Randomised trial of software algorithm-driven regional citrate anticoagulation versus heparin in continuous renal replacement therapy: the Filter Life in Renal Replacement Therapy pilot trial

Matthew J Brain, Owen S Roodenburg, Natalie Adams, Phoebe McCracken, Lisen Hockings, Steve Musgrave, Warwick Butt and Carlos Scheinkestel

Continuous venovenous haemodiafiltration (CVVHD-F) is the default mode of renal replacement therapy (RRT) in many intensive care units. Unplanned interruptions decrease therapy effectiveness and unnecessary replacements of the extracorporeal circuit increase cost.[1,2] Circuit anticoagulation is a modifiable element in preventing unplanned filter loss. Heparin is the predominant anticoagulant and is often used regionally to avoid a systemic effect by either minimising heparin dosage or neutralising heparin with protamine in returning blood.

Some reports have suggested that circuit calcium sequestration with citrate may improve filter life.[3-9] Compared with heparin, citrate increases therapy complexity and cost[6,10] by requiring systemic calcium monitoring and supplementation to avoid patient hypocalcaemia.[6,8] Methods to simplify citrate delivery include predilution fluids incorporating citrate that mean separate citrate infusions are not necessary and, more recently, software algorithms incorporated into continuous renal replacement therapy (CRRT) machines to control calcium delivery. A consequence of fixed-concentration citrate fluids is higher pre-dilution flow rates, with high effluent dose[11] or a compensatory reduction in dialysate dosage.

In our prospective randomised pilot study, we compared the efficacy and safety of an established regional heparin-based protocol with an 18 mmol/L citrate pre-dilution fluid and paired dialysate solution, delivered using integrated, software-supported algorithms for citrate and calcium delivery. We recorded end points of mortality and dialysis dependence as a feasibility pilot study for an outcomes trial.

Methods

The Alfred and the Monash University human research and ethics committees approved the study protocol, and later approved an amendment for empirical and/or pre-emptive hypocalcaemia management in those receiving citrate therapy (see Appendix 1 at http://www.cicm.org.au/journal.php). Approval was granted for

ABSTRACT

Objective: The effectiveness of continuous renal replacement therapy (CRRT) increases when unplanned circuit failure is prevented. Adequate anticoagulation is an important component. Although heparin is the predominating anticoagulant, calcium chelation with citrate is an alternative, but systemic calcium monitoring and supplementation increase the complexity of CRRT. We assessed efficacy and safety of citrate delivery via integrated software algorithms against an established regional heparin protocol.

Design: Prospective computer randomisation allocated eligible patients to regional citrate or heparin between April and December 2012. Citrate fluids were Prismocitrate 18 mmol/L predilution and Prism0cal B22 dialysate. Hemosol B0 was the default fluid for heparin. The primary outcome was filter running time. Electively terminated circuits were censored. Intention-to-treat (ITT) and per-protocol analyses were performed. Filter survival was compared by log-rank tests and hazard ratios were explored with a mixed-effects Cox model.

Results: 221 filters were analysed from 30 patients (of whom 19 were randomly allocated to citrate filters and 11 to heparin filters). Patients randomly allocated to citrate were older, sicker, with a higher male:female ratio, but of similar weight. Mortality was 37% in the citrate arm and 27% in the heparin arm. All deaths were attributed to underlying disease. Significant crossover occurred from the citrate arm to use of heparin. Median filter survival, by ITT, was not significantly different (citrate, 34 hours; heparin, 30.7 hours; $P = 0.58$). Per-protocol survival favoured citrate (citrate, 42.1 hours; heparin, 24 hours; $\chi^2 = 8.1$; $P = 0.004$). Considerable variation in filter life existed between patients, and between vascular access sites within patients. Safety end points were reached in one heparin and three citrate patients.

Conclusion: Although the per-protocol results favoured citrate when it was actually delivered, the significant crossover between treatment arms hampered more definitive conclusions. Until further studies support improved patient outcomes, increased complexity and complications suggest that anticoagulation choice be made using patient-specific indications.

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Table 1. Baseline characteristics and patient outcomes

Characteristic at randomisation	Citrate	Heparin
Number of patients	19	11
Age (years), mean (SD)	64 (13)	51 (17)
Sex (male), number (%)	12 (63%)	7 (64%)
APACHE III-j score, median (IQR)	80 (58–99)	61 (52.5–91.5)
Weight (kg), mean (SD)	80 (26.3)	78.2 (16.3)
Reason for CRRT,* no. of patients (%)		
Oliguria (urine output < 100 mL in 6-hour period) unresponsive to fluid resuscitation	8 (42%)	7 (64%)
Volume overload (not correctable by diuretics in spite of adequate blood pressure and serum creatinine > 100 µmol/L)	6 (32%)	3 (27%)
Increase in serum creatinine > 300 µmol/L or BUN > 25 mmol/L	13 (68%)	4 (36%)
Increase in serum potassium > 6.5 mmol/L due to AKI	2 (11%)	1 (9%)
Lactic acidosis	1 (5%)	1 (9%)
ICU admission to start CRRT (hours), median (IQR)	43.2 (22.1–89)	10.2 (5–48.8)
Admission details, no. of patients (%)		
Non-operative	12 (63%)	7 (64%)
Cardiovascular system	3 (16%)	4 (36%)
Respiratory system	5 (26%)	1 (9%)
Genitourinary system	2 (11%)	2 (18%)
Septic shock	4 (21%)	1 (9%)
Trauma	1 (5%)	2 (18%)
Other system	4 (21%)	1 (9%)
Mechanical ventilation	17 (89%)	10 (91%)
Mechanical ventilation (hours), median (IQR)	179 (81–398.5)	144 (86–151)
Outcome at 28 days, no. of patients (%)		
Mortality	7 (37%)	3 (27%)
Remained in hospital (% of survivors)	8 (67%)	4 (50%)
Dialysis dependent (% of survivors)	2 (17%)	3 (38%)

APACHE = Acute Physiology and Chronic Health Evaluation. CRRT = continuous renal replacement therapy. BUN = blood urea nitrogen. AKI = acute kidney injury. ICU = intensive care unit. IQR = interquartile range. * > one reason per patient.

obtaining delayed consent from the patient or person responsible if the patient was unable to give informed consent at the time of therapy initiation. Funding was via an Alfred small projects grant and recruitment occurred between April and December 2012. The trial was registered with the Australian New Zealand Clinical Trials Registry. Due to an administrative error, the trial was not declared registered until 18 July 2012 (ACTRN12612000765820), and is recorded as retrospectively registered.

