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ORIGINAL ARTICLE

Regional citrate anticoagulation for pediatric CRRT using integrated citrate software and physiological sodium concentration solutions

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Abstract
Background In continuous renal replacement therapy (CRRT), regional citrate anticoagulation offers an attractive alternative to heparinization, especially for children with a high bleeding risk.
Methods We report on a new management approach to CRRT using integrated citrate software and physiological sodium concentration solutions. Convective filtration was performed with pre-filter citrate anticoagulation using an 18 mmol/L citrate solution and a post-filter replacement fluid. The citrate flow rate was automatically adjusted to the blood flow rate by means of integrated citrate software. Similarly, calcium was automatically infused into children to maintain their blood calcium levels within normal range.
Results Eleven CRRT sessions were performed (330 h) in seven critically ill children aged 3–15 years (extreme values 15–66 kg). Disease categories included sepsis with multiorgan dysfunction (n=2) and hemolytic uremic syndrome (n=5). Median effluent dose was 2.1 (extreme values 1.7–3.3) L/h/1.73 m^2. No session had to be stopped because of metabolic complications. Calcium levels, both in the circuits and in the circulating blood of the children, remained stable and secure.
Conclusions Regional citrate anticoagulation can be used in children with a body weight of >15 kg using integrated citrate software and commercially available solutions with physiological sodium concentrations in a safe, effective and convenient procedure.

Keywords Continuous venovenous hemofiltration · Children · Citrate anticoagulation · Acute kidney injury · Continuous renal replacement therapy · Pediatric intensive care

Introduction

In continuous renal replacement therapy (CRRT), regional citrate anticoagulation offers an attractive alternative to heparinization, especially in patients with a high bleeding risk since they do not have to be anticoagulated [1–4]. In this therapeutic modality, anticoagulation occurs only in the extracorporeal circuit through the infusion of citrate which chelates ionized calcium, resulting in very low calcemia. Blood calcium levels and blood coagulation factors are restored after the hemofilter before returning to the child. Many North American pediatric intensive care units (PICU) have adopted regional citrate anticoagulation [5–9], but this technique has proven difficult to implement in units where the nurse to child ratio is 1 to 2 and where ongoing support from nephrology cannot be considered. Among the difficulties linked to the implementation of this technique are the meticulous adjustment of citrate and calcium perfusions to the blood flow rate, as well as the lack of commercially available physiological fluids and the complexity of various protocols using many different solutes and strategies.

We report here on the implementation of regional citrate anticoagulation in continuous venovenous hemofiltration (CVVH) in a university-affiliated 12-bed PICU using integrated citrate software, commercially available solutions containing physiological sodium concentrations and simplified procedures.

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Materials and methods

Patients

After the arrival of the CRRT machine with integrated software for citrate dosing and calcium management, the medical and nursing teams received training using a new protocol. Children already receiving heparin for other extracorporeal assistance or for mechanical heart valve were not included in the study. Children with a body weight of <10 kg or with liver failure with a prothrombin activity percentage of <40 % were excluded due to an increased risk of citrate accumulation.

Over a 12-month period (December 2011 to December 2012) we treated seven thrombocytopenic or postsurgical children by CRRT with citrate anticoagulation to achieve a regional citrate anticoagulation and thus limit the risk of bleeding. During this period, 828 children (624 aged >28 days) were hospitalized in our unit. A total of ten children were treated with CRRT, but two children were already receiving heparin for other extracorporeal assistance and another one weighed <10 kg.

This study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki. The parents of the participating children provided written consent for publication of the findings.

Continuous renal replacement therapy

We used a commercially available hemofilter with automated procedures (Prismaflex System, Hospal-Gambro, Lund, Sweden; software version 16.0). In this procedure, blood, citrate and calcium pumps are coupled, which means if the blood pump stops, the citrate pump and the calcium infusion also stop. In addition, when integrated citrate software is used, the citrate flow rate is automatically regulated according to the blood flow rate and the selected citrate dose, whereas the infusion rate of calcium is automatically regulated to the blood flow rate, the replacement fluid flow rate and the net negative balance rate.

