Citrate-Based Anticoagulation for Hemofiltration Is Here to Stay, Probably!*

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Continuous renal replacement therapies (CRRTs) in the ICU require anticoagulation of the extracorporeal circuit and hemofilter to prevent clotting and maintain function. The most common method used is the continuous infusion of unfractionated heparin, implying systemic anticoagulation and, therefore, not infrequently complicated by bleeding (1). Citrate-based anticoagulation (CBA) of the extracorporeal circuit during CRRT was first described in 1990 (2) with the aim to reduce the risk of bleeding. CBA achieves regional anticoagulation, that is, limited to the blood of the extracorporeal circuit, avoiding systemic anticoagulation and the associated risk of bleeding. The infusion of sodium citrate at the origin of the arterial blood line induces hypocalcemia in the extracorporeal circuit by chelating calcium ions and thereby interrupting the coagulation cascade. The citrate-calcium complex is partially filtered and eliminated with the ultrafiltrate, and calcium chloride is infused to compensate for the calcium loss. Citrate reaching the systemic blood is metabolized by the liver, muscle, and renal cortex in the Krebs cycle.

CBA has also shown to be significantly more efficient in maintaining patency of the hemofilter (3) compared with unfractionated and low-molecular-weight heparin and, actually, significantly prolongs filter running time in critically ill patients with acute kidney failure during CRRT with CBA (2, 4). Recent randomized controlled trials (RCTs) in this patient population confirm these observations (5, 6).

The practice of CBA, however, used to be a complex and costly procedure (2), requiring preparation of daily customized replacement solutions by pharmacy departments as well as intensive monitoring and intervention in order to avoid or correct metabolic complications. Metabolic alkalosis, hypernatremia, and hypocalcemia were frequent concerns and barriers to implementation of CBA. Citrate accumulation seems to be particularly worrisome in patients with severe shock with lactic acidosis. It is suggested that in this condition lactate competes with citrate for entering the Krebs cycle. In addition, this oxygen-dependent metabolic pathway is impaired due to concomitant severe intracellular hypoxia (7). Potential complications of CBA also include the binding of other electrolytes, metabolic alkalosis, citrate accumulation in patients with severe liver failure (8), overfeeding, effects on other calcium-regulated processes, and alterations of bone metabolism if ionized calcium concentrations are not kept within a normal range (9).

Recent technological developments have significantly increased safety and reduced workload associated with CBA. Commercially available systems with automatic coupled adjustments of flow rates of citrate, calcium, ultrafiltrate, and blood and specific software used in recent RCTs seem to have greatly reduced metabolic adverse events (5, 6) and promoted the use of CBA.

In this issue of *Critical Care Medicine*, Gattas et al (10) report on the results of a multicenter RCT performed in six centers in Australia and one in New Zealand comparing CBA with regional anticoagulation with unfractionated heparin and protamine for CRRT in adult critically ill patients. Although not a standard method in many regions of the world, heparin-protamine anticoagulation was chosen as a control group because it reflects local practices. CRRT modalities were left to the discretion of the attending physician and well balanced between study groups, with venovenous hemodiafiltration being the predominant mode. The main findings of the trial are in line with a recent Dutch multicenter (6) and a Swiss single center RCT (5) and show a significantly reduced frequency of circuit clotting and almost doubling of the first filter's running time in patients undergoing CBA. Interestingly, adverse events were significantly more frequent in the heparin-protamine group than with CBA (10). Although adverse events were uncommon in the trial by Gattas et al (10) and other recent trials (5, 6), CBA, even with automated systems, requires certain specific knowledge of citrate metabolism in order to adequately adjust for variations in circuit and systemic calcium concentrations and acid-base status and avoid citrate accumulation.

No differences in bleeding events or mortality were observed in the study by Gattas et al (10) and the two above-mentioned RCTs. Mortality and cost were significantly reduced in a single-center RCT performed by Oudemans-van Straaten et al (11) comparing CBA with nadroparin.

The choice of the control group may have influenced trial results. For example, most RCTs with heparin-based control groups, for obvious reasons, explicitly excluded patients at high risk or actively bleeding. If considered during the screening phase of a trial, these cases could have been reflected as control group failures. In addition, in this group of patients, CRRT is usually performed without or with low-dose anticoagulation, leading to frequent clotting of the circuit, which

*See also p. 1622.

Key Words: citrate-based anticoagulation; clotting; continuous renal replacement therapy; hypocalcemia; metabolic alkalosis

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has been observed to be associated with increased cost and blood loss (11). In summary, data generated in RCT refer to low-risk bleeding patients and probably explain that no difference in the incidence of bleeding was found by Gattas et al (10). Experience with the potential comparative benefits and drawbacks of CBA in actively bleeding or high-risk patients with severe thrombocytopenia or coagulation abnormalities is therefore lacking. Other subgroups, like patients in septic states, in which heparin-based anticoagulation is less effective, and patients with suboptimal vascular access, in whom clotting is a frequent complication, need to be addressed in future CBA clinical research.