All patients deemed by the duty intensivist to require initiation of RRT were screened for eligibility by treating staff using predefined inclusion and exclusion criteria (see Appendix 2 at http://www.cicm.org.au/journal.php). Enrolled patients were prospectively randomised in an unblocked trial design to receive regional citrate or regional heparin protocols (see Appendix 1). Due to the significant differences in fluids and monitoring, blinding of researchers to treatment protocols was not practical.

The primary outcomes were filter life and treatment safety. Filter life was defined as the time blood was flowing within the extracorporeal circuit. Data for numbers of circuits and blood flow time were extracted from minutely data captured and stored by the Prismaflex machines (Gambro, Australia; software version 6.1) and validated against hourly paper-based observations, with replacement of missing or corrupted digital data from the paper record. Individual circuits were identified by serial number from digital data. For paper-based data, one circuit was assumed per uninterrupted treatment block. The clinical reasons for therapy stoppage (circuit failure or elective cessation), anticoagulation method used, and vascular access site were also recorded with other CRRT parameters (see Appendix 1). Effluent dose was calculated by two methods with different time denominators: the dose over the time that blood was actually flowing, and the dose over the total time that the extracorporeal circuit was loaded.

Thirteen Prismaflex machines were used for CVVHD-F, with integrated proprietary algorithms to control calcium replacement based on expected losses with the prescribed citrate dose, fluid calcium concentrations and prescribed flow rates. Modification of a previously published citrate–calcium algorithm[12] was used for titration of citrate therapy based on measured patient and circuit ionised calcium (iCa^{2+}) levels. Regional heparin titration followed the ICU's standard delivery protocol (see Appendix 1).

Fluids used for citrate were Prismocitrate 18 mmol/L as predilution and Prism0cal B22 as dialysate. Hemosol B0 was the default fluid for heparin. Pretrial staff training on changes to the machines and fluids was provided by Gambro Australia and nursing educators with extensive experience in CRRT delivery. An additional period of intense education on prolonging filter life was provided by Gambro when an earthquake in northern Italy in May 2012 resulted in a shortage of AN69 ST100 filters. Consequently, in the late trial phase, Prismaflex M100 and ST150 circuits were used for some treatments.

Statistical analysis and figure creation were performed in R (R Development Core Team), version 3.0.2[13] (with dependent packages[14-16]), using intention-to-treat and per-

Table 2. Circuit parameters by group, mean (SD)

Circuit parameter	Intention-to-treat group		Per-protocol group	
	Citrate	Heparin	Citrate	Heparin
Patients, *n*	19	11	19	18
Circuits, *n*	96	125	65	156
CRRT period, days	117.1	153.9	95.1	176
Total treatment period, days	144.55	194.6	NA	NA
Circuit blood flow (Qb)				
Maximum, mL/minute (SD)	202 (38)	232 (30)	188 (32)	231 (31)
Mean, mL/minute (SD)	191 (40)	217 (37)	176 (33)	218 (36)
% Run time at maximum Qb, % (SD)	62.2 (32)	59 (35)	64 (33)	59 (36)
Effluent dose (mL/kg/hour$_{run time}$), mean (SD)	50.3 (10.4)	53.2 (10.1)	50.2 (11)	52.6 (9.9)
Effluent dose* (mL/kg/hour$_{circuit loaded time}$), mean (SD)	37.9 (11.6)	44.8 (10.9)	38.6 (11.3)	43.1 (11.6)
Extracorporeal circuit type, *n* (%)				
ST100	85 (89%)	67 (54%)	56 (86%)	96 (62%)
ST150	6 (6%)	10 (8%)	6 (9%)	10 (6%)
M100	2 (2%)	44 (35%)	1 (2%)	45 (29%)
Not recorded	3 (3%)	4 (3%)	2 (3%)	5 (3%)
Vascular access vein, *n* (%)				
Internal jugular	34 (35%)	23 (18%)	22 (34%)	35 (22%)
Subclavian	5 (5%)	8 (6%)	5 (8%)	8 (5%)
Femoral	56 (58%)	35 (28%)	37 (57%)	54 (35%)
Tunnelled internal jugular	1 (1%)	59 (47%)	1 (2%)	59 (38%)

CRRT = continuous renal replacement therapy. NA = not applicable. * Effluent dose for circuit-loaded time is calculated from the time the circuit was loaded to the time taken down; for circuits with missing digital data, cumulative time from paper observations was used.

protocol comparisons. Univariate circuit survival analysis was compared by log-rank tests and visually by Kaplan–Meier curves. Hazard ratios were calculated using a mixed-effects Cox model[16] (a shared frailty model[17]) with sequential optimisation of terms by comparison of likelihood ratios.

