

# Regional citrate anticoagulation for continuous renal replacement therapy in children

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## Abstract

**Background** Anticoagulation of the continuous renal replacement therapy (CRRT) circuit is an important technical aspect of this medical procedure. Most studies evaluating the efficacy and safety of citrate use have been carried out in adults, and little evidence is available for the pediatric patient population. The aim of this study was to compare regional citrate anticoagulation versus systemic heparin anticoagulation in terms of the lifetime of hemofilters in a pediatric population receiving CRRT at a pediatric center in Bogota, Colombia.

**Methods** This was an analytical, observational, retrospective cohort study in which we assessed the survival of 150 hemofilters (citrate group 80 hemofilters, heparin group 70 hemofilters) used in a total of 3442 hours of CCRT (citrate group 2248 h, heparin group 1194 h). Hemofilter survival was estimated beginning at placement and continuing until filter replacement due to clotting or high trans-membrane pressures.

**Results** Hemofilter survival was higher in the citrate group than in the heparin group (72 vs. 18 h;  $p < 0.0001$ ). Bivariate analysis

showed that the hemofilter coagulation risk was significantly increased when heparin was used, regardless of hemofilter size and pump flow (hazard ratio 3.70, standard error 0.82, 95% confidence interval 2.39–5.72;  $p < 0.00001$ ).

**Conclusions** Regional citrate anticoagulation could be more effective than heparin systemic anticoagulation in terms of prolonging the hemofilter lifetime in patients with acute renal injury who require CRRT.

**Keywords** Anticoagulation · Citrate · Heparin · Continuous renal replacement therapy · Dialysis · Children

## Introduction

Continuous renal replacement therapy (CRRT) is a treatment for patients with acute kidney injury (AKI), fluid overload, and severe metabolic disturbances in the pediatric intensive care unit (PICU) [1]. Circuit anticoagulation is an important technical issue in this therapy, and its primary purpose is to prevent thrombotic processes once the blood comes in contact with the extracorporeal circuit. Heparin is the most widely used anticoagulant. However, heparin therapy is associated with an increased risk of bleeding and thrombocytopenia, the development of resistance to its action in critically ill patients, and the stimulation of proinflammatory effects by impaired phagocytosis [2].

Citrate anticoagulation offers an interesting alternative as its anticoagulation effect is regional (reversed immediately postfilter) and is therefore associated with lower rates of bleeding complications [2]. Since its introduction for clinical use in 1980, there have been several studies in adults trying to establish the safety and efficacy of regional citrate anticoagulation [3–8]. A systematic review and meta-analysis [9, 10] have shown, with some limitations due to the heterogeneity of the selected studies, that citrate may be more effective than other alternatives for anticoagulation

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The original version of this article was revised to correct the rendering of the name of the author Jaime Fernández Sarmiento.

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because it will extend the lifetime of the circuit (due to a lower risk of bleeding) and, although it has been associated with an increased risk for metabolic disorders, these had no relevant clinical consequences. However, citrate must be handled by experienced personnel due to the potential for increased complications inherent to the treatment.

If regional citrate anticoagulation decreases the frequency of bleeding complications and prolongs the lifetime of hemofilters, it could decrease the costs of CRRT. Given the potential benefits of regional citrate anticoagulation, it is therefore important to know the results of the use of this therapy in the pediatric patient population. However, relevant studies on this patient population are scarce [11]. Since Bunchman et al. [12, 13] established the first protocol for CRRT using citrate in children, there have been only nine additional pediatric studies reporting the use of this strategy [11, 14–23].

The main objective of this study was to compare the lifetime of hemofilters using regional citrate anticoagulation versus systemic heparin anticoagulation in a population of children needing CRRT in the PICU.

## Materials and methods

An analytical, observational, retrospective cohort study was carried out in which patients were followed from admission through to discharge from the PICU of the Fundación Cardioinfantil in Bogotá, Colombia.

