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Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial

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Abstract

Background. Continuous venovenous haemofiltration (CVVH) in the intensive care setting requires anticoagulation to prevent clotting of the extracorporeal circuit. Several protocols avoiding heparin and using regional citrate anticoagulation have been developed to diminish bleeding risks. However, data from randomized trials comparing citrate anticoagulation with systemic heparinization are very limited.

Methods. One hundred and seventy-four patients on mechanical ventilation, requiring renal replacement therapy for acute renal failure, were included in this prospective randomized multicentre trial comparing regional citrate with systemic heparin. The study was performed at nine different intensive care units at university or academic teaching hospitals. The participants were randomized to either CVVH using regional citrate anticoagulation or CVVH using systemic anticoagulation with unfractionated heparin. The primary outcome was to compare treatment efficacy represented by the patients' acid base status on Day 3 and on each consecutive day. Several parameters of safety and efficacy were analysed as secondary outcomes.

Results. Comparison of standard bicarbonate from Day 3 to Day 11 revealed no difference between both treatment modalities. Use of citrate resulted in less systemic anticoagulation, a lower risk of bleeding and a longer haemofilter patency. Episodes of hypercalcaemia, hypocalcaemia and the need for additional bicarbonate infusions occurred more often under citrate. The patients' high mortality was not influenced by the mode of anticoagulation.

Conclusions. Citrate may be used as a regional anticoagulant and the only buffering agent in CVVH with adequate treatment efficacy and safety. However, neither citrate nor heparin anticoagulation should be regarded as a therapeutic standard, since there is no advantage of one of these substances with regard to patient mortality.

Keywords: acute renal failure; anticoagulation; citrate; haemofiltration

Introduction

In-hospital mortality in critically ill patients with acute renal failure is often exceeding 50% [1–4]. Though there is still no consensus for the optimal renal replacement therapy [5–7], continuous venovenous haemofiltration (CVVH) is often preferred to intermittent techniques in order to provide tight control of volume and acid base status. However, a major disadvantage of continuous procedures is the need for continuous anticoagulation to prevent clotting of the extracorporeal circuit. In clinical practice, systemic anticoagulation with unfractionated heparin is common. As this can be associated with severe adverse effects, such as heparin-induced thrombocytopenia (HIT) or an increased risk of bleeding, regional anticoagulation with citrate was developed to avoid systemic anticoagulation.

Citrate acts as an anticoagulant in the extracorporeal system through chelation of ionized calcium. Systemic anticoagulation does not occur, since the patient's ionized calcium is restored through instant dilution of the citrate–calcium complexes when the blood re-enters the patient's systemic circulation and through rapid metabolization of citrate in the liver and other tissues. In addition to its function as an anticoagulant, citrate serves as a buffer sub-

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stance, since each molecule of citrate is metabolized yielding three molecules of bicarbonate.

Apart from a lower bleeding risk and no risk of HIT, an improved biocompatibility of citrate was advocated in both intermittent and continuous renal replacement therapy [8–10]. Recently, data from a prospective single-centre study suggested a beneficial effect of citrate anticoagulation on the patients' in-hospital as well as 3-month mortality, even though the mean duration of citrate exposure was only 2.7 days [10].

A considerable drawback of regional anticoagulation with citrate is the risk of iatrogenic metabolic derangements that may occur due to citrate, affecting the patients' calcium, sodium and acid base balance [11,12].

In this study, we investigated a further pre-dilution CVVH system originally described by Palsson in 1999 [13]. In this approach, trisodium citrate is part of the haemofiltration substitution solution itself and not infused as a separate concentrate. It acts as a regional anticoagulant for the extracorporeal circuit and at the same time provides a buffering agent. The calcium substitution flow is defined as the only parameter to be varied in the clinical setting.

The aim of this study was to compare this system to a standard CVVH system that uses systemic heparinization with a focus on the correction of metabolic acidosis, patient mortality, filter 'life' before clotting and the risk of bleeding.

Materials and methods

Study design

The study was a multicentre, controlled, randomized, open, prospective, phase III clinical trial with parallel group design at nine different intensive care units at university hospitals or academic teaching hospitals in Germany.

Regulatory issues

The study was carried out in accordance with the 'Declaration of Helsinki', and it was approved by the ethics committee of the North Rhine Physician's Council and by the institutional review boards at each of the participating study centres. The study was registered at German Clinical Trial Register (www.germanctr.de) number DRKS00000224 and at EudraCT with number 2005-004734-40.

