Original Article

Regional citrate anticoagulation in continuous venovenous haemodiafiltration using commercial solutions

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Abstract

Background. Treatment with trisodium citrate provides an effective means of regional anticoagulation during continuous renal replacement therapy (CRRT). We evaluated the efficacy, safety and cost of a regional citrate anticoagulation protocol using commercial solutions in 17 critically ill patients treated with continuous venovenous haemodiafiltration (CVVHDF). We performed a total of 22 sessions.

Methods. We delivered an A.C.D-A541® solution containing 112.9 mmol/l disodium citrate (3.22%) at a median rate of 260 (190–280) ml/h via the pre-filter port of a COBE PRISMA with an AN-69 dialyser, while adjusting the rate to maintain post-filtered ionized calcium (iCa2+) between 0.25 and 0.4 mmol/l. Plasma iCa2+ was maintained at >1.1 mmol/l by infusion of calcium chloride at a median rate of 1.70 (1.36–2.27) mmol/l/h. The dialysate was easily modified according to the acid–base status of each patient. Both replacement and dialysate solutions were delivered at 1200 ml/h. Each session was scheduled for 48 h and biological parameters were assessed every 6 h.

Results. The mean dialyser survival was 39 ± 11 h (median 41.5 h; range 13–48 h). We observed dialyser clotting in four cases (18%). There were no bleeding events or modifications of coagulation parameters. The citrate solution, replacement solution and dialysate were obtained as commercial products. Both the replacement and dialysate solutions contained calcium. The extra cost of this technique was 25 €/day as compared to anticoagulation with heparin.

Conclusions. We designed an efficient method of regional citrate anticoagulation for CVVHDF by using commercial solutions. The monitoring of patients was as intensive as during heparin anticoagulation for CRRT. Because of the higher cost of this method, it should be proposed only for patients with high bleeding risk.

Keywords: bleeding complications; citrate; commercial solutions; critically ill patients; haemodiafiltration; regional anticoagulation

Introduction

Continuous renal replacement therapy (CRRT) is currently used for treatment of acute renal failure in critically ill patients with haemodynamic instability, even though it has not been shown to improve patient survival over that of intermittent haemodialysis [1]. A main disadvantage of CRRT is the requirement of anticoagulation therapy to maintain filter patency and thereby prevent clotting of the extracorporeal circuit. Heparin is the most frequently used anticoagulant, but is associated with a risk of bleeding that is seen in 4–30% of patients [2–4]. Moreover, heparin may not provide ideal anticoagulation in patients that have intrinsic clotting system activation, antithrombin III deficiency or evidence of intravascular coagulation [5]. In addition, despite the low incidence of the heparin-induced thrombocytopenia (1–3%) [6,7], it may preclude the use of heparin in some cases. Various alternative methods have been developed to ensure anticoagulation in the extracorporeal circuit, including regional heparinization [8], low molecular weight heparin [9,10], saline flushes [11], prostacyclin [12,13], the serine proteinase inhibitor nafamostat [14], hirudin [15] and regional citrate anticoagulation [16–21].

Citrate exerts anticoagulation activity through its ability to chelate ionized calcium in the extracorporeal
circuit. A major portion of the citrate–calcium complex is filtered. The uncleared fraction is diluted by the total blood volume and is rapidly metabolized to bicarbonate by the tricarboxylic pathway in the liver and other tissues, including the kidney and skeletal muscle. The rapid metabolism of citrate to bicarbonate releases calcium and, therefore, does not confer systemic anticoagulation. However, patients with severe liver failure and lactic acidosis may have difficulties in metabolizing citrate, resulting in citrate accumulation and toxicity. The infusion of hypertonic trisodium citrate may lead to hypernatraemia and/or alkalosis, unless adapted replacement solutions and/or dialysates are used. A balance of sodium and bicarbonate can be maintained with a hypotonic calcium solution that is bicarbonate free. Unfortunately, this type of replacement solution is not available on the French market. Therefore, we designed a prospective study to evaluate the efficiency, safety, feasibility and cost of a regional citrate anticoagulation method that uses a calcium-containing standard commercial isotonic solution in 17 critically ill patients treated by continuous venovenous haemodiafiltration (CVVHDF).

