods: standard heparinization and RA procedure with a calcium-free and citrate-free dialysate.

Results. In our study of 15 patients on chronic hemodialysis which compared 30 RA sessions versus 28 heparin-based anticoagulation session, we observed a 100% success rate with a median session duration of 240 min in both RA and heparin groups. No early extracorporeal circulation (ECC) loss was reported. However, we noted significant differences in the post-dialysis ECC thrombosis scores, with higher Global Thrombosis Index (GTI) and higher membrane coagulation scores in the RA group ($P < .007$ and $P < .02$, respectively). No hypocalcaemia or hypercalcemia symptoms occurred. Median post-filter ionized calcium levels were 0.32 (0.29–0.39) mmol/L at 30 min and median patient ionized calcium levels was 1.19 (1.135–1.28) mmol/L at 60 min. No significant difference in per-dialysis arterial blood pressure was observed between groups.

Conclusion. Our study evaluated the RA approach using a calcium-free, citrate-free acetate dialysate in a chronic hemodialysis center and found it effective. Although an acid-free dialysate was not used in this study, our findings suggest it could be the next frontier in the evolution of advanced dialysis techniques.

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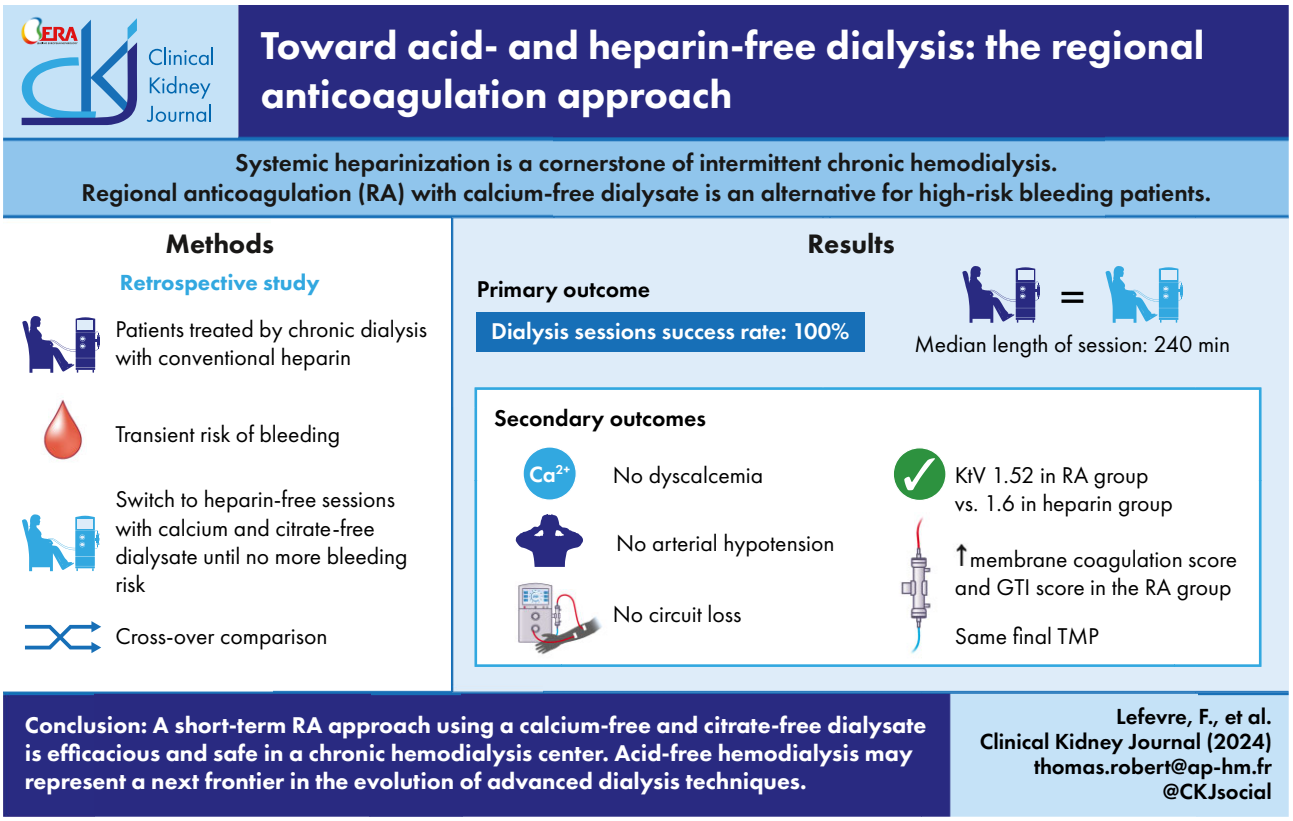
GRAPHICAL ABSTRACT



