A safe citrate anticoagulation protocol with variable treatment efficacy and excellent control of the acid–base status*

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Objective: **Citrate anticoagulation is an excellent alternative to heparin anticoagulation for critically ill patients requiring continuous renal replacement therapy. In this article, we provide a safe and an easy-to-handle citrate anticoagulation protocol with variable treatment doses and excellent control of the acid–base status.**

Design: **Prospective observational study.**

Setting: **University hospital.**

Patients: **One hundred sixty-two patients with acute renal failure requiring renal replacement therapy were enrolled in the study.**

Intervention: **A continuous venovenous hemodialysis-based citrate anticoagulation protocol using a 4% trisodium solution, a specially designed dialysate fluid, and a continuous calcium infusion were used. The study period was 6 days. Hemofilters were changed routinely after 72 hours of treatment. The patients were grouped according to body weight, with patients below 60 kg body weight in group 1, patients with at least 60 kg and up to 90 kg body weight in group 2, and patients with a body weight of above 90 kg in group 3. Dialysate flow was adapted according to body size and matched approximately 2 L/hr for a patient with average body size. Blood flow, citrate flow, and calcium flow were adjusted according to the dialysate flow used.**

Measurements and Main Results: **Median filter run time was 61.5 hours (interquartile range: 34.5–81.1 hours). Only 5% of all hemofilters had to be changed because of clotting. The prescribed treatment dose was achieved in all patients. Acid–base and electrolyte control were excellent in all groups. In the rare cases of metabolic disarrangement during citrate anticoagulation, acid–base values were rapidly corrected by modifying either the dialysate flow or alternatively the blood flow rate. Eight patients (5%) developed signs of citrate accumulation indicated by an increase of the total calcium >3 mmol/L or a need for high calcium substitution.**

Conclusions: **We provide a safe and an easy-to-handle citrate anticoagulation protocol that allows an excellent acid–base and electrolyte control in critically ill patients with acute renal failure. The protocol can be adapted to patients' need, allowing a wide spectrum of treatment doses. (Crit Care Med 2009; 37:2018–2024)**

KEY WORDS: continuous venovenous hemodialysis; regional anticoagulation with citrate; hemofilter lifetime; treatment dose; acid–base control; hypercalcemia

Continuous renal replacement therapy (CRRT) is established for the treatment of acute renal failure. However, anticoagulation is difficult in CRRT and can rarely be avoided. All systemic anticoagulants also increase the bleeding risk; therefore, regional anticoagulation is advocated, which is most often based on the chelating properties of citrate for calcium ions (1).

Citrate anticoagulation has already been suggested in 1983 for the hemodialysis of patients with acute renal failure but was not widely accepted due to the occurrence of severe side effects including alkalosis (2) and severe hypocalcemia. The development of metabolic alkalosis results from the metabolic conversion of citrate to bicarbonate. To our knowledge, the first routine implementation of citrate anticoagulation in this patient group has been reported in the early 1990s by Mehta et al (3–5). The use of an alkali-free dialysis fluid by Mehta and Ward alone was at the applied, fixed dose of 1000 mL/hr apparently not sufficient to correct for the indirect buffer base infusion with the citrate. By adding the infusion of isotonic saline in predilution and, thus, the removal of buffer bases by the corresponding filtrate volume, the issues with alkalosis were controlled.

We have previously shown that increasing the dialysate flow and, thereby, the diffusive removal of buffer bases, mostly bicarbonate and citrate, from the patients' blood can be used to compensate the tendency toward alkalosis (6). Drawbacks with that protocol were that we were not able to realize widely accepted dose standards of about 2 L/hr CRRT dose and to adapt the realized CRRT dose to the body weight of the patient (7). To avoid higher blood flows and the associated higher citrate infusion requirements, this required the addition of a buffer base to the dialysis fluid (8). Accordingly, we now use a dialysate with 20 mmol/L bicarbonate for citrate-based continuous venovenous hemodialysis (CVVHD).

The aim of this clinical study is to show that our protocol can easily, and with a high flexibility, be adapted to the desired CRRT dose. For this, we prospectively separated the patients by their body weight into a small, medium, and large group and

*See also p. 2128.

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Supported, in part, by a financial grant from Fresenius Medical Care, Bad Homburg, Germany.

Dr. Morgera has received grant support from the Department of Nephrology as well as honoraria. Professor Neumayer has received honoraria and grant support from Fresenius. The remaining authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3181a00a92

treated each group at an appropriate but different dose level.

