Chapter 9

Metabolic effects of citrate-based versus bicarbonate-based substitution fluid in continuous venovenous hemofiltration: a prospective sequential cohort study

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Abstract

Background. Studies investigating the metabolic effects of citrate-based substitution fluids are lacking. This study aims to compare the effect of citrate-based versus bicarbonate-based substitution fluid used during continuous venovenous hemofiltration (CVVH) for acute kidney injury on acid-base balance and electrolytes in critically ill patients.

Methods. This was a prospective sequential cohort study in patients with a contra-indication for systemic anticoagulation. The first cohort was treated by bicarbonate-based CVVH (n=10) and the second cohort was treated by CVVH with citrate-based substitution fluid (n=19). Flow of the latter was coupled to blood flow and ionized calcium concentrations were monitored and kept constant by calcium-glubionate infusion.

Results. No major differences between the two groups were found in baseline acid-base parameters. In both groups, arterial pH increased after initiation of treatment and normalized on the average within 18h in either group. No differences were found in bicarbonate concentrations. Electrolyte control was comparable for the groups.

Conclusion. Citrate-based substitution fluid is comparable to bicarbonate-based substitution fluid during CVVH in critically ill patients with acute kidney injury, concerning acid-base balance and electrolyte control. This implies complete conversion of citrate to bicarbonate in the patients studied

Key words

- Acid-base – citrate - continuous venovenous hemofiltration - electrolyte control

Introduction

Continuous venovenous hemofiltration (CVVH) is a suitable modality to replace renal function during acute kidney injury in the intensive care unit (ICU).

Citrate has been used for almost 20 years as a regional anticoagulant during CVVH, to prevent filter clotting.[1-12] After administration, citrate is converted to bicarbonate at a ratio of 1:3, thus providing an important buffer source during CVVH. To date, there are only few studies focusing on the metabolic effects of citrate.[9,14-16] In these studies, continuous techniques other than CVVH were used [14,15] or a control group was absent.[9,15,16] In addition, most of these studies focused on subacute metabolic changes.[9,14,15] The effects of citrate-based CVVH on acid-base balance are diverse, with metabolic alkalosis as the most common finding.[1,2,4,5,7,11,14,15] Concentrated citrate infusion gave rise to high concentrations of bicarbonate in patients with a normal conversion of citrate. In severe hepatic failure, however, the conversion of citrate may be diminished, resulting in accumulation of citrate and a resultant high anion gap metabolic acidosis.[3,16-18] Finally, citrate-based CVVH may alter electrolyte concentrations, such as those of sodium [1,2,4,9] and calcium.[1-6,9,11,19-21] In fact, potentially dangerous metabolic side effects may relate to the high citrate concentration fluids that have been used in addition to buffered substitution fluids and may have hampered, up till now, widespread introduction of citrate for regional anticoagulation and buffering in CVVH. Therefore, we developed a citrate-based substitution fluid according to the concept described by Palsson and Niles which, by theory, does not have the metabolic hazards of the infusion of concentrated citrate.[3] An often mentioned drawback of this concept is that the buffer cannot be dosed separately from substitution fluid, which can be a problem in severe acidosis. Studies investigating the metabolic effects of citrate-based substitution fluid are lacking. Initial data on filter survival have been reported and the current study is an analysis of this prospective clinical trial.[12]

We hypothesized that our mode of citrate-based substitution fluid corrects metabolic acidosis as rapidly and fully as bicarbonate-based treatment with comparable electrolyte control, during CVVH for acute kidney injury in the ICU.

Methods

Patients. From August 2004 to February 2006 a prospective observational sequential cohort study was carried out at the ICU of the VU University Medical Centre in Amsterdam. The study protocol was approved by the local committee on ethics and

performed in accordance with the Declaration of Helsinki. The study started one year prior to availability of a custom-made citrate-based replacement fluid. Until that time all consecutive patients (n=31) with acute renal failure and high bleeding risk were treated by anticoagulant-free CVVH (bicarbonate- or lactate-buffered) and were prospectively observed. Patients with acute kidney injury and high risk for bleeding were treated in our hospital by anticoagulant-free CVVH. Patients with high serum lactate levels (> 5 mmol/l) were routinely treated by bicarbonate-buffered CVVH (n=13). Since the availability of citrate-based solution in may 2005, the following 20 consecutive patients with a bleeding tendency were treated by CVVH using this new solution, which became the first choice of treatment in patients a high bleeding risk. Since all patients were treated according to local standards at that time, the need for informed consent was waived. CVVH was started for acute kidney injury and ongoing hypercatabolism, diuretic-resistant volume overload, respiratory distress, multi-organ failure or any combination of these features. High risk for bleeding was defined as a platelet count below 40 $x10^9$/l, an activated partial thromboplastin time (aPTT) >60 sec, a prothrombin time (PT) >2.0 INR, a recent major bleeding, or significant active bleeding. There were no exclusion criteria.