For the descriptive analysis, we included subjects between 1 month and 18 years of age with AKI or exacerbated chronic kidney disease who had received CRRT during hospitalization in the PICU from January 2008 to July 2013. The subjects were divided into two groups: one group comprising patients who received regional citrate anticoagulation and the second group comprising those who received anticoagulation with unfractionated heparin. Patients who had received alternative forms of anticoagulation during the study period were excluded from the analysis.

Therapy was defined as various renal replacement therapies, including slow continuous ultrafiltration, continuous venovenous hemodiafiltration, continuous venovenous hemofiltration (CVVH), and continuous venovenous hemodialysis, which patients received for a total of >12 h over a number of sessions. The therapy modality was selected according to the patient's clinical condition (hemodynamic stability, primary diagnosis), and the objective of the therapy (solute removal, water removal, cytokine removal, etc.). All of the therapies received one of the two types of anticoagulation.

In the heparin anticoagulation protocol, an initial intravenous bolus of unfractionated heparin in the range of 20–50 IU/kg body weight was administered, followed by continuous

infusion of heparin at a rate of 5 to 20 IU/kg/h, adjusted to achieve a target partial thromboplastin time (PTT) ratio of approximately 1.5- to 2-fold the control or a postfilter PTT of between 180–200 s [24].

In the citrate group, 3.22 % acid citrate dextrose formula A (ACD-A) was administered in the prefilter port, with an infusion rate (in ml/h) equivalent to 1.5-fold the pump flow ( $Q_b$ ) ( $Q_b \times 1.5$  in ml/h), in order to maintain a concentration of ionized calcium postfilter (venous port) from 0.25 to 0.4 mmol/L. A calcium gluconate infusion was administered in the postfilter port at a concentration of 20 mg/dl, with an infusion rate (in ml/h) corresponding to 25% of the  $Q_b$  ( $Q_b$  in ml/h/4) in order to maintain the concentration of prefilter ionized calcium (arterial port) at between 1.0 and 1.2 mmol/L. The monitoring of the concentrations of ionized calcium and venous blood gases pre- and postfilter were determined at the first, second, and fourth hour of therapy, and then every 4 h until the therapy was concluded. At the same time intervals, the acid–base status of the patient was monitored by the analysis of arterial blood gases obtained through the arterial prefilter port. The infusion rate adjustments of both calcium gluconate and ACD-A were made based on changes in ionized calcium concentrations determined in the pre- and postfilter ports.

In addition to establishing and comparing the total lifetime of hemofilters in the two study groups, we determined and compared the average length of stay of the patient in the PICU, the incidence of mortality, and the frequency of severe bleeding (defined as bleeding associated with hypotension, tachycardia, need for red blood cell transfusion or a 2 g/dl drop in hemoglobin within 24 h). The frequency of metabolic complications, such as hypocalcemia (ionized calcium concentration of <1 mmol/L or serum total calcium concentration of <9 mg/dl), hypercalcemia (total ionized calcium concentration of >1.2 mmol/L or serum total calcium concentration of >11 mg/dl), metabolic alkalosis (bicarbonate concentration of >24 meq/L), hypomagnesemia (plasma magnesium concentration of <1.4 mg/dl), and hypernatremia (sodium plasma concentration of >145 mEq/L) were only measured in the regional citrate anticoagulation group due to incomplete records in the systemic heparin anticoagulation group.

The protocol was submitted for review and the study was approved by the institutional ethics committee.

## Statistical analysis

Four units of analysis were considered in this study, according to the outcome of interest: patients, admissions, therapies, and hemofilters, keeping in mind that the same patient may have been admitted more than once to the PICU and that each hemofilter may have been used for more than one therapy.