Current Kidney Disease Improving Global Outcome guidelines consider CBA to be the method of choice for CRRT anticoagulation, if no contraindications for citrate infusion exist (12). With 212 randomized patients and 857 circuits, the trial by Gattas et al (10) is the largest multicenter RCT published so far in the field of CBA. The data generated have significant external validity because of the pragmatic design accepting variability inherent to clinical practice. Also, the main study results are highly significant and lend support to the recommendations. Based on the data given in Gattas et al (10) and other recent studies (5, 6), if no contraindications for citrate infusion exist, CBA should be considered a safer and cheaper option than conventional heparin-based anticoagulation and no longer be reserved for patients at high risk of bleeding.

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HIV Infection and Severe Sepsis: A Bitter Pill to Swallow*

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Infection with HIV affects over 1.3 million people in the United States and over 35 million people worldwide (1). Despite improvements in treatment, HIV is still associated with increased morbidity and mortality. Although infectious complications of HIV and AIDS have decreased, noncommunicable diseases such as cardiovascular disease, chronic obstructive pulmonary disease, end-stage renal disease, and diabetes are becoming more common in HIV-infected persons as they are living longer with highly active antiretroviral therapy (HAART) (2).

***See also p. 1638.**

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A Randomized Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults*

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The Participating Sites and Investigators are listed in **Appendix 1**.

Trial Registration (ACTRN12609001079235): A randomized controlled study comparing the effect of two different anticoagulation regimens on filter life during Continuous Renal Replacement Therapy–The Heparin Citrate Study. Date registered December 16, 2009.

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Objective: To determine whether regional anticoagulation of continuous renal replacement therapy circuits using citrate and calcium prolongs circuit life and/or affects circulating cytokine levels compared with regional anticoagulation using heparin and protamine.

Design: Multicenter, parallel group randomized controlled trial.

Setting: Seven ICUs in Australia and New Zealand.

Patients: Critically ill adults requiring continuous renal replacement therapy.

Interventions: Patients were randomized to receive one of two methods of regional circuit anticoagulation: citrate and calcium or heparin and protamine.

Measurements and Main Results: The primary outcome was functional circuit life measured in hours, assessed using repeated events survival analysis. In addition, we measured changes in interleukin-6, interleukin-8, and interleukin-10 blood levels. We randomized 212 subjects who were treated with 857 continuous renal replacement therapy circuits (median 2 circuits per patient [interquartile range, 1–6], 390 in citrate group vs 467 in heparin group). The groups were well matched for baseline characteristics. Patients receiving regional continuous renal replacement therapy anticoagulation with heparin and protamine were more likely to experience circuit clotting than those receiving citrate and calcium (hazard ratio, 2.03 [1.36–3.03]; $p < 0.0005$; 857 circuits). The median lifespan of the first study circuit in each patient was 39.2 hours (95% CI, 32.1–48.0 hr) in the citrate and calcium group versus 22.8 hours (95% CI, 13.3–34.0 hr) in the heparin and protamine group (log rank $p = 0.0037$, 204 circuits). Circuit anticoagulation with citrate and calcium had similar effects on cytokine levels compared with heparin and protamine anticoagulation. There were more adverse events in the group assigned to heparin and protamine anticoagulation (11 vs 2; $p = 0.011$).

Conclusions: Regional citrate and calcium anticoagulation prolongs continuous renal replacement therapy circuit life compared with regional heparin and protamine anticoagulation, does not affect cytokine levels, and is associated with fewer adverse events. (*Crit Care Med* 2015; 43:1622–1629)

Key Words: continuous renal replacement therapy; intensive care; randomized controlled trial; regional citrate anticoagulation

Maintaining the patency of the circuit during continuous renal replacement therapy (CRRT) is an important clinical goal, and anticoagulation of the extracorporeal blood is part of the strategy to achieve it (1). Clotting of blood within the circuit, including the hemofilter, reduces the effectiveness of CRRT and may cause blood loss and decreased solute clearance (2). It also increases treatment cost and workload by shortening circuit life. For these reasons, anticoagulation is commonly used during CRRT. However, systemic anticoagulation may increase bleeding risk. Therefore, techniques have been developed to anticoagulate the CRRT circuit but not the patient. Such techniques are referred to as regional circuit anticoagulation.

