Implementation of a simplified regional citrate anticoagulation protocol for post-dilution continuous hemofiltration using a bicarbonate buffered, calcium containing replacement solution

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Running title: Regional citrate anticoagulation for post dilution CRRT

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Abstract

Background / Aims

Recent updates to the Nikkiso Aquarius continuous renal replacement therapy (CRRT) platform allowed us to develop a post dilution protocol for Regional Citrate Anticoagulation (RCA) using standard bicarbonate buffered, calcium containing replacement solution with Acid Citrate Dextrose Formula-A (ACD-A) as a citrate source. Our objective was to demonstrate the protocol was safe and effective.

Methods

Prospective audit of consecutive patients receiving RCA for CRRT within ICU, who were either contraindicated to heparin or had poor filter lifespan (<12 hours for 2 consecutive filters) on heparin.

Results

We present the first 29 patients who used 98 filters. After excluding 'non-clot' filter loss, 50% had duration of >27 hours. Calcium supplementation was required for 30 (30%) filter circuits, in 17/29 (58%) patients. One discontinuation due to metabolic alkalosis and no adverse bleeding events.

Conclusion

Post dilution RCA system is effective and simple to use on the Aquarius platform and results in comparable filter life for patients relatively contraindicated to heparin.

Keywords: Citrate, Critical Care, Hemofiltration, Haemofiltration, Renal Replacement Therapy, Regional Citrate Anticoagulation, Protocol

Introduction

Regional citrate anticoagulation (RCA) has been used routinely for continuous renal replacement therapy in treatment of critically ill patients for over 25 years [1] and is the recommended form of anticoagulation for both patients with and without contra-indication to heparin in the international Kidney Disease Improving Global Outcomes Acute Kidney Injury guidelines of 2012 [2]. Recent evidence has confirmed the superiority of regional citrate compared with systemic heparin anticoagulation both to maintain patency of the extracorporeal circuit and to reduce bleeding complications[3-6]. Despite this weight of favorable evidence uptake of RCA has been limited in many countries, including the UK[7]. Perception of RCA as complex to deliver and concerns regarding potential complications and additional cost of therapy may underlie this lack of enthusiasm.

In the UK CRRT is almost universally delivered in the intensive care unit (ICU) by the bedside nurse who, while highly skilled, has numerous demands and is not specialized to the administration of RRT. This system has the advantage that CRRT can be commenced rapidly at any time when clinically indicated. However, assurance of quality and safety for citrate in delivered by a single bedside nurse requires RCA delivery integrated into a microprocessor controlled CRRT device using simple reliable protocols. As a consequence, Heparin remains the anticoagulant of choice for CRRT in most UK ICUs while patients with contra-indications to systemic anticoagulation are managed with no anticoagulation. Wide use of no anti-coagulation can result in poor circuit lifespan, inadequate delivered CRRT dose and blood loss associated with frequent filter clotting.

RCA can be delivered in a number of CRRT modalities [8, 9]. In addition to citrate and calcium replacement solutions, calcium free dialysate or pre-dilution replacement fluid are required to maintain effective anticoagulation during dialysis, hemodiafiltration or pre-dilution hemofiltration, increasing expense and complexity. Conversely in post-dilution hemofiltration, conventional replacement solutions can spare the need for costly supplemental calcium infusions [10].

Recent release of the Nikkiso Aquarius CRRT platform 'Version 6-RCA' (Nikkiso Europe GmbH, Hannover, Germany) has now enabled the integrated delivery of RCA-CRRT with machine-controlled pumps, enabling the development of

RCA with this device in a UK ICU environment. This paper describes the implementation of a simple and reliable RCA protocol for post-dilution CRRT on the Aquarius device at the Royal London Hospital Adult Critical Care Unit (ACCU), London, UK. The ACCU is a mixed medical / surgical ICU servicing a major London trauma center and renal unit where approximately 40% CRRT treatments have a contra-indication to heparin anticoagulation - presenting a significant impetus to the development of alternative anticoagulant strategies locally.

Methodology

RCA Protocol Development

Development of the RCA protocol was constrained by availability of only a conventional haemofiltration replacement solution; Accusol (Nikkiso Europe GmbH, Hannover, Germany): a bicarbonate buffered solution, containing 1.75mmmol/L of Calcium (Table 1). Use of this calcium containing replacement solution necessitated the use of post-dilution continuous veno-venous hemofiltration (CVVH), however this modality is simple to employ, and use of a single solution results in both logistical and cost advantages.