The demographic and clinical characteristics of the study subjects and the variables associated with the filter were

described. Relative frequency measures, comparative tables, and histogram-type frequency distribution graphs were used for qualitative variables, where applicable. Central tendency measures (mean, median, and mode) and dispersion or variability measures (percentiles, range or standard deviation, coefficient of variation or homogeneity) were used for quantitative variables, depending on the normality of the distribution of the data, which was evaluated using the Shapiro–Wilk test. The unit of analysis was the hemofilters and, since a patient could provide more than one filter, it was adjusted for the additional variance caused by clustering. For calculating the useful life of hemofilters using citrate anticoagulation versus heparin anticoagulation, we performed an analysis for each specific event, the event being the lifetime of the filter from the time it was placed until it was replaced/discontinued due to therapy completion, thrombotic occlusion, or system dysfunction with transmembrane pressures of >280 mmHg.

Hemofilter changes due to discharge of the patient from the PICU as a result of improvement or death were taken as censorship. Survival estimates were made using the Kaplan–Meier method. The median survival for each group, with its respective 95% confidence intervals (CIs), was reported, and a comparison of the curves was tested using a log-rank test. The magnitude of the effect of the anticoagulant on clotting in the filter was analyzed using Cox’s non-parametric proportional hazards model, which was adjusted for potential confounding variables (size of the filter and pump flow) that could affect the lifetime of the filter.

A sample size of 120 filters, 60 per group, was calculated to be sufficient to identify a significant difference in time to occlusion of the filters, with a type I error of 5% and a power of 80%, estimating a percentage of censure of 5% and taking into account the intra-patient variation that might arise. The sampling was non-probabilistic and included the entire study population. All analyses were performed using STATA version 9 software (StataCorp LP, College Station, TX).

## Results

### Description of the population

Thirty-two patients (17 in the citrate group and 15 in the heparin group) with 46 admissions (30 in the citrate group and 16 in the heparin group) were included in the analysis. The demographic and clinical characteristics of the patients were similar in both groups (Table 1), except for the length of hospital stay, which was higher in the heparin group ( $p=0.021$ ).

### Description of hemofilters

A total of 150 hemofilters were used in all therapies, 80 in the citrate patient group and 70 in the heparin patient group. A

significant difference was observed in the size distribution of the filter between the two groups ( $p=0.007$ ). In both groups, the most frequently used filter size was 0.7 m<sup>2</sup>. However, the proportion of 0.4-m<sup>2</sup> filters was much lower in the citrate group than in the heparin group. Similarly, there was a significant difference in the number of therapies per filter between the two groups ( $p=0.0045$ ), with the number being higher in the citrate group (Table 2).

### Description of therapies

A total of 3442 h of dialysis therapy (citrate group 2248 h heparin group 1194 h) were included in the analysis. The characteristics of the therapies were similar in both groups, except for one significant difference in the distribution of the type of therapy ( $p=0.000$ ) and in the Qb used ( $p=0.0027$ ). For example, there was a higher proportion of CVVH in the citrate anticoagulation group. In both anticoagulant therapy groups the average Qb was 3.45 ml/kg, and the most frequently used Qb was between 100 and 200 ml/min. However, the proportion of Qb at <100 ml/min was much higher in the citrate group than in the heparin group. The patients’ pH was normal, and a tendency towards alkalosis was seen in the citrate group, which suggests accumulation (Table 3).

### Analysis of hemofilter lifetime

In the citrate anticoagulation group there were 56 events (hemofilter removal due to clotting or dysfunction of the circuit evidenced by transmembrane pressures of >280 mmHg). The heparin group presented 63 events. The median duration of hemofilters was significantly higher in the group receiving citrate as anticoagulant than in the group receiving heparin as anticoagulant [72 (95% CI 48–96) vs. 18 (95% CI 12–24) h;  $p < 0.0001$ ] (Fig. 1). A bivariate analysis was performed with the possible confounding variables according to clinical experience, and no statistical relationships between the size of the filter and Qb and the duration of the hemofilter were found (Table 4). Cox’s proportional risk analysis showed that the risk of hemofilter clotting when heparin was used as an anticoagulant is 3.7-fold higher than when citrate was used (hazard ratio 3.70, standard error 0.82; 95% CI 2.39–5.72;  $p < 0.00001$ ).