Due to the severity of illness, patients were commonly not legally competent, and written informed consent had to be obtained from a patient's legal representative. However, if a legal representative was not available and treatment could not be delayed due to medical reasons, the responsible physician in charge was allowed to decide whether or not to include the patient according to the assumed patient's will. This decision was made under careful consideration of the patient's relative opinion regarding the patient's will. Simultaneously, the appointment of a legal representative through the responsible judge at the local court (Amtsgericht) was requested within the next working day.

As soon as a legal representative was appointed by the local judge, written informed consent was obtained from this representative. At any time, if patients regained decision-making capacity, consent was then sought directly from the patients.

Patient eligibility

Inclusion and exclusion criteria (see Table 1) were assessed in all adult patients on mechanical ventilation with acute renal failure requiring renal replacement therapy. With regard to heparinization, patients could not be included into the study, when there was a need for effective systemic anticoagulation defined as an aPTT goal >20% above the upper limit of normal (as given by the local laboratory institution). However, when this need arose at any time after inclusion and randomization, the patients could remain in the study, regardless whether they were randomized to regional citrate or systemic anticoagulation. The presence of any liver disease was not an exclusion criterion. Patients with HIT were excluded from the study due to 50% probability to be randomized to the group being treated with heparin anticoagulation, which is contraindicated in these cases.

Table 1. Criteria for inclusion, exclusion and patient withdrawal

Inclusion criteria
Written informed consent given
Adult patients >18 years
Diagnosis of acute renal failure and indication for renal replacement therapy as assessed by one of the following criteria: (i) volume overload, not correctable by diuretics in spite of adequate blood pressure and creatinine >1.2 mg/dL; (ii) increase of serum creatinine >2.5 mg/dL or BUN >50 mg/dL; and (iii) increase of serum potassium >5.5 mmol/L due to oligoanuria
Patients who at the time of inclusion had not yet started with renal replacement therapy
Arterial line as vascular access
Mechanical ventilation
Exclusion criteria
HIT
Need to continue effective systemic heparin anticoagulation with an aPTT >20% above the upper limit of the normal range
Metabolic alkalosis as defined by a pH >7.50 and base excess of >+4 mmol/L
Pregnancy, lactation period
Patient on chronic renal replacement therapy
Participation in another study during the preceding 3 months
Previous participation in the same study
Patient withdrawal and dropout
Severe metabolic alkalosis as defined by an increase of pH >7.55 and base excess of >+8 mmol/L without possibility of respiratory/ventilational compensation
Severe citrate accumulation as defined by pH <7.20 and BE <−10 mmol/L and no obvious cause other than citrate overload, especially no intoxication, ketoacidosis, or lactacidosis
HIT developing during study
By wish of the patient or legal representative (withdrawal of the declaration of consent)
General deviation from the study protocol
Decision of the investigator

Treatment intervention

After 1:1 randomization, one group (HF-Citrate group) was treated with a citrate-based CVVH solution as regional citrate anticoagulation, and the other group (HF-Bicarbonate group) was treated with systemic heparin anticoagulation and a bicarbonate-based CVVH solution. The day, when CVVH treatment was initiated, was characterized as Day 0. The study comprised a treatment phase and a follow-up phase. The treatment phase was equal to the time on CVVH until death, recovery of renal function or switch to another renal replacement therapy. The follow-up phase was the time from discontinuation of CVVH until discharge from the intensive care unit up to a maximum of 30 days.

A detailed description of the citrate CVVH system has been published earlier [14]. In summary, all CVVH treatments were performed in a pre-dilution mode using standardized equipment (HF Multifiltrate system, AV600S high-flux membrane, surface area 1.4 m^2, both Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany). Flow rates of blood and substitution fluid were adopted to the equivalent of ~4 mmol citrate per 1000 mL of treated whole blood and then adapted to the patient's weight range (see Figure 1). Calcium losses caused by the extracorporeal clearance of citrate–calcium complexes were substituted by intravenous infusion of a 5.5% calcium chloride solution. Pre-dilution substitution flow rates varied between 2000 and 4000 mL/h based on generally accepted dosing recommendations, whereby the dilution of uraemic