Keywords: acid-free dialysate, calcium-free dialysate, intermittent hemodialysis, regional anticoagulation

KEY LEARNING POINTS

What was known:

- Systemic heparinization is the cornerstone of intermittent hemodialysis to prevent clotting.
- Regional anticoagulation (RA) with calcium-free dialysate is a major alternative to heparin for high-risk bleeding patients in chronic hemodialysis.
- Acid-containing dialysate is the most widely used technique for chronic intermittent hemodialysis.

This study adds:

- A calcium- and citrate-free dialysate effectively prevents clotting without heparin, achieving adequate chronic intermittent dialysis.

Potential impact:

- Acid-free and heparin-free chronic hemodialysis may represent the next step in the development of intermittent hemodialysis, potentially avoiding many adverse events and improving patient care.

INTRODUCTION

In France, the national prevalence of end-stage renal disease (ESRD) treated with dialysis or transplantation is 1294 per million inhabitants [1]. As of 2017, the Renal Epidemiology and Information Network (REIN) registry recorded approximately 50 000 ESRD patients undergoing treatment exclusively through hemodialysis. Hemodialysis poses a significant public health challenge and serves as a crucial lifeline for patients either awaiting kidney transplantation or when transplantation is not an option.

Extracorporeal circuit (ECC) anticoagulation is the cornerstone of intermittent hemodialysis technique to prevent clotting and addressing the potential risk of bleeding complications [2]. Unfractionated or low-molecular weight heparins are the most commonly used systemic anticoagulant [3]. We estimate that a patient is exposed to around 600 000 IU of unfractionated

heparin (UFH) per year in our center. Given their conditions, ESRD patients are at a heightened risk of bleeding, making regional anticoagulation techniques a compelling alternative [4]. The European Best Practice Guidelines (EBPG) Expert Group on Hemodialysis categorizes patients at high risk of bleeding as follows: those with active or recent bleeding (within the last 7 days), recent trauma or surgery, recent stroke, retinal hemorrhage, arteriovenous malformation or aneurysm, uncontrolled hypertension or coagulopathy (including thrombocytopenia and intravascular coagulation disease) [5]. The EBPG recommend avoiding anticoagulation in high-risk patients. Furthermore, chronic dialysis patients may periodically face an elevated risk of bleeding or an effective bleeding, necessitating temporary adjustments to their anticoagulation regimen, making regional anticoagulation (RA) techniques of interest. Some patients have permanently high bleeding risk, necessitating an alternative method of anticoagulation. High-quality dialysis without heparin remains a real challenge.

Currently, various methods of dialysis without systemic anticoagulation are possible [2]. One approach involves hemodialysis without anticoagulation, but necessitates a complete circuit and dialyzer change every 2 h during a session [6]. However, this method is cost-ineffective and time-consuming for nurses [7]. In contrast, regional citrate anticoagulation, a common method used for continuous renal replacement therapy, avoids the need for heparin. It involves infusing an anticoagulant–citrate–dextrose formulation (i.e. ACD-A) according to blood flow to reach a citrate blood concentration between 3 and 4 mmol/L into the arterial line along with a calcium-free dialysate with calcium reinfusion after the filter [8–12]. The standard regional citrate anticoagulation requires close monitoring of systemic calcium levels to prevent hypocalcemia and exposes the patient to high citrate concentrations, which represents challenges for nurses in chronic dialysis units. To address these challenges, we have developed a simplified RA procedure. This method utilizes a calcium-free dialysate containing citrate (citrate concentration 0.8 mmol/L) without the need for calcium monitoring. Blood calcium diffuses out through the membrane into the effluent dialysate, resulting in ionized calcium concentration at the membrane outlet of <0.4 mmol/L, effectively inhibiting the coagulation process. To prevent hypocalcemia, the eliminated calcium is reinfused to the patient before the venous needle via a 50 mL syringe of 10% calcium chloride. This simplified RA procedure routinely used in our center for chronic dialysis patients with high risk of bleeding offers an efficient and practical alternative to traditional anticoagulation methods in dialysis units [13, 14]. Faguer *et al.* demonstrated in critically ill patients the superiority of regional anticoagulation with calcium-free dialysate versus the use of heparin-grafted membrane, with early cessation of the session for coagulation in 3% of cases versus 19% respectively [15]. In addition, they showed that citrate and calcium-free dialysate was effective for regional anticoagulation, suggesting that citrate was not mandatory in this procedure [15–17]. Thus, we can assume that the absence of calcium in the dialysis bath should be sufficient to obtain a post-filter ionized calcium level <0.4 mmol/L, and that the small amount of citrate in the bath would not be necessary for proper anticoagulation of the circuit of dialysis.