Anticoagulation with citrate has been recommended as the most suitable form of CRRT regional circuit anticoagulation (3). When added to blood, citrate induces hypocalcemia, which inhibits coagulation. Calcium is then infused into the patient's bloodstream to maintain systemic normocalcemia and reverse anticoagulation. Regional citrate anticoagulation is particularly suitable for patients at increased risk of bleeding and has been used successfully for many years by early adopters at single sites (4). It has now been developed commercially and has become widespread in various healthcare systems making large-scale evaluation of efficacy and safety desirable.

Regional circuit anticoagulation can also be achieved by infusing heparin at full anticoagulation dose prehemofilter and reversing its effects before blood returns to the patient by means of protamine infusion posthemofilter. This method of regional anticoagulation was used in around 20% of patients recruited in a recent large randomized controlled trial (RCT) of CRRT intensity (5).

It remains unknown in the era of widespread use whether citrate and calcium regional anticoagulation and heparin and protamine regional anticoagulation are equivalent in terms of prolonging circuit life or whether one of these two techniques is superior. Citrate-induced hypocalcemia in the extracorporeal blood may also modulate other calcium-dependent processes, including neutrophil function and arterial stiffness (6, 7); it is unknown if this affects cytokine blood levels differently to other anticoagulation methods.

To address these questions, we conducted a prospective multicenter RCT. We tested the hypothesis that citrate and calcium anticoagulation would be superior to heparin and protamine in maintaining circuit patency and that these two techniques would have different effects on circulating cytokines.

MATERIALS AND METHODS

Trial Design and Setting

This study is a prospective, parallel-group (1:1), RCT and was conducted in the ICUs of seven hospitals: four tertiary referral units and three metropolitan units. Six ICUs were in Australia and one was in New Zealand. The trial was approved by the Sydney Local Health District Ethics Review Committee (RPAH Zone, X09-0068) and by each local ethics committee. There were no changes to the study design after the commencement of recruitment.

Eligibility Criteria

Critically ill adults in ICU were eligible for the study if they fulfilled four criteria: 1) acute renal failure requiring CRRT, 2) suitability for regional anticoagulation of the CRRT circuit, 3) clinical equipoise regarding the method of circuit anticoagulation, and 4) informed consent was given or sought soon after enrolment. Patients were ineligible for the study if they fulfilled any exclusion criterion: 1) expected stay in ICU less than 24 hours, 2) age less than 18 years, 3) pregnant or breastfeeding, 4) suspected ischemic hepatitis or liver failure, 5) known allergy to heparin or protamine, 6) suspected or confirmed heparin-induced thrombocytopenia (HIT), and 7) chronic kidney disease requiring dialysis prior to ICU admission.

Interventions

The study compared two methods for regional anticoagulation of a CRRT circuit. The intervention was regional citrate anticoagulation with maintenance of systemic normocalcemia (citrate group). The control was regional heparin anticoagulation with protamine reversal to avoid systemic anticoagulation (heparin group). The CRRT protocols used at each study site are summarized in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B273) (8). Variation was expected and accepted between study sites with regard to machine, modality, fluids, and initial machine settings. Within each site, other determinants of circuit life were designed to be as similar as possible in the study and control groups (modality, predilution or postdilution, and starting flow rates). CRRT was delivered according to manufacturer's specifications, including scheduled circuit changes after 72 hours of use. CRRT was prescribed by intensivists and delivered by intensive care nursing staff in all study sites. The decision to start or stop CRRT, and determination of the reason for stopping, was carried out by ICU clinicians as usual. Study personnel collected this information at a later time.

Cytokine Measurement

At two study sites, blood was collected from a convenience sample of study patients for serum cytokine measurement. This was done when research staff were immediately available at the commencement of CRRT for the first sample collection and again at 48–72 hours after commencement of CRRT. Samples were centrifuged immediately and serum stored at –70°C for subsequent batch analysis. Samples were assayed by custom-designed human multiplex-cytokine bead array kits (Millipore, Billerica, MA) and analyzed on a Luminex 100 system (Luminex, Austin, TX).

Data Collection

We collected baseline data regarding age, gender, weight, source of admission to ICU, severity of illness (Acute Physiology and Chronic Health Evaluation score II), diagnostic group,

presence of sepsis, mechanical ventilation, inotropes, and basic laboratory variables pertaining to renal function and hematology. Study interventions were discontinued when CRRT was stopped indefinitely or if patients developed a contraindication to their allocated circuit anticoagulation.

Outcomes

The primary outcome was functional circuit life (measured in hours). The functional life of a CRRT circuit commences upon extracorporeal circulation of blood and ends when that circuit is discontinued by ICU staff. ICU staff stopped circuits for one of the following reasons: 1) transmembrane pressure across the circuit exceeded 300 mm Hg, 2) visible clot was obstructing flow through the machine, 3) the blood pump was unable to rotate due to clot obstruction, or 4) other (free-text entry by bedside staff). The first three reasons were considered to be a clotted circuit.