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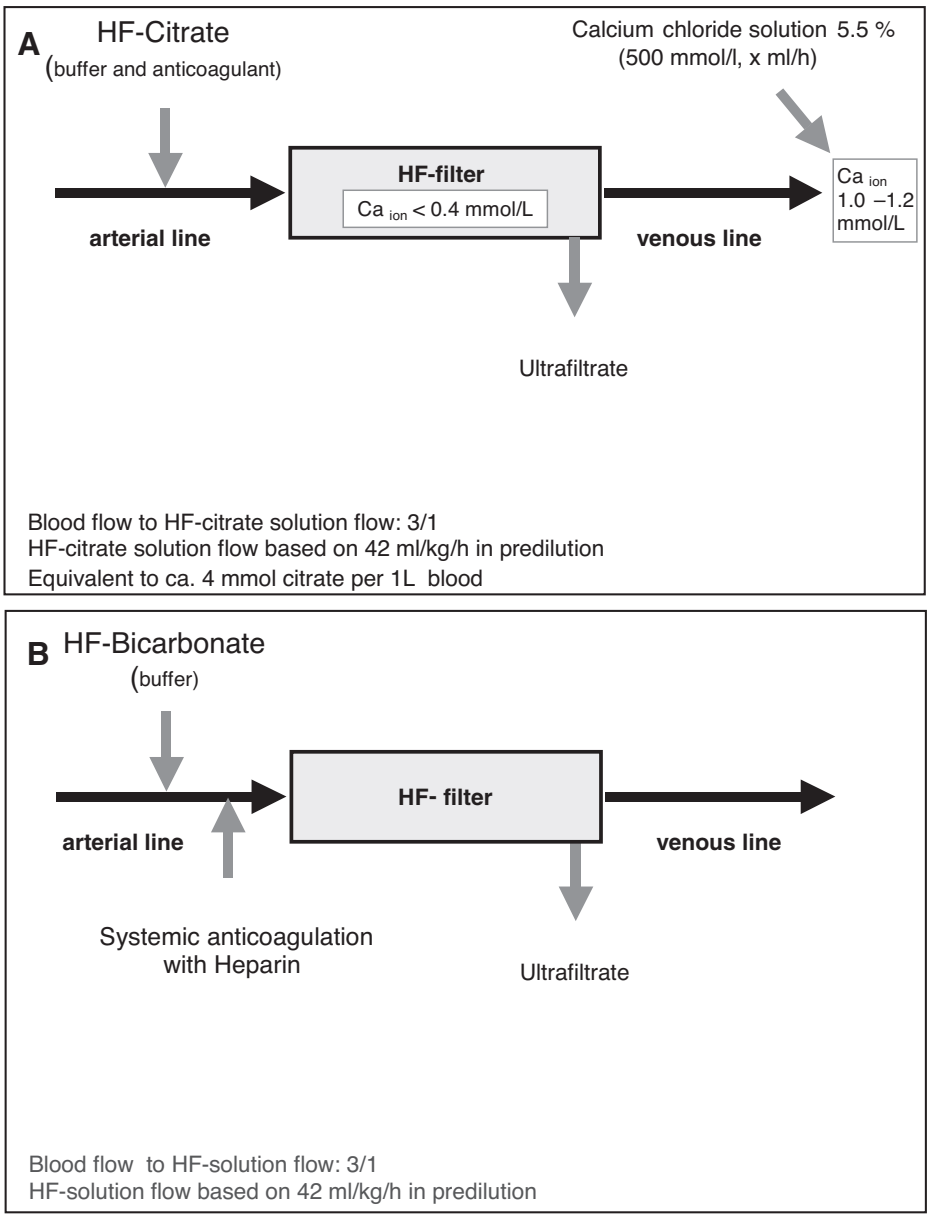


Fig. 1. CVVH circuit with HF-Citrate (**A**) and HF-Bicarbonate (**B**).

toxins by pre-dilution was compensated by adequately increasing the substitution flow to ~42 mL/kg/h [6,15]. The composition of the two haemofiltration solutions HF-Citrate and HF-Bicarbonate is listed in Table 2.

Table 2. Composition of the study solutions HF-Citrate and HF-Bicarbonate

	HF-Citrate	HF-Bicarbonate
Sodium (mmol/L)	140	140
Potassium (mmol/L)	2.0	2.0
Calcium (mmol/L)	–	1.5
Magnesium (mmol/L)	0.75	0.5
Chloride (mmol/L)	104.7	111
Citrate (mmol/L)	13	–
Bicarbonate (mmol/L)	–	35
Glucose (g/L)	1	1
Theoretical osmolality (mosmol/L)	266	296
pH value	6.5–7.8	7.25–7.45

Objectives

The primary objective was to evaluate the efficacy of HF-Citrate in comparison with HF-Bicarbonate. The chosen parameter of efficacy was the patients' acid base status on Day 3 and on each consecutive day.

Secondary objectives were to evaluate efficacy and safety of HF-Citrate in comparison with HF-Bicarbonate with particular focus on control of uraemia, intensity of anticoagulation, mortality, the incidence of HIT and bleeding, disturbances of calcium homoeostasis, and haemofilter patency.