For the current evaluation, data from the cohort treated by citrate-based CVVH were retrieved and compared to data from the cohort treated by bicarbonate-based CVVH. We omitted 1 patient in the citrate group and 3 patients in the bicarbonate group from analysis as a result of missing data. All patients had an arterial catheter for blood pressure monitoring. Though our primary goal was a comparison between citrate- and the physiologic bicarbonate-buffered fluid, we also made a comparison with the patients treated with lactate-buffered fluid in order to put the analysis in a wider perspective.

Treatment. CVVH was performed using a Braun Diapact hemofiltration machine (DIAPACT, B. Braun Medical, Germany). Vascular access was obtained by the insertion of an 11-Fr double lumen catheter (GamCath, Gambro, Germany) into either the femoral, subclavian, or internal jugular vein. A 1.9 m^2 highly permeable cellulose triacetate filter (NIPRO UF-205, Nissho Corp., Japan) was used in all treatments. The composition of the different substitution fluids used in this study is shown in Table 1. For bicarbonate-based CVVH a commercially prepared buffer solution was available (HF 32 bic, Dirinco, Rosmalen, The Netherlands); for the use of citrate a substitution fluid was custom-made by Dirinco BV, according to the protocol developed by Palsson and Niles.[3] Blood flow rate was set at 180 ml/min in both groups. Substitution fluid was administered at a standard rate

Table 1. Substitution fluids.

	Bicarbonate HF 32 Bic®	Citrate HF CitPre®	Lactate BH 504®
Sodium (mmol/l)	140.0	139.9	140
Potassium (mmol/l)	2.0	3.0	1.5
Magnesium (mmol/l)	0.5	0.5	0.5
Calcium (mmol/l)	1.75	---	1.5
Chloride (mmol/l)	111.5	104.0	103
Glucose (mmol/l)	1.0	5.0	11.1
Citrate (mmol/l)	---	13.3	---
Bicarbonate (mmol/l)	32.0	---	---
Lactate (mmol/l)	3.0	---	42.0

of 2000 ml/h in the bicarbonate group. Since administration of substitution fluid in the citrate group was continuously coupled to blood flow rate, substitution fluid rate in the citrate group was set at 2400 ml/h. Substitution fluids were infused in predilutional mode. Patients receiving citrate-based therapy had a separate intravenous infusion with calcium-glubionate (Calcium Sandoz^{R}, containing calcium 0.225 mmol/ml, Novartis Consumer Health, The Netherlands). Calcium administration was adapted to concentrations of ionized calcium by a specially designed algorithm.[12] In brief, ionized calcium was kept at 1.0-1.1 mmol/l. In normocalcaemic patients calcium was infused at a rate of 12 ml/h. If ionized calcium concentration was 0.9-1.0 mmol/l, infusion rate was increased to 14 ml/h, and to 18 ml/h if the concentration was below 0.8 mmol/l, together with a bolus injection of 2.25 mmol calcium-glubionate. In case of high ionized calcium (>1.1 mmol/l) infusion rate was lowered to 10 ml/h**.** Citrate CVVH was stopped, if the patient fulfilled one of the following criteria: total to ionized calcium ratio of more than 2,5, persistent metabolic alkalosis with a base excess of more than 10 mmol/l, clinical signs of hypocalcemia (tetanic symptoms or prolonged QT interval) or progressive non-lactic acidosis (pH<7.20) during CVVH combined with an increase in anion gap (>13 mmol/l) without the presence of endo- or exogenous acids other than citrate, suggesting citrate accumulation. If there were signs of citrate accumulation, predilution CVVH was continued without anticoagulation using bicarbonate-based replacement fluid.