In cases where "other" was recorded by bedside staff or the reason for stopping was missing, adjudication was required. Two senior staff intensivists who were independent of the study reviewed these cases independently and adjudicated the reason for stopping. Disagreements were resolved by mutual consensus. There were three possible outcomes for these adjudicated circuits (clotted, did not clot, or unclear). Circuits stopped electively for process of care reasons (e.g., intrahospital transfer) were deemed "did not clot."

The secondary outcomes were 1) change in interleukin-6, interleukin-8, and interleukin-10 between commencement of CRRT and 48–72 hours later, 2) units of red cells transfused, 3) duration of CRRT (hours), 4) ICU length of stay, and 5) hospital mortality.

Sample Size

A sample size of 220 was planned; this provided for around 200 evaluable patients after 10% withdrawal or loss to follow up. For estimation of the detectable difference in circuit life, we assumed that each subject would contribute at least one study circuit and that subsequent circuits from the same patient would require adjustment for repeated measures in the calculation. Two hundred eighteen study subjects in a study design with two repeated measurements provide 80% power to detect a difference in mean circuit survival of 4 hours (compound symmetry covariance structure, SD 14.80, correlation between observations on the same subject 0.01, α 0.05). Patients stayed in the group allocated at randomization, and all circuits received by those patients were included and analyzed as study circuits.

Randomization

Randomization was stratified by site. Each site used a randomly generated sequence of numbers in permuted block sizes of 4, 6, and 10 to allocate the study group. This was concealed using sequentially numbered, opaque sealed envelopes prior to study commencement by nonstudy personnel. Patients were screened and entered into the study by ICU clinical staff who opened the next envelope in sequence. The statistician was blinded to group allocation until completion of the primary outcome analysis.

Statistical Methods

The primary outcome (circuit life) was analyzed using repeated events survival analysis (9). Heterogeneity across individual trial subjects was expected, along with correlation of the circuit life experienced by multiple circuits from an individual subject. Event dependence within subjects (where the event is a clotted circuit) was excluded prior to analyzing circuit life using a proportional hazard conditional frailty model (an extension of Cox regression). The advantage of the frailty model is that it takes into account the within-cluster correlation. We assumed a shared frailty mode in which the cluster effects are incorporated in the model as normally distributed random variables. The circuits that were stopped without clotting or were stopped for unclear reasons were censored in the survival analysis. A plot of the Kaplan-Meier estimate for the survival function of each subject's first trial circuit was performed, and median circuit life in the two groups was compared using a log-rank test. Median circuit life of the subset of circuits that clotted was also compared. Continuous outcomes that were normally distributed were compared using a *t* test; otherwise, a Mann-Whitney *U* test was used. Proportions were compared using a chi-square test. The survival analysis was carried out using SAS (Enterprise Guide v5.1; SAS Institute Inc., Cary, NC): the syntax used in the PHREG procedure is presented in the **supplemental material** (Supplemental Digital Content 2, http://links.lww.com/CCM/B274). Other analyses were carried using IBM SPSS Statistics for Windows (v20; IBM Corp., Armonk, NY). All patients and circuits remained in their allocated group for analysis according to intention to treat.

RESULTS

Participants and Recruitment

Two hundred twelve subjects were randomized between May 2010 and January 2013. Recruitment was stopped when sample size exceeded 200, and loss to follow up for the primary outcome was known to be low. The flow of participants into the trial is shown in **Figure 1**. Overall, 857 study circuits (390 in citrate group and 467 in heparin group) were used by the study subjects during the study period. Eight subjects (five in citrate group and three in heparin group) were randomized but did not receive CRRT using a study circuit. The remaining 204 patients contributed a median of two circuits (interquartile range [IQR], 1–6) each. The distribution of the number of circuits per subject is shown in **Figure S1** (Supplemental Digital Content 2, http://links.lww.com/CCM/B274).

The demographic and clinical characteristics of the trial subjects at the time of randomization are summarized in **Table 1**. Although 24 of 105 patients (22.9%) in the citrate group were admitted to the ICU from the emergency department, compared with 38 of 107 (35.5%) in the heparin group, the groups were well otherwise well matched at baseline with respect to severity of illness and common renal and hematological laboratory variables.