Data collection and statistical analysis

Clinical parameters, CVVH parameters and blood gas analyses were collected every 6 h in defined time frames. Other laboratory parameters, reasons for interruptions of CVVH treatment and concomitant medications were collected every 24 h. All bleeding episodes, whether classified as mild (no systemic symptoms), moderate (systemic symptoms and/or Hb drop >2 g/dL/day) or severe (need for transfusion), were documented as well.

To evaluate the primary objective of the study, the 'principle of confidence interval inclusion' was used. A hierarchical test principle was applied

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starting at the first value for standard bicarbonate at Day 3 and continued stepwise for each consecutive value (obtained every 6 h) until the test failed significance. A two-sided 95% confidence interval for the difference of the group means (HF-Citrate minus HF-Bicarbonate) of the standard bicarbonate values at the respective time point was calculated. If this confidence interval was entirely within an interval (from −3 to +3 mmol/L), the two solutions were considered clinically equivalent.

Sample size calculation was performed with an alpha of 5% (two-sided), an assumed standard deviation of 3.5 mmol/L for standard bicarbonate [16], and an expected group difference of 1 mmol/L. Assuming that >90% of all patients would have been eligible for the per-protocol set, the power of the first test at Day 3 at morning would have been clearly >80% with a sample size of 120 patients, i.e. 60 per group.

All statistical analyses were performed using SAS® version 9.1.3. The data are presented as number of observations (percent of patients), means (95% confidence interval) or medians (interquartile ranges). We compared variables using Student's *t*-test or Mann–Whitney *U*-test, as appropriate.

Results

Patient recruitment and analysis sets

In total, 174 patients were randomized to one of the two treatment strategies with equal distribution of 87 patients within each group. Four patients randomized to HF-Bicarbonate received no study medication. Thus, the full analysis set for all safety analyses comprises 170 patients – 87 of them in the HF-Citrate group and 83 patients in the HF-Bicarbonate group. All analyses of efficacy were done in 62 patients in the HF-Citrate group and 47 patients in the HF-Bicarbonate group, who were on CVVH treatment at least until Day 3. This per-protocol set derived from the full analysis set as shown in Figure 2.