Subjects and methods

Patients

Beginning from March 2001, the first 17 adult patients requiring CVVHDF that were hospitalized in the Department of Nephrology and intensive care units of Toulouse University Hospitals were treated with the described method to establish a new citrate anticoagulation protocol using commercial products. The patients were included even when conventional anticoagulation, such as heparin, was not contraindicated. We excluded only patients with severe liver failure (prothrombin time <30% and factor V <20%), because citrate is metabolized by the liver. Twenty-two sessions were performed and each session was scheduled for 48 h.

Methods

CRRT was performed using the COBE PRISMA CFM set (Hospal, Lyon, France) with an AN-69 pre-dilution acrylonitrile dialyser (effective surface area 0.6 m²). A double-lumen 12F catheter (Arrow International Corporation, Pennsylvania, USA) was inserted exclusively into the femoral vein to avoid cardiac citric acid intoxication, even though serum citrate concentrations were lower than toxic levels. The blood flow rate was initially 125 ml/min.

A.C.D-A541 (BRAUN, Boulogne, France), a preformed 1000 ml solution that contains 123.6 mmol/l glucose, 224.4 mmol/l sodium, 114.2 mmol/l hydrogen ion and 112.9 mmol/l citrate (3.22%) was delivered, pre-filter driven, by an independent pump (AVI270; 3M, Minnesota, USA) at an initial rate of 250 ml/h. Post-filter ionized calcium (iCa²⁺) levels were measured to assess the adequacy of anticoagulation. The citrate infusion rate was titrated at increments of 10 ml/h to maintain post-filter iCa²⁺ between 0.25 and 0.4 mmol/l. This target was established according to a previous report [18]. The loss of calcium through the dialysate was compensated by infusion of a calcium chloride solution. An aliquot of 1.83 g calcium chloride (45.6 mmol/l) in 11 isotonic glucose was initially infused at a rate of 30 ml/h (1.37 mmol/l). The calcium infusion rate was titrated at increments of 10 ml/h to maintain plasma iCa²⁺ > 1.1 mmol/l. Haemofilters were primed with 10000 U heparin in 21 of 0.9% saline.

The replacement solution, composed of 4750 ml Hemosol® B0 solution (Hospal, Lyon, France) combined with 250 ml Hemosol® B0 5.88% HCO₃Na solution (Hospal, Lyon, France; sodium 144 mmol/l, bicarbonate 35 mmol/l, calcium 1.75 mmol/l, magnesium 0.5 mmol/l, lactate 3 mmol/l), was delivered at a rate of 1200 ml/h.

In the next bag, the dialysate composition was adapted to the acid–base status of the patient. In case of metabolic acidosis (pH < 7.2), the dialysate was made from 4750 ml Hemosol® B0 solution and 250 ml Hemosol® B0 5.88% HCO₃Na solution. In the absence of acidosis, only 125 ml of the Hemosol® B0 5.88% HCO₃Na solution was added to the Hemosol® B0 solution. In this case, the dialysate composition was modified to contain sodium 126 mmol/l, bicarbonate 17 mmol/l, calcium 1.75 mmol/l, magnesium 0.5 mmol/l and lactate 3 mmol/l. In case of hypernatraemia ([Na⁺] > 145 mmol/l) or metabolic alkalosis (pH > 7.5 and/or[HCO₃⁻] > 40 mmol/l), Hemosol® B0 5.88% HCO₃Na solution was not added to the Hemosol® B0 solution. The dialysate was delivered at a rate of 1200 ml/h. The net ultrafiltration was adjusted according to patient condition by adapting the rate of the total fluid input (Figure 1).