Circuit Life

Patients receiving regional CRRT anticoagulation with heparin were more likely to experience circuit clotting than those receiving citrate (hazard ratio, 2.03 [1.36–3.03]; $p < 0.0005$;

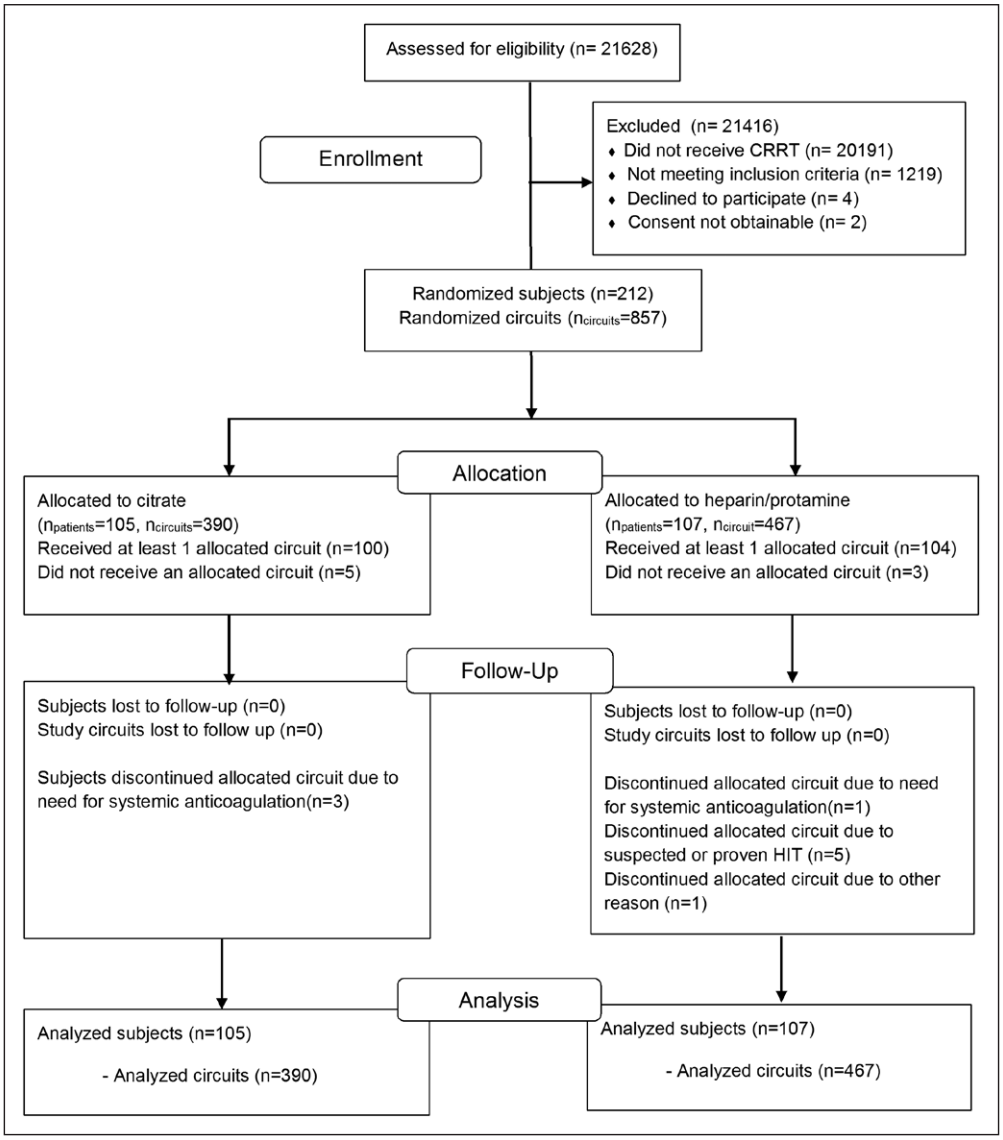

Figure 1. Flow diagram of participants showing assessment of eligibility, enrollment, treatment allocation and follow-up in the trial. CRRT = continuous renal replacement therapy, HIT = heparin-induced thrombocytopenia.

857 circuits using a frailty model; variance [SD] of the random effect 1.23 [0.19]). The probability of the first circuit from each trial subject experiencing loss due to clotting and the median circuit life of the first circuit favored regional citrate anticoagulation for the prolongation of CRRT circuit life (median citrate circuit life of 39.2 hr [95% CI, 32.1–48.0 hr] versus median heparin circuit life of 22.8 hr [95% CI, 13.3–34.0 hr]; log rank $p = 0.0037$; 204 circuits) (**Fig. 2**). Furthermore, 226 of 390 circuits (57.9%) in the citrate group were stopped due to clotting, compared with 310 of 467 (66.4%) in the heparin group ($p < 0.02$). The median circuit life of these clotted-only circuits was 16.5 hr [IQR, 21.1 hr] in the citrate group compared with 11.8 hr [IQR, 14.3 hr] in the heparin group ($p < 0.0001$).