CRRT was performed with a pre-filter citrate anticoagulation and a post-filter replacement fluid (Fig. 1). To minimize the risk of mistake only two standard solutions with physiological sodium concentrations were employed. Regional citrate anticoagulation was realized with an 18 mmol/L citrate solution [Prismocitrate 18/0 (in mmol/L: citrate, 18; sodium, 140; chloride, 86); Hospal-Gambro]. This convective CVVH was performed using a phosphate-containing post-filter solution (Phoxilium 1.2 mmol/l phosphate, Hospal-Gambro; in mmol/L: calcium, 1.25; magnesium, 0.6; sodium, 140; chloride; 115; hydrogen phosphate, 1.2; hydrogen carbonate; 30; potassium, 4). No continuous diffusion was used, so as not to introduce an additional solution.

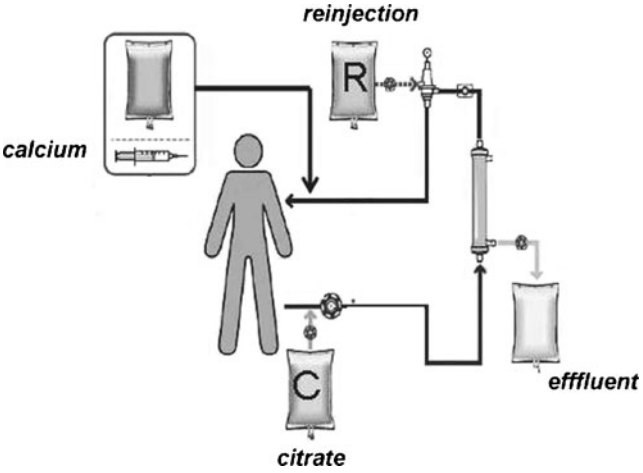

Fig. 1 Schema of the citrate–continuous venovenous hemofiltration (CVVH) setup. Convective CVVH was performed with a pre-filter citrate anticoagulation with a citrate solution (*C*) and a post-filter fluid replacement (*R*). Beyond the filter, calcium was continuously infused in the return line of the hemofiltration catheter to restore the blood ionized calcemia levels to between 0.90 and 1.30 mmol/L. Net negative balance was adjusted according to the patient's clinical state during the treatment

The hemofilter set and catheter were selected according to the child's weight, with a blood volume in the extracorporeal circuit of <10 % of the child's circulatory volume [10]. Hemofilters were primed with 1 L of 0.9 % saline containing 5,000 U of heparin. Children with a body weight of <25 kg underwent CRRT using a Prismaflex ST 60 set (AN-69 filter; 0.6 m^2), whereas a Prismaflex ST 100 set (1 m^2) was used for children weighing >25 kg. Depending on the size of the access catheter, the blood flow rate was 2–4 mL/kg per minute up to a maximum of 150 mL/min.

Firstly, we set the blood flow rate and the citrate dose. Based on these parameters, the software then regulated the citrate flow rate. When an 18 mmol/L citrate solution was used, this citrate flow rate was quite high and resulted in a pre-filter dilution. Secondly, we set a post-filter replacement fluid flow rate equal to the citrate flow rate (giving a pre-filter dilution to post-filter dilution ratio of 1:1). This post-filter replacement fluid flow rate increased the effluent dose and rebalanced blood levels of potassium, magnesium and phosphate. In doing so, these settings provided a dose of effluent of around 2 L/h/1.73 m^2 and a filtration fraction within the filter of around 20 %. Small adjustments were sometimes necessary in subsequent steps when adding a net negative fluid balance rate, and the ratio pre-post dilution could be changed to maintain an efficient dose of effluent with a low filtration fraction. We considered that these parameters provided a good compromise between the risk of thrombosis in the hemofilter and the effectiveness of the CRRT session.

The initial citrate dose was set at 2.2 mmol/L, which could be modified to obtain circuit ionized calcium level of <0.5 mmol/L. The citrate solution was provided by the pre-blood pump line of the Prismaflex machine.

Beyond the filter, calcium was continuously infused on the return line of the hemofiltration catheter to restore the blood calcium levels of the children to within normal range. The software evaluated calcium loss in the effluent depending on the therapy flow rates and the anticoagulation settings. Calcium compensation was defined as the percentage of supplemented calcium solution when compared to calcium loss. The calcium compensation rate was initially set at 100 %. Calcium infusions were performed with 10 % calcium gluconate (223 mmol/L) or with 10 % calcium chloride (456 mmol/L), according to the hemofilter set used (calcium gluconate for filter up to 0.6 m^2). The lowest concentration of calcium (223 mol/L) could deliver small amounts of calcium (especially when low blood flow rates are used) while remaining above the minimum flow rate permitted by the machine (2 mL/h). The highest concentration (456 mmol/L) could deliver greater amounts of calcium without many changes of the syringe. These two forms of calcium are commercially available at these concentrations. However, changing from one concentration to another was not possible after starting the CRRT session for safety reasons.