Results

Enrolment and randomisation

Between April and December 2012, of 30 patients requiring CRRT, 19 were randomly allocated to citrate and 11 to regional heparin (Figure 1). Group size imbalance was due to unblocked randomisation. All patients randomised to citrate received citrate anticoagulated circuits, but crossover from citrate to heparin occurred in 31 of 96 circuits, with reasons only documented in four cases: nursing preference, workload, unfamiliarity and error. No crossover occurred from heparin to citrate. One heparin and one citrate patient were randomised for significant lactic acidosis without meeting other predefined inclusion criteria, and their results were included in the analysis.
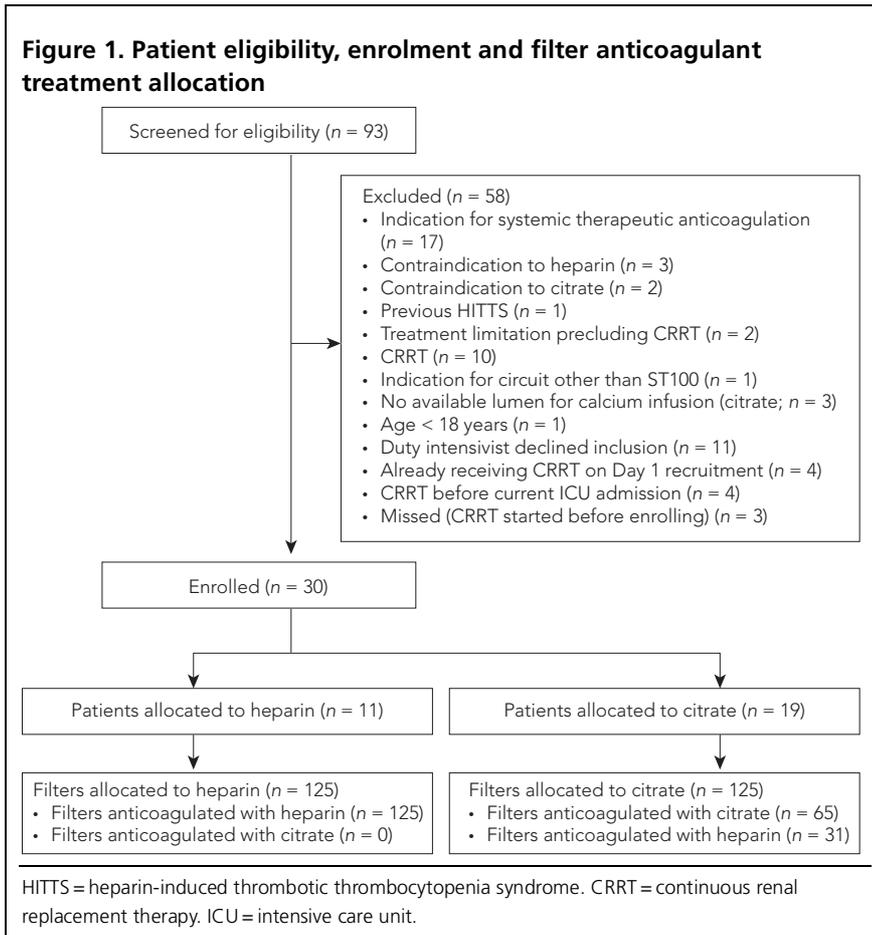
Baseline characteristics and outcomes

Baseline characteristics and outcomes of the two groups are shown in Table 1. All deaths were attributed to underlying disease. Patients randomised to citrate were older and had higher Acute Physiology and Chronic Health Evaluation III-j scores but were of similar weight (73.2 kg compared with 75.8 kg). Time to initiation of CRRT was longer in the citrate group and septic shock a more common diagnosis. A patient who was an outlier in the heparin group received the equivalent of 81 days' RRT over 120 ICU days; this patient contributed to 56 of 59 heparin filters run via a tunnelled internal jugular line.

Circuit parameters and data sources

Digital data were available for 209 of 221 circuits. Two patients had missing digital data for their entire CRRT treatment (one heparin patient and one citrate patient), six patients had missing digital data for at least one filter that was documented on paper charts. Detailed paper observations were missing in one patient for six of 17 treatments that were recorded digitally and confirmed in the progress notes. Circuits that were loaded onto a machine but did not

Figure 1. Patient eligibility, enrolment and filter anticoagulant treatment allocation

Screened for eligibility (*n* = 93)

Excluded (*n* = 58)
- Indication for systemic therapeutic anticoagulation (*n* = 17)
- Contraindication to heparin (*n* = 3)
- Contraindication to citrate (*n* = 2)
- Previous HITTS (*n* = 1)
- Treatment limitation precluding CRRT (*n* = 2)
- CRRT (*n* = 10)
- Indication for circuit other than ST100 (*n* = 1)
- No available lumen for calcium infusion (citrate; *n* = 3)
- Age < 18 years (*n* = 1)
- Duty intensivist declined inclusion (*n* = 11)
- Already receiving CRRT on Day 1 recruitment (*n* = 4)
- CRRT before current ICU admission (*n* = 4)
- Missed (CRRT started before enrolling) (*n* = 3)

Enrolled (*n* = 30)

Patients allocated to heparin (*n* = 11)

Patients allocated to citrate (*n* = 19)

Filters allocated to heparin (*n* = 125)
- Filters anticoagulated with heparin (*n* = 125)
- Filters anticoagulated with citrate (*n* = 0)

Filters allocated to citrate (*n* = 125)
- Filters anticoagulated with citrate (*n* = 65)
- Filters anticoagulated with heparin (*n* = 31)

HITTS = heparin-induced thrombotic thrombocytopenia syndrome. CRRT = continuous renal replacement therapy. ICU = intensive care unit.

run were not included in the results. Circuit parameters are shown in Table 2.

Anticoagulation efficacy

Kaplan–Meier survival estimates did not show a statistically significant difference in median run time when filter survival was analysed by randomised group (citrate 34 hours, heparin 30.7 hours, χ^2 = 0.3, $P = 0.58$) (Figure 2). When filter survival was compared by anticoagulation protocol, citrate was superior (citrate 42.1 hours, heparin 24 hours, χ^2 = 8.1, $P = 0.004$) (Figure 2).

Analyses using an optimised mixed-effects Cox model are shown in Table 3, Table 4, Table 5 and Table 6. Compared with temporary internal jugular access, femoral vascular access catheters consistently provided a lower risk of filter failure, and risk for tunnelled internal jugular lines reached significance only in the per-protocol analysis. Subclavian access was not significantly different to temporary internal jugular access.