Citrate was given in the form of Acid Citrate Dextrose Formula-A (ACD-A) solution (Haemonetics, Glasgow, UK) (Table 1); ACD-A solution is routinely used for anticoagulation of extra-corporeal circuits for apheresis and plasma exchange in the UK and for citrate anti-coagulated CRRT in Europe and the USA [11, 12]. As an advantage over the widely used tri-sodium citrate solution (TSC), ACD-A has both lower sodium content and less buffer generation after metabolism (2 molecules of bicarbonate per molecule of citrate in comparison with 3 from TSC). ACD-A solution (containing 113mmol/L citrate) was given to achieve a calculated pre-filter citrate concentration in blood of 2.8mmol/L [10] (i.e. 2.8/113 = 1/40 of blood flow). This citrate dose, while lower than in some RCA protocols, has been widely used for safe and effective RCA CRRT, achieving filter iCa^{2+} concentrations of around 0.35 mmol/L [10, 13], and was felt to represent the best balance between effective anticoagulation and risk of the development of metabolic alkalosis.

Development of the complete CVVH-RCA dosing schedule involved a stepwise process (Figure 1). The initial dose of 35 ml/kg/h was chosen to ensure a dosing schedule capable of accommodating the demands of initial treatment in sicker patients and to accommodate the local use of CRRT-dosing based on *Ideal Body Weight* (Devine formula). As ACD-A delivery also provides an element of pre-dilution fluid (around 10%), the calculations were then iterated to maintain a consistent CRRT dose, before tabulation as post-dilution replacement rates, blood flow rates and ACD-A flow rates in weight ranges (<50, 50-59, 60-69, 70-79 and >80) (Table 2). Using this protocol thus involves only estimation of patient weight and programming of the indicated flow rates. Following the same process, a 25 ml/kg/h protocol was developed stepped down of dose if required (Table 2).

We aimed to maintain plasma ionised Calcium in the range 0.9-1.2 [8]. Calcium replacement was principally by via the post-dilution Accusol replacement solution, which contains 1.75 mmol/L calcium, equating the initial calcium replacement employed in many other RCA protocols (3.5mmol/h with a 2L exchange). If required, additional calcium was administered via the integrated pump on the Aquarius device as a Calcium Chloride 10 mmol/L solution in 0.9% Saline. To avoid abrupt fall in iCa^{2+} additional Calcium was administered if initial arterial iCa^{2+} was <1.0 mmol/L or if iCa^{2+} fell below 0.9 mmol/L on 3hrly monitoring thereafter (Table 3).

As a bicarbonate buffered replacement solution was used in addition to citrate there is the potential for development of metabolic alkalosis when using this CVVH-RCA protocol. To mitigate this tendency, a relatively low (2.8 mmol/L) dose of citrate and ACD-A solution (rather than tri-sodium citrate) was chosen. Arterial pH and bicarbonate were monitored every 3h. If whole blood HCO_3 was >40 or pH >7.5 while on a CRRT dose of 35 ml/kg/h, then intensity was reduced to 25 ml/kg/h (Table 2), reducing bicarbonate donation by around 25%. If metabolic alkalosis persisted, a third 25 ml/kg/h RCA protocol a reduction in blood flow to 4 times hemofiltration rate (filtration ratio of 25%) in tandem with a reduction in citrate flow to keep the concentration in the blood at 1/40, was used to reduce citrate delivery by a further

20% (Table 4). Persistent metabolic alkalosis despite these measures triggered a switch to non-RCA CRRT.

Impaired citrate metabolism can occur in severe liver dysfunction or refractory shock with poor tissue perfusion causing citrate accumulation. Although RCA has been safely applied to patients with appropriate monitoring with chronic liver disease [14], in our developmental study we excluded patients with advanced chronic liver disease, acute liver or with refractory shock (Table 5). In addition, we monitored the Total to Ionized Calcium ratio twice daily to assess for citrate accumulation and if this was greater than 2.5, RCA was discontinued.