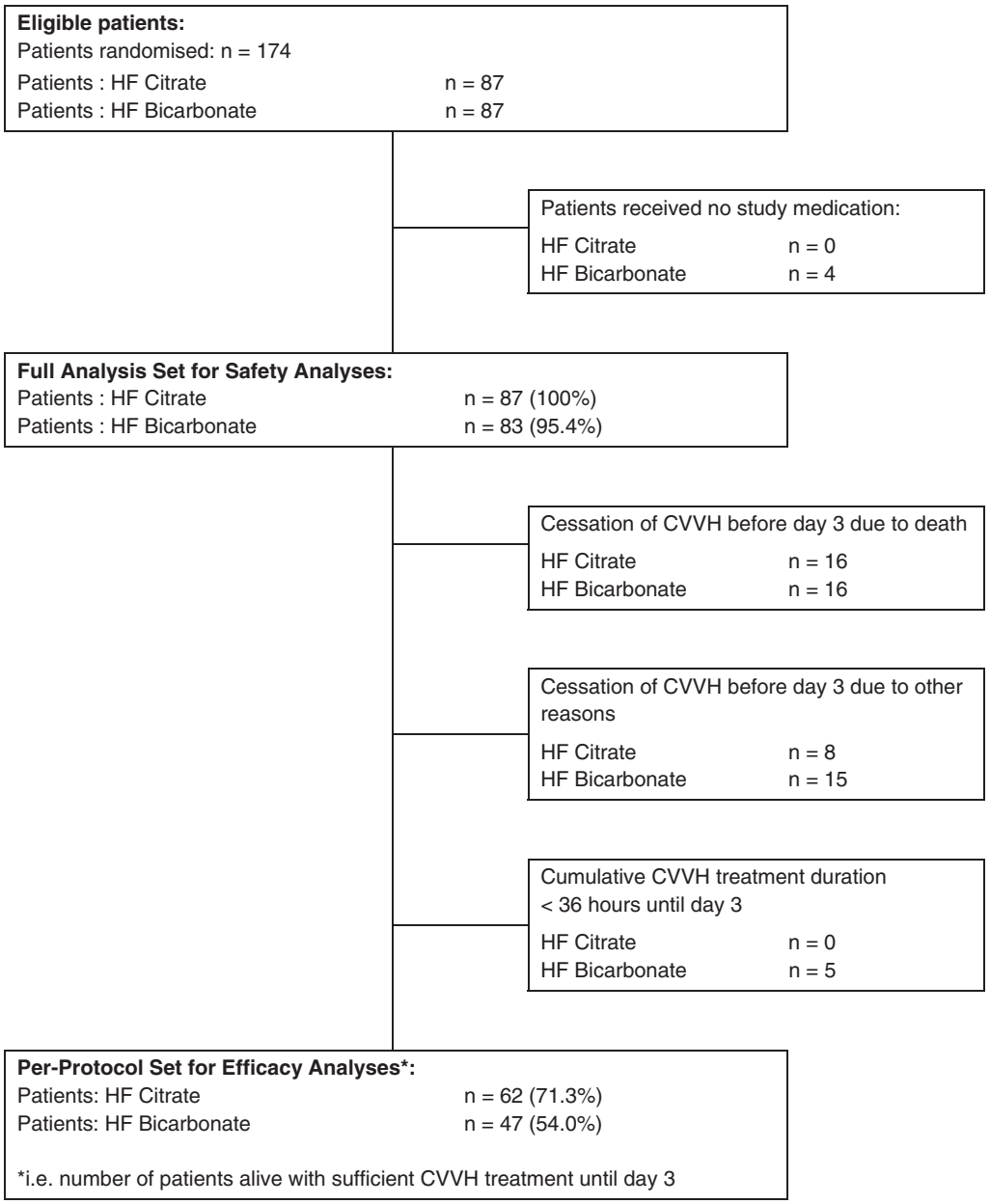


Fig. 2. Patient recruitment and analysis sets.

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Baseline data

Table 3 shows the demographic parameters of the study population. Baseline characteristics as well as the mean Sequential Organ Failure Assessment (SOFA) summary scores and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were similar between the two treatment groups. In the calculation of APACHE II scores, the Glasgow Coma Scale was not included because sedation and mechanical ventilation in all patients prevented an accurate assessment of this parameter. As mentioned above, the presence of liver disease was not an exclusion criterion. Twenty-five percent of the patients in the HF-Citrate group had a medical history of hepatobiliary disorders, including 6% with known liver cirrhosis. In the HF-Bicarbonate group, 15% of the patients had a history of hepatobiliary disorders including 5% with known liver cirrhosis. Sepsis was the major reason for acute renal failure (79.0% in the HF-Citrate group and 76.6% in the HF-Bicarbonate group). In 46.8% of patients in the HF-Citrate group and 48.9% of patients in the HF-Bicarbonate group, acute renal failure occurred after surgery.

Primary efficacy outcome

The comparison of mean standard bicarbonate on Day 3 as the primary efficacy parameter confirmed equivalence between citrate- and bicarbonate-buffered CVVH treatment. At inclusion, standard bicarbonate values were similar between the two treatment groups. Mean standard bicarbonate values at the morning of Day 3 (start of testing for equivalence) were 24.2 mmol/L in the HF-Citrate group ($n = 62$) and 25.1 mmol/L in the HF-Bicarbonate group ($n = 47$) – a difference of −0.8 mmol/L. At noon on Day 11, mean standard bicarbonate results were 24.7 mmol/L in the HF-Citrate group ($n = 20$) and 23.3 mmol/L in the HF-Bicarbonate group ($n = 12$) – a difference of 1.4 mmol/L. The hierarchical test procedure ended at noon on Day 11 when the confirmatory test procedure for equivalence was no longer statistically significant (Table 4).

Due to safety reasons, additional sodium bicarbonate infusions according to the physician's judgment were allowed in the study population. Compared with the HF-Bicarbonate group, more patients in the HF-Citrate group (23% versus 12%, P = 0.07) received additional sodium bicarbonate at least once at some point during the study.

Secondary efficacy outcome

Control of uraemia. Control of uraemia was evaluated on Day 3 in order to provide steady-state data that reflect the intensity and effective treatment time of the applied CVVH dose. Mean plasma urea levels on Day 3 were 73 ± 26 mg/dL in the HF-Citrate group and 74 ± 30 mg/dL in the HF-Bicarbonate group ($n = 62/47$). Reduction of urea levels from baseline values in these patients (155 ± 71 mg/dL in the HF-Citrate group and 146 ± 68 mg/dL in the HF-Bicarbonate group) was comparable in both groups.