Net negative fluid balance rate (net ultrafiltration rate) was then adjusted according to the patient's clinical state during the treatment. Children were carefully monitored for hypotension. Monitoring body temperature, preventing hypothermia and timely provision of external heat were carried out [11]. The ionized calcium concentrations were measured, both in the children and in the extracorporeal circuit, 1 h after the start and at each change in settings; otherwise, they were measured every 6 h. Acid–base parameters and electrolytes (ionized calcemia) were measured in the PICU by a blood gas analyzer (GEM Premiere 4,000, Instrumentation Laboratory UK Ltd, Warrington, UK). Other electrolytes (total calcium, magnesium, phosphate) were usually measured every 12 h. As recommended by the manufacturers, the hemofilters were changed routinely after 72 h of treatment.

Complications

Electrolyte disturbances were defined as metabolic alkalosis with a pH of >7.50, hypernatremia with a Na level of ≥150 mmol/L, hypokalemia with a potassium level of ≤3.0 mmol/L, hypophosphatemia with a PO_4 level of ≤0.8 mmol/L, low ionized Ca level with an iCa level of ≤0.90 mmol/L, and a total-to-ionized calcium ratio of >2.5.

Presentation of results and calculations

The results are displayed as the median with the extreme (lowest–highest) values.

The dose of effluent (L/h/1.73 m^2) was calculated as (CFR + RFR + NBR) × 1.73/BSA × 1,000, where CFR is the citrate flow rate (mL/h), RFR post-filter replacement fluid flow rate (mL/h), NBR is the net negative balance rate (mL/h) and BSA is the body surface area (m^2). Filtration fraction (%), which reflects the hematocrit leaving the hemofilter, was calculated as 100 × (RFR + NBR)/(PFR + CFR) where RFR, NBR and CFR are as described above and PFR is the plasmatic flow rate [(1 − hematocrit/100) × blood flow rate (ml/h)]. Filter survival is expressed graphically using the Kaplan–Meier technique.

Results

The characteristics of the children included in the study are given in Table 1. All of these children were critically ill and had acute kidney injury (*Injury* to the kidney, as defined by

Table 1 Characteristics of the pediatric patients[a] enrolled in the study

Patient	Age (years)	Weight (kg)	PIM2 (%)	Disease	Duration of CRRT (days)	Venous access	AST/ALT levels (UI/L)	Prothrombin time (percentage of activity)	Outcome
1	15	45	10.5	Postsurgical septic shock with MODS	4	Jugular, 11Fr	75/193	63	Survived
2	11	66	3.9	HUS with colitis	5	Femoral, 8Fr	291/244	80	Survived
3	13	45	13.0	Septic shock (Group A *Streptococcus*)	4	Jugular, 11Fr	146/62	90	Survived
4	6	20	1.2	HUS with kalemia >6.5 mmol/L	2	Femoral, 8Fr	35//38	76	Survived
5	9	31	2.8	HUS with severe enterocolitis	4	Jugular,11Fr	134/68	45	Survived
6	12	45	1.5	HUS with pancreatitis	4	Jugular, 13.5Fr	127/59	74	Survived
7	3	15	2.8	Atypical HUS	2	Femoral, 8Fr	194/41	62	Survived

PIM2, Revised version of the Pediatric Index of Mortality [28]; MODS, multiple organ dysfunction syndrome; HUS, hemolytic-uremic syndrome; AST aspartate aminotransferase, ALT, alanine aminotransferase

[a] The patient cohort comprised 3 girls and 4 boys

modified RIFLE criteria [12]). All children underwent a course of CRRT as part of the management of their condition.

The median time of therapy was 4 (extreme values 2–5) days. Eleven CRRT sessions were performed for a total of 330 h. Mean blood flow rate was 2.7 (1.8–3.7) mL/kg/min, and median effluent dose was 2.1 (1.7–3.3) L/h/1.73 m^2. Other CRRT settings are reported in Table 2.

Within the first 24 h of CRRT, the median percentages of the decrease in blood urea nitrogen (BUN) and creatininemia were 42.7 % (12–62 %) and 49.4 % (7–64 %), respectively (Table 3). The poor performance described for child 7 resulted from a session which had to be quickly interrupted due to a technical issue (an error message indicating a dysfunction of the calcium line).