Data collection. Demographic parameters and clinical data were recorded at baseline and presented in Table 2, together with admission diagnosis. Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) were employed to assess severity of illness at baseline and during treatment. Mean arterial

pressure (MAP) was recorded continuously. Arterial blood was taken from an arterial catheter before start of CVVH (Baseline) and during the study period (of 72 h). Blood gas analysis was performed every 6h on the ICU, using a Bayer RapidLab 865 Blood Gas Analyser (Bayer, Leverkusen, Germany), or in the hospitals clinical laboratory, using a Radiometer ABL800 Flex (Radiometer, Copenhagen, Denmark). The pH (n 7.35-7.45), PCO_2 (n 35-45 mmHg), base excess (n -2.0-+3.0 mmol/l) and plasma concentrations of bicarbonate (n 22.0-26.0 mmol/l) and ionized calcium (n 1.1-1.3 mmol/l) were recorded. The latter was routinely measured only during citrate-based treatment. A multichannel analyzer was used to measure six hourly the levels of sodium (n 136-146 mmol/l), potassium (n 3.6-4.8 mmol/l) and chloride (n 98-108 mmol/l) (Hitachi Modular ISE 900, Roche Diagnostics, Mannheim, Germany) and the levels of total calcium (n 2.20-2.60 mmol/l), magnesium (n 0.70-1.00 mmol/l), albumin (n 35-52 g/l), phosphate (n 0.70-1.40 mmol/l), lactate (n <2.2 mmol/l), creatinine (n 60-110 μmol/l) and urea (n 3.0-7.5 mmol/l) (Hitachi Modular P800, Roche Diagnostics, Mannheim, Germany). Values for albumin were taken once daily during the whole study period and was measured with a colorimetric assay (Modular analytics, Roche Diagnostics, Mannheim, Germany). Average values of data from the second and third day of treatment were calculated and presented as t=48h and t=72h data. Study duration was 72h, except for patients in whom CVVH ended earlier due to death or recovery of renal function. The down-time and duration of CVVH treatment within the study period were recorded. Down-time was defined as the time that CVVH was not applied as a result of filter change or patient transport. In addition, mortality until 28 days within the ICU was considered (Table 2).

Evaluation of acid-base status. We calculated the anion gap (AG) and the anion gap corrected for albumin (AGc). For these calculations the following equations were used: AG (mEq/l) = $[Na^+] + [K^+] - [Cl^-] - [HC0_3^-]$ (in mmol/l), AGc (mmol/l) = AG + 0.25 x (normal [albumin]-measured [albumin]), with albumin in g/l and normal [albumin] of 40 g/l. We also analysed data according to Stewart and Figge,[22-24] wherein acid-base balance is determined by the difference in strong ions (SID), the total concentration of weak acids and the partial pressure of carbon dioxide (PCO_2). The apparent strong ion difference (SIDa) can be calculated from: SIDa (mEq/l) = $[Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-]$ - [lactate]. For the total concentration of weak acids the partial carbon dioxide pressure (PCO_2), the weak acid phosphate (PO_4^{3-}) and albumin are taken into account. The effective strong ion difference (SIDe): SIDe (mEq/l) = 2.46×10^{-8} x ($PCO_2/10^{-pH}$) + [albumin] x 0.123 x (pH-

Table 2. Patient characteristics.

	Bicarbonate n=10	Citrate n=19
Male/female	4/6 (40/60)	12/7 (63/37)
Age (years)	57 ± 18	62 ± 16
Weight (kg)	82 ± 13	79 ± 16
APACHE II	26.7 ± 9.6	24.5 ± 6.7
SOFA Baseline	16 ± 4.1	13 ± 3.6
SOFA 72h	16 ± 4.9	13 ± 2.8
Creatinine (µmol/l)	257 ± 136	278 ± 120
Urea (mmol/l)	15.4 ± 9.6	22.5 ± 12.7
Vasopressor dependency	9 (90)	16 (84)
MAP (mmHg)		
Baseline	79 ± 11	80 ± 9.7
24h	79 ± 16	80 ± 9.0
48h	89 ± 13	81 ± 12.1
72h	87 ± 18	80 ± 7.6
Admission Diagnosis		
Sepsis	4 (40)	9 (47)
Trauma	0	1 (5)
Aortic aneurysm	2 (20)	1 (5)
Pancreatitis	0	1 (5)
Glomerulopathy	0	1 (5)
Cardiogenic shock	3 (30)	2 (11)
Postoperative	0	1 (5)
Others	1 (10)	3 (16)
Mechanical ventilation	10 (100)	19 (100)
Mortality until 28 days within the ICU	7 (70)	7 (37)

Mean ± SD or number of patient (percentage), where appropriate. Abbreviations: MAP=mean arterial pressure, APACHE II=acute physiology and chronic health evaluation, SOFA=sequential organ failure assessment.

0.631) + $[PO_4^{3-}]$ x 0.309 x (pH-0.469), with PCO_2 in mmHg, [albumin] in g/l and [phosphate] in mmol/l. The strong ion gap (SIG) is the difference between SIDa and SIDe. This difference is zero, unless unmeasured anions are present, like sulphate, ketoacids, citrate, pyruvate, and acetate. The calculations were performed at baseline and once daily, for daily averaged values from t=24 to 72h.