Table 3. Patient characteristics at baseline

Characteristic	HF-Citrate	HF-Bicarbonate
Total (*n*)	87	83
Gender (*n*, male)	57 (65.5%)	59 (71.1%)
Age (years)	61.72 (15.29)	65.11 (12.46)
Ethnic group (*n*, Caucasian)	85 (97.7%)	81 (97.6%)
Sepsis (*n*)	67 (77%)	61 (73.5%)
Post-operative (*n*)	41 (47.1%)	41 (49.4%)
SOFA score	9.95 (2.95)	9.55 (2.59)
APACHE II score (Glasgow Coma Scale excluded)	21.83 (5.07)	22.04 (5.51)

Data are given as mean (SD) or *n* (%).

Table 4. Comparison of the mean morning standard bicarbonate as the primary parameter of efficacy

Visit	*n* HF-Citrate/ HF-Bicarbonate	HF Citrate mean (SD) (mmol/L)	HF Bicarbonate mean (SD) (mmol/L)	Difference	95% CI
Day 0 morning	61/47	22.2 (4.7)	22.9 (4.6)	–	–
Day 1 morning	62/47	23.1 (3.3)	24.1 (4.0)	–	–
Day 2 morning	62/47	24.0 (2.8)	24.6 (2.5)	–	–
Day 3 morning	62/47	24.2 (3.1)	25.1 (2.7)	−0.827	(−1.948–0.294)
Day 4 morning	55/39	24.3 (2.6)	25.2 (2.5)	−0.850	(−1.927–0.228)
Day 5 morning	50/34	24.7 (3.4)	25.0 (2.6)	−0.317	(−1.703–1.069)
Day 6 morning	43/28	24.9 (2.9)	24.2 (2.3)	0.645	(−0.672–1.961)
Day 7 morning	33/22	24.8 (3.1)	24.3 (2.9)	0.489	(−1.182–2.160)
Day 8 morning	29/19	24.7 (3.1)	24.4 (2.6)	0.307	(−1.422–2.036)
Day 9 morning	27/17	24.7 (3.5)	24.8 (2.3)	−0.013	(−1.947–1.921)
Day 10 morning	20/15	24.4 (2.7)	24.0 (2.8)	0.392	(−1.501–2.286)
Day 11 morning	20/12	24.6 (2.9)	24.2 (2.5)	0.393	(−1.669–2.456)
Day 11 noon	20/12	24.7 (2.8)	23.3 (2.8)	1.397	(−0.682–3.475)

An overview of the morning standard bicarbonate values. The hierarchical test procedure started on Day 3 and ended at noon on Day 11 when the confirmatory test procedure for equivalence was no longer statistically significant.

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Anticoagulation. The mean daily heparin dose in the HF-Citrate group was 5428 ± 6029 IU (median 3240 IU, n = 62) compared with 13 174 ± 7440 IU (median 12 639 IU, n = 47) in the HF-Bicarbonate group ($P < 0.001$). Corresponding to these different heparin doses, mean aPTT values were significantly higher in the HF-Bicarbonate group throughout the study (data not shown).

Safety outcome

Mortality. Mortality was high in the study population. Forty-one patients in the HF-Citrate group (47%) and 34 patients in the HF-Bicarbonate group (41%) died during the study period. As outlined above, 16 patients in both study groups (19% of all patients) died within the first 2 days.

The mortality rates per day both for the treatment phase and for the complete study period (treatment phase and follow-up phase) were similar across the treatment groups. Mortality during CVVH treatment was 3.1% per day in the HF-Citrate group and 3.1% per day in the HF-Bicarbonate group (n = 87/83). During the whole study period, mortality was 3.8% per day in the HF-Citrate group and 3.4% per day in the HF-Bicarbonate group (n = 87/83). A Kaplan–Meier survival analysis showed that there was no statistically significant difference in survival up to Day 30 between the two treatment groups ($P = 0.67$) (see Figure 3).

HIT. The incidence of HIT was higher in the HF-Bicarbonate group compared with the HF-Citrate group both during the treatment phase (7.2% versus 3.4% of all patients) as well as the whole study period (9.6% versus 4.5% of all patients). One surviving patient in the HF-Bicarbonate group retained permanent health defects that were attributed to HIT, and the other patients experienced no secondary complications as judged by the local investigator.

Bleeding complications. More patients in the HF-Bicarbonate group (14.5%) had bleeding episodes under CVVH than patients in the HF-Citrate group (5.7%). The patients' risk of bleeding per CVVH day was assessed by calculating the occurrence rates of bleeding during CVVH (number of days with bleeding complications per patient/number of days of CVVH per patient). The mean occurrence of bleeding per CVVH day was 0.03 ± 0.13 in the HF-Citrate group and 0.05 ± 0.18 in the HF-Bicarbonate group (n = 87/81, $P = 0.06$). Most bleeding episodes were classified as mild (no clinical symptoms, no drop in haemoglobin concentration >2 g/dL/day). Moderate and severe bleeding episodes, defined as a drop in haemoglobin concentration >2 g/dL/day or the need for red cell transfusions, were documented in four patients in the HF-Citrate group and five patients in the HF-Bicarbonate group.