Hazard ratios for random effects at an SD of 1 show considerable variation in

Figure 2. Kaplan–Meier estimate of filter survival versus run time.* Median survival times for each curve are 34 hours (citrate) and 30.7 hours (heparin) for intention-to-treat analysis (A), and 42.1 hours (citrate) and 24 hours (heparin) for per-protocol analysis (B)
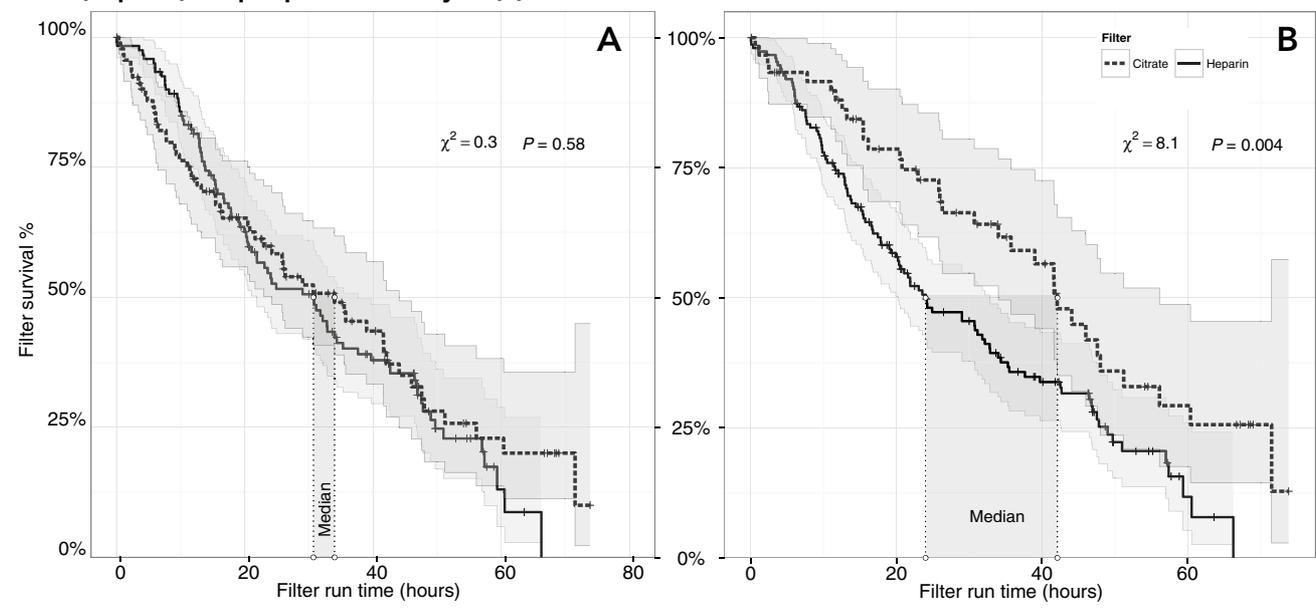
* Black crosses denote censored data.

Table 3. Fixed effects from intention-to-treat analysis of hazard ratios from Cox mixed-effects model for factors influencing filter survival relative to continuous renal replacement therapy, delivered by a temporary internal jugular catheter with citrate anticoagulation

Factors	Hazard ratio (95% CI)	P (Wald test)
Heparin anticoagulation (compared with citrate)	1.62 (0.75–3.5)	0.22
Vascular access (compared with temporary internal jugular vein)		
Temporary subclavian vein	0.48 (0.14–1.68)	0.25
Temporary femoral vein	0.34 (0.16–0.69)	0.0029
Tunnelled internal jugular vein	0.3 (0.08–1.06)	0.061

Table 4. Random effects from intention-to-treat analysis of hazard ratios from Cox mixed-effects model for factors influencing filter survival relative to continuous renal replacement therapy, delivered by a temporary internal jugular catheter with citrate anticoagulation

Source of variation	SD (95% CI)	HR (95% CI), 1 SD above mean	HR (95% CI), 1 SD below mean
Between pts	0.52 (0–1.14)	1.68 (NC–3.13)	0.6 (0.32–NC)
Site of access, within pt	0.56 (0.29–0.74)	1.75 (1.33–2.1)	0.57 (0.48–0.75)

HR = hazard ratio. pt = patient. NC = not calculable.

risk of filter failure between patients and between vascular access sites within patients.

Safety and outcomes

Safety end points requiring treatment-arm interruption were reached in one patient receiving heparin and three receiving citrate. Two citrate interruptions were deemed prophylactic (based on the potential for hypocalcaemia to compound vasoplegia in severe shock). Two incidents were

deemed definitely treatment-related: one patient was given an inadvertent heparin bolus that resulted in an activated partial thromboplastin time of >300 seconds, with no clinical sequelae; and one patient with an intracerebral malignancy had a seizure when their $[iCa^{2+}]$ was 0.84 mmol/L while on citrate. The seizure led to an addition to the study protocol about the management of significant hypocalcaemia that involved rapid empirical correction in addition to the calcium infusion rate changes.

Transfusion requirements

Ten patients randomised to the citrate protocol received 60 units of packed red cells (0.42 units/day of total treatment period); six patients randomised to the heparin protocol received 76 units of blood (0.39 units/day of total treatment period). No significant bleeding episodes requiring treat-

Table 5. Fixed effects from per-protocol analysis of hazard ratios from Cox mixed-effects model for factors influencing filter survival relative to continuous renal replacement therapy, delivered by a temporary internal jugular catheter with citrate anticoagulation*

Factors	Hazard ratio (95% CI)	P (Wald test)
Heparin anticoagulation (compared with citrate)	2.89 (1.61–5.17)	0.0001
Vascular access (compared with temporary internal jugular vein)		
Temporary subclavian vein	0.5 (0.14–1.82)	0.3
Temporary femoral vein	0.31 (0.15–0.68)	0.003
Tunnelled internal jugular vein	0.24 (0.06–0.92)	0.037

* Hazard ratios demonstrate the variability at 1 SD above and below the mean, eg, 15.9% of patients had at least a 40% higher risk of filter failure and 15.9% had at least a 29% lower risk of filter failure.