Statistics. The Kolmogorov Smirnov test showed that measurement fulfilled normal distribution. Continuous data are presented as mean ± standard deviation (SD). The independent samples t-test was used to compare groups at the time points of the study. The paired-samples t-test was used for paired data, followed by the Bonferroni-Holm test for

repeated testing. A P-value <0.05 was considered to be statistically significant, and exact values are reported.

Results

Demographic, clinical and treatment data at baseline are presented in Tables 2 and 3; groups were comparable. In Table 4, data on acid-base balance and electrolytes are summarized. Groups were comparable for mean arterial pressure (Table 2) and vasopressor administration (data not shown) during the observation period.

Table 3. Treatment characteristics.

	Bicarbonate	Citrate
Blood flow (ml/min)	180	180
Substitution flow (ml/h)	2000	2400
Net fluid removal (ml)		
24h	596 ± 1204	563 ± 753
48h	1161 ± 1904	1104 ± 1176
72h	1239 ± 1787	1587 ± 1423
Observation period (h)	54 ± 27	63 ± 17
CVVH time (h)	51 ± 25	61 ± 16
First Filter life (h)	29 ± 27	38 ± 22
Down-time (h)	2.9 ± 4.1	2.4 ± 3.3
Decrease in creatinine		
0-72 h (µmol/l)	42 ± 92	98 ± 106
Decrease in urea		
0-72 h (mmol/l)	1.4 ± 3.8	8.0 ± 10.7

Mean ± SD. CVVH: continuous venovenous hemofiltration

Table 4. Acid-base balance and electrolytes.

	Buffer	Baseline	T=6	T=12	T=18	T=24	T=48	T=72h
PCO_2 (mmHg)	B	40 ± 19	36 ± 9	35 ± 7	33 ± 6	33 ± 5	34 ± 5	37 ± 3
	C	40 ± 7	38 ± 7	38 ± 6	39 ± 8	39 ± 7	38 ± 6	39 ± 7
Base Excess (mmol/L)	B	-9.0 ± 4.4	-8.9 ± 7.1	-6.9 ± 6.2	-6.8 ± 8.0	-6.8 ± 8.2	-1.8 ± 2.9 ¶¶†	-1.4 ± 1.9 ¶¶†
	C	-5.2 ± 5.7	-6.9 ± 5.6 ¶¶	-4.9 ± 4.7	-4.1 ± 4.3	-4.1 ± 3.7	-2.7 ± 3.2 ¶¶	-1.5 ± 2.9 ¶¶
Sodium (mmol/L)	B	142 ± 10	142 ± 8	142 ± 7	141 ± 7	140 ± 6	137 ± 4	137 ± 2
	C	141 ± 6	142 ± 6	140 ± 3	139 ± 3	139 ± 2	137 ± 2 ¶	137 ± 3 ¶¶
Potassium (mmol/L)	B	4.5 ± 0.8	4.9 ± 1.1	4.2 ± 0.4	4.5 ± 0.5	4.6 ± 0.7	4.5 ± 0.7	4.3 ± 0.6
	C	4.5 ± 0.8	4.3 ± 0.7	4.3 ± 0.4	4.4 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.2 ± 0.3
Chloride (mmol/L)	B	106 ± 11	113 ± 11	113 ± 14 ¶	111 ± 10 * ¶†	110 ± 5.6 * ¶	104 ± 3 ¶¶	103 ± 1 ¶¶
	C	107 ± 8	106 ± 6	107 ± 4 ¶	106 ± 3 ¶	104 ± 3 ¶¶	104 ± 4 ¶¶	102 ± 2 ¶¶
Total Calcium (mmol/l)	B	1.63 ± 0.23 *	1.58 ± 0.22 **	1.71 ± 0.17 *	1.81 ± 0.15 ** ¶	1.89 ± 0.15 * ¶	1.96 ± 0.16 ¶	1.99 ± 0.21 ¶
	C	1.90 ± 0.27	1.89 ± 0.22	1.94 ± 0.20	1.99 ± 0.16 ¶	2.04 ± 0.14 ¶	2.08 ± 0.16 ¶¶	2.07 ± 0.13 ¶
Magnesium (mmol/L)	B	0.88 ± 0.16	0.88 ± 0.15	0.86 ± 0.13	0.82 ± 0.08	0.81 ± 0.08	0.84 ± 0.16	0.87 ± 0.16
	C	0.92 ± 0.20	0.94 ± 0.14	0.88 ± 0.12	0.84 ± 0.13	0.84 ± 0.13	0.81 ± 0.10	0.81 ± 0.70
Phosphate (mmol/L)	B	1.55 ± 0.91	1.59 ± 0.92	1.51 ± 0.91	1.57 ± 0.84	1.53 ± 0.84	1.19 ± 0.48	1.12 ± 0.26
	C	1.54 ± 0.71	1.59 ± 0.67	1.26 ± 0.48 ¶¶	1.20 ± 0.46 ¶¶	1.11 ± 0.37 ¶¶	1.06 ± 0.24 ¶¶	0.97 ± 0.18 ¶
Lactate (mmol/L)	B	6.5 ± 4.0	8.3 ± 3.6	7.9 ± 6.6	8.3 ± 8.6	9.2 ± 8.4 *	4.0 ± 1.9 **	3.7 ± 1.4 **
	C	4.6 ± 8.3	6.1 ± 11.2	2.7 ± 1.7	2.3 ± 2.2	2.0 ± 1.8	1.9 ± 1.0	1.6 ± 0.64 ¶
Albumin (g/L)	B	17 ± 3	15 ± 4	16 ± 4	17 ± 4	18 ± 4	17 ± 4	16 ± 5
	C	17 ± 5	17 ± 4	17 ± 4	17 ± 4	17 ± 4	15 ± 5	15 ± 4