The target citrate dose was easy to achieve. The calcium compensation rate was set at 100 % without any changes required, except for three sessions (the first two and at the end of a third one). After the first two sessions, we favored normalizing serum calcium by infusing calcium rather than by changing the calcium compensation setting. These temporary infusions of calcium were performed only four times during the 11 CRRT sessions.

No session had to be stopped because of metabolic complications. Only one transient metabolic alkalosis occurred with spontaneous resolution. No citrate accumulation occurred: the calcium total to ionized calcium ratio remained under 2.5 (Table 3). In order to demonstrate the safety of this procedure the following measurements, performed after the first hour, are given in Table 4: the two extreme values of plasmatic ionized calcemia, total calcemia, natremia, blood pH and phosphatemia. No child had bleeding complications.

The median hemofilter life was 24.0 h (extreme values 7–69; total 330 h). Reasons for discontinuing CRRT were normal scheduling (6/11 sessions, 55 %), catheter dysfunction (2/11 session), catheter clotting (1/11 sessions), alarm handling/technical issues (2/11 sessions). Figure 2 illustrates filter run time.

Discussion

To our knowledge, this report is the first to date that describes the use of automated regional citrate anticoagulation for CRRT in children. To minimize risks, only physiological sodium concentration solutions and simplified procedures were used. Based on our results, we conclude that regional citrate anticoagulation can be used for CRRT in children with a body weight of >15 kg using integrated citrate software, in a safe, effective and convenient procedure.

First, our results demonstrate that regional citrate anticoagulation can be safely used for hemofiltration in children using standardized methods. In system used on our patients, the citrate flow rate was automatically regulated according to the blood flow rate, and the calcium infusion rate was automatically regulated according to the blood flow rate, the replacement fluid flow rate and the net negative balance rate. The stability of the blood calcium levels was ensured both in the circuits and in the circulating blood of the children. Very few changes in settings were necessary.

Citrate infusion can cause side effects, of which the primary one is the citrate accumulation phenomenon where excess citrate binds to free calcium, causing an increase in the ratio of total calcium to ionized calcium to levels of >2.5 mmol/L. Patients with liver failure who cannot metabolize citrate effectively are especially prone to the risk of citrate accumulation [13–15]. Our strategy has been to focus all measures on reducing the risk of citrate accumulation. Therefore, we chose not to use this method of anticoagulation in children weighing <10 kg or with liver failure with a low percentage of prothrombin activity. As an additional measure to reduce the risk of citrate accumulation, we also reduced the amount of citrate

Table 2 Continuous renal replacement therapy settings[a]

Patient	Blood flow rate, mL/min (ml/kg/min)	Citrate dose (mmol/L)	Citrate flow rate[b] (mL/h)	Replacement fluid flow rate (mL/h)	Net negative fluid balance (mL/h)	Effluent dose[c], L/h/1.73 m^2 (mL/kg/h)	Filtration fraction[b] (%)
1	150 (3.3)	2.5 then 2.2	1,250	1,250	150	3.3 (59)	22
2	120 (1.8)	2.2	733	900	100	1.7 (26)	20
3	120 (2.7)	2.2	880	900	0	2.2 (40)	18
4	60 (3.0)	2.2	480	500	0	2.1 (49)	20
5	80 (2.6)	2.2 then 2.3	587	600	50	2.0 (40)	19
6	120 (2.7)	2.2 then 2.4	880	700	80	2.1 (37)	15
7	55 (3.7)	2.2	403	400	20	2.2 (55)	18

[a] Very little change in flow settings were necessary

[c] The citrate flow rate was automatically set by the hemofilter in accordance with the blood flow rate and the citrate dose

[c] The effluent dose and the filtration fraction were calculated as described in the Materials and methods section

Table 3 Biological data (24 h efficiency)

Patient	BUN at H0 (mmol/L)	BUN at H24 (mmol/L)	Percentage of decrease in BUN during first 24 h (%)	Creatininemia at H0 (μM)/L	Creatininemia at H24 (μM)/L	Percentage of decrease in creatininemia during first 24 h (%)	Total/ionized calcium ratio (%)
1	8.5	7.2	15	100	78	22	2.09
2	26.0	17.0	35	647	318	51	2.07
3	31.4	14.3	54	448	217	52	1.95
4	81.4	31.0	62	1358	492	64	2.00
5	31.9	15.7	51	431	218	49	1.89
6	32.1	18.4	43	875	477	45	1.79
7[a]	28.1	24.8	12	244	228	7	1.89