Table 6. Random effects from per-protocol analysis of hazard ratios from Cox mixed-effects model for factors influencing filter survival relative to continuous renal replacement therapy, delivered by a temporary internal jugular catheter with citrate anticoagulation*

Source of variation	SD (95% CI)	HR (95% CI), 1 SD above mean	HR (95% CI), 1 SD below mean
Between pts	0.34 (0.27–0.71)	1.402 (1.32–2.04)	0.713 (0.49–0.76)
Site of access, within pt	0.66 (0.15–1.16)	1.94 (1.16–3.21)	0.51 (0.31–0.86)

HR = hazard ratio. pt = patient. * Hazard ratios show the variability at 1 SD above and below the mean, eg, 15.9% of patients had at least a 40% higher risk of filter failure and 15.9% had at least a 29% lower risk of filter failure.

ment-arm cessation or cases of heparin-induced thrombo-cytopenia were reported.

Discussion

Our study provides insight into the practicalities of RRT in a large metropolitan ICU. Similarly to previous studies[4-8,18] filter life was prolonged in filters that received citrate anticoagulation, but intention-to-treat analysis did not support any advantage of one anticoagulation modality. Interpretation and clinical implications of the results of our pilot study are tempered by the significant baseline imbalances, and significant crossover from citrate to heparin, which affect internal statistical validity. Complications were observed with the citrate protocol and, unlike previous studies,[5] transfusion requirements were not reduced in the citrate arm (although the study size and significant protocol crossover limit interpretation of these events).

As a pilot for an outcomes study of RRT anticoagulation strategies, the amount of crossover from the citrate arm has significant implications for feasibility. Documentation of the reasons for crossover was poor; human error, staff familiarity with and preference for heparin, and perceptions of associated increased workload were given as contributors to the high occurrence of crossover. Considering that this trial was initiated early after rolling out new technology for citrate delivery, these factors may be modifiable. These human factors all influence CRRT and have implications for change management in future ICU studies that involve these therapies. Unanticipated external factors such as the AN69 and ST100 filter supply shortage resulted in an intense focus on filter management midway through the study, and eventually alternative filters were used; both these factors may have affected the results.

The mixed-effects model highlights vascular access and patient factors as being nearly as important as anticoagulation method in influencing variability of filter survival in the study population. Because the limited sample size increased the risk that the optimised model was not generalisable, this requires further investigation. These factors may also vary between ICUs, as local policy, practices and equipment vary.

Despite several limitations, we were able to accurately assess filter life using digital data capture. We showed that citrate administered by machine-controlled algorithms improved filter survival, but our interpretation (until further randomised studies may show improved patient outcomes) is that the choice of anticoagulant for CRRT should be made by clinicians. They should use patient-specific indications and contraindications; assess the risks of bleeding, reactions to heparin or protamine, and hypocalcaemic sequelae; and include staff factors. Future work should continue to simplify citrate administration while improving

safety features to capitalise on its increased filter patency. Other factors such as adequate vascular access and the impact of human factors in CRRT management require further exploration.

Competing interests

As The Alfred ICU solely uses Gambro products for RRT, Gambro have an ongoing relationship with The Alfred that includes support and education. M B and O R liased with Gambro about training staff for this project, accessing the Prismaflex data and supply of fluids. All fluids for this study were supplied to The Alfred at the same price. We have not received any other financial, employment or other benefits, and have no other competing interests.

Author details

Matthew J Brain, Intensive Care Specialist[1,2,3]
Owen S Roodenburg, Intensive Care Specialist,[1] and Deputy Director[3]
Natalie Adams, Registered Nurse[3]
Phoebe McCracken, Research Coordinator[3]
Lisen Hockings, Intensive Care Specialist[3]
Steve Musgrave, Registered Nurse[3]
Warwick Butt, Intensive Care Specialist[3]
Carlos Scheinkestel, Intensive Care Specialist and Director[3]

1 School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia.
2 Department of Medicine, Launceston General Hospital, Launceston, TAS, Australia.
3 Department of Intensive Care and Hyperbaric Medicine, The Alfred, Melbourne, VIC, Australia.

Correspondence: matthew.brain@monash.edu

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Appendix 1. Study treatments

Target CRRT blood flow was stratified in each group by patient weight as shown in Appendix 1, Table 1.

Appendix 1, Table 1. Target CRRT blood flow, by patient weight	
Patient weight (known or best estimate)	Blood flow (Qb)
70 kg or less	150 mL/min
71–100 kg	200 mL/min
> 100 kg	250 mL/min

CRRT dose for heparin patients will follow the existing Alfred protocol (Appendix 1, Figure 1). Fluid flow rates for heparin patients will be a prefilter dilution rate of 1250 mL/hour, postfilter replacement at 100 mL/hour, and dialysate rate of 30 mL/kg/hour to a maximum of 5 L/hour.

CRRT dose for citrate patients will be determined by the blood flow and citrate dose (reflected in the preblood pump [PBP] rate) with a fixed postfilter replacement rate of 100 mL/hour. The dialysate flow (Q_D) rate was fixed at 30 mL/kg/hour (up to a maximum 3 L/hour) as for the heparin group with the solution being the calcium-free Prismocal B22.

The PBP rate of Prismocitrate 18/0 will be determined by the Prismaflex machine after the operator enters the initial citrate dose according to the equation below.

Heparin protocol

Delivery of anticoagulation in this arm will follow the ICU protocol for administration of regional heparin as shown in Appendix 1, Figure 1. As per the protocol, in the event of two failed circuits in less than 24 hours on heparin, protamine may be added.