### Description of complications

#### Bleeding

Among all of the subjects in the study, 15 episodes of severe bleeding occurred, with the frequency of this type of adverse event being similar in both groups ( $p=0.605$ ). At least one risk factor for bleeding was identified in the citrate group (disseminated intravascular coagulation, plasmapheresis,

**Table 1** Description of the population

Variable	Anticoagulant treatment group		p value
	Citrate	Heparin	
Demographic variables			
Total number of patients	17	15	
Female	10 (58.8%)	10 (66.7%)	
Male	7 (41.2%)	5 (33.3%)	0.647
Average weight (kg)	29.14 ± 15.56	33.6 ± 18.07	0.458
Weight (kg)			
<10	1 (5.8%)	1 (6.6%)	
10–20	6 (35.2%)	3 (20%)	
>20	10 (58.8%)	11 (73.3%)	
Average age (years)	8.8 ± 5.25	9.35 ± 4.63	0.777
PICU admissions per patient	Median 1 [0]	1 [0]	0.160
Type of renal failure			
AKI	6 (32.5%)	8 (53.3%)	0.305
CKD-WD	9 (52.9%)	5 (33.3%)	0.265
CKD-PD	2 (11.7%)	2 (13.3%)	0.893
Description of clinical events for admissions			
Total admissions	30	16	
Need of PLP	3 (10%)	1 (6.2%)	0.667
Need of MV	11 (64.7%)	10 (66.6%)	0.094
Need of VS	12 (70.5%)	11 (73.3%)	0.063
Time on MV (days)	6 [12]	12.5 [14]	0.157
Time on VS (days)	6.5 [9]	4 [9]	0.578
Sepsis	19 (63.3%)	13 (81.2%)	0.208
DIC	5 (16.7%)	3 (18.8%)	0.859
Liver disease	4 (13.3%)	4 (25%)	0.320
Other coagulation disorders	1 (3.3%)	0 (0%)	0.460
Hematocrit at admission	28.2 ± 5.5 (range 18.3–39)	29.79 ± 6.54 (range 17.6–41)	0.394
Death	5 (16.7%)	3 (18.8%)	0.859
Length of stay in PICU (days)	8.5 [13]	17.5 [24.5]	0.021

Values in table are presented as a number with/without the percentage in parenthesis, as the average ± standard deviation (SD), or as the median with the interquartile range (IQR) in square brackets, as appropriate

AKI, Acute kidney injury; CKD-WD, chronic renal disease without previous dialysis; CKD-PD, chronic renal failure with previous dialysis; PLP, plasmapheresis; MV, mechanical ventilation; VS, vasoactive support; DIC, disseminated intravascular coagulation; PICU, pediatric intensive care unit

prolonged clotting times and other coagulation defects) in 77.7% of cases, compared with 66.6% for the heparin group. Both groups had a 30% incidence of bleeding episodes which, given the complexity of the patients and the risk factors, we consider to be a reasonable figure (Table 5).

#### Metabolic complications in the citrate group

There were no episodes of hypernatremia. The most frequent complication was metabolic alkalosis (86.6%), followed by hypocalcemia (60%), hypomagnesemia (46.6%) and hypercalcemia (13.3%). Phosphate levels were not recorded (Fig. 2). No association was found between metabolic

complications and the average flow of citrate or the average ratio of total calcium to ionized calcium (T/I Ca<sup>2+</sup>) above or below 2.25. The only association found was between the mean postfilter flow of calcium gluconate and hypomagnesemia, with the former being higher when hypomagnesemia was present ( $p = 0.0028$ ).