Secondary and CRRT Process Outcomes

There was no significant difference between the citrate and heparin groups in the change of circulating levels of interleukin-6, interleukin-8, and interleukin-10 between randomization and 48–72 hours later (**Table 2**). The clinical and CRRT process outcomes are shown in **Table 3**. Overall, 28 of 105 patients (26.7%) in the citrate group died in ICU, compared with 25 of 107 patients (23.4%) in the heparin group ($p = 0.58$). There was no significant difference in ICU length of stay, hospital mortality, or red cell transfusion. Patients in the citrate group used 390 circuits for a cumulative total of 8,281 hours of renal replacement therapy, compared with 467 circuits and a cumulative total of 8,015 hours of therapy in the heparin group. Dialysis catheter site, CRRT modality, and starting blood flow rates are shown in **Table S2** (Supplemental Digital Content 2, http://links.lww.com/CCM/B274).

Adverse Events

There were more adverse events in the heparin group (11 events, three serious) compared with the citrate group (two events, one serious) ($p = 0.011$ for all events) (**Table S3**, Supplemental Digital Content 2, http://links.lww.com/CCM/B274).

The most common adverse event was suspected or confirmed HIT, resulting in discontinuation of study treatment.

DISCUSSION

Key Findings

The key findings of this study are that regional citrate anticoagulation is superior to regional heparin/protamine regional anticoagulant for the prolongation of circuit life during CRRT and is associated with fewer adverse events. The additional key finding is that citrate anticoagulation did not affect circulating cytokine levels differently.

Relationship to Previous Studies

Previous RCTs evaluating citrate have shown longer circuit life compared with heparin controls (10–13) but others have not (14–16). Three of the studies that have shown superior circuit life were multicenter studies where the control group was systemic anticoagulation with heparin (11–13). Our study is the only study to compare another regional method of circuit anticoagulation.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Intervention and Control Groups

Variable	Citrate (*n* = 105)	Heparin (*n* = 107)
Age, yr	66.4 (14.3)	66.8 (14.9)
Male gender, *n*/total (%)	74/105 (71)	72/107 (67)
Weight		
Measured (vs estimated), *n*/total (%)	46/105 (44)	50/107 (47)
Weight (kg)	85.0 (20.6)	84.3 (22.9)
Source of admission to ICU, *n*/total (%)		
Emergency department	24/105 (22.9)	38/107 (35.5)
Hospital ward	27/105 (25.7)	19/107 (17.8)
Operating theatre, elective	31/105 (29.5)	33/107 (30.8)
Operating theatre, emergency	4/105 (3.8)	3/107 (2.8)
Transfer from another hospital	4/105 (3.8)	6/107 (5.6)
Transfer from other ICU	9/105 (8.6)	6/107 (5.6)
Not available	6/105 (5.7)	2/107 (1.9)
Time from ICU admission to randomization (hr)		
Median (interquartile range)	25.1 (44.5)	21.5 (44.0)
APACHE III diagnostic group, *n*/total (%)		
Coronary artery bypass grafts	14/105 (13.3)	13/107 (12.1)
Renal disorders	10/105 (9.5)	7/107 (6.5)
Sepsis with shock, nonurinary	8/105 (7.6)	7/107 (6.5)
Other respiratory diseases	6/105 (5.7)	7/107 (6.5)
Valvular heart surgery	5/105 (4.8)	6/107 (5.6)
Other	62/105 (59.0)	67/107 (62.6)
APACHE II score, mean (SD)	25.6 (7.6)	25.0 (6.9)
Meeting criteria for severe sepsis, *n*/total (%)	45/105 (42.9)	32/107 (29.9)
Sequential Organ Failure Assessment score: patients scoring 3+ at time of randomization, *n*/total (%)		
Renal	45/101 (44.5)	51/106 (48.1)
Cardiovascular	69/101 (68.3)	68/106 (64.2)
Respiratory	46/101 (45.5)	51/106 (48.1)
Coagulation	5/101 (5.0)	3/106 (2.8)
Liver	3/101 (3.0)	7/106 (6.6)
Mechanically ventilated, *n*/total (%)	77/105 (73.3)	75/107 (73.3)
Receiving inotropes, *n*/total (%)	74/105 (68.4)	71/107 (66.4)
Renal variables, mean (SD)		
Urea (mmol/L)	21.9 (13.3)	23.4 (13.8)
Creatinine (μmol/L)	309 (157)	322 (177)
Phosphate (mmol/L)	2.02 (0.83)	1.94 (0.94)
Urine output in 6 hr prior to randomization (mL)	170 (262)	190 (222)

Continued

TABLE 1. (*Continued*). Baseline Demographic and Clinical Characteristics of the Intervention and Control Groups

Variable	Citrate ($n = 105$)	Heparin ($n = 107$)
Hematologic variables, mean (SD)		
Hemoglobin (g/L)	98.0 (16.6)	98.3 (26.2)
Platelet count (× 10^9/L)	209 (146)	215 (143)
International normalized ratio	1.5 (1.2)	1.4 (0.52)
Activated partial thromboplastin time (s)	40 (18)	40 (14)

APACHE = Acute Physiology and Chronic Health Evaluation score.
Criteria for severe sepsis is defined as two or more signs of systemic inflammatory response syndrome.