MATERIALS AND METHODS

The protocol was approved by the ethics committee of the Charité. Between August 2004 and December 2006, 162 consecutive patients had been included in this clinical study at the Charité Berlin Campus Mitte. All the patients fulfilled the inclusion criteria: written informed consent, age at least 18 years, and acute renal failure clinically requiring CRRT. The diagnosis of acute renal failure was based on clinical and laboratory grounds and is in accordance with the recommendation made by the Acute Dialysis Quality Initiative (www.adqi.net). The Acute Dialysis Quality Initiative classification of acute renal failure is divided into three levels (risk, injury, and failure) based on either glomerular filtration rate or urine output criterion, whichever is more severe. All patients included into this study reached the failure level. Pregnant patients and patients participating in another clinical study were not included. Treatment was not started in one patient (due to nonavailability of a vascular access and death of the patient before insertion of a double-lumen central venous catheter). Thus, data of 161 patients were available for analysis.

The study lasted in each patient up to 6 days. The duration was shorter, when CRRT was no longer clinically needed. Filters were changed routinely after 72 hours of treatment. To avoid filter changes during periods of limited staff availability, a tolerance of ±12 hours was allowed.

For practical reasons, the patients were categorized by body weight into three groups and each group was treated at a matching efficacy level. As the predilution by the infusion of the 4% citrate solution is minimal and as at least for small molecules like urea and creatinine a complete saturation of the effluent can be expected, we used the effluent flow as a surrogate for treatment efficacy. This is in line with other studies using the effluent flow as a surrogate for the applied treatment intensity (9). The dose adaptation was done approximately proportional to the body surface. This scaling method is based on the fact that metabolic processes, including the generation of renally excreted waste products, have empirically been found to scale clearly better proportional to body surface area compared with body weight (10). Compared with scaling, the dose proportional to body weight, this results in a smaller dose decrease for small patients and a smaller dose increase for larger patients. Of note, scaling the treatment dose proportional to body surface area is commonly used in pediatric nephrology, i.e., for very small patients (11, 12). Using the empirical formula $0.1173\ m^2 \times \text{body weight}^{0.6466}$ (13) for the relation between body weight and body surface area, the recommended effluent flow of 2000 mL/hr for an average 70 kg patient (7) corresponds to a required effluent flow of 2350 mL/hr for a 90-kg patient [$2000\ mL/hr \times (90\ kg/70\ kg)^{0.6466}$]. The prescription for group 2 sums already up to 2220 mL/hr, with the effluent flow resulting from fluid removal not yet included but clinically known to fill the remaining gap. Thus, the prescription made for group 2 is adequate for patients up to 90 kg. Analogously, the prescription made for group 1 is adequate for patients up to 60 kg. Thus, patients below 60 kg body weight were included in group 1, patients with at least 60 kg and up to 90 kg body weight in group 2, and patients with a body weight of above 90 kg in group 3. CVVHD with citrate anticoagulation was started at predefined treatment settings in each group (compare Table 1 and Figure 1) and adjusted as clinically required. The dialysate used in this study was developed recently in our unit (8) and is now commercially available (Ci-Ca Dialysate K2, Fresenius Medical Care, Bad Homburg, Germany). The composition is as follows: potassium 2 mmol/L, sodium 133 mmol/L, chloride 116.5 mmol/L, magnesium 0.75 mmol/L, bicarbonate 20 mmol/L, zero calcium, and glucose 1 g/L. The infusion of the 4% trisodium citrate solution (136 mmol/L citrate; Fresenius Kabi Bad Homburg, Germany) was adjusted in steps of 5 mL/hr depending on the postfilter ionized calcium with the goal to have the latter in the range 0.25–0.35 mmol/L. The infusion of pharmacy-prepared calcium chloride solution (91 mmol/L calcium [8]) was similarly adjusted in steps of 5 mL/hr according to the systemic ionized calcium concentration to keep this parameter in the normal range. Figure 1 gives an overview of the setup of our CVVHD system.

The fine tuning of the acid–base status was mostly done by changing the dialysis fluid flow, where changes of 20% of the dialysis fluid flow have been found to be usually appropriate as was the case with our previous protocol (8). Alternatively, the dialysis fluid flow could be kept constant and the effect on the acid–base status be modified by increasing the citrate infusion whereby the parallel in-

Table 1. Distribution of the 161 included patients in the three groups and predefined starting values for blood, dialysate, citrate solution, and calcium solution flows; the net fluid removal was prescribed as clinically required

	Group 1 (Below 60 kg Body Weight)	Group 2 (Between 60 and 90 kg Body Weight)	Group 3 (Above 90 kg Body Weight)
Number of patients included	19	97	45
Predefined starting values			
Blood flow (mL/min)	80	100	120
Dialysate flow (mL/hr)	1500	2000	2500
Citrate solution flow (mL/hr; 4% sodium citrate, containing 136 mmol/L citrate ions)	140	170	205
Calcium solution flow (mL/hr; 91 mmol/L calcium ions)	38	50	65