Appendix 1, Table 2. Citrate starting rates, by arterial ionised calcium concentration					
Arterial ionised calcium	Citrate dose	Arterial ionised calcium	Citrate dose	Arterial ionised calcium	Citrate dose
0.74	1.4	0.98	2.5	1.32	3.4
0.75	1.5	1.01	2.6	1.37	3.5
0.76	1.6	1.04	2.7	1.43	3.6
0.79	1.7	1.07	2.8	1.50	3.7
0.80	1.8	1.10	2.9	1.57	3.8
0.83	1.9	1.13	3.0	1.64	3.8
0.86	2.1	1.16	3.0	1.74	4.0
0.89	2.2	1.19	3.1	1.84	4.1
0.92	2.3	1.22	3.2	1.95	4.2
0.95	2.4	1.27	3.3	2.08	4.3

Citrate protocol

The Prismaflex citrate anticoagulation will be set up according to the Prismaflex Operator Manual Chapter 8, Anticoagulation methods: citrate – calcium via Prismaflex syringe pump, and requires the dedicated Prismaflex calcium infusion line. The machine will be preconfigured (factory set) to operate in with Prismocitrate 18/0 only.

Preparation

The following items will need to be available in addition to the Prismaflex machine and circuit:
■ Prismocitrate 18/0 5 L bag for use as the PBP
■ PrismoCal B22 5 L bag for use as dialysate
■ 0.9% normal saline 1 L for use as postfilter replacement
■ 50 mL leur lock syringe for use in the Prismaflex syringe driver
■ 5 x 10 mL ampules of 100 mg/mL (10%) calcium chloride
■ Prismaflex calcium infusion line (total volume 0.6 mL)
■ Patient's weight (1st option: known if possible; 2nd: dietitian's assessment; 3rd: an estimate).

The calcium chloride infusion will be prepared in the 50 mL syringe for use in the Gambro syringe driver. This will contain 5 x 10 mL ampules of 100 mg/mL calcium chloride for a concentration of 680 mmol/L calcium (see Prismaflex Operators Manual[1] page 8: 12 and figure 8.1). Note: the machine is preconfigured via service mode to accept this concentration only.

After priming the line, this will be connected via the dedicated calcium line to the central venous catheter (CVC). If no CVC is available then it may be connected to the return line of the vascath.

Prepare circuit as per the Alfred ICU CRRT Guideline, including circuit prime with heparin, but instead of Hemosol B0 use Prismocitrate 18/0 for the PBP bag and Prism0Cal B22 for the dialysate bag. In patients with a history of heparin-induced thrombosis–thrombocytopenia syndrome or other reaction to heparin, prime circuits with saline only.

Anticoagulation setup

In the machine setup procedure (setup mode) the "Enter anticoagulation settings" will be displayed. Enter initial blood flow according to Appendix 1, Table 1.

Calculate the initial citrate dose using the following equation (a table of values is shown in Appendix 1, Table 2):

$$\text{citrate dose} = 5.81 - 3.23/[iCa^{2+}_{art}]$$

where citrate dose is mmol citrate/L blood flow and iCa^{2+} is the arterial ionised calcium. This should fall within a range of 1.7–4.0 mmol citrate / L blood flow. If starting emergently before an arterial blood gas has been taking then set citrate dose to 3 mmol/L blood flow. *Note*: This calculation step is only performed on treatment initiation or if the patient has been off CRRT for over 24 hours. When restarting at other times, use the last dose. (This was implied but not explicit in the previous protocol.) *Amendment*: For patients with an initial arterial ionised calcium less than 1.10 mmol/L, 10 mL of calcium gluconate (2.2 mmol) will be administered before starting therapy.

Appendix 1, Table 3. Default calcium compensation (syringe infusion rates)

Ionised calcium level	Calcium compensation (%)
> 1.1 mmol/L	90%
1.0–1.1 mmol/L	100%
< 1.0 mmol/L	110%

The default calcium compensation (syringe infusion rate) will be set according to Appendix 1, Table 3.

Leave replacement fluid calcium concentration at 0 mmol/L (for 0.9% sodium chloride on the postfilter replacement hook).

Set dialysate (Prismocal B22) flow rate at 30 mL/kg/hour using the same estimated weight as for blood flow.

Monitoring and adjustment of therapy

After initiation check the systemic ionised calcium and the extracorporeal circuit prefilter ionised calcium after the first hour. The target prefilter ionised calcium concentration is 0.30 to 0.44 mmol.L^{-1}.

The target prefilter ionised calcium (iCa^{2+}) is 0.3–0.44 mmol/L. Modify the dose of citrate according to the following protocol (Appendix 1, Table 4). *Amendment*: If at any point the circuit ionised calcium is undetectable, drop the citrate dose to 2.5 mmol citrate/L blood flow then continue with flow chart below. If it remains undetectable then the medical staff must review in regard to further drops or if an unrecognised contraindication to citrate may exist (this was implied in staff education but not explicit in prior version).

The arterial iCa^{2+} target is 1.0–1.1 mmol/L. The calcium compensation default start is defined in Table 3. Adjust the calcium chloride infusion according to the following protocol (Appendix 1, Table 5). *Amendment*: If at any point the patient arterial ionised calcium falls below 0.85 then 10 mL of calcium gluconate (2.2 mmol) should be given. If it remains low then the medical team must review dosing and evaluate reasons for persistent hypocalcaemia (eg, unrecognised rhabdomyolysis, massive transfusion, new unrecognised hepatic failure, etc.) and ongoing use of citrate.

Appendix 1, Table 4. Monitoring and adjustment of citrate dose

- Citrate dose (Prismocitrate 18/0): set initial citrate dose using Table 2. After 60 minutes, adjust rate according to the following:

  ▸ if prefilter iCa^{2+} > 0.50 mmol.L^{-1}, increase citrate dose by 0.3 mmol/L blood; reassess in 60 minutes

  ▸ if prefilter iCa^{2+} is 0.45–0.50 mmol.L^{-1}, increase citrate dose by 0.1 mmol/L blood; reassess in 60 minutes

  ▸ if prefilter iCa^{2+} is 0.30–0.44 mmol.L^{-1}, maintain rate; *this is the target*. Reassess in 2 hours if new circuit or rate change has been made in the previous 2 hours, or if there is an identified trend towards the upper or lower limit; otherwise reassess in 4 hours

  ▸ if prefilter iCa^{2+} < 0.3 mmol.L^{-1}, reduce citrate dose by 0.2 mmol/L blood; reassess in 60 minutes.