Mean ± SD; * $p<0.05$ between groups; ** $p<0.01$ between groups; ¶ $p<0.05$ compared to baseline; ¶¶ $p<0.01$ compared to baseline; † $p<0.05$ for changes between groups. Abbreviations: B=Bicarbonate group, C=Citrate group.

Acid-base balance. Before treatment, groups were comparable, with a relatively low pH and bicarbonate. Over 72h of treatment, the groups differed only in lactate concentration. After start of CVVH, acid-base balance similarly normalized in the groups (Fig. 1a and b), without additional infusion of bicarbonate. Within 18h, pH-values increased to the reference range, similarly in both groups. The rise in bicarbonate concentration was somewhat faster in the bicarbonate group, however.

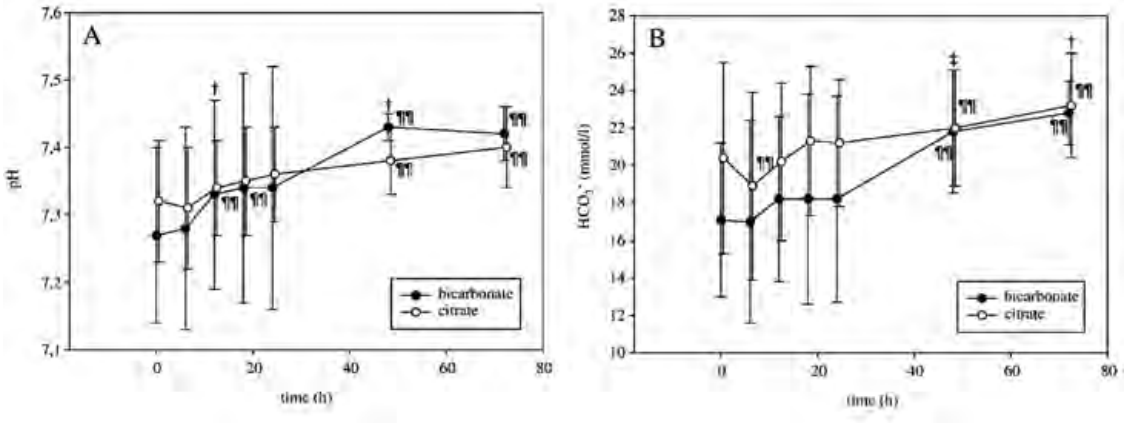

Fig 1. Arterial pH (A) and plasma bicarbonate concentrations (B) in patients treated with bicarbonate- or citrate-based CVVH. Data presented as mean ± SD. * $p<0.05$ between groups; † $p<0.05$ for changes between groups; ‡ $p<0.01$ for changes between groups; ¶¶ $p<0.05$ compared to baseline.

