Regional citrate anticoagulation is safe in intermittent high-flux haemodialysis treatment of children and adolescents with an increased risk of bleeding

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Abstract
Background. Regional citrate anticoagulation (RCA) is strongly recommended for adults with an increased risk of bleeding complications. The objective of this retrospective analysis was to evaluate an RCA protocol concerning feasibility and safety in intermittent high-flux haemodialysis (iHD) treatment in children and adolescents.

Methods. Eighteen children and adolescents aged 5–17 years (median 15 years) underwent 74 iHD treatment sessions with RCA. Twelve of 18 patients presented with overt local or diffuse haemorrhage before beginning the HD sessions, and six had an increased risk of haemorrhagic complications. Forty children on acute haemodialysis with general heparin anticoagulation, matched for bleeding risk, age and body surface area, served as a control group. Citrate flow was adapted to achieve a post-filter ionized calcium of 50.30 mmol/L; calcium substitution was adapted to maintain the patients’ serum calcium levels within the physiological range. Calcium-free dialysis fluid was used. The blood flow rate ranged from 3 to 5 mL per minute and kilogram body weight.

Results. Regional anticoagulation was successfully achieved within the extracorporeal blood circuit, while the coagulation of all 18 patients remained within physiological parameters. No adverse effects of RCA were observed. In all 18 children, neither new haemorrhage nor worsening of the bleeding situation occurred, and in 10/12 patients, bleeding stopped during dialysis with RCA.
In contrast, one-third of the control group developed new hemorrhagic complications or presented with worsening of pre-existing bleeding during haemodialysis (P = 0.006).

**Conclusion.** RCA is feasible, safe and effective in paediatric intermittent haemodialysis treatment.

**Keywords:** ACD-A; acute renal failure; children; citrate dialysis; intermittent haemodialysis treatment.

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**Introduction**

Extracorporeal blood purification techniques are associated with clotting of the extracorporeal circuit; therefore, with the exception of some coagulation disorders, anticoagulation is mandatory [1–3]. The anticoagulant most commonly used is unfractionated heparin [1,4]. Although the introduction of heparin has been one of the major advances in the history of haemodialysis, its side effects can be significant. The most grave of these, bleeding, is reported to occur in up to 50% of the adult population [5–8]. Data on adults as well as children strongly recommend either dialysis without heparin or by regional citrate anticoagulation (RCA) in patients who are actively bleeding, or at risk of bleeding, e.g. within 3 days of a bleeding episode, a surgical or accidental wound, or <2 weeks from cerebral or retinal haemorrhage [4–7,9]. In addition, heparin cannot be used in case of a heparin-induced thrombocytopenia. Citrate decreases the free (ionized) serum calcium by forming chelate complexes [1,2]. Thus, calcium is not available anymore for the activation of tenase and prothrombinase complexes within the coagulation cascade. In this way, sufficient anticoagulation is achieved. This effect is easily reversed by calcium substitution. This provides the means for regional anticoagulation exclusively in the extracorporeal blood circuit.

First described by Morita in 1961 [10], RCA has been used scarcely for more than three decades [11,12]. Within the past decade, RCA has gained more frequent use in adult and paediatric nephrology units throughout the world, especially in continuous renal replacement therapy (CRRT) [13–19]. In North American centres participating in the prospective paediatric continuous renal replacement therapy registry, 56% of CRRT sessions were performed with RCA [19].

Recently, a revival of RCA in intermittent haemodialysis (iHD) has been noticed in the adult population [17,18,20]. Studies on RCA iHD in children, unlike CRRT, are scarce [21]. The objective of this retrospective analysis was to evaluate the feasibility and safety of an RCA protocol for intermittent haemodialysis treatment in children with an increased risk of bleeding.

**Materials and methods**

From 2003 to 2008, 18 children and adolescents (11 male, 7 female) underwent iHD with RCA. Eight patients were dialysed because of acute renal failure, and 10 patients suffered from end-stage kidney disease and were chronic haemodialysis patients. No patients presented a contraindication for RCA. Ages ranged from 5 to 17 years with a median of 15 years. Body surface areas (BSA) ranged from 0.76 to 2.02 m² with a median of 1.43 m². Vascular access was achieved by Cimino fistula in three patients and Splitsith* or Permacht® catheters (Gambro, Plaegg-Martinsried, Germany) in the other patients (size depending on age and weight). All patients received haemodialysis treatment with RCA because they had overt bleeding or were at high risk of bleeding complications, e.g. were within 3 days of a bleeding episode, or a surgical or accidental wound, or <2 weeks after cerebral haemorrhage [4–7,9]. Clinical data are given in Table 1.