This comparator was chosen because regional anticoagulation with heparin and protamine is extensively used in Australia/New Zealand (5) and elsewhere. Overall, systematic reviews and practice guidelines have recommended the use of citrate on the basis of expert opinion and weak evidence (3, 4, 17–20).

The adverse effect profile also favored citrate in this trial, a finding similar to that of other studies (10–13, 15, 16). Our study was not able to detect any novel benefits associated with citrate, such as modification of circulating cytokines, and there was no significant difference in mortality. The aforementioned multicenter studies also reported no difference in mortality. One study that compared regional citrate with systemic low-molecular-weight heparin reported a mortality benefit in the citrate group (16), and we hypothesize that the choice of a different control group may be relevant if this was not a chance observation.

Implications of Study Findings

These data provide a compelling argument for the use of regional citrate anticoagulation in order to maximize the effective delivery of CRRT in ICU patients. There are also clear potential cost-saving implications from our results if ICUs realize the benefits of less circuit downtime and fewer circuit changes. We recommend the use of regional citrate anticoagulation during CRRT as first-line treatment in suitable patients.

Strengths and Limitations

This study has several strengths. It is a very large study compared with other RCTs evaluating regional citrate anticoagulation with 857 circuits randomized (10–16). The treatment effect was large and obvious, not only in terms of the hazard ratio for the primary outcome but also in terms of the median lifespan of the first circuit, and the median lifespan of the circuits that were stopped due to clotting. A higher proportion of circuits in the citrate group did not clot, and fewer citrate circuits were used to achieve an overall longer cumulative duration of time on CRRT. Citrate performed better than heparin even though control group circuit life was relatively high (median, 22.8 hr). Furthermore, the generalizability of our study is high because of its multicentric design and our pragmatic acceptance of variation in CRRT citrate protocols between sites. Finally, this trial also reflects modern CRRT practice patterns: regional citrate anticoagulation is widespread, commercially developed, and technically easier to deliver than in the past. Other ICUs are likely to experience similar benefits, including cases where the citrate CRRT protocols are not identical to our own.

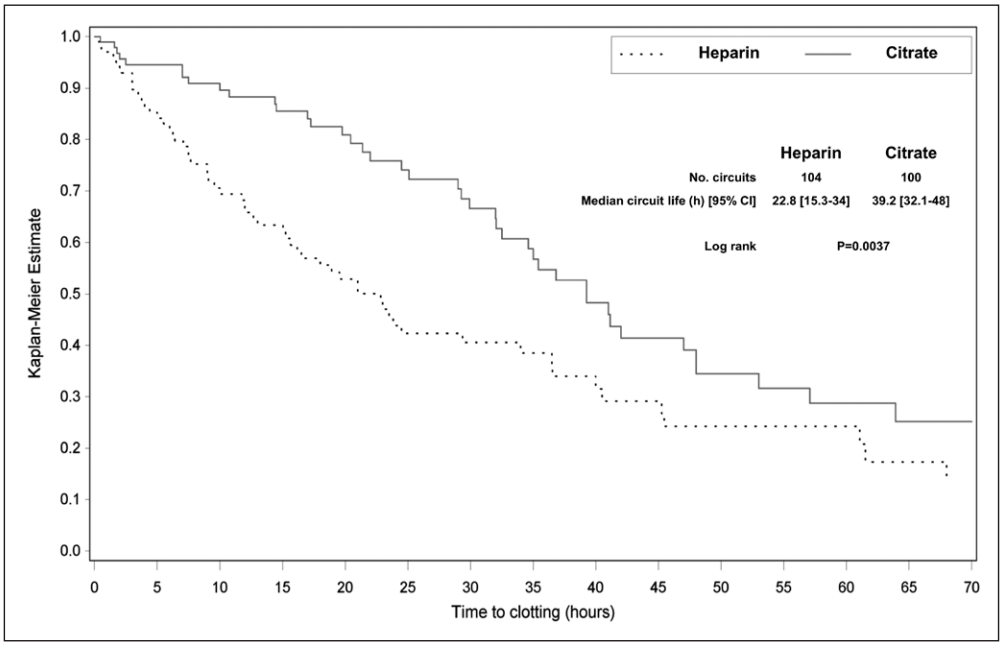

Figure 2. Kaplan-Meier estimate of the probability of continuous renal replacement therapy circuit survival for the first circuit.