BUN, Blood urea nitrogen; H0, Baseline (before initiation of continuous renal replacement therapy (CRRT); H24, 24 h after initiation of CRRT

[a] For this child, the session was prematurely interrupted and not restarted in this 24-h period

employing two different methods. First, we used low concentrations of citrate (2.2 mmol/L) while setting an ionized calcium level in the circuit (<0.5 mmol/L) of slightly higher than those usually recommended [2]. Morabito et al. successfully used this threshold for treating critically ill cardiac surgery adults with multiple organ dysfunction syndrome (MODS) [15]. Secondly, since the pre-filter citrate flow rate depends on the blood flow rate through an automated control mechanism, we decreased the amount of citrate by lowering the blood flow rate. While sustaining a recommended effluent dose of 2 L/h/1.73 m^2 [16] with the usual hemoconcentration within the filter, we were able to set blood flow rates slightly lower than those regularly reported in other PICU [17].

The only alkalosis episode we observed happened at the beginning of our study when a higher level of citrate concentration was prescribed (2.5 mmol/L). No alkalosis episode occurred when the citrate concentration was 2.2 mmol/L.

Recent publications have reported that regional citrate anticoagulation could be a reasonably safe form of anticoagulation for maintaining the efficiency and patency of the dialyzer in critically ill patients with liver dysfunction [18, 19]. To identify adult patients at risk of citrate accumulation in terms of a total calcium to ionized calcium ratio of ≥2.5, Schultheiss et al. reported that the baseline serum lactate level (threshold ≥3.4 mmol/L) and prothrombin time (threshold ≤26 %) may be useful biomarkers for risk prediction in daily clinical practice [19]. In children, the relevancy of these thresholds remains to be confirmed. With respect to age, even though regional citrate anticoagulation has already been used in newborns without obvious side effects [8], data remain sparse for children with a body weight of <10 kg [6, 9, 20].

In our study, the phosphate-containing post-dilution solution prevented the occurrence of hypophosphatemia. Severe hypophosphatemia can cause generalized muscle weakness, paralysis of the respiratory muscles, myocardial dysfunction and reduced peripheral vascular resistance [21]. Santiago et al. [22] showed that the incidence of hypophosphatemia in children on CRRT is very high and that the addition of phosphate to the replacement solution is safe and reduces the incidence of hypophosphatemia.

Table 4 Biological data (safety) after 1 h of Continuous renal replacement therapy (CRRT)

Patient	Lowest ionized calcemia (mmol/L)	Highest ionized calcemia (mmol/L)	Highest total calcemia (mmol/L)L	Lowest natremia (mmol/L)	Highest natremia (mmol/L)	Lowest blood pH	Highest blood pH	Lowest phosphatemia (mmol/L)
1	0.96	1.17	2.81	140	146	7.13[a]	7.51[a]	1.00
2	1.11	1.22	2.42	131	136	7.31	7.39	1.76
3	1.00	1.16	2.18	132	136	7.29	7.49	0.97
4	0.99	1.04	2.30	131	135	7.31	7.45	2.04
5	1.15	1.21	2.26	132	135	7.29	7.46	1.06
6	1.11	1.18	2.51	135	137	7.35	7.43	1.82
7	0.98	1.08	2.16	133	137	7.33	7.40	2.21

Among all the measures performed after the first hour, the two extreme values of plasmatic ionized calcemia, total calcemia, natremia, blood pH, and phosphatemia are reported here

[a] These values of blood pH were observed in the first 24 h when mechanical ventilation was ongoing

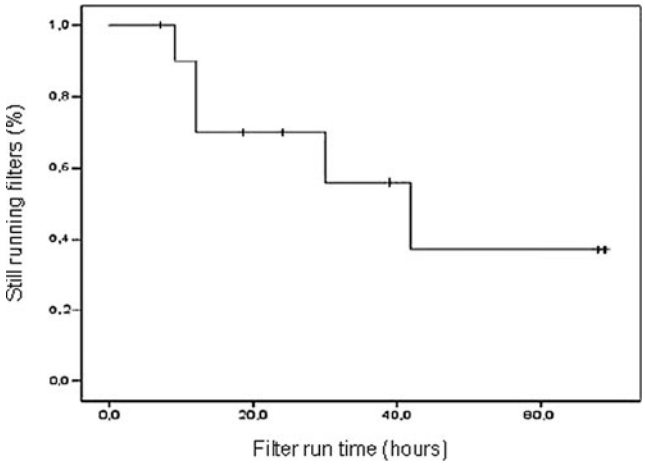

Fig. 2 Continuous renal replacement therapy (CRRT) session ends were indicated by a vertical mark if discontinued for non-CRRT reasons (Scheduled change or intentional stoppage)

Oudemans-van Straaten et al. reported that the implementation of regional anticoagulation with citrate is a worthwhile approach to reduce bleeding risk [2]. No hemorrhagic episode occurred among our patients during these CRRT sessions using regional anticoagulation.