As a control group, we compiled the data on 40 paediatric haemodialysis patients from 1999 to 2010 retrospectively who met the same high risk bleeding definition, or who were overtly bleeding but received standard anticoagulation treatment with heparin. Median heparin dosage was 11 (3–70) μg/kg body weight × h. The patients were matched according to age (± 1.0 year), body surface area (± 0.20 m²) and blood flow velocity (± 20 mL/min). Statistically, the groups were not significantly different in age, body surface area and blood flow rate.

We set up an RCA protocol for iHD, adapting the work of Nathall et al. and Mitchell et al. on RCA in continuous veno-venous haemofiltration (CVVH) [2,22]. This protocol was established as standard for RCA at our dialysis units in 2003. Data protocol sheets, the dialysis protocols and the patients’ files were retrospectively reviewed for this analysis.

Pre-conditions for RCA were a body weight of ≥10 kg and a dialysis catheter or fistula with no blood flow instability. The indications for RCA were defined according to Janssen et al. [7]. RCA was not considered in patients with poor hepatic function, considerably reduced muscle mass and/or significantly reduced organ perfusion, due to an impaired citrate metabolism.

The dialysis modalities were as follows: The AK200 (Gambro, Plaegg-Martinsried, Germany) paediatric haemodialysis system was used with polysulphone high-flux dialysers (F/Fl-series, Fresenius, Bad Homburg, Germany). A calcium-free salt concentrate was used to generate the dialysis fluid (SK-F 219-0, Fresenius, Bad Homburg, Germany). Flow rate was 500 mL/min. Blood gas analysis and electrolyte sampling were done prior to iHD. To prevent sodium overload by trisodium citrate solution, the sodium concentration of the dialysis fluid was adjusted to 134 mmol/L. In addition, bicarbonate concentration of the dialysis fluid was reduced to 26–30 mmol/L in order to prevent metabolic alkalosis by citrate metabolism. Blood flow rate was 3–5 mL/body weight × minute corresponding to 70–200 mL/min. In Hannover, ACD-A solution [14] (3% citrate, Baxter Deutschland GmbH, Unterschleissheim, Germany) was used for anticoagulation. In Essen, a 10-fold concentrated solution [22] (30% citrate, local pharmacy) was used, but at one-tenth of the protocol’s ACD-A flow velocity. Thus, the citrate dose administered was identical in both centres. For analysis, the Essen data was converted to match 3% citrate, and all results are given in relation to a 3% citrate solution. The citrate solution was placed on an external IV pump and connected to the former ‘heparin line’ of the dialysis circuit. Calcium gluconate 10% (B. Braun AG, Melsungen, Germany) was placed on an IV pump and connected by a three-way stop cock to the ‘venous’ port of the dialysis catheter or the shunt needle. Calcium infusion was always begun at the beginning of the dialysis session, simultaneously with ACD infusion.

Assuming a plasma citrate concentration of ~6 mmol/L would be necessary for successful anticoagulation [2], we calculated an initial ACD-A (3% citrate) solution infusion rate at 3.3% of the blood flow rate. This calculation can be simplified by the following formula: citrate 3% rate (mL/h) = blood flow rate (mL/min) × 2. ACD solution flow rate was adapted thereafter for post-filter ionized calcium blood levels aiming at ≤0.30 mmol/L. The flow sheets used by the dialysis nurse are shown in Tables 2 and 3. Due to the accessory loss of calcium to the dialysate, a parenteral calcium substitution was necessary. We began with a 10% calcium gluconate solution at a rate of 0.4% of the blood flow rate. The calculation can be simplified by the formula: calcium gluconate 10% rate (mL/h) = blood flow rate (mL/min) / 4. For example, a blood flow rate of 100 mL/min would lead to the calculation as follows: ACD (3% citrate) rate = 0.033 × 100 mL/min = 3.3 mL/min = 198 mL/h [simplified: ACD (3% citrate) rate = 100 × 2 = 200 mL/h]; calcium gluconate (10%) rate = 0.004 × 100 mL/min = 0.4 mL/min = 24 mL/h [simplified: calcium gluconate (10%) rate = 100 / 4 = 25 mL/h].