To examine this, we applied our simplified regional anticoagulation procedure with a citrate and calcium-free, acetate-containing dialysate and assessed the efficacy in comparison with standard heparinization.

MATERIALS AND METHODS

Study population

We conducted a retrospective, observational, monocentric, crossover study in a hemodialysis center in Marseille, France (Fig. 1). We included all patients on chronic hemodialysis who had been dialyzed with conventional heparin treatment (hemodialysis or predilutional hemodiafiltration only) for at least 1 month without incident, in order to exclude the dialysis initiation period. We selected all the patients who presented with a periodic contraindication to heparin and switched to a RA technique using a calcium-free and citrate-free dialysate for at least two sessions between October 2020 and April 2021. The criteria for periodic heparin contraindication included at least one of the following conditions: active hemorrhage, a high bleeding risk characterized by situations such as recent bleeding within the past 7 days, recent post-operative periods of <7 days, recent head trauma within the past 7 days, recent invasive procedures within the past 7 days, recent stroke, uremic pericarditis or non-exteriorized deglobulization. Concerning the exclusions criteria, patients who experienced regular extracorporeal circuit losses with heparin, used hemofiltration techniques, had dysfunctional vascular access, exhibited hypercalcemia exceeding 3 mmol/L, or were undergoing curative anticoagulant treatment were excluded from our analysis. The hemofiltration regimen was excluded due to the absence of diffusive transfer through the membrane (no dialysate circulation in the membrane) making it impossible to achieve a post-filter ionized calcium level below 0.4 mmol/L. The dialysis sessions were performed using the DDB-EXA generator (NIKKISO, Paris, France) within our chronic unit of dialysis. The ultrafiltration rate was adjusted based on the patient's dry weight, and the effective blood flow rate and session duration were tailored to the medical prescription. A constant dialysate flow rate of 500 mL/min and a dialysate temperature of 36°C were maintained for all patients and high-flux synthetic membranes were used for all the patients. After at least two sessions of dialysis with the RA technique, if the bleeding risk was resolved based on clinical evaluation, the patient resumed their conventional session with heparin. If the bleeding risk persisted as determined by the clinician, the RA technique was continued until the bleeding risk subsided.

RA procedures

The RA procedure necessitated the use of a dialysate that was free from both calcium and citrate (D506, Hemotech, Toulouse, France). The final composition of the dialysate, achieved after diluting the acid concentrate with the sodium bicarbonate concentrate, remained consistent across all dialysis sessions. It included the following components: citric acid at 0 mmol/L, acetic acid at 2 mmol/L, glucose at 5.5 mmol/L, chloride at 107 mmol/L, potassium at 3 mmol/L, calcium at 0 mmol/L and magnesium at 0.5 mmol/L. The composition of sodium and bicarbonate varied according to the medical prescription. To replace calcium, we administered a continuous intravenous injection of a 10% calcium chloride solution via an electric syringe in the venous return line after the venous bubble trap. The flow rate of reinjection was set at 42 mL/h, resulting in a plasma calcium concentration equivalent to that achieved with a dialysate containing 1.5 mmol/L of calcium concentration as previously described. We monitored ionized calcium levels using an automatic blood gas analyzer in our unit. This involved assessing a post-filter ionized calcium level at 30 min to ensure