#### Discussion

A small number of analytical observational studies have been carried out in the pediatric population that have analyzed the safety of citrate versus heparin as anticoagulant in renal

**Table 2** Description of hemofilters

Hemofilter variables	Anticoagulant treatment group		p value
	Citrate group	Heparin group	
Total number of hemofilters	80	70	
Number of filters per patient	4 [5]	3 [6]	0.66
Number of treatments per filter	2 [1]	1 [1]	0.0045
Filter size (m <sup>2</sup> )			
0.4	3 (3.75%)	14 (20%)	0.007
0.7	41 (51.2%)	29 (41.4%)	
1.2	36 (45%)	27 (38.5%)	

Values in table are presented as the median with the IQR in square brackets or as the number with/without the percentage in parenthesis, as appropriate

replacement therapy. The authors of three studies [25–27] considered citrate to be more effective in preventing clotting of the circuit and prolonging its lifetime, although its use

required greater monitoring of pH and electrolytes, which in turn requires nurses with specialized skills. The major limitation to any definitive drawing of conclusions based on the results of these studies is the low number of patients included.

Studies in adult populations aimed at analyzing the lifetime of hemofilters anticoagulated with citrate versus heparin have produced variable results, with some reporting that citrate is better [4–6] and others failing to demonstrate this outcome [7–9].

In the systematic review by Zhang et al. [10], six randomized controlled trials in adults met the selection criteria. Four of these studies compared regional citrate anticoagulation versus systemic anticoagulation with unfractionated heparin [4–6, 8]. In the other two studies, the control group received regional anticoagulation with unfractionated heparin or systemic anticoagulation with nadroparin [7, 8]. Of the four trials whose control groups received systemic anticoagulation with heparin, three (302 circuits, with 153 in the heparin group and 149 in the citrate group) reported a significantly higher filter

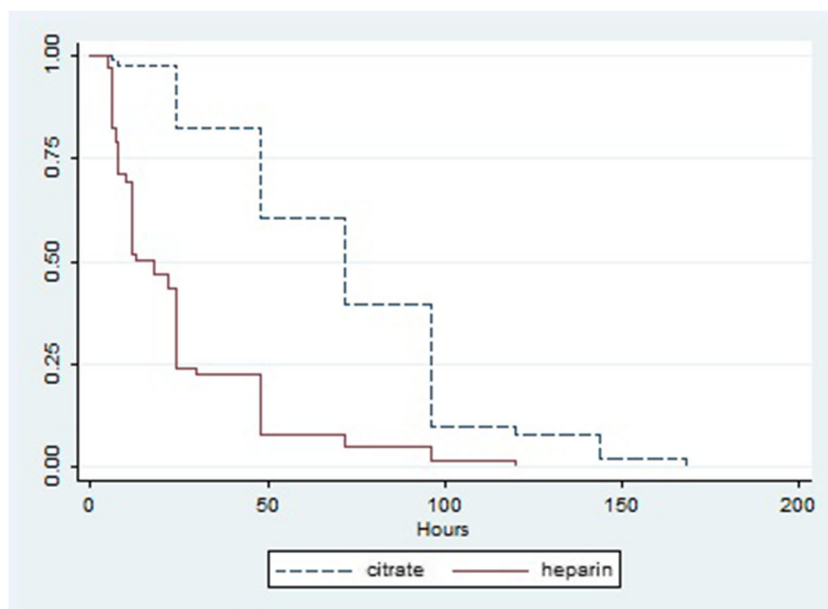
**Table 3** Description of therapies with citrate and heparin as anticoagulants