During citrate-based CVVH, only one case of alkalosis (pH >7.45) was observed. The alkalosis, however, was of respiratory rather than of metabolic origin. In Table 5, the calculated data are presented. In the bicarbonate group, the elevated AG normalized during treatment (Table 5), presumably as the consequence of a reduction of Na^+ concentrations (Table 4) and a rise in HCO_3^- concentrations. In the citrate group, AG rose within the first 6h of treatment (Table 5), but fell thereafter. The early increase in AG can be partially explained by the decrease in HCO_3^- concentration (by mean 1,5 mEq/l), while for the remaining 1.4 mEq/l unmeasured anions should be taken into account. There were no differences between groups in Stewart-Figge parameters (Table 5). SIDa tended to be lower in the bicarbonate group, reflecting the higher lactate concentrations in this group. SIG tended to be higher in the citrate group, although SIG differed from zero only at t=24h. The SIG similarly correlated to the AGc in both groups: $r=0.73$ ($p=0.002$) in the bicarbonate group and $r=0.75$ ($p<0.001$) in the citrate group. The acid-base balance in the patients treated by lactate-based substitution fluid also normalized in a similar way when compared to the bicarbonate- and citrate group (data not shown).

Electrolytes. Electrolyte concentrations prior to treatment were similar in the groups (Table 4). The total calcium level in the citrate group was higher at start of treatment, which might be explained by a slightly higher albumin level, but after two days there was no difference. In both groups there was a comparable increase in total calcium during the three days. Serum levels of ionized calcium decreased after start of treatment in the citrate group but returned to normal within approximately 12 hours (Fig. 2a); after an initial increase the first 6-18 hours, the total to ionized calcium ratio remained stable (fig 2b). In general, no differences in chloride were seen between the groups. However, during the first 18h of treatment, increases were greater in the bicarbonate group. Hypernatremia was not observed (Table 4). Hyponatremia (< 133 mmol/l) was never recorded.

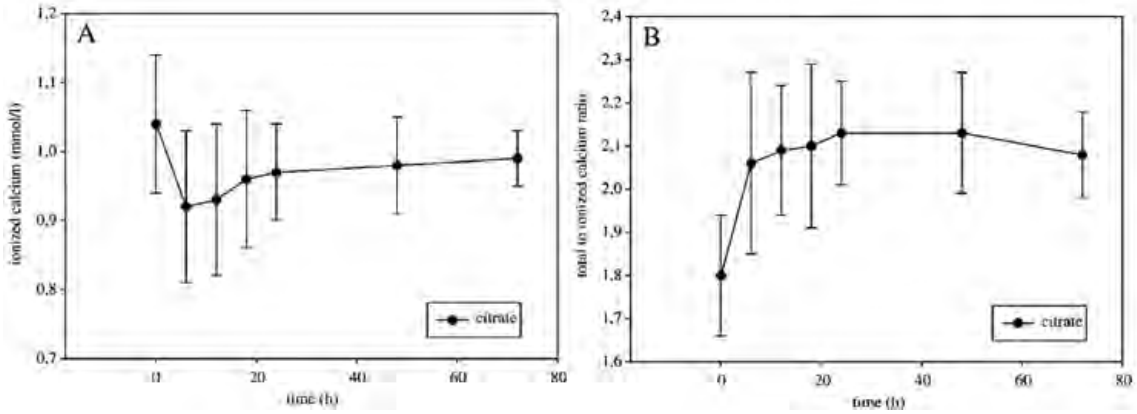

Fig 2. Levels of ionized calcium (A) and total to ionized calcium ratio (B) in patients treated by citrate-based CVVH. Data presented as mean ± SD.

Discussion

In this study, the effect of CVVH with citrate-based substitution fluid on acid-base balance and electrolytes appeared similar to that by bicarbonate-based CVVH suggesting complete metabolism of citrate, indicating that this treatment is safe in our patients. These metabolic effects in patients treated by lactate-based substitution fluid were also similar to the patients treated by citrate- or bicarbonate-based fluid. The comparability between lactate- and bicarbonate-based fluids was demonstrated earlier by Thomas et al..[25] The composition of the fluids used in the latter trial was largely similar as compared to those we used (table 1).

In 1990, Mehta et al. were the first to describe a protocol for citrate-based continuous arteriovenous hemodialysis, using infusion of concentrated trisodium citrate. Metabolic alkalosis was found in 27% [1] and 26% [2] of patients. Studies using a similar