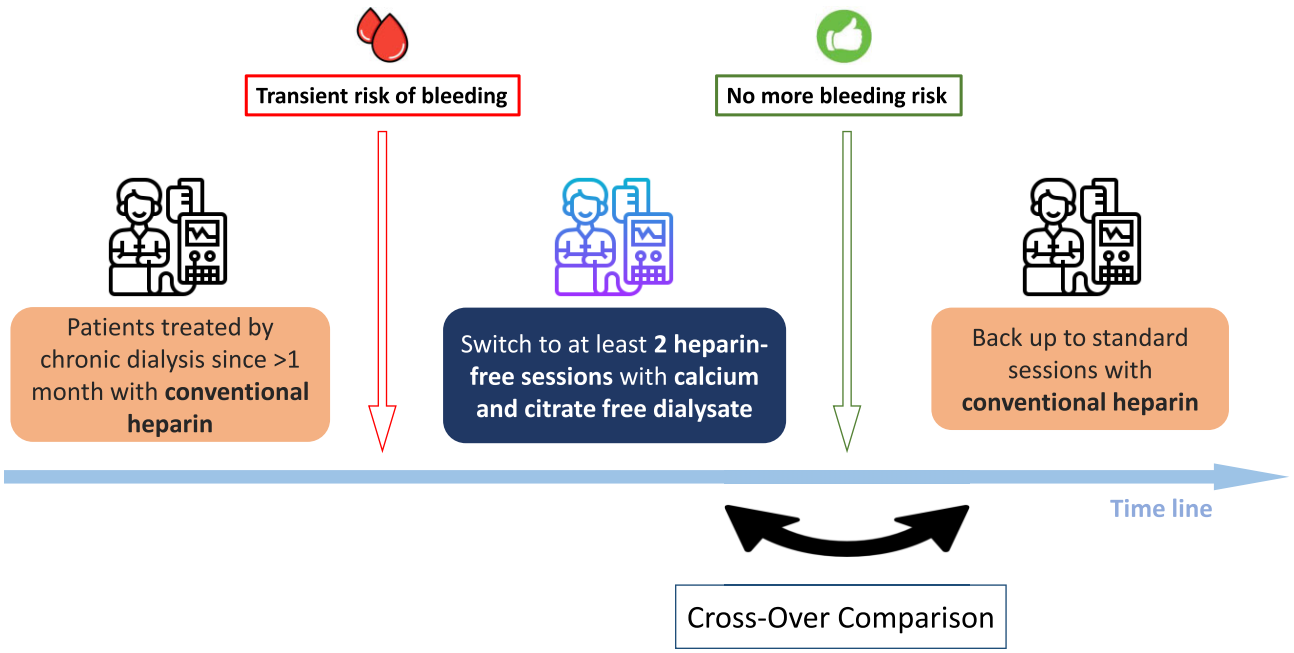


Figure 1: Study design.

efficiency (with a target of <0.4 mmol/L) and a patient ionized calcium level at 60 min for safety (target >1.1 and <1.35 mmol/L). In cases where the patient's ionized calcium level was found to be inadequate, adjustments to the calcium reinjection rate were made, as outlined in Supplementary data, Table S1. During a session with the RA procedure, any abnormality reported by the patient (spasmophilia with positive Chvostek's and Trousseau's signs, muscle cramps, tetany, cardiac rhythm disorders, perioral or extremity paraesthesia, digestive disorders, hypertension, hypotension or confusion) triggered an immediate measurement of the patient's ionized calcium levels as per our protocol. No change in dialysis regimen (hemodialysis or hemodiafiltration) were made between the RA sessions and the heparin sessions.

Standard heparinization procedure

The continuous infusion of unfractionated heparin (UFH) was performed on the arterial line throughout the session. Total UFH dose was 50 IU/kg/session with 25 UI/kg during the first hour and then 12.5 UI/kg during the session [18]. Heparinization was stopped at the fourth hour session for arteriovenous fistula (AVF).

Dialysis membranes

All patients dialyzed with Toraysulfone TS dialysis membrane, a high-flow polysulfone dialyzer. No dialysis membrane changes were made between sessions.