Variable	Therapies with citrate	Therapies with heparin	p value
Total number of therapies	141	97	
Average number of therapies per patient	8.29 ± 6.52	6.07 ± 4.99	0.291
Therapy time (h) per patient	120 [174]	66 [97]	0.161
Therapy time			
CVVH	33 (23.4%)	4 (4.12%)	0.0000
CVVHD	98 (69.5%)	79 (81.44%)	
CVVHDF	7 (4.96%)	13 (13.4%)	
SCUF	3 (2.13%)	1 (1.03%)	
Qb (ml/min)			
Average Qb	100 [IQR 70] (3.4 ml/kg)	120 [80] (3.5 ml/kg)	0.0027
Qb therapy			
<100	62 (43.97%)	17 (17.53%)	0.000
100–200	73 (51.77%)	74 (76.29%)	
>200	6 (4.26%)	6 (6.19%)	
Qd (ml/h)			
Qd in CVVHD	450 [300]	700 [500]	0.000
Average Qd in CVVHDF	581.4 ± 213	530 ± 269.4	0.669
Q citrate (ml/h)			
Average citrate Q	171.75 ± 72.18	NA	
Q gluconate (ml/h)			
Average gluconate Q	42.63 ± 21.94	NA	
T/I Ca <sup>2+</sup> ratio			
<2.25	10 (33.3%)	NA	
2.25–2.4	11 (36.7%)	NA	
>2.4	9 (30%)	NA	

Values in table are presented as a number with/without the percentage in parenthesis, as the average ± SD, or as the median with the interquartile range (IQR) in square brackets, as appropriate

CVVH, Continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous haemodiafiltration; SCUF, slow continuous ultrafiltration; Q, flow; Qb, pump flow; Qd dialysate flow; NA, not applicable; T, Total calcium; I, Ionized calcium

**Fig. 1** Kaplan–Meier survival function for the entire lifetime of the hemofilters



lifetime in the citrate group compared to the control group [4–6], while the other study (142 circuits) found no difference between the two groups [8]. Despite the heterogeneity of the studies included ( $I^2 = 99\%$ ), overall circuit survival was significantly higher in the citrate group than in the control group, with a mean difference of 23 h (95% CI 0.45–45.61).

In the current study, the total lifetime of the hemofilters was significantly higher in the citrate group than in the heparin group, with a mean difference of 54 h regardless of pump flow and the size of the hemofilter. Taking into account that the descriptive analysis revealed that there was a higher proportion of therapies with a  $Q_b$  of  $<100$  ml/min in the citrate group than in the heparin group (43.9 vs. 17.53%), it can be deduced that the use of citrate prolongs the lifetime of hemofilters despite the use of a lower  $Q_b$ , which is especially important in the pediatric population as these patients often need a low  $Q_b$ .

The available evidence in children is limited. However, compared with other pediatric studies, the lifetime of hemofilters anticoagulated with citrate in our study (72 h, 95% CI 48–96 h) is similar to that reported by Bunchman et al. [2] ( $71.3 \pm 7.2$  h), but higher than that observed by

Elhanan et al. [15] ( $55.6 \pm 22.0$  h), Brophy et al. [20] ( $44.7 \pm 35.9$  h) and Chadha et al. [22] ( $51 \pm 8$  h).

The main problem with heparin is that it causes systemic anticoagulation in addition to circuit regional anticoagulation [2]. In Zhang et al.'s systematic review [10], in a total of 517 patients (citrate group 257, control group 260), 12 and 47 bleeding episodes were reported in the citrate group and the control group, respectively. The calculated relative risk (RR) was 0.28 (95% CI 0.15–0.50), although the definition of bleeding events was not uniform across the studies. The bleeding rate was also significantly lower in the citrate group than in the control group, findings which are similar to those reported in a meta-analysis carried out by Wu et al. [9] (RR 0.34, 95% CI 0.17–0.65) and Yu-jie et al. [28] (odds ratio 0.25, 95% CI 0.12–0.54).