Weaknesses of this trial include the fact that it was unblinded. However, blinding was not practical. Furthermore, our study was also underpowered to detect significant differences in patient-centered outcomes, such as mortality, time in ICU, time in hospital, and renal recovery. Follow-up time was short and limited to ICU with the exception of hospital outcome, and no

TABLE 2. Change in Interleukin-6, Interleukin-8, and Interleukin-10 Levels Between 0 and 48–72 Hr Following Commencement of Continuous Renal Replacement Therapy

	Citrate[a]			Heparin[b]			
Variable	*t* = 0 Hr	*t* = 48–72 Hr	Change Score	*t* = 0 Hr	*t* = 48–72 Hr	Change Score	*p*[c]
IL-6, median, pg/mL (IQR)	102.7 (214.0)	48.3 (58.1)	−29.3 (171.5)	141.7 (285.6)	53.8 (99.0)	−66.5 (262.1)	0.4
IL-8, median, pg/mL (IQR)	108.0 (114.0)	54.7 (42.6)	−26.2 (127.4)	115.8 (132.4)	53.8 (48.8)	−25.8 (131.0)	0.86
IL-10, median, pg/mL (IQR)	40.3 (63.3)	36.7 (44.9)	−0.7 (39.6)	37.7 (143.0)	36.2 (53.2)	−6.9 (111.1)	0.76

t = time (hours from start of continuous renal replacement therapy circuit), IL = interleukin, IQR = interquartile range.

[a]Subset of 22 paired samples in the citrate group.

[b]Subset of 21 paired samples in the heparin group.

[c]Comparison of median change scores in the citrate and heparin groups (Mann-Whitney *U* test).

Blood was collected at *t* = 0 hr in an additional 12 patients but the circuit was stopped in less than 48 hr (for clotting in four patients and other reasons in eight patients).

TABLE 3. Clinical Outcomes and Continuous Renal Replacement Therapy Process Measures

Variable	Citrate (*n* = 105)	Heparin (*n* = 107)	Total	*p*
Clinical				
ICU mortality, *n*/total (%)	28/105 (26.7)	25/107 (23.4)		0.58
ICU length of stay, median (IQR), d	9.0 (12)	9.0 (13)		0.79
Hospital mortality, *n*/total (%)	33/105 (31.4)	31/107 (29.0)		0.7
Red cells transfused				
Patients transfused, *n*/total (%)	52/101 (52)	48/103 (47)		0.58
Volume of red cells, mean (SD)	908 (770)	872 (917)		0.83
CRRT process				
Filter outcome				
Clotted	226	310	536	
Did not clot	127	112	239	
Unclear	37	45	82	
TOTAL	390	467	857	
Duration of CRRT				
Total patient time on circuit (hr)	8,281	8,015	16,296	
Per patient on circuit (hr), median (IQR)	55.7 (86.6)	50.6 (73.4)		0.6

IQR = interquartile range, CRRT = continuous renal replacement therapy.

information is available about other clinical outcomes after discharge from ICU. However, the focus of this study was on circuit life.

CONCLUSIONS

Regional citrate and calcium anticoagulation prolongs CRRT circuit life compared with regional heparin and protamine anticoagulation, does not affect cytokine levels, and is associated with fewer adverse events.

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Appendix 1. Participating Sites and Investigators

Chief investigator: David Gattas

Management committee: David Gattas, Dorrilyn Rajbhandari, Celia Bradford, Rinaldo Bellomo

Seven participating hospitals (site investigator is listed first, followed by research team members)

1. Royal Prince Alfred Hospital (NSW, Australia): David Gattas, Dorrilyn Rajbhandari, Heidi Buhr, Megan Keir, Jodie Cowell
2. Austin Hospital (VIC, Australia): Rinaldo Bellomo, Glenn Eastwood, Leah Peck, Helen Young
3. Auckland City Hospital (New Zealand): Shay McGuinness, Rachael Parke, Eileen Gilder, Jodi Brown
4. Royal North Shore Hospital (NSW, Australia): Celia Bradford, Simon Finfer, Elizabeth Hickson, Heather Low, Lewis Macken, Anthony Delaney, Richard Lee, Carole Foot, Julie Potter, Anne O'Connor, Susan Ankers, Simon Bird
5. Monash Medical Centre (VIC, Australia): Craig Walker, Pauline Galt, Tammy Lamac
6. Frankston Hospital (VIC, Australia): John Botha, Jodi Vuat, Sharon Allsop, David Lewis, Cameron Green
7. Dandenong Hospital (VIC, Australia): Sanjiv Vij, Katherine Shepherd, Bridget O'Bree