For each patient, we recorded demographic factors, medical diagnosis, the presence or absence of renal failure and the simplified acute physiology score (SAPS)-II illness severity score at the time of admission [22]. Mortality was defined as death at any point during the hospitalization. We also assessed the rate of dialysate cloting, hemorrhagic episodes (acute bleeding requiring transfusions or fall in haemoglobin level of > 2 g/day), activated partial thromboplastin time (APTT) and platelet count. We detected citrate toxicity by monitoring changes in serum sodium, serum bicarbonate, serum pH, serum iCa²⁺ and post-filter iCa²⁺. Serum electrolytes, arterial blood gases, post-filter iCa²⁺, platelet counts and APTT were measured at baseline, at 2 and 12 h and then every 12 h. Blood urea nitrogen and serum creatinine levels were assessed before and after each session in order to evaluate the efficiency of the extrarenal epuration.

Statistical analysis

Results are presented as medians and interquartile ranges. Quantitative variables were compared by the non-parametric Friedman test for serial measurements. Blood urea nitrogen, serum creatinine levels, platelet count and APTT ratio before and 36h after the beginning of CRRT sessions were compared by the Wilcoxon test. Biological parameters assessed at 48 h were not included in the analysis, because of the low number of sessions. Dialyser survival was estimated using a Kaplan–Meier test [23]. A P-value of < 0.05 was considered to be statistically significant.
Results

Patient characteristics

Table 1 shows data for patient characteristics. There were 12 male and five female patients. Their median age was 54 years (range 24–77 years). All patients had circulatory failure with vasopressor dependency and required mechanical ventilation. Their median SAPS-II score at the time of admission was 74 (range 38–84). Twelve of the 17 (70%) patients had oliguric acute renal failure. Three patients had an elevated risk of bleeding (patients 6, 14 and 16). Five patients (29%) died during the hospitalization. These deaths were related to underlying processes, such as acute respiratory distress syndrome in one patient (patient 6), uncontrolled septic shock in three patients (patients 10, 11 and 12) and cardiac shock (patient 15) and not to CRRT complications.

Efficacy

We performed 22 sessions. Clotting of the dialyser was observed in only four sessions (18%) at 13, 18, 40 and 41 h (median 29 h). In one of these four sessions, the patient presented with catheter dysfunction with an initial high venous pressure. In nine patients (41%), CRRT was voluntarily stopped due to non-clotting problems, such as catheter dysfunction (n = 2), diagnostic procedures (n = 4) and patient death (n = 3). Overall, the mean dialyser survival was 39 ± 11 h (median 41.5 h; range 13–48 h). The Kaplan–Meier survival curve for dialyser life is shown in Figure 2. Dialyser survival was 77% at 36 h and 41% at 48 h. The average infusion rate of citrate needed to maintain post-filter iCa\(^{2+}\) < 0.4 mmol/l was 260 ml/h (range 190–280 ml/h) or 29.37 mmol/h (range 21.46–31.63 mmol/h).

There was a significant decrease in blood urea nitrogen [8.45 (range 2.2–28) from 15.5 (range 3.1–39) mmol/l; P < 0.0001] and serum creatinine levels [117.5 (range 35–302) from 172 (range 48–633) μmol/l; P < 0.0001] during each session.

Citrate toxicity

The average infusion rate of calcium chloride needed to maintain a plasma iCa\(^{2+}\) > 1.1 mmol/l was 37.5 ml/h (30–50 ml/h) or 1.70 mmol/h (range 1.36–2.27 mmol/h) of elemental calcium. There was no difference in median serum ionized calcium levels during the study period (Table 2) and the patients did not present with cardiac or neuromuscular manifestations related to hypocalcaemia. Two patients presented with asymptomatic hypocalcaemia (lowest iCa\(^{2+}\) level 0.73 mmol/l).