Recirculation procedure

The Gambro Prismaflex platform allows saline recirculation for up to 120 minutes to maintain filter patency while the patient is disconnected for procedures or investigations. This saves filters, fluids and cost of treatment. The procedure is described in the operating manual and can be used for all patients in the FLIRRT study.

Recirculation is recommended whenever a patient requires disconnection for what is predicted to be a short period and no instruction to cease CRRT has been received.

Data collection and sampling

Arterial blood gas monitoring is commonly performed 1–4 hourly in the ICU depending on the patient's condition. Circuit ionised calcium also requires monitoring via the prefilter port of the machine (see Appendix 1, Table 5).

In addition to standard haemodynamic monitoring performed in all ICU patients, the study will collect flow and alarm data stored in the Prismaflex machines and records of vascular access site.

Study end points

Primary outcomes

1. Safety: defined as the absence of adverse events[2] necessitating consideration of or actual discontinuation of the study anticoagulant or an additional therapy such as blood transfusion (with choice of an alternate anticoagulant strategy or additional treatments to be determined by treating physician).

Predefined safety endpoints:

- After starting CRRT, the new development of severe metabolic alkalosis as defined by an increase of pH > 7.55 and base excess of > + 8 mmol/L deemed to result from CRRT.
- Severe citrate accumulation as defined by the new development of a positive anion gap metabolic acidosis (pH < 7.20 and BE < − 10 mmol/L) with no obvious cause other than citrate overload, especially not due to ketoacidosis, lactic acidosis or other drug toxicity. Note this does not preclude patients with a pH < 7.2 being randomised to citrate.
- Development of heparin-induced thrombocytopenia during

Appendix 1, Table 5. Monitoring and adjustment of calcium chloride infusion

- Calcium chloride infusion (680 mmol/L made up as 5 x 10 mL ampoules of 100 mg/ml calcium chloride): commence at 100% compensation if arterial iCa^{2+} is within the normal range. Commence at 90% compensation if iCa^{2+} > 1.1 mmol/L. Commence at 110% compensation if iCa^{2+} < 1.0 mmol/L. Adjust rate according to the following:

  ▸ if serum iCa^{2+} > 1.1 mmol.L^{-1}, reduce calcium compensation by 10%; reassess in 1 hour

  ▸ if serum iCa^{2+} is 1.0–1.1 mmol.L^{-1}, maintain current rate. Reassess in 2 hours if a rate change had been made in the previous 2 hours, or if there is an identified trend toward the upper or lower limit; otherwise reassess in 4 hours

  ▸ if serum iCa^{2+} < 1.0 mmol.L^{-1}, increase compensation rate by 10%; reassess in 1 hour.

study period.

- Development of a reaction to protamine during therapy: defined as mild or severe, depending on whether treatment with protamine requires cessation:
  - mild: hypotension, rash, flushing
  - severe: anaphylaxis, paradoxical bleeding.
- Bleeding episodes, classified as mild, moderate or severe:[3]
  - mild: bleeding identified with no systemic symptoms and Hb drop less than 1 g/dL/day
  - moderate: documented blood loss with clinical evidence of hypovolaemia and/or Hb drop > 2 g/dL/day
  - severe: documented blood loss with clinical evidence of hypovolaemia requiring transfusion.
- Total units of packed red cells or other blood products will be recorded over CRRT period.

2. Efficacy:

- Circuit survival: will be measured directly and indirectly:
  - directly with actuarial classification of each circuit (haemofilter failure, line-related failure, procedure or planned cessation of treatment)
  - indirectly by monitoring filter pressure drop, TMP and K_{UF} against filter time (see Appendix 2).
- Control of uraemia: reduction of urea from baseline to level at Day 3; time to urea < 25 mmol/L.
- Filter performance as determined by clearances of urea, creatinine, phosphate, uric acid and vitamin B12 (funding permitted).
- Technical complications:
  - filter clotting: repeated filter clotting defined as filter lifespan less than 24 hours on two consecutive days[4] *or* filter had to be changed because of increased drop in end-to-end pressure or transmembrane pressure > 300 mmHg
  - vascular access malfunction: inability of the catheter to deliver the prescribed blood flow,[5] defined as being unable to maintain prescribed Qb with access pressure more negative than 250 mmHg for 1 hour and unresponsive to patient repositioning or saline flushes[5]
  - complications of vascular access catheter: including insertion complications, site infection and vessel thrombosis after insertion.
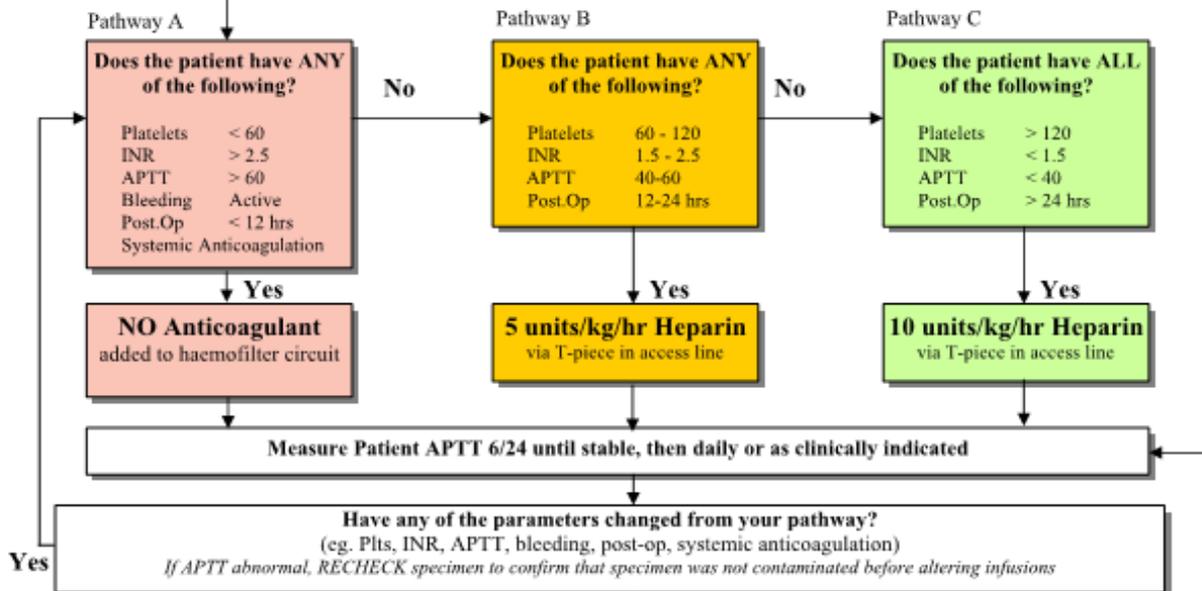
Secondary outcomes

Secondary outcomes are dialysis independence at ICU and hospital discharge; survival to ICU and hospital discharge; and 3-month mortality.