Table 5. Calculated values

	Buffer	Baseline	T=6	T=12	T=18	T=24	T=48	T=72h
AG (mmol/L)	B	24.3 ± 3.7	18.6 ± 10.6	16.5 ± 9.4‡	21.1 ± 15.5‡	19.0 ± 3.3 ¶‡	13.7 ± 1.8 ¶¶‡	12.7 ± 2.0†
	C	17.5 ± 10.8	20.4 ± 10.8 ¶¶	17.0 ± 4.7	17.6 ± 4.1	17.5 ± 3.7	15.8 ± 3.9	15.2 ± 2.6
AGc (mmol/L)	B	31.1 ± 4.3	24.8 ± 7.3†	22.3 ± 8.1†	20.3 ± 4.5 ¶†	23.7 ± 4.1 ¶	22.7 ± 5.7‡	19.6 ± 0.91
	C	26.8 ± 13.1	24.7 ± 3.6	23.7 ± 4.4	23.8 ± 4.2	23.7 ± 3.7	21.9 ± 4.8	21.9 ± 3.8
SIDa (mEq/L)	B	36.4 ± 5.7	N/A	N/A	N/A	33.9 ± 4.1 *	37.6 ± 3.3	35.7 ± 1.6 *
	C	37.7 ± 5.8	N/A	N/A	N/A	39.3 ± 2.6	39.4 ± 3.2	40.3 ± 1.5
SIDe (mEq/L)	B	35.0 ± 6.3	N/A	N/A	N/A	34.5 ± 6.2	38.5 ± 5.8 ¶¶‡	38.8 ± 5.1 ¶¶
	C	36.5 ± 7.2	N/A	N/A	N/A	36.1 ± 5.3	38.0 ± 5.8	38.1 ± 5.2
SIG (mEq/L)	B	6.6 ± 1.6	N/A	N/A	N/A	-1.3 ± 4.9 *	-3.6 ± 3.1†	0.4 ± 1.8
	C	2.2 ± 7.9	N/A	N/A	N/A	4.0 ± 3.5	3.2 ± 5.9	2.7 ± 4.7

Mean ± SD. * $p<0.05$ between groups; ¶ $p<0.05$ compared to baseline; ¶¶ $p<0.01$ compared to baseline; † $p<0.05$ for changes between groups; ‡ $p<0.01$ for changes between groups. Abbreviations: B=Bicarbonate group, C=Citrate group, AG=Anion Gap, AGc=Anion Gap corrected for albumin, SIDa=apparent Strong Ion Difference, SIDe=effective Strong Ion Difference, SIG=Strong Ion Gap, N/A=Not Applicable.

citrate regimen found metabolic alkalosis as well, with frequencies ranging from 6% to 67%.[4,7,11,14,15] Furthermore, in a few cases diminished conversion of citrate led to citrate accumulation, which resulted in high anion gap metabolic acidosis.[3,16,18]. Palsson and Niles developed a citrate-based CVVH regimen, in which citrate and electrolytes were at isotonic concentrations in the substitution fluid. No metabolic complications were reported in their study, except two cases of citrate accumulation as a result of severe hepatic failure and septic shock.[3] Trials evaluating comparable citrate protocols did not show acid-base disturbances either.[6,10] Aforementioned studies, however, focus on the anticoagulant effect of citrate and to date there are only few studies focusing primarily on the metabolic effects of citrate.[9,14-16] In these studies, other continuous renal replacement therapy (CRRT) modalities were used,[14,15] or a control group was absent.[15,16] In our study, CVVH was performed according to the CVVH system designed by Palsson and Niles,[3] and our study carries the advantage of a comparison with a control group and consequently, this is the first controlled study on the effects of CVVH using citrate-based substitution fluid on acid-base balance and electrolyte control and the first to report on both acute and subacute metabolic effects of citrate-based CVVH.

Correction of the acute kidney injury induced-metabolic acidosis appeared to be as fast in CVVH with citrate-based as in bicarbonate-based substitution fluids. The rise of pH was essentially due to rising concentrations of bicarbonate in both groups (Fig.1). However, the increase in bicarbonate concentrations appeared to be faster in the bicarbonate group. A reasonable explanation is the fact that in citrate-buffered therapy, citrate needs conversion into bicarbonate, while in bicarbonate-buffered therapy the physiological buffer is available immediately. In critically ill patients, acute kidney injury is indeed often accompanied by multi-organ failure and the consequent changes in liver and muscle blood flow may lead to a diminished conversion of citrate.[17,18] In our study an increase in AG attributable to unmeasured anions of 1.4 mmol/l was found at t=6h, which may reflect a trisodium citrate concentration of 0.7 mmol/l, although the SIG of 4.0 mEq/l at t=24h may indicate a higher concentration. Nevertheless, AG normalized in our study at t=48h and t=72h, while SIG did not differ from zero, so that the increase in plasma citrate concentrations may have been transient in the first 24h after start of treatment. Otherwise, the additive value of analysis according to Stewart and Figge appeared limited, even during citrate-based CVVH, since for instance the AGc highly correlated to the SIG, as reported earlier.[26] The course of the plasma bicarbonate concentration in the control group is in

accordance with previous literature on bicarbonate-buffered CVVH,[27,28] although observation intervals in these studies are rather long (24h).