As with calcium, median serum sodium did not change during CVVHDF. However, one patient developed hypernatraemia (serum sodium 148 mmol/l), two patients developed a serum pH > 7.5 (maximum recorded pH 7.52) and two other patients developed serum bicarbonate > 35 mmol/l (36.8 and 37.8 mmol/l, respectively). In these patients, the dialysate composition was modified in the subsequent bag. The initial dialysate, composed of 4750 ml Hemosol® B0 solution combined with 250 ml Hemosol® B0 5.88% HCO\(_3\)Na solution was replaced by a dialysate composed of 4750 ml Hemosol® B0 solution alone. Thereafter, we corrected metabolic alkalosis and hypernatraemia. Overall, a total of 145 Hemosol® bags were used. The initial dialysate composition was modified in these cases (3.4%). Median serum pH and bicarbonate levels were similar during the CVVHDF sessions.
After the first 48 h, when CRRT with regional citrate anticoagulation was continued (n = 4), we observed no further hypernatraemia or metabolic alkalosis.

Complications

None of the patients suffered from bleeding during the session, except for one patient (patient 16) that was hospitalized for hemorrhagic shock following a broken leg. The bleeding had started before the initiation of CRRT and continued during the session.

There was no significant modification of median platelet count from the beginning [155 × 10^9/l (range 59 × 10^9–489 × 10^9/l)] to the end of the session [156.5 × 10^9/l (range 51 × 10^9–660 × 10^9/l); P > 0.05]. The median activated partial thromboplastin time ratio was also similar at initiation [1.23 (range 0.97–2.15)] and at therapy completion [1.17 (range 0.97–1.88); P > 0.05].

Feasibility

The fluids used to perform the present technique were not manufactured by the hospital pharmacy department. The citrate solution, replacement solution and dialysate were commercial products. The dialysate was easily and rapidly modified by the nurses in the patient room according to patient acid–base status. All biological parameters were monitored four to five times a day.

Cost

When CVVHDF was required at our institution, Hemosol® solutions and AN-69 haemofilters were used with all of the anticoagulation methods. The use of heparin for anticoagulation costs ~0.38 €/day. A 1 l bag of A.C.D-A® costs 2.92 €. The median delivered quantity of A.C.D-A® was 6.250 l. Consequently, the daily cost of A.C.D-A® was ~20 €. The glucose and the calcium chloride combined cost 5 €/day. Overall, the extra cost of a CRRT session using regional citrate anticoagulation was 25 €/day. Since the dialysate modification was done in the subsequent bag, we did not use additional Hemosol® bags and consequently there was no additional cost. Nevertheless, Hemosol® solutions are expensive with one bag at a cost of 12.2 €.

Discussion

In current practice, CRRT is frequently used for the treatment of acute renal failure in critically ill patients. This technique requires systemic or regional anticoagulation in order to prevent haemofilter clotting. In the present study, we evaluated the efficacy, safety, feasibility and cost of a regional citrate anticoagula-

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
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<th>Sex</th>
<th>SAPS-II</th>
<th>ARF</th>
<th>Death</th>
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<td>1</td>
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<td>M</td>
<td>84</td>
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<td>2</td>
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<td>78</td>
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<td>No</td>
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<tr>
<td>4</td>
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<tr>
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<td>10</td>
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<td>78</td>
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<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Peritonitis/septic shock</td>
<td>72</td>
<td>F</td>
<td>84</td>
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<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>ARF/AAA repair/septic shock</td>
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<td>M</td>
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<tr>
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<td>ARDS/pneumonia</td>
<td>54</td>
<td>F</td>
<td>67</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*SAPS-II score at the initiation of CRRT. ARF, acute renal failure; ARDS, acute respiratory distress syndrome; AAA, abdominal aortic aneurysm; M, male; F, female.
method using preformed commercial solutions in 17 patients treated by CVVHDF. Our findings suggest that this method provides effective regional anticoagulation and may furnish an alternative to standard systemic anticoagulation treatment.