Calcium homeostasis. Only one patient in the HF-Citrate group had to be withdrawn from the study according to the protocol due to assumed citrate accumulation. This patient with known liver cirrhosis developed a high ratio of total to ionized calcium due to vigorous calcium supplementation in order to counterbalance the drop of ionized calcium caused by citrate accumulation. This phenomenon relieved quickly after cessation of citrate infusion. Though citrate was tolerated by all patients except for one, derangements of calcium homeostasis occurred more often in the HF-Citrate group compared with the HF-Bicarbonate group. The risk of hypocalcaemia ($Ca^{++} < 0.9$ mmol/L) and hypercalcaemia ($Ca^{++} > 1.35$ mmol/L) was evaluated by dividing the number of values outside these limits per patient by the number of total measurements per patient. For both parameters, the mean occurrence rates were significantly higher in the HF-Citrate group compared with the HF-Bicarbonate group (hypercalcaemia: 0.08 ± 0.14 versus

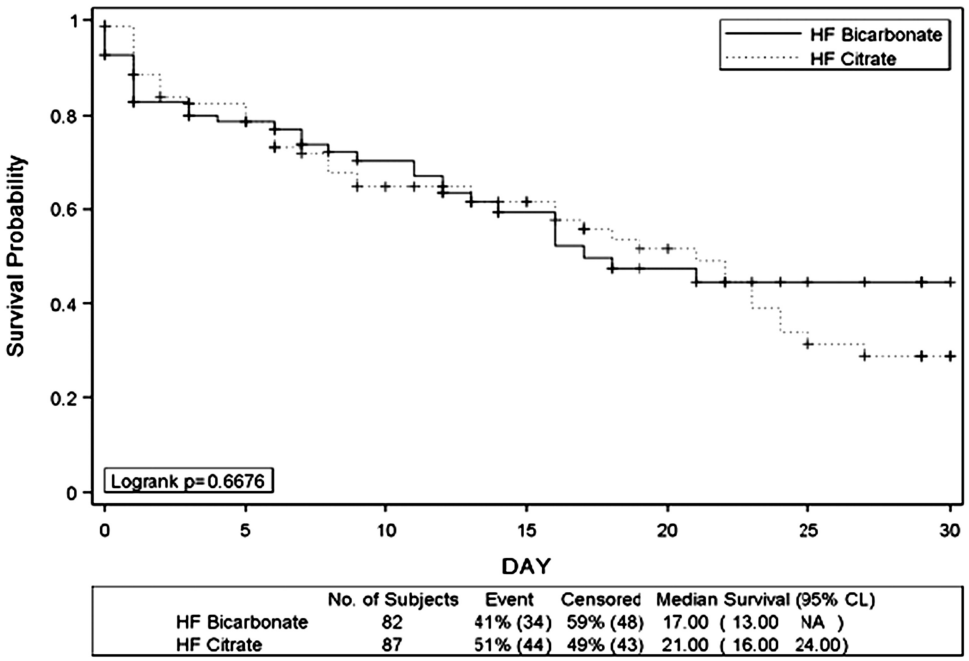


Fig. 3. Kaplan–Meier survival analysis up to Day 30.

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0.03 ± 0.12, P < 0.001; hypocalcaemia: 0.08 ± 0.16 versus 0.05 ± 0.20, P < 0.001).

Haemofilter patency. Mean haemofilter patency as a parameter of technical safety was significantly longer in the HF-Citrate group compared with the HF-Bicarbonate group (37.5 ± 23 h versus 26.1 ± 19 h, P < 0.001, n = 87/81). The mean duration of interruption of CVVH was 1.7 h per day in the HF-Citrate group compared with 2.8 h per day in the HF-Bicarbonate group, a difference that was not statistically significant.

Discussion

The present study is, to our knowledge, the first randomized prospective multicentre trial comparing systemic heparin anticoagulation with regional citrate anticoagulation in critically ill patients requiring continuous renal replacement therapy. Since 1990, when Mehta introduced citrate anticoagulation in CRRT [17], only three rather small randomized trials comparing citrate with unfractionated heparin for a limited treatment time revealed less bleeding and longer or similar circuit survival with citrate but did not focus on other clinical outcomes or mortality [18–20].