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Anticoagulation in Continuous Renal Replacement Therapy (CRRT)

Prime Haemofilter circuit twice with:
first: 1L 0.9%Sodium Chloride + 10,000units heparin
second: 1L 0.9%Sodium Chloride

Pathway A

Does the patient have ANY of the following?

Platelets	< 60
INR	> 2.5
APTT	> 60
Bleeding	Active
Post.Op	< 12 hrs
Systemic Anticoagulation	

→ **No**

↓ **Yes**

NO Anticoagulant added to haemofilter circuit

Pathway B

Does the patient have ANY of the following?

Platelets	60 - 120
INR	1.5 - 2.5
APTT	40-60
Post.Op	12-24 hrs

→ **No**

↓ **Yes**

5 units/kg/hr Heparin via T-piece in access line

Pathway C

Does the patient have ALL of the following?

Platelets	> 120
INR	< 1.5
APTT	< 40
Post.Op	> 24 hrs

↓ **Yes**

10 units/kg/hr Heparin via T-piece in access line

Measure Patient APTT 6/24 until stable, then daily or as clinically indicated

Have any of the parameters changed from your pathway?
(eg. Plts, INR, APTT, bleeding, post-op, systemic anticoagulation)
If APTT abnormal, RECHECK specimen to confirm that specimen was not contaminated before altering infusions

Yes →

↓ **No**

Has the filter clotted 2 or more times in 8 hours? → **No**

↓ **Yes**

Commence Regional Heparinisation at

Heparin	1000 units/hour	(via T-piece in access line)
Protamine	10 mg/hour	(via T-piece in return line)

Check <u>Patient</u> & <u>Circuit</u> APTT after 6 hours
then titrate according to the table below
(circuit APTT from red port at bottom of filter)

		Patient APTT (sec)	
		Normal (<38)	*High (>38)*
Circuit APTT (sec)	*Low (<50)*	↑Heparin by 150 units/hr Recheck filter & patient APTT 6/24	(N/A)
	Target (50-80)	No Change Daily patient APTT	↑Protamine by 1.5 mg/hr * Recheck patient APTT 6/24
	High (>80)	↓Heparin by 150 units/hr Recheck filter APTT 6/24	↓ Heparin by 150 units/hr ↑ Protamine by 1.5 mg/hr* Recheck filter & patient APTT 6/24

*NB. Usual ratio of Protamine:Heparin is 1mg:100units.
If this ratio exceeds 2mg:100units then liase with the consultant re. management of CRRT anticoagulation.*

Page 2 of 2	Target: All ICU Nursing and Medical Staff	Developed: Dec 2004	Last Review: Dec 2004
	Maintained by: Linda Wight	Review Due: June 2005	Approved by: A/Prof C.Scheinkestel
	Contact: L.Wight@alfred.org.au	Title: CRRT Anticoagulation (Heparin)	

Figure 1. Alfred ICU regional heparin anticoagulation protocol

Appendix 2. Screening and enrolment

Inclusion criteria

- Adult patients > 18 years.
- Diagnosis of acute renal failure with an indication for renal replacement therapy as assessed by one or more of the following criteria:
  - oliguria (urine output < 100 mL in a 6-hour period) unresponsive to fluid resuscitation
  - volume overload, not correctable by diuretics in spite of adequate blood pressure and creatinine > 100 μmol/L
  - increase of serum creatinine > 300 μmol/L or BUN > 25 mmol/L
  - increase of serum potassium > 6.5 mmol/L due to AKI.
- Patients who at the time of inclusion had not yet started RRT.

Exclusion criteria

- Patient weight < 30 kg (machine specification for citrate dosing and ST100 membrane).
- Inability to enter randomisation due to a contraindication to one of the treatment arms:
  - indication for systemic anticoagulation with heparin (therapeutic range APTT) or an equivalent therapeutic dose of low-molecular weight heparin (this does not include routine thromboprophylaxis)
  - prior development of heparin-induced thrombocytopenia
  - history of anaphylaxis to heparin, protamine or citrate.
- Pregnancy or lactation.
- Patients on CRRT before ICU presentation.
- Indication for therapeutic hypothermia.
- Previous participation in the same study.
- Indication for a filter set other than the AN69 ST100 1m^2 set or a specific dialysis prescription differing from the study protocol (which is based on the standard Alfred protocol).

Patient withdrawal from study

- Development of a safety endpoint (predefined or unforeseen) that precludes continuation of the anticoagulation in that arm.
- By wish of the patient or legal representative (withdrawal of the declaration of consent).
- Significant deviation from the study treatment protocol.
- Decision of the treating physician.

Patients withdrawn from the randomised treatment for any reason will be followed up according to the study follow-up schedule and analysed according to the intention-to-treat principle.

Screening log

A screening log was maintained to document patients who met eligibility criteria but had an exclusion or were not enrolled for another reason.

Randomisation and allocation of initial treatment

Randomisation to either anticoagulation method was conducted through an unblocked, computer-generated, random allocation that was accessed from the bedside intensive care computers and stored on a central secure server in the Alfred ICU. The randomisation algorithm was managed by the Alfred ICU information technology staff who were independent from the investigators.