Excellent control was achieved in both groups for sodium, potassium, magnesium, phosphate, chloride and calcium. In previous studies citrate-based CRRT is often associated with hypernatremia caused by the administration of concentrated trisodium citrate with sodium concentrations ranging from 210 to 420 mmol/l.[1,2,4,9] Due to the composition of the substitution fluids used in our study, hypernatremia did not occur. In the bicarbonate group, a transient increase in chloride concentrations was observed shortly after start of treatment. This can be explained by the chloride concentration of the substitution fluid (Table 1), being 111.5 mmol/l in the bicarbonate group versus 104.0 mmol/l in the citrate group.[25] Despite the fact that patients in the citrate group received more chloride per hour of treatment due to the differences in the substitution flow, the correction of metabolic acidosis was adequate and comparable to the bicarbonate group. Finally, lactate concentrations were lower in the citrate group throughout the observation period, since patients with severe lactate acidosis are per protocol treated by bicarbonate-buffered hemofiltration in our hospital.

We monitored ionized calcium levels to adjust infusion rates and considered total/ionized calcium ratios to indicate citrate accumulation, when increasing above 2.5.[19-21] Ionized calcium was not monitored in patients treated by bicarbonate. After an initial decrease during the first hours of treatment, the correction of ionized calcium level was fast and complete in the citrate group. This transient decrease, in parallel with the transient bicarbonate decrease, could be explained by the lag time for conversion of citrate to bicarbonate, as unconverted citrate will form calcium-citrate complexes with ionized calcium. Low plasma levels of ionized calcium is a common finding during citrate administration and has been well described before.[1-5,6,9,11,19-21] The calcium infused via the peripheral catheter should balance the calcium lost in the ultrafiltrate. We designed an algorithm in order to prevent hypocalcemia and its complications,[17] but in spite of this algorithm, hypocalcemia (<0.9 mmol/l) occurred in 7 patients, especially during the first day of treatment. No patient had a significant change in clinical status as a result of hypocalcemia, however. In one patient with a rapidly progressive post renal transplantation lymphoproliferative disorder with severe liver dysfunction, regional citrate anticoagulation had to be discontinued because of citrate accumulation with a total to ionized calcium ratio of 2.75. After conversion to predilution bicarbonate-based CVVH the total to ionized calcium ratio rapidly normalized. Liver failure is not an

absolute contra-indication for treatment by CVVH with citrate-based substitution fluid, though it is known that liver cirrhosis is associated with a higher level of metabolic complications as a result of a decreased citrate clearance. There is, however, a substantial inter-individual variation in citrate clearance which makes the prediction hard. Moreover, Kramer et al. demonstrated the feasibility of citrate anticoagulation in patients with advanced liver cirrhosis.[29] When the safety monitoring is performed according the protocol, citrate accumulation can be recognized timely before the onset of serious adverse events.

In order to achieve sufficient anticoagulation, the substitution flow was set at a higher rate in the citrate group (Table 3). As a result, the hourly administration of buffer in citrate-based treatment was 20% higher as compared to bicarbonate-based treatment. Together with similar down-times, the lower buffer administration may have attenuated the rise in plasma bicarbonate concentrations in the bicarbonate group.[30,31] Limitations of this study comprise the relatively small number of patients and the absence of randomisation, though the groups were comparable. A retrospective power analysis revealed that this study was powered enough to demonstrate the potential differences observed. Yet, it is conceivable that more subjects are warranted to find smaller differences with statistical significance; the clinical relevance would be doubtful, however.

In conclusion, CVVH using citrate-based substitution fluid is largely comparable to bicarbonate-buffered CVVH concerning acid-base balance and electrolyte control, if adequate monitoring of ionized calcium is performed.

List of abbreviations

CVVH=Continuous Venovenous Hemofiltration, ICU=Intensive Care Unit, aPTT=activated Partial Thromboplastin Time, PT=Prothrombin Time, R=Range, APACHE II=Acute Physiology and Chronic Health Evaluation, SOFA=Sequential Organ Failure Assessment, MAP=Mean Arterial Pressure, N=Normal range for laboratory data, iCa^{2+}=Ionized calcium, AG=Anion Gap, AGc=Anion Gap corrected for albumin, SIDa=apparent Strong Ion Difference, SIDe=effective Strong Ion Difference, SIG=Strong Ion Gap, CRRT=Continuous Renal Replacement Therapy.

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Competing interests

The authors declare that they have no competing interests.

Conflict of interest statement

The results presented in this paper have not been published previously in whole or part, except in abstract format

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