In a study of 18 children on intermittent hemodialysis with a history of bleeding or at high risk for bleeding complications who were receiving regional citrate anticoagulation [23], no patients developed new bleeding events. In contrast, in the control group of 14 children on acute hemodialysis and receiving systemic anticoagulation with heparin, a third of the patients developed new bleeding complications or worsening

**Table 4** Hazard ratio estimates for the duration of the hemofilter

Half-life of hemofilters				
Variables	Hazard ratio	Standard error	<i>p</i> value	95% Confidence interval
Size 0.4 m <sup>2</sup>	1.189176	0.4145021	0.619	0.6005503–2.35474
Size 0.7 m <sup>2</sup>	0.8352619	0.154889	0.332	0.5807348–1.201344
Pump flow $<100$	1.47	0.7578872	0.449	0.5390875–4.03792
Pump flow 100–200	1.883189	0.7924947	0.133	0.8254416–4.29636

**Table 5** Frequency of severe bleeding episodes among all admissions in each group

Variable	Anticoagulant treatment group		p value
	Citrate group	Heparin group	
Severe bleeding event	9/30 (30%)	6/16 (32.6%)	0.605
Type of bleeding event			
Upper gastrointestinal bleeding	1 (11.1%)	3 (26.6%)	0.095
Catheter insertion	3 (33.3%)	0 (0%)	0.114
Intra-abdominal	4 (44.4%)	2 (33.3%)	0.667
Central nervous system	1 (11.1%)	2 (33.3%)	0.292

Values in table are presented as the number with the percentage in parenthesis

of previous bleeding ( $p=0.006$ ). Systemic bleeding was not documented in the study of Elhanan et al. [15], involving 22 children on CRRT and regional citrate anticoagulation.

As opposed to previously reported results, the frequency of episodes of severe bleeding in our study cohort was similar in both groups ( $p=0.605$ ). However, in the citrate group at least one risk factor for bleeding was identified in 77.7% of cases, compared to 66.6 % of cases in the heparin group. In addition, 100% of the bleeding events in the heparin group were systemic (upper gastrointestinal, central nervous system, intra-abdominal bleeding), while in the citrate group local bleeding (high flow catheter insertion site) made up 30% of the events. There was also no significant difference in mortality between the two groups ( $p=0.859$ ) and no deaths attributable to bleeding. On the contrary, the proportion of deaths in this study was lower (25%) than that reported in studies published since 2000, in which the mortality in children with AKI receiving CRRT varies from 32.1 to 58.9 % [29, 30].

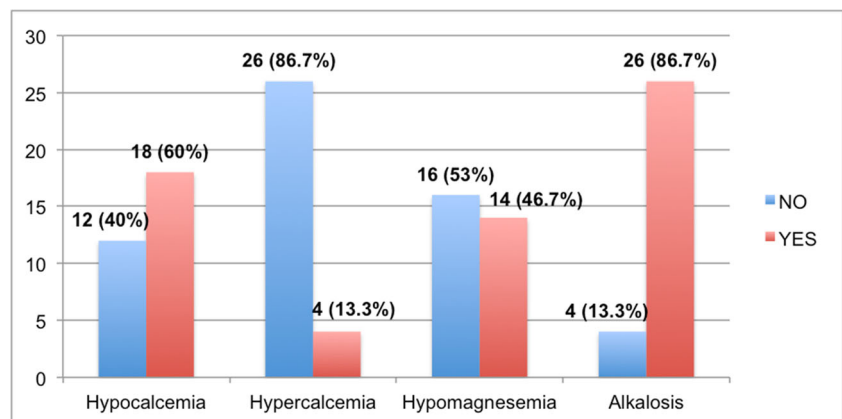
The reported frequency of metabolic complications associated with the use of regional citrate anticoagulation is variable in both adult and pediatric patient population studies. For example, in a study of 209 adults (37 received only citrate, 87 received low-dose heparin + citrate, and 85 received only heparin), metabolic alkalosis was seen in 50% of patients treated with citrate [31]. Zhang et al. [10], in their systematic review, found that metabolic events were reported very

heterogeneously across the studies and, therefore, it was not possible to analyze them. However, in the meta-analysis conducted by Wu et al. [9], there was no significant difference in the incidence of metabolic alkalosis in the citrate group compared to the heparin group (RR 0.92, 95% CI 0.23–3.68), while the overall incidence of hypocalcemia in patients with citrate was higher (4.8 vs. 0.8%) (RR 3.51, 95% CI 1.17–10.60).