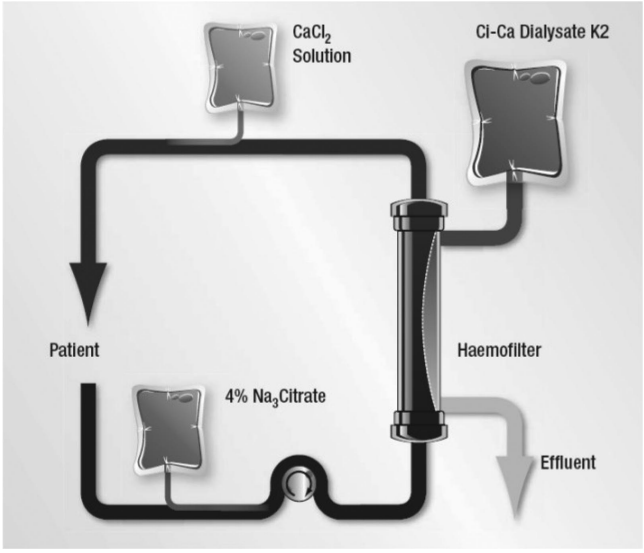

Figure 1. Sketch of the citrate-continuous venovenous hemodialysis setup.

Table 2. Number of patients, baseline acid–base status, baseline renal function, and etiology in each of the three groups and in all patients

	All	Group 1	Group 2	Group 3	*p*
n	161	19	97	45	—
Male	104 (65%)	4 (21%)	66 (68%)	34 (76%)	—
Age (yrs)	69.8 (61.3–76.2)	75.1 (64.8–79.3)	71.1 (62.1–76.4)	66.3 (59.9–72.3)	0.046
Weight (kg)	80.0 (65.0–95.0)	55.0 (52.0–56.0)	75.0 (68.0–82.0)	100.0 (100.0–110.0)	<0.001
Acute Physiology and Chronic Health Evaluation II	28 (23–35)	27 (21–30)	29 (22–35)	28 (24–35)	0.52
Acid–base status at baseline					
pH	7.36 (7.30–7.41)	7.35 (7.31–7.41)	7.37 (7.31–7.42)	7.33 (7.23–7.37)	0.006
Base excess (mmol/L)	−2.7 (−6.1 to 0.7)	−2.7 (−3.9 to 0.0)	−1.1 (−4.6 to 1.8)	−4.6 (−8.7 to −2.3)	0.001
Bicarbonate (mmol/L)	22.0 (19.3–25.0)	22.2 (20.3–24.1)	23.0 (20.0–25.7)	19.7 (17.4–22.3)	0.002
Lactate (mg/dL)	16 (11–40)	15 (13–21)	16 (10–34)	22 (11–77)	0.34
Renal function at baseline (mg/dL)					
Urea	93 (62–141)	66 (56–85)	96 (70–141)	109 (65–155)	0.01
Creatinine	2.4 (1.6–3.4)	1.9 (1.2–2.9)	2.2 (1.6–3.4)	2.9 (2.0–3.8)	0.073
Hepatic function at baseline					
Bilirubin (mg/dL)	1.0 (0.6–1.9)	0.7 (0.6–1.0)	1.3 (0.6–1.9)	0.7 (0.6–1.3)	0.29
Patients with bilirubin ≥1.5 and <5 mg/dL (n)	19	1	16	2	—
Patients with bilirubin ≥5 mg/dL (n)	6	1	4	1	—
Etiology of the acute renal failure					
Cardiovascular failure					
Septic	21 (13%)	2 (11%)	14 (15%)	5 (12%)	—
Postsurgical	66 (42%)	10 (53%)	37 (39%)	19 (44%)	—
Internistic	31 (20%)	2 (11%)	20 (21%)	9 (21%)	—
Not specified in detail	3 (2%)	0 (0%)	2 (2%)	1 (2%)	—
Prerenal	21 (13%)	1 (5%)	13 (14%)	7 (16%)	—
Postrenal	4 (3%)	0 (0%)	3 (3%)	1 (23%)	—
Not specified	10 (6%)	4 (21%)	5 (5%)	1 (23%)	—

Due to rounding, the sum of the individual percentages of the different etiologies is not exactly 100%, continuous data are given as median (interquartile range); indicated *p* values were determined by the Kruskal-Wallis test, significance indicates group differences.

crease of the blood flow keeps the regional anticoagulation unchanged.

The treatment was performed using the multiFiltrate (Fresenius Medical Care, Bad Homburg, Germany) in combination with two external infusion pumps for citrate and calcium infusion. At the end of the study period, the multiFiltrate Ci-Ca with integrated citrate and calcium pumps was also used. All treatments were done with the AV600S hemofilter, a 1.4 m^2 high-flux polysulfone dialyzer.

On a six hourly basis, we documented results of blood gas analyses (for acid–base status and systemic ionized calcium, sodium, potassium, and lactate) and values of the postfilter ionized calcium. As clinically required, we assessed bilirubin, total calcium, total magnesium, and phosphate concentrations as well as blood cell counts on a daily basis.