We monitored dialysis parameters (transmembranous pressure, pressure in the arterial and venous lines), patient haemodynamics (systolic, diastolic and mean blood pressure, heart rate), patient ionized calcium (iCa), potassium, sodium and base excess, post-filter ionized calcium (ABL Radiometer, Radiometer GmbH, Willich, Germany). Additionally, in a subgroup of 14 patients, blood samples were drawn for monitoring citrate metabolization.
activated coagulation time (ACT, ACTester, Quest Medical Inc., Allen, TX, USA) in the systemic and extracorporeal (post-dialyser) circuit. Following the dialysis session, the dialysis nurse examined the extracorporeal circuit for blood clots.

During the first time of the dialysis session, the patient’s systemic blood iCa, sodium and base excess, and the extracorporeal post-filter iCa were monitored at 15-min intervals. These intervals were consecutively prolonged to 30 min and 1h afterwards. As necessary (e.g. unstable parameters), the monitoring intervals were shortened again. The extracorporeal iCa was assessed using the blood sampling port at the post-filter site of the circuit and was targeted at 0.20–0.30 mmol/L [21]. The citrate flow rate was adjusted, as shown in Table 2 to maintain the targeted range. The patients’ blood iCa was either assessed from a pre-existing arterial line (intensive care patients) or using a blood sampling port located proximal to the citrate line at the ‘arterial’ line of the extracorporeal circuit. Calcium gluconate infusion was adjusted to maintain the patient’s systemic blood iCa within the physiological range (1.00–1.30 mmol/L) as shown in Table 3.

Statistical analysis was performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL, USA). Normal distribution was tested by using Kolmogorov–Smirnov test. Normally distributed data are reported as means ± SD. For test significance, the t-test was used for normally distributed data; otherwise, the Mann–Whitney U-test was used. The level of significance was set at a P < 0.05.

Results

We analysed 74 iHD sessions with RCA in 18 patients. Median number of HD sessions with RCA per patient was 3 with a range from 1 to 16. Median duration of one dialysis session was 240 min.
iHD with RCA was well tolerated. Unspecific side effects of dialysis (e.g. nausea, headache, muscle cramps)
were not observed. All patients remained haemodynamically stable during dialysis therapy. Mean arterial pressure was 86 ± 13 mmHg with a slight, but not statistically significant decrease at the end of dialysis.

Twelve of 18 patients presented with overt local or diffuse haemorrhage before HD session commencement. The remaining six had an increased risk of haemorrhagic complications. Eleven of 18 patients had surgery (including biopsy) prior to dialysis.

The mean systemic blood ACT of the patients with RCA was 91 ± 8 s during dialysis therapy, compared to 166 ± 37 s in the control group (P < 0.001). ACT in the in the RCA group was significantly below 120 s (P < 0.001), which is the recommended minimum for ACTester™-based ACT in dialysis patients (Quest Medical Inc., Allen, TX, USA). The consecutive systemic blood ACTs measured during dialysis therapy did not differ significantly from those obtained before treatment.

In all 18 children with RCA, neither new haemorrhage nor worsening of the bleeding situation occurred during dialysis therapy or within 24 h. In 10 of 12 patients with overt bleeding, haemorrhage had stopped during the dialysis procedure with RCA and had considerably improved in the remaining two. None of the six patients with no active bleeding before beginning dialysis with RCA developed haemorrhagic complications. In contrast, 13 of 40 patients (33%) in the control group developed new haemorrhagic complications (P = 0.006). In addition, pre-existing haemorrhage worsened in 7/24 children during the dialysis procedure in the control group (P = 0.047).

The mean extracorporeal, post-filter blood iCa level was 0.26 ± 0.05 mmol/L. The median post-filter ACT measured in the extracorporeal circuit was 186 s, with a range of 121–600 s. Median citrate flow rate to achieve these iCa levels was 3.3% (2.2–5.5%) of the blood flow rate. The intra-individual variation coefficient of the citrate flow/blood flow ratio was 0.11; the inter-individual variation coefficient was 0.08. The initial target of post-filter iCa was met in 68/73 dialysis sessions (93%).

In 17/18 patients, the extracorporeal circuits were free of relevant blood clots. In one patient, a relevant clot formation was found in both bubble catchers. The iCa within the extracorporeal circuit was found to be correctly targeted (<0.30 mmol/L anytime controlled). Unfortunately, the patient did not belong to the subgroup with ACT monitoring.