Endpoint definition

Our primary endpoint was to compare dialysis sessions success rate between both anticoagulation procedures defined by complete restitution of extra-corporeal circuit after reaching the prescribed dialysis time. Each patient was his own comparison. As secondary objectives, we also compared: the circuit loss rate, early ECC restitution rate (defined as recovery 30 min or more before the end of the prescribed duration), prolonged AVF bleeding at the end of dialysis (defined by compression time extended more than 20 min) and the post-dialysis ECC thrombosis degree using a semi-quantitative scoring system, dialyzer Membrane Coagulation Score and the Global Thrombosis Index (GTI) score. The GTI score [13] assesses the presence of thrombotic material within different parts of the ECC, including venous or arterial bubble traps, lines and dialyzer (0 point if clear, 0.5 point if fibrin deposits, 1 point if blood clots). This score is not a validated score but a descriptive score assessed visually at the end of each dialysis session which offers a valuable and real-time evaluation of thrombosis in the dialysis circuit, with its potential clinical implications. The dialyzer Membrane Coagulation Score evaluates after the restitution the percentage of residual blood within the dialyzer fibres, with a scale ranging from no residue to substantial levels (1 point if no residue, 2 points if less the 10%, 3 points if 10%–25%, 4 points if 25%–50% and 5 points if >50%). In the initial description of this score [19], it was presented as a five-item score ranging from 0 to 4. However, for statistical convenience, we opted to change the scoring from 1 to 5. This adjustment was made to simplify statistical analysis and interpretation. We monitored clinical tolerance by assessing symptoms suggestive of hypocalcaemia, such as paraesthesia, metallic taste, discomfort sensation, hot flushes, unusual intense asthenia or palpitations, per-dialytic hypotension rate was defined by a systolic blood pressure drop of at least 20 mmHg, accompanied by clinical signs like lipothymia, syncope, abnormal movements, abdominal pain, nausea, vomiting and the subsequent need for crystalloid resuscitation. We compared dialysis parameters: final transmembrane pressure (TMP), Kt/V, mean ultrafiltration rate, vascular access, blood flow rate (mL/min) and mean dialysis time (min).

Statistical analysis

Quantitative variables results were expressed as medians and quartiles (Q1 and Q3). Qualitative variables were reported as

Table 1: General population characteristics.

Patient characteristics[a]	$n = 15$ (%)
Age (years)	72.9
Gender, male	10 (66)
Dialysis method: HD/predilution HDF	3 (20)/12 (80)
AVF/tunnelled catheter	9 (60)/6 (40)
Active cancer	1 (7)
AVF thrombosis history	1 (7)
History of pulmonary embolism or deep venous thrombosis	2 (13)
Diabetes	9 (60)
Arterial hypertension	13 (86)
Coronary artery disease	10 (66)
Peripheral artery disease	4 (26)
History of bleeding event	1 (6)
Cause of bleeding high risk situations	
Invasive procedure	5
Post-operative period	5
Cerebral traumatism	1
Fistulography	4
Dual antiplatelet aggregation	2 (13)

[a]For quantitative variables, values are expressed as median. For qualitative variables, values are expressed as *n* (%).
HD: hemodialysis; HDF: hemodiafiltration.

numbers and percentages. Non-parametric Wilcoxon–Mann–Whitney tests were conducted to compare the characteristics of each group. Categorical variables were compared using Fisher's exact test. All test were two-tailed. A value of $P < .05$ was considered statistically significant. The data were analysed using Prism software (GraphPad Prism Software, San Diego, CA, USA) and JMP Pro V14 software.

RESULTS

General characteristics of the study population

In our study, we analyzed a cohort of 15 patients, comparing 30 sessions of RA with 28 sessions of standard heparin-based anticoagulation using a crossover design. Two heparin dialysis sessions were excluded from analysis due to missing data. The median age of the patients was 72.9 years, with males representing 66% of the study population. The primary cause of nephropathy was diabetes, accounting for 35%, closely followed by nephroangiosclerosis at 28%. Predilution hemodiafiltration was the predominant dialysis method, utilized in 80% of the sessions. Sixty percent of the patients had an AVF, and only one patient had a history of AVF thrombosis. Common comorbidities included diabetes (60%), arterial hypertension (86%) and coronary artery disease (66%). Only one patient was under dual antiplatelet aggregation treatment. Temporary contraindications to heparin primarily stemmed from high bleeding risks due to invasive procedures or post-operative recovery (Table 1).