Several methods have been used to prevent haemofilter clotting during CRRT sessions. When systemic anticoagulation with conventional or fractionated heparin is contraindicated, such as with high bleeding risk, heparin-induced thrombocytopenia or other rare pathologies including aortic dissection, several alternative techniques are usually recommended. Although CRRT without anticoagulation of the haemofilter provides a possible alternative, this requires iterative saline flushes, high blood-flow rates and a low platelet count [24]. Tan et al. [25] previously reported a 32 h mean filter-life in critically ill patients treated by CVVHDF without anticoagulation or saline flush. Nevertheless, all of the patients in this study had a low platelet count. Regional heparinization is technically complicated because of the difficulty in estimating the amount of protamine required to antagonize post-filter heparin [8]. Intravenous prostacyclin has been successfully used in patients with combined hepatic and renal failure [26]. This molecule inhibits platelet aggregation without modifying haemostatic parameters. However, major limitations of its use include vasodilatation and the accompanying hypotension as well as an elevated cost. Previous studies have demonstrated the efficiency of regional citrate anticoagulation [16–21]. Nevertheless, in all of these studies but two [20,21], the authors used replacement and dialysate solutions specially prepared by the hospital pharmacy department.

In the current study, we evaluated a method of regional citrate anticoagulation that used only commercial solutions. It is difficult to compare the present results with previous reports that used different techniques, including continuous arteriovenous haemodialysis (CAVHD) [16], continuous venovenous haemofiltration (CVVHF) [17,20], continuous venous haemodialysis (CVVHD) [19] and CVVHDF [18,21]. Nevertheless, a comparison of dialyser survival revealed a 48 h survival of 70% for dialysers in the studies by Kutsogiannis et al. [18] and Hofmann et al. [20], 61% in a study by Tolwani et al. [19] and 41% in a study by Gabutti et al. [21] compared with 41% in our study. However, patients that died within 48 h of initiating CRRT and patients with incomplete dialysis records were excluded from the studies by Kutsogiannis et al. [18] and by Tolwani et al. [19]. When we used the same exclusion criteria, our haemofilter patency was 70% survival at 48 h.

The mean dialyser survival was ~48 h in the study by Mehta et al. [16], 29.5 h in Palsson et al. [17], 82 h in Kutsogiannis et al. [18], 28 h in Gabutti et al. [21] and 45 h in Hofmann et al. [20], compared with 39 h in our study. Our survival time appeared to be shorter because we voluntarily stopped each session at 48 h to change haemofilters. In contrast, our survival times were longer than in high-risk bleeding patients not
treated with heparin, treated with low doses of heparin (100–700 IU/h) or with high doses (>700 IU/h) of heparin (22.1 ± 14.8, 24.7 ± 13.2 and 23 ± 9.6 h, respectively) [27]. Mehta et al. [16] reported a higher haemofilter life span in CAVHD-treated patients treated with citrate anticoagulation than in patients given fractionated heparin (61.5 and 39.7 h, respectively). Hofbauer et al. [28] reported that citrate sodium anticoagulation during haemodialysis induced a lower activation of coagulation than both conventional and fractionated heparin. In a combined prospective retrospective study, Gabutti et al. [21] reported a higher median lifespan for regional citrate anticoagulation than that for heparin in 12 haemodynamically unstable patients treated by CVVHDF.

The incidence of haemofilter clotting in the current study was lower (18%) than in previous reports by Palsson et al. [17] (25%), by Kutsogiannis et al. [18] (38%) and by Mehta et al. [16] (49%). The average amount of citrate that we delivered was slightly higher than in previous reports [17–21] (Table 3) and this may be due to our use of calcium in the replacement solution, which was not used in the other studies. These findings suggest that a calcium-free replacement solution is not necessary to obtain a low incidence of clotting.

The incidence of bleeding episodes during CRRT combined with all of the anticoagulation methods ranged from 10% to 50% and mortality caused by bleeding was as high as 15% [3,21,27]. In previous reports, the use of regional citrate anticoagulation during CRRT was associated with hemorrhagic episodes that ranged from 0% to 25% [17–21]. In the current study, only one patient (4.5%), who was hospitalized for hemorrhagic shock, continued bleeding during the CRRT session. None of our patients died from bleeding complications during this study. In agreement with previous studies, there was no effect on coagulation parameters.