All patients received intravenous calcium substitution. Thereby, the patients’ mean ionized serum calcium levels were maintained at 1.18 ± 0.08 mmol/L throughout the HD session. Ionized calcium was below 1.00 mmol/L (minimum 0.84 mmol/L) in 5 of 563 measurements (<1%). There was no statistically significant difference between ionized calcium levels prior to a dialysis session and at its end. The median flow rate of calcium gluconate 10% was 0.44% of the blood flow rate with a range of 0–0.67% showing huge inter-individual differences. The calcium infusion rate in relationship to the ACD-A infusion rate ranged from 0% to 30% providing 0.12–0.38 mmol of calcium per 1 mmol of citrate infused. We calculated a mean calcium requirement of 5.7 ± 2.5 mmol/m² BSA × h (range 0.6–14.8 mmol/m² BSA × h).

Serum sodium levels remained within the physiological range during RCA. Mean systemic sodium levels were 139 ± 4 mmol/L. A comparison of sodium levels before and after dialysis did not show any statistically significant differences. Mean systemic bicarbonate levels were 24.5 ± 4 mmol/L. A comparison of sodium levels before and after the RCA session. Neither severe acidosis nor severe alkalois occurred while on RCA iHD or in the following 24 h.

No adverse event was experienced, including hypercalcaemia or hypercalcaemia, hypomagnesaemia, severe alkalosis or acidosis, citrate intoxication or hypernatraemia. Also, no other serious adverse event was observed. None of the extracorporeal circuits clotted severely, except for one of the 74 extracorporeal circuit clot formation, as mentioned above. These blood clots did not cause any harm, but we have not been able to elucidate on the cause.

**Discussion**

Intermittent haemodialysis as a standard procedure of extracorporeal blood purification in adults has also been used in haemodynamically stable children and adolescents for three decades [23–25]. In recent years, citrate anticoagulation was more frequently used in paediatric CRRT [4,13,19]. To the best of our knowledge, data on the safety and feasibility of RCA in paediatric intermittent haemodialysis are missing.

After setting up a protocol for RCA in iHD treatment, we assessed its feasibility and adequacy in 18 children with overt bleeding or at high-risk for haemorrhagic complications. RCA iHD did not affect haemodynamic stability. It was administered without any technical problems. RCA was well tolerated; adverse reactions were not ob-
served. The bleeding improved in all patients with overt haemorrhage; no new haemorrhagic complications occurred during RCA dialysis therapy and for the following 24 h. In contrast, bleeding complications were frequent in the high-risk control group with standard heparinization (>30%) and similar to the findings of van de Wetering et al. [5] and of our workgroup [26].

In all but one patient, no relevant clot formation was found in the extracorporeal circuit. Gubensek et al. used a visual pseudo-quantitative clotting score [17] and found almost no signs of clotting in both bubble catchers and the dialyser. This is comparable to our findings.

Most data published on monitoring of anticoagulation refers to post-filter blood ionized calcium levels. The targeted iCa varied between 0.25 and 0.50 mmol/L [2,14–18,27,28]. In our dialysis circuits, a median post-filter iCa of 0.26 mmol/L was associated with a median ACT of 186 s. Both results matched the standards referred to previously. Recently, our workgroup showed that post-filter iCa levels should be targeted below 0.30 mmol/L to provide adequate anticoagulation in high-flux HD with RCA [21].

All extracorporeal post-filter ACTs measured in a subgroup of our patients exceeded 120 s which is the recommended minimum target for dialysis patients (Quest Medical Inc., Allen, TX, USA).

Elhanan et al. [16] used a citrate protocol in children with CRRT, based on animal research [2]. Citrate flow at start of CRRT was calculated using blood flow and replacement flow rates. This resulted in an ACD-A flow rate (millilitre per hour) of the 1.5–2-fold of the blood flow rate (millilitre per minute) [equivalent to 2.5–3.3% of the blood flow rate (millilitre per hour)] [16]. Bunchman et al. started the ACD-A infusion rate at 2.5% of the blood flow rate [13,14]. Chadha et al. used a starting ACD-A rate of 1.6–3.7% of the blood flow rate in children [15]. We regularly started with an ACD-A flow of 3.3% of blood flow, and in our CRRT patients (not reported here), it was lower, too. The median ACD-A flow during dialysis also was 3.3% (range 2.2–5.5%) of the blood flow. Most publications report only minor changes of the ACD-A infusion rate [12–17]. In high-flux iHD in adults, citrate clearance proved to be higher than in CRRT [20], with a ratio of citrate removed with dialysate of 83% versus 20–30% [15,16]. Therefore, our protocol would seem to make sense because more citrate may be needed for high-flux iHD than for CRRT. The variation coefficients of the citrate flow/blood flow ratio in our 18 patients were rather low. There is no comparable published data on children and adolescents.