Characteristics and outcomes in citrate-free dialysate

We analysed two sessions with the RA technique per patient. In our evaluation of sessions using citrate-free dialysate, we observed a 100% success rate with a median duration of 240 (240–240) min in both the RA and heparin groups. There was no instance of early ECC restitution or ECC loss observed in either group. Statistical differences were observed in the median GTI scores between the RA group and the heparin group, with values of 1.25 (range 1–2) and 0.5 (range 0.5–1), respectively ($P = .007$). Similarly, the median membrane coagulation scores differed significantly, registering 2 (range 2–3) in the RA group and 1.5 (range 1–2) in the heparin group ($P = .02$) as shown in Table 2. However, no significant difference was found in the median final transmembrane pressure, which was 175 mmHg (range 149.5–235.3) in the RA group compared with 167 mmHg (range 155–207) in the heparin group ($P = .67$). Furthermore, dialysis adequacy was close, with median Kt/V at 1.52 (1.4–1.6) and 1.6 (1.5–1.7), respectively, in RA and heparin groups (Table 2). None of the patients experienced symptoms of hypocalcemia or hypercalcemia during dialysis sessions. Thirty minutes after the initiation of each dialysis sessions, the median post-filter ionized calcium level was 0.32 (0.29–0.39) mmol/L, while at 60 min after initiation, the median patient ionized calcium level was 1.19 (1.135–1.28) mmol/L. No significant differences in per-dialysis systolic/diastolic arterial blood pressure were observed between the two groups.

DISCUSSION

Our study provides evidence that citrate-containing dialysate is not an absolute requirement for achieving successful intermittent hemodialysis sessions. This opens the possibility of using acid-free dialysate baths. We have shown that citrate-free dialysate induces a substantial transfer of calcium from the blood into dialysate to lower ionized calcium levels below 0.4 mmol/L. We hypothesize that this lead to the inactivation of the cascade coagulation and platelet aggregation as evidenced by a reduction in median GTI and median membrane coagulation score [12, 20].

One of the most noteworthy implications of our findings is the potential to liberate hemodialysis patients from the long-term use of heparin. Chronic dialysis patients are routinely exposed to significant amounts of UFH, totalling up to 600 000 IU every year according to our protocol. Dialysis methods based on heparin for patients at risk of bleeding such as heparin-grafted membrane or reduced doses of heparin are available [7, 21]. However, besides the risk of bleeding, heparin also exacerbates osteoporotic risks in conjunction with the pre-existing osteopathy linked to chronic kidney disease [2]. Moreover, our technique offers the added benefit of avoiding allergic reactions associated with heparin, such as heparin-induced thrombocytopenia or anaphylactic responses to contaminants like oversulfated chondroitin sulfate [22, 23]. Furthermore, recent studies have raised concerns about potential cardiovascular risks associated with heparin use, demonstrating that heparin could lead to cardiac hypertrophy secondary to the secretion of fibroblast growth factor-23 [24].

Our innovative technique also lays the foundation for chronic acid-free hemodialysis. In a neutral pH environment, bicarbonate ions in the dialysate can precipitate with divalent cations (such as Ca^{2+} and Mg^{2+}). This precipitation can occlude the fluid pathway, leading to system malfunction and increased maintenance requirements. Acidifying the dialysate either with acetic acid, citric acid or hydrochloride acid dissolves CO_2 to prevent formation of these insoluble precipitates. These commonly used acids have no established superiority among them in randomized crossover studies [25–27]. However, it is essential to acknowledge that these acids are not without side effects, including alterations in phosphocalcic and acid–base metabolism, cramps, hypomagnesemia, changes in parathyroid hormone levels, and potential long-term impacts on mineral and bone metabolism [28]. Additionally, the use of acidified dialysate can

Table 2: Comparison of dialysis session characteristics.

Secondary endpoints	RA, $n = 30$	Heparin, $n = 28$	P
Successful session	30 (100)	30 (100)	
Length of session (min)	240	240	
Post-filter ionized calcium level (mmol/L)	0.32		
Patient ionized calcium level (mmol/L)	1.19		
ECC loss	0	0	
Early ECC restitution	0	0	
GTI score	1.25 (0.5–1.25)	0.5 (0.5–1)	**.007**
Mean membrane coagulation score	2 (2–3)	1.5 (1–2)	**.02**
Coagulated arterial bubble trap	4	3	.35
Coagulated venous bubble trap	1	0	.75
Intradialytic arterial hypotension	1	0	.32
Symptoms suggestive dyscalcemia	0	0	
Kt/V	1.52 (1.4–1.6)	1.6 (1.5–1.7)	**.02**
UF rate (L/session)	2.35 (1.5–2.9)	2.35 (1.8–3.1)	.33
Bleeding AVF duration (min)	6 (5–10)	6 (5–7.5)	.35
Final TMP (mmHg)	175 (149.5–235.3)	167 (155–207)	.67