Statistical Analysis. We tested, whether adequate control on the acid–base status can be achieved in the complete study population and whether there are differences among the three groups. The base excess (BE) after about 24-hour treatment was chosen for the confirmative analysis; specifically for each patient the value measured closest to 24 hours after start of treatment, where only values between 22 and 30 hours after treatment start were accepted. The predefined analysis contained two steps. In the first step of the confirmative analysis, the median of the BE was tested to be in the range of ±3 mmol/L. It was prespecified to accept this, if the respective 95% confidence interval is completely within the mentioned interval. As a second step of the confirmative analysis, the Kruskal-Wallis test was used to search for group differences.

In addition to these confirmative statistical analyses, we performed a descriptive analysis of the data. When not specified otherwise, continuous data are reported as median (interquartile range). For visualization of time-dependent data, we linearly interpolated data between two subsequent measurements. As the variability over time of the flows, flow ratios, and corresponding laboratory parameters was low, we compared these parameters statistically among groups by using the median documented value per patient. The Kruskal-Wallis test was used to identify differences among the three studied groups. The Wilcoxon's signed rank test was used to compare baseline data with the last documented value. For all statistical tests, a significance level of 5% was used.

RESULTS

Patients Characteristics. Table 2 shows the patients' characteristics in the three groups. As expected, the body weight differs significantly among groups. There is also a difference in the gender distribution of the groups, which is expected as gender and body weight are typically linked.

Efficacy of the CRRT Protocol. Concerning efficacy of the treatment, the effluent flows applied in the three groups are significantly different (compare Table 3), as to be expected from our protocol. A comparison of the creatinine concentrations measured in the three groups by analysis of variance does not reach significance.

Table 4 shows a comparison for several parameters between baseline and the final value measured during the study period. Most of the significant changes are expected consequences of the CVVHD treatment: the lowering of urea, creatinine, and potassium concentrations, and the improvement in the acid–base status.

Acid–Base Status—Confirmative Analysis. Favorable results were found for the confirmative analysis regarding acid–base control after 24 hours of citrate anticoagulation. In the overall group, BE was well controlled with a median of −0.4 (−2.7–1.5) mmol/L at 24 hours. The 95% confidence interval of the median is −1.1 to 0.6 mmol/L, that is, completely within the prespecified range of ±3 mmol/L. A comparison of the

Table 3. Median and interquartile range for four pairs of treatment parameter and laboratory value assessing the corresponding effect and the respective change to baseline where appropriate

	Group 1		Group 2		Group 3		
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	*p*
Regional anticoagulation (mmol/L)							
Citrate dose	3.97	3.53–4.02	3.85	3.74–3.97	3.87	3.74–3.97	0.88
Postfilter ionized calcium	0.275	0.261–0.310	0.282	0.269–0.300	0.292	0.266–0.310	0.71
Calcium homoeostasis (mmol/L)							
Calcium dose	1.75	1.61–2.00	1.72	1.61–1.91	1.88	1.64–2.05	0.16
Systemic ionized calcium	1.157	1.114–1.173	1.159	1.134–1.181	1.166	1.133–1.195	0.22
Change of systemic ionized calcium vs. baseline	−0.036	−0.068 to 0.022	0.026	−0.053 to 0.075	0.044	−0.040 to 0.109	0.28
Acid–base status							
Dialysate-to-blood-flow ratio (%)	31.3	25.0–31.3	33.3	30.0–33.3	33.3	30.0–34.7	0.008
Base excess (mmol/L)	0.90	−1.40 to 2.10	0.60	−1.40–2.30	−1.25	−3.25 to 0.85	0.035
Change of base excess vs. baseline (mmol/L)	2.90	−2.20 to 4.90	1.60	−1.70 to 5.70	3.20	0.10–5.67	0.32
Continuous renal replacement therapy efficacy							
Effluent flow (mL/hr)	1800	1734–1863	2259	1945–2327	2613	2335–2779	<0.001
Creatinine (mg/dL)	1.40	1.10–2.05	1.70	1.40–2.20	2.30	1.80–2.60	0.003
Change of creatinine vs. baseline (mg/dL)	−0.43	−0.74 to −0.10	−0.45	−1.45 to −0.05	−0.45	−1.52 to 0.00	0.89

p value is determined by Kruskal-Wallis test is given, significance indicates a difference among the three investigated groups.