In our study we documented no episodes of hypo- or hypernatremia. The most frequent complication was metabolic alkalosis followed by hypocalcemia, hypomagnesemia, and hypercalcemia. No analyses were made in the heparin group because the records were incomplete. Although the frequency of metabolic complications is not negligible, these events were not clinically significant, and only in one case was it necessary to suspend citrate therapy due to severe metabolic alkalosis. This was possibly related to the close monitoring these patients undergo according to institutional protocol, through a determination of acid–base status and pre- and postfilter concentrations of total and ionized calcium, based on which timely adjustments are made to ACD-A and calcium gluconate infusion rates.

The variability in the frequency of electrolyte and acid–base disturbances depends in part on the accuracy with which the protocols are applied [2]. However, two factors have reported in children which are associated with the increased risk

**Fig. 2** Frequency of metabolic complications among total admissions in the citrate anticoagulant group



of citrate toxicity in this patient population. First, it has been determined that the citrate load administered to children is higher than that administered to adults, taking into account that the pediatric dose depends on blood flow (calculated in ml/kg/min) [11]. Second, lower citrate clearance rates have been reported in CRRT, compared to intermittent hemodialysis, and the rates are even lower when this therapy is used in children [32–34]. In adults, clearance rates of 35–50 % have been reported, compared with rates of only 20 % in pediatric patients [22].

The T/I  $\text{Ca}^{2+}$  ratio is proportional to the serum concentration of citrate. It has been established that a ratio of  $>2.25$  suggests an accumulation of citrate and that one of  $>2.4$  is an independent risk factor for 28-day mortality in critically ill patients with AKI on CRRT with citrate as anticoagulant [28]. Although in 66.6 and 30% of admissions the average T/I  $\text{Ca}^{2+}$  ratio was higher than 2.25 and 2.4, respectively, we found no association between the development of some form of metabolic complication and a T/I  $\text{Ca}^{2+}$  ratio that was higher or lower than 2.25 ( $p =$  not significant), and there was no difference in mortality between the citrate and heparin groups ( $p = 0.859$ ). Based on these results, we infer that the population could have other risk factors and/or triggers for complications apart from citrate use.

The main limitation of this study arises from possible data confusion and selection bias, given its retrospective nature. Incomplete data in the medical records made it difficult to evaluate various aspects, such as the association between hematocrit and the lifetime of hemofilters, as well as the frequency of metabolic complications in the heparin group. For this reason, conclusions cannot be drawn from this study regarding the relationship between anticoagulation modalities and the risk of metabolic complications. With the current design, we also could not assess the effect of the T/I  $\text{Ca}^{2+}$  ratio related to medium-term mortality and, due to the low number of bleeding events, it was not possible to establish a statistical association between these and bleeding risk factors unrelated to circuit anticoagulation.

Despite these limitations, the social and theoretical relevance of the study is that, to date, most studies evaluating the efficacy and safety of citrate have been carried out in adult populations and, therefore, the evidence available for the pediatric patient population is limited. Furthermore, this study is among those reporting the greatest number of therapy hours to date in the pediatric population and provides the first local description of the use of this anticoagulation strategy in children.

## Conclusions

Regional citrate anticoagulation could be more effective than heparin systemic anticoagulation in terms of prolonging the

lifetime of the hemofilter. This finding suggests that citrate anticoagulation is an effective strategy for anticoagulation in pediatric CRRT. Further research protocols are needed to assess the safety of using citrate in this population.

## Compliance with ethical standards

**Conflict of interest** The authors declare there exists no conflict of interest.

**Ethics statement** This study was approved by the institutional ethics committee.

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