Citrate infusion may expose patients to metabolic complications, such as hypernatraemia, alkalosis and hypocalcaemia. Mehta et al. [16] reported a high rate of metabolic alkalosis (4%) when using hypertonic sodium citrate. Two methods have been proposed to prevent this complication. The first consists of using a replacement solution containing a hypotonic citrate sodium solution (2%) [17,19]. However, this system lacks flexibility. In order to maintain an adequate citrate infusion rate, the ultrafiltration rate cannot be modified unless the citrate concentration is changed when administering the replacement solution. The second method consists of modifying the sodium and bicarbonate concentrations in the dialysate [16,18]. To avoid hypernatraemia and metabolic alkalosis, we infused a separate preformed solution (A.C.D-A541R, 2.8%) containing disodium citrate that is usually used for plasmapheresis. The A.C.D-A541R solution was used several years ago by Flannigan et al. [29] for regional citrate anticoagulation during haemodialysis. Hemorrhagic complications were more frequent in patients following low-dose controlled heparin anti-

<table>
<thead>
<tr>
<th>Number of sessions</th>
<th>Made of CRRT</th>
<th>Blood flow rate (ml/min)</th>
<th>Average citrate delivered (mmol/h)</th>
<th>Rate of elemental calcium infused (mmol/h)</th>
<th>Incidence of haemofilter clotting</th>
<th>48 h dialyser survival</th>
</tr>
</thead>
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<tr>
<td>Palsson et al. [17]</td>
<td>17</td>
<td>CVVHDF</td>
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<td>9</td>
<td>CVVHDF</td>
<td>125</td>
<td>25</td>
<td>3.1</td>
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<td>Tolwani et al. [19]</td>
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<td>CVVHD</td>
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<td>25</td>
<td>3.1</td>
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<td>Hoffman et al. [20]</td>
<td>58</td>
<td>CVVHF</td>
<td>125</td>
<td>25</td>
<td>3.1</td>
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<tr>
<td>Gabutti et al. [21]</td>
<td>12</td>
<td>CVVHDF</td>
<td>125</td>
<td>25</td>
<td>3.1</td>
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<td>CVVHDF</td>
<td>125</td>
<td>25</td>
<td>3.1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Calcium chloride was initially delivered as 6.3 meq/h and adapted thereafter to maintain normal serum ionized calcium levels. When using the same exclusion criteria as Kutsogiannis et al. [19] and Tolwani et al. [19], haemofilter patency in our series was 70% survival at 48 h. N.A. not available.
coagulation than during hypertonic citrate therapy. The commercial dialysate solution was easily adapted to patient acid–base status (see above). In our study, only one patient presented with moderate hypernatraemia and two others presented with serum bicarbonate > 35 mmol/l. In both cases, we easily modified the dialysate composition. Asymptomatic hypocalcaemia was observed in all of the previous protocols [16–19,21]. In our study, two patients presented with asymptomatic hypocalcaemia. Systemic ionized calcium levels were normalized by infusion of elemental calcium at a rate of 1.82 ± 0.36 mmol/h, which is lower than previously reported [17–19,21] (Table 2). This lower infusion rate probably resulted from the presence of calcium in the replacement solution. This finding underscores the importance of close monitoring of iCa\(^{2+}\) levels, particularly in critically ill patients who frequently present with ionized hypocalcaemia [30].

Regional anticoagulation with citrate is not currently used because of the complex methodology that includes specialized replacement solutions and specialized dialysates. In the current study, several of these difficulties were avoided. First, we used commercial replacement and dialysate solutions. Second, citrate was delivered as a preformed commercial solution that does not require preparation by the hospital pharmacy department. Third, the extra cost was minimal at 25 €/day since Hemosol\textsuperscript{®} solutions are currently used in our institution. Finally, this method did not require more monitoring of biological parameters than other anticoagulation methods and therefore did not change the daily routine of the dialysis nurses.

In conclusion, we tested a simplified method of regional citrate anticoagulation during CVVHDF that uses commercial hypotonic citrate and reinjection solutions. This technique is practical, effective and can be used safely in critically ill patients, particularly in those who have a high risk of bleeding. In future studies, we will compare conventional heparin and citrate anticoagulation during CVVHDF in critically ill patients.

Conflict of interest statement. None declared.

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