Table 4. Comparison of laboratory and clinical parameters at baseline with the final value recorded during the study period, median (interquartile range) values, and Wilcoxon's signed rank test has been used for statistical comparison

	Baseline	End	*p*
pH	7.36 (7.30–7.41)	7.41 (7.35–7.46)	<0.00001
Base excess (mmol/L)	−2.7 (−6.1 to 0.7)	1.2 (−2.2 to 2.8)	<0.00001
Bicarbonate (mmol/L)	22.0 (19.3–25.0)	24.7 (22.1–26.9)	<0.00001
P_{CO_2} (mm Hg)	41 (35–46)	39 (34–44)	0.104
P_{O_2} (mm Hg)	106 (85–130)	98 (78–122)	0.027
Lactate (mg/dL)	16 (11–40)	12 (9–19)	<0.0001
Sodium (mmol/L)	139 (136–145)	140 (138–143)	0.046
Potassium (mmol/L)	4.7 (4.4–5.3)	4.4 (4.1–4.8)	<0.00001
Systemic ionized calcium (mmol/L)	1.13 (1.06–1.19)	1.15 (1.11–1.20)	0.061
Total calcium (mmol/L)	2.1 (1.8–2.2)	2.2 (2.1–2.4)	<0.01
Total magnesium (mmol/L)	0.9 (0.8–1.1)	0.8 (0.8–0.9)	<0.0001
Phosphate (mmol/L)	1.52 (1.12–1.87)	0.92 (0.64–1.32)	<0.001
Urea (mg/dL)	93 (62–141)	54 (41–74)	<0.00001
Creatinine (mg/dL)	2.4 (1.6–3.4)	1.5 (1.1–2.0)	<0.00001
Hematocrit (%)	30 (28–34)	31 (29–33)	0.802
Leukocytes (g/L)	14.4 (10.8–18.7)	14.7 (10.3–19.6)	0.850
Platelet count (g/L)	142 (85–199)	89 (53–160)	<0.00001
Activated partial thromboplastin time (s)	50 (42–62)	46 (41–56)	<0.01
Quick (%)	61 (32–92)	71 (35–95)	<0.00001
Total bilirubin (mg/dL)	1.0 (0.6–1.9)	1.1 (0.6–2.6)	0.748
Albumin (g/dL)	2.3 (1.8–2.6)	2.2 (1.9–2.6)	0.584
Total protein (g/dL)	4.8 (4.1–5.6)	5.0 (4.3–5.5)	0.731
Systolic blood pressure (mm Hg)	110 (100–120)	120 (105–130)	<0.01
Diastolic blood pressure (mm Hg)	55 (45–60)	50 (50–60)	0.986
Heart rate (L/min)	90 (75–100)	90 (80–100)	0.351

creatinine concentrations measured in the three groups by analysis of variance does not reach significance ($p = 0.21$). Thus, both postulated hypotheses were confirmed as expected. In addition, acid–base control was tested using the same criterion as for the overall study population for the three groups separately. For all the three groups, the 95% confidence interval of the median BE after 24 hours of treatment was in the range of ±3 mmol/L.

Figure 2 shows the ratio dialysate-to-blood-flow in combination with the BE as a parameter for the acid–base status of the patient. The results are similar for pH and bicarbonate (data not shown). Statistically, a difference in the acid–base control is present, with lower dialysate-to-blood-flow ratios being used in lighter patients and a slight metabolic acidosis in the heaviest patient group (Table 3).

Figure 3 shows the incidence of metabolic acidosis and alkalosis over time. After resolution of the initial metabolic acidosis, the patients' acid–base status was well controlled with low and equal percentages of metabolic acidosis and alkalosis episodes. Except for a higher frequency of initial metabolic acidosis in group 3, results were similar for the three groups (data not shown).

Postfilter Ionized Calcium and Filter Patency. The postfilter ionized calcium as a measure of the citrate effect as well as the citrate dose, which was defined as the amount of citrate infused per liter treated blood was stable with the same levels in all three groups. There is no indication for a group difference concerning the regional citrate anticoagulation (compare Table 3).

Of the 216 hemofilters documented, the majority was stopped due to reaching the scheduled filter lifetime (n = 86, 40%) or due to various non–CRRT-related reasons, like discharge from the intensive care unit, change to intermittent dialysis, need for surgery, or death of patients (n = 111, 51%). Ten filters (5%) were stopped because of clotting. For the