The calcium substitution maintained the serum calcium of all of our patients within normal range while on dialysis. We found considerable differences between individual patients and dialysis sessions of a single patient concerning the need for calcium reflected by the wide range of 0.6–14.8 mmol/m² BSA × h. Alterations of calcium homeostasis and bone metabolism have been described after extended use of RCA in CRRT [29]. Chadha et al. report of 1/5 children with hypercalcaemia while on CRRT with RCA [15]. In contrast, like us, Bunchman et al. and Elhanan et al. did not experience alterations in the patients’ calcium homeostasis when treated with RCA [14,16]. We gave between 0.12 and 0.38 mmol of calcium per 1 mmol of citrate infused into the extracorporeal circuit. This finding in iHD matches very well the data of Chadha et al. who infused 0.16–0.32 mmol/mm in children on CRRT [15]. This setting is comparable because they have applied also in CRRT, like us in iHD, a dialysis fluid free from calcium. On the whole, details concerning the amount of calcium actually used in paediatric RCA are scarce in the literature. In contrast to the findings of Schneider et al. in adult iHD with RCA, we found no statistically significant changes in pre- and post-dialysis iCa levels of the patients.

In the paediatric literature on CRRT with RCA, no new bleeding complications occurred during the dialysis procedure with RCA [13–16]. Chadha et al. reported that overt bleeding stopped in two patients while on CRRT with RCA [15]. However, the majority of publications do not comment on overt haemorrhage. In the adult literature, bleeding while using RCA is found occasionally [30]. Normally, this is associated with critical illness, sepsis and other coagulation disturbances, and poor hepatic function [29,30]. About two-thirds of our patients presented with overt bleeding at start of dialysis sessions. In nearly 90% of them, bleeding stopped while on dialysis with RCA; in the remainder, bleeding improved significantly. Beyond this, we did not observe any events of new haemorrhage during or after treatment.

In the past, citrate accumulation and intoxication were experienced in association with massive blood transfusions [31–33] and in autologous peripheral blood progenitor cell harvesting [34]. Accordingly, common side effects of RCA are alterations of the calcium homeostasis and metabolic alkalosis [2,10–18,20,29–34]. Six of 34 patients reported by Mehta had to be treated with diluted intravenous hydrochloric acid due to severe or prolonged alkalosis [12]. Magnesium depletion was rarely seen [33]. In patients with poor hepatic function and/or severely reduced muscle mass, citrate accumulates leading primarily to acidosis and hypocalcaemia. Cardiac depression has been reported as an adverse reaction to massive citrate buffered blood transfusions, to citrate infusion in healthy test persons with citrate serum levels exceeding 1.6 mmol/L [31,35], and in one case, related to RCA [36]. Calculating the total/ionized calcium ratio published by Bakker et al. [37] seems to be a useful tool in detecting pre-clinic signs of citrate intoxication.

Citric acid/sodium citrate (trisodium citrate) solutions, such as ACD-A solution from Baxter or the more concentrated solution from Essen [22], both used by us for RCA, delivered a relevant sodium load to the patient. This may result in hypernatraemia. By means of reducing sodium and bicarbonate concentration in dialysis fluid below standard, we experienced neither alkalosis nor hypernatraemia in our patients on iHD. All our patients remained haemodynamically stable while on dialysis. Cardiac depression was not seen. A thorough monitoring and adaptation of the prescription prohibit diverse side effects.

We are well aware that our study is limited due to the comparatively small number of patients and to the retrospective nature. However, our data may serve as the basis for a prospective multi-centre trial, which will be necessary to establish guidelines for paediatric RCA in blood purification therapy.
Conclusion

According to our experience, RCA is feasible, safe and effective in paediatric intermittent haemodialysis. The hemorrhagic situation in patients with overt bleeding can even be improved while on HD with RCA. Furthermore, there may be no danger of new bleeding while on HD treatment. Reduction of the sodium and bicarbonate content of the dialysis fluid is recommended, and the patients should be closely monitored for electrolyte and acid–base disturbances.

Conflict of interest statement. None declared.

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