[a]For quantitative variables, values are expressed as median. For qualitative variables, values are expressed as *n* (%).
Kt/V: K—urea dialyzer clearance, t—dialysis duration, V—volume of urea distribution; UF: ultrafiltration; TMP: transmembrane pressure.

stimulate interleukin-1 secretion, leading to inflammation and lymphocyte activation [29], as well as bradykinin and nitric oxide activation. Acid-free dialysate, like acetate-free biofiltration, is more biocompatible and exhibits superior clinical tolerance, with reduced instances of per-dialytic hypotension [25]. In a narrative discussion about bicarbonate in dialysis, Marano even suggests that acid, regardless of the anion (acetate, citrate or chloride), leads to hemodynamic intolerance due to CO_2 overload. Marano proposes using the new label "acid-free biocompatible dialysate" as a potential solution [30]. Using a calcium-free dialysate helps prevent the precipitation of Ca^{2+} cations with bicarbonate, and in this sense our technique may pave the way for an acid-free dialysate as calcium carbonate precipitates in the fluid pathway of dialysate delivery systems that dispense bicarbonate-containing dialysate. However, an acid-free dialysate can still result in the precipitation of bicarbonate ions with Mg^{+} cations, despite their low concentration (0.5 mmol/L). Further investigations are needed to address this issue.

Nonetheless, our technique does come with limitations, primarily in terms of safety. Incorrect usage of calcium-free dialysate without proper reinjection of calcium chloride into the venous line, or inadvertent injection of calcium chloride into the venous line using conventional dialysate containing calcium, poses a risk of iatrogenic hypercalcemia or hypocalcemia. Collaboration with dialysis machine manufacturers is urgently needed to develop dedicated machines equipped with secure calcium chloride reinjection mechanisms and safety alarms. The manufacturers of dialysis generators could thus incorporate a peristaltic pump synchronized with the blood pump featuring an appropriate setting for the controlled calcium reinfusion and design an extracorporeal circuit with a calcium reinfusion site after the venous bubble trap but before the air detector to ensure the absence of gas embolism risk through the venturi effect. While our study has its inherent limitations due to its retrospective nature, the crossover design helps mitigate some of its effects. The relatively small number of patients, although sufficient for drawing significant conclusions, remains a limitation. Additionally, the short duration of the study precludes the exploration of medium- and long-term effects of the absence of acid and calcium in the dialysate on biocompatibility, bone metabolism, magnesemia and inflammatory parameters. The absence of long-term heparin uses and its potential impacts on cardiovascular and osteoporotic risk also warrant further investigation. Furthermore, the study design does not allow investigation of the rates of systemic bleeding in both groups.

To address these limitations and gain a more comprehensive understanding, a prospective, long-term randomized trial involving a larger patient cohort and comparing conventional heparinization with calcium-free dialysate and with calcium and citrate-free dialysate would be highly valuable. Such a study could provide valuable insights into the safety, efficacy and potential benefits of acid-free dialysate and reduced heparin usage in the context of chronic intermittent hemodialysis.

CONCLUSION

In this observational and retrospective analysis, a short-term RA approach using a calcium-free and citrate-free, acetate-containing dialysate was effective and safe in a chronic hemodialysis center compared with systemic heparinization. While we did not use an acid-free dialysate in this study, our findings suggest that acid-free hemodialysis may represent the next frontier in the evolution of advanced dialysis techniques and now need further prospective studies.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

AUTHORS' CONTRIBUTIONS

F.L., S.G., S.B. and T.R. designed the study. F.L. and T.R. were responsible for data collection, data analysis and interpretation, and drafting the article. T.R. analysed the data. F.L. generated the tables and figures. All authors were involved in revising the manuscript and approved of the final, submitted version.

DATA AVAILABILITY STATEMENT

Anonymized data used in conducting the analyses will be made available upon request directed to the corresponding author. Proposals will be reviewed and approved by the authors with scientific merit and feasibility as the criteria. After approval of

a proposal, data can be shared via a secure online platform after signing a data access and confidentiality agreement. Data will be made available for a maximum of 5 years after a data sharing agreement has been signed.

CONFLICT OF INTEREST STATEMENT

TR has received speaker fees from hemat medical.

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