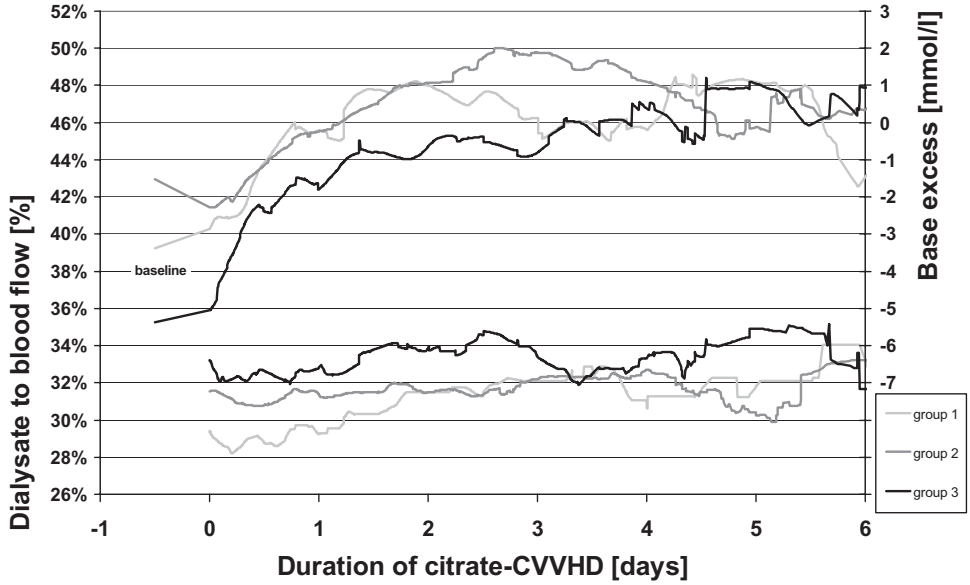

Figure 2. Dialysate-to-blood-flow ratio and base excess during the observation period for the three study groups. *CVVHD*, continuous venovenous hemodialysis.

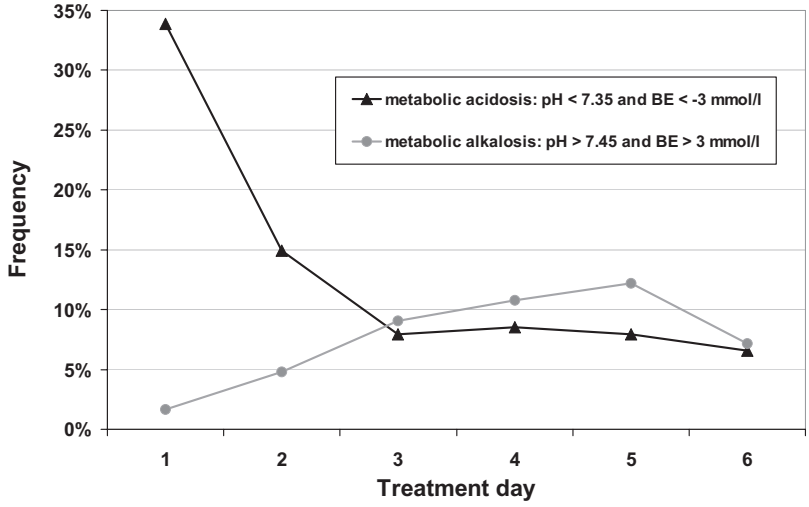

Figure 3. Incidence of metabolic acidosis and metabolic alkalosis during the study period. *BE*, base excess.

remaining nine filters (4%), reasons for filter stopping were not available. The filter lifetimes of all 216 hemofilters and in the subgroup of the clotted hemofilters were 61.5 hours (34.5–81.1 hours) (median, interquartile range) and 43.7 hours (21.8–50.1 hours), respectively. When censoring the hemofilters discontinued for non–CRRT-related reasons, the median filter patency clearly exceeds the maximum in-use time of 72 hours as specified by the manufacturer, Figure 4.

Systemic Calcium and Signs for Citrate Accumulation. The systemic ionized calcium concentration and the calcium dose, which is defined as calcium infusion in mmol per liter generated effluent, showed an evolution over treatment time. In the initial treatment phase, a slight decrease of the systemic ionized calcium concentration was apparent (due to the iatrogenic increase of the blood citrate concentration and the chelating effect of citrate with the circulating ionized calcium). With the calcium substitution dose increasing to around 2.0 mmol/L, the systemic ionized calcium concentration increased within the first two treatment days toward the upper desired range. Thereafter, the systemic ionized calcium concentration was kept stable with the calcium dose lowered to approximately 1.6 mmol/L.

The lowest measured systemic ionized calcium concentration was 0.61 mmol/L and was measured immediately after start of the treatment in a patient with an already low baseline concentration of 0.67 mmol/L. During the citrate-CVVHD, the systemic ionized calcium concentration of this patient increased after several increases of the calcium substitution according to our protocol. There was also a transient overcompensation with a systemic ionized Ca concentration of 1.50 mmol/L and a total Ca concentration of 3.3 mmol/L after approximately 36 hours of citrate-CVVHD. Thereafter, both the ionized and the total Ca concentrations stabilized in the respective normal ranges after a further approximately 24 hours of treatment. The patient had no liver failure and the short-time hypercalcemia was an iatrogenic complication.

Two patients received an additional calcium substitution shortly after start of the citrate-CVVHD. This additional calcium need was due to a slight increase of the systemic citrate concentration in the initial treatment phase, which is known to lead to a slight drop of the systemic ionized calcium concentration.