However, the absence of reported incidents does not necessarily predict that this procedure is safe in all cases. In the past, Hanley and Lippman-Hand [23] informed the medical community about the hazards of overinterpreting zero numerator events. They calculated that no occurrence in 300 observations still allows a 95 % chance that the true incidence is as high as approximately 1 %.

Our protocol provided effective plasma purification. The recommended adult effluent dose was routinely about 35 mL/kg/h. To deliver a similar effluent dose irrespective of age, we calculated this dose from the BSA (2 L/h/1.73 m^2) as recommended [4, 14, 24]. If we had calculated the effluent dose in units of milliliters per kilogram per hour rather than in liters per hour per 1.73 m^2, this dose would be too low for the youngest children (for a child weighing 3 kg, the effluent dose would be more than twofold lower).

Although there was no continuous diffusion, plasmatic BUN and creatininemia was halved within 24 h of treatment initiation. Adding a continuous dialysis would have required a third type of solution without calcium and would have complicated the procedure while increasing the risk that the different solutions would be confused by the healthcare providers. Parakininkas et al. reported that post-dilution CVVH and continuous venovenous hemodialysis (CVVHD) can achieve equivalent BUN and creatinine clearances [25].

Finally our protocol is convenient. The commercially available solutions could be used as provided, without any addition of electrolyte. This reduced the workload of nurses and also improved safety by reducing the risk of error.

We observed a low median filter life. Most children had hemolytic-uremic syndrome (HUS), and peritoneal dialysis was the preferred option treatment in these cases as soon as the acute phase of HUS had subsided. Therefore, the median filter life was reduced. Nevertheless, a fairly large percentage of unscheduled stops still persisted (45 %). Two of the unscheduled stops were related to a catheter dysfunction and one was linked to clotting in the return line of the catheter. Contrary to what is recommended by the manufacturer, we preferred to inject calcium in the return line of the hemofiltration catheter—and not in a separate central line—for vein preservation purposes in these children at risk of chronic kidney disease. However, in doing so, the return line was not anticoagulated. Using this same strategy, but in adults, Dorval et al. [26] reported 13 % catheter dysfunction. The two other unscheduled stops occurred after an error message, indicating a dysfunction of the calcium line. It turned out later that the syringes used for the reinjection of calcium had been changed by the manufacturer without any warning notice. Since then, a new version of hemofilter software takes these changes into consideration.

We also chose a low dose of citrate in order to reduce the risk of metabolic complications, which is higher at the start of a regional citrate anticoagulation program. Using the same approach, Gabutti et al. [27] started with a citrate dose of 2.1 mmol/L to treat 17 severely ill adults and reported a median filter life of 24.2 h. In a later study, Monchi et al. [3] reported a median filter life of 70 h using a citrate dose of 4.3 mmol/L. Our main objective was to remove the risk of hemorrhagic complications for the children requiring CRRT, but without increasing the risk of metabolic complications. Higher doses of citrate are probably needed to increase the life of filters, but the overriding concern is that the healthcare team is able to prevent serious metabolic complications linked to the citrate accumulation phenomenon.

Finally, integrated regional citrate anticoagulation software and solutions with physiological sodium concentrations allowed us to safely implement the regional anticoagulation in a pediatric unit where ongoing support from nephrology cannot be considered. The main limitation of this study is the low number of sessions that were performed. Validation of our single-center findings is warranted in a larger prospective, multicenter cohort study with a longer follow-up period. It also remains to be seen if this strategy can be used on children weighing <15 kg. Nevertheless, this strategy allows an efficient reduction of urea and creatinine blood levels, and a negative balance rate up to 150 mL/h. It reduces the risk that children requiring CRRT will experience hemorrhagic complications by way of the regional anticoagulation, which was our main objective. We hope that this report will encourage further work in this field.

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