Our primary objective, the control of acid base status, is a major therapeutic goal in patients with multi-organ failure needing renal replacement therapy. Our concept of using citrate as the only buffer substance to be applied through haemofiltration is safe and effective since the equivalence of standard bicarbonate in both patient groups from Day 3 to Day 11 could be demonstrated. More patients in the HF-Citrate group needed additional bicarbonate infusions compared with the patients treated with heparin; however, this did not reach statistical significance. Comparisons with other previously described systems cannot be made since, to our knowledge, data focusing on the need of additional bicarbonate infusions to control metabolic acidosis are missing in previous published studies. However, since other systems allow a variable combination of bicarbonate-free and bicarbonate-containing haemofiltration solutions [10] or variations of citrate, blood and dialysate flow rates [12] in accordance to the patient's acid–base status, these might allow a more rapid correction of metabolic acidosis compared with our system. The risk of metabolic alkalosis with the use of combinations of citrate and bicarbonate is low [10,12] and possibly even lower than in a standard bicarbonate CVVH as long as treatment algorithms are accurately followed [10].

Regional anticoagulation with citrate does not eliminate any need for heparin since, as seen in our study, many other indications for systemic anticoagulation may emerge during therapy. We saw no adverse effects of the combined therapy with regional citrate and systemic heparin. As other studies suggest [10,12,18–20], we were able to demonstrate that lower doses or even no heparin in the HF-Citrate group transfers to lower risks of bleeding and HIT when citrate is used for regional anticoagulation. Moreover, clotting in the extracorporeal circuit can be more effectively controlled by citrate, leading to prolonged haemofilter patency compared with heparin use. An important consideration in the development of our study protocol was to reduce the complexity of the system and to allow only variations in the calcium substitution flow. Therefore, the ratio of citrate to blood flow—though principally possible—was not adjusted to the post-filter calcium concentration. This might explain the slightly shorter filter lifetime compared with others [12].

Irrespective from the advantages of citrate that were seen in our study, we cannot confirm a beneficial effect of citrate anticoagulation on mortality, which was a finding of a randomized single-centre trial comparing regional citrate with systemic nadroparin [10]. In our study, the daily mortality rates during CVVH treatment were 3.1% in both patient groups. As in many other units, sepsis was the predominant reason for death in our patients. There is a variety of different pathophysiological mechanisms that lead to organ failure in septic patients. The complexity of the sepsis syndrome renders the question whether any single procedure will ever have a clear-cut effect on mortality. Therefore, it is comprehensible for us that we could not demonstrate an effect of the anticoagulation protocol on mortality in our patients even though the exposure to citrate was considerably longer (8.5 days versus 2.7 days) compared with the aforementioned trial that suggested a survival benefit in a citrate population [10].

Though we were able to simplify regional citrate anticoagulation compared with other systems, metabolic derangements occurred significantly more often compared with heparin anticoagulation. These are largely inherent to the mechanism of citrate providing anticoagulation through chelating calcium ions [11]. In particular, we saw more episodes of hypocalcaemia as well as hypercalcaemia in the patients treated with citrate. Though most episodes were not judged as serious by the local investigators, there is an additional risk for the patients that has to be outweighed against the risks of systemic heparin.

In conclusion, this multicentre randomized trial comparing regional citrate anticoagulation with systemic heparin anticoagulation confirmed equivalence between citrate and bicarbonate with regard to treatment efficacy. Using citrate as the only buffer substance appears to be appropriate even though some patients needed additional bicarbonate. In our study, citrate anticoagulation has distinct advantages with regard to haemofilter patency and the risk of HIT and bleeding. However, there were more metabolic disturbances with citrate anticoagulation, and we saw no beneficial effect on mortality. Of course, these findings only apply to our system and our patient population. However, in general, we feel that neither citrate nor heparin should be regarded as therapeutic standards. A decision based on a careful assessment of individual patients' risks is therefore required.

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Conflict of interest statement. R.H. is employed by Fresenius Medical Care.

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(See related article by Morgera. Survival benefit with regional anticoagulation with citrate in CRRT: the end of a myth? *Nephrol Dial Transplant* 2011; 26: 9–11.)

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Is fetuin-A a mortality risk factor in dialysis patients or a mere risk marker? A Mendelian randomization approach

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Abstract

Background. Low levels of circulating fetuin-A are associated with increased mortality in dialysis patients. This study aimed to examine a potential causative role for fetuin-A on mortality by investigating whether a functional polymorphism in the alpha2-Heremans–Schmid glyco-

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