Citrate accumulation as a complication of a disturbed hepatic metabolism was suspected both in case of an elevated total calcium concentration and in case of an unusually high calcium substitution need as judged by the calcium substitution per liter generated effluent. By using empirically defined cutoff levels, patients with a total calcium concentra-

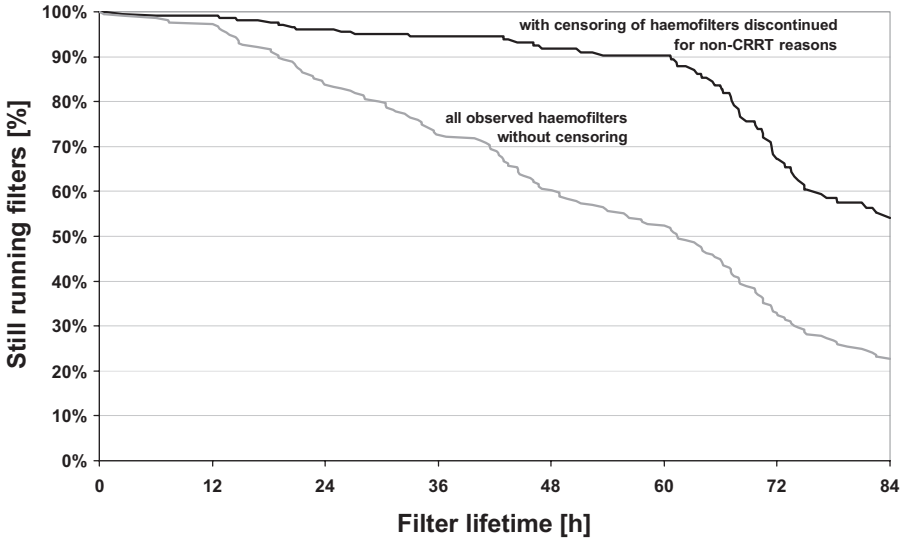

Figure 4. Filter patency during the study for all filters as observed during the study (*gray line*) and with censoring of filters discontinued for noncontinuous renal replacement therapy (*CRRT*) reasons (*black line*).

tion of 3 mmol/L or more (any measurement within the study) and patients receiving >3 mmol calcium substitution per liter generated effluent (at any time point within the study) were evaluated in more detail. We identified a total of eight patients with suspected citrate accumulation: one by elevated total calcium, six by receiving high calcium substitution, and one fulfilling both criteria. In only two of these patients, citrate anticoagulation was stopped and switched to heparin anticoagulation. Both patients had a multiorgan failure syndrome and a bilirubin value >5 mg/dL at baseline. All other patients were continued with citrate anticoagulation. Elevated calcium concentrations in these patients did not appear to be related to citrate accumulation. In one patient, the systemic calcium concentration increased at a standard calcium infusion, potentially due to calcium release from another compartment. In the latter patient, a normalization was achieved by reducing the calcium infusion. In the remaining patients, calcium concentration was transiently elevated due to a too high calcium substitution rate, which was not readily detectable by the dialysis/intensive care unit staff in the setup with external infusion pumps.

DISCUSSION

Management of the Acid–Base Status. Changes in pH, BE, and systemic bicarbonate were basically in parallel and indicate that an initial metabolic acidosis has been resolved during the treatment period. Correction of acid–base abnormalities is apparently a slow process, which is complete only after about 2 days (compare Fig. 2). This is congruent with other studies. Rocktaschel et al (14), for example, showed a trend to alkalosis during a 3-day observation period when using a hemofiltration solution containing 46 mmol/L lactate in continuous venovenous hemofiltration. This slow process is plausible as the distribution volume of bicarbonate, which is the quantitatively dominating physiologic buffer base, is in the magnitude of the total body water and thus exceeds by far the hourly applied CRRT dose (15).

In our protocol, control of acid–base status can be achieved not only by adapting the dialysate flow but also by modifying the blood flow (in certain limits). In patients with metabolic acidosis where a reduction of the CRRT dose is not desired, it would be possible to increase the blood flow in parallel with the citrate solution flow. Thus, more citrate would be systemically infused and, after metabolization, contribute to the correction of the metabolic acidosis.

Anticoagulation. As theoretically expected, the required citrate flow was proportional to the blood flow. In this study, a median citrate dose of 3.87 mmol (3.74–3.97) citrate per liter treated blood was required. After finding the correct citrate dose for each patient in the first hours of the treatment, little further changes of the citrate flow were needed.

Adjusting the citrate dose according to the goal of a postfilter ionized calcium in the range between 0.25 and 0.35 mmol/L had already been shown to provide excellent filter lifetimes (6). This was again confirmed in this study. Excellent filter lifetimes have been reported in many citrate anticoagulation protocols with similar citrate doses (16, 17).

We did see a slight decrease of the platelet count during the application of our citrate-CVVHD protocol. This is not unusual during CRRT (18) and might be explained by the action of the roller pumps used to circulate the blood in the extracorporeal circuit.

Calcium Balance. Our protocol allows to titrate the systemic ionized calcium values as clinically required or desired. Because our dialysate contains no calcium, the amount of calcium needed to be substituted is directly linked to the dialysate flow (8). We aimed for a systemic ionized calcium concentration in the normal range, which was easily achieved and maintained during the study. An initial dip in the ionized calcium usually occurs during citrate anticoagulation and is due to the chelating effect of the infused citrate on circulating calcium ions (8). We observed a slight increase in the total calcium from baseline to the end of the study. Plausible reasons for this increase are: 1) net infusion of calcium, because most of the patients were hypocalcemic before citrate anticoagulation and 2) increased amount of circulating Ca-citrate complexes due to the citrate infusion, which leads to an elevation of the citrate blood level (19).

CRRT Efficacy. Although it is obvious that the CRRT dose should be adapted to the size of the patient, the scaling method is not completely clear. Although in adults dosing is generally based on body weight (7, 20), pediatricians prefer to scale proportional to body surface area (11, 12). This scaling method is based on the fact that metabolic processes, including the generation of renally excreted waste products, have empirically been found to scale clearly better proportional to body surface area compared with body weight (10), thus enabling a better and more flexible adaptation of the treatment efficacy to patients' need. We decided to use the surface area-based scaling approach and were able to realize the desired treatment efficacy corresponding to 2000 mL/hr in a 70-kg patient. In case that even higher treatment efficacies or doses are desired, it can be realized by proportionally increasing the following four flows: blood flow, dialysate flow, citrate, and calcium solution flows. By doing so, dialysate flow rates up to 4000 mL/hr can be safely used in critically ill patients

without running a higher risk for metabolic disarrangements (Kindgen-Milles D, unpublished observation).

Safety. We observed a slight reduction of plasma magnesium into the lower normal range as well as a drop of the plasma inorganic phosphate concentration. Sometimes the latter required phosphate substitution. These findings are in line with the electrolyte balance studies by Tan et al (26). Effective CRRT therapy is associated with substantial phosphate loss into the effluent, which often requires substitution to avoid adverse clinical effects due to hypophosphatemia. Tan et al observed a neutral magnesium balance with 0.75 mmol/L magnesium in the substitution solution. However, citrate does not only build complexes with calcium but also with magnesium. This leads to a shift of magnesium from nondiffusible protein complexes to diffusible citrate complexes. As a consequence hypomagnesemia might occur. We think that in our protocol, despite the 0.75 mmol/L magnesium in the dialysate, a slightly negative magnesium balance had occurred that led to a stabilization of the plasma magnesium concentration in the low normal range.

We observed a low frequency of citrate-CVVHD–specific treatment complications. Of note, only a minority of the patients developed signs of citrate accumulation who required a modification or discontinuation of the CVVHD treatment. In some patients, we observed a transient hypercalcemia. This could retrospectively be traced back to a calcium substitution that overcompensated the calcium removal with the effluent resulting in a positive calcium balance and increasing calcium concentrations. At that time, we used an external calcium pump and had to choose the calcium substitution as calcium flow. Thus, the calcium dose that is calcium substitution in relation to the effluent flow was not directly available. This value might well have been useful in avoiding a mismatch of the calcium substitution.

Nevertheless, we would like to stress that particularly patients with liver failure are at risk of citrate accumulation and toxicity. We, therefore, recommend to be cautious with the use of citrate anticoagulation in these patients. A close monitoring of the ionized calcium and total calcium is mandatory.

To further increase the safety of the treatment, an integration of the citrate and calcium pumps into the CRRT device is required. This enables not only safety features like automatic stop in case of alarms but also enables the possibility to select all treatment parameters on a single-user interface. This, in turn, is a prerequisite to implement the parameters citrate dose and calcium dose, which clearly eases treatment prescription as they are largely independent of the prescribed efficacy level, and, thus, further increases safety. Similarly, prefixed connections of citrate and calcium lines close to the catheter connections can safely avoid mixing up of these lines in case the catheter is connected in reverse way. The multiFiltrate Ci-Ca used at the end of this study includes these safety features.

CONCLUSION

We have shown that our citrate anticoagulation protocol can safely be applied at different CVVHD doses. This enabled an effective treatment of acute renal failure and excellent control on the acid–base status as well on the systemic ionized calcium in combination with negligible clotting issues. Furthermore, our results have important implications for a safe implementation of citrate anticoagulation on a CRRT device.

ACKNOWLEDGMENT

We thank Dr. R. Pohlmeier from Fresenius Medical Care for his technical and scientific support.

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