Both the 2.5% Dextrose content of ACD-A Solution and citrate itself represent sources of energy. ACD-A contains ~700 KJ/L energy of which 560 KJ/L would be delivered to the patient at a filtration ratio of 20%. This energy intake was factored into feeding requirements by clinician dieticians and blood glucose was monitored for hyperglycaemia 3 hourly.

Pilot Service Implementation

We considered the introduction of RCA as a clinically indicated service improvement and examined our implementation process in a prospective clinical audit. Patients were eligible if they had conventional reasons to need RRT within the ICU (new or on-going treatment) and were considered by the treating physician to either have a contraindication to heparin anticoagulation, or had a filter lifespan of <12h for >2 filter sets despite use of heparin. Contra-indications to commencement of RCA during the service implementation pilot, aimed at avoiding metabolic complications or citrate accumulation, are set out in Table 5. The first thirty consecutive CVVH-RCA treatments were evaluated.

Systemic arterial blood gas analysis including ionized calcium, pH, bicarbonate, sodium and glucose were performed before RCA, one hour after initiation and then every three hours or as dictated by the Calcium replacement protocol. Central laboratory bloods for urea & electrolytes, calcium and magnesium levels were obtained before treatment and then 12 hourly allowing calculation of

the total to ionized calcium ratio. We also recorded post-filter ionised calcium (these values were not used to adjust the protocol or treatment), circuit lifespan, quantity of additional calcium infusion required and the reason to discontinue use of RCA-CRRT.

Results

The first thirty patients treated with CVVH-RCA received 112 RCA anticoagulated CRRT circuits in total (Supplementary Table 2). One patient, whose diagnosis was necrotising pancreatitis due to a triglyceride level of 18.9 mmol/L was excluded from final analysis (14 filters median life span 6.5 hours range 4-12.5). The remaining 29 patients used 98 filters with a median (range) filter life span of 21 hours (1-72). Reasons for filter cessation are shown in table 6. After excluding filter losses due to planned discontinuation for medical reasons (e.g. procedures, imaging, recovery of renal function) and technical failures of the CRRT circuit 50% of filters had duration of greater than 27 hours (Figure 2).

Metabolic characteristics of CVVH-RCA treatments are presented in Table 7. Post-filter [iCa^{2+}] was measured twice a day to monitor the efficacy of the citrate protocol, across all samples taken the median value was 0.39, range 0.28-0.64 – only one measured value was >0.5 mmol/L.

Calcium supplementation, in addition to the 1.75 mmol/L in Accusol, was required for 30 (30%) filter circuits, in 17/29 (58%) patients. Only three patients (eight filters) required supplementary calcium throughout the whole time they were receiving RCA-CVVH, one of who had necrotising pancreatitis. Five patients (nine filters) developed a need for additional calcium during treatment having not initially required it. In the remaining nine patients (thirteen filters) that required additional calcium on commencing RCA-CVVH the calcium infusion was administered for a median of 50% (range 1-91%) of the time on therapy.

One patient discontinued RCA due to metabolic alkalosis refractory to protocol-directed adjustment of RCA therapy. There were no adverse bleeding events while on RCA-CVVH.

Discussion

Main findings

This paper describes the successful development and implementation of an RCA protocol on the commonly utilizing integrated microprocessor-controlled pumps for citrate and calcium infusions on the Aquarius CRRT platform. Several features of our protocol differ from other commercially available systems adding to the range of options available for clinicians. Post-dilution CVVH results in purely convective solute clearance with predictable dosing, and a conventional replacement solution has savings in terms of simplicity and minimizing cost of addition calcium solution. Our protocol was well tolerated, despite use of the bicarbonate buffered replacement only one of 30 patients had to discontinue CVVH-RCA for alkalosis. Use of additional calcium was relatively low with 70% of circuits used not requiring additional calcium supplementation, representing potential savings in consumables and nursing time. There were no instances of clinical citrate accumulation. Filter lifespans were acceptable and similar to some previous reports of RCA-CRRT [15], but lower than median values (39-46 hours) reported in recent randomised trails comparing citrate to heparin [5, 6]. It should be noted that our patients were selected for having contraindications to heparin or prior poor filter lifespans and were thus likely to be predisposed to poorer filter lifespans, by comparison historical data suggests typical filter lifespan using no anticoagulation in our unit were three fold worse than those achieved with citrate in this pilot [16]. Based in our experience in this pilot, we expect that adoption of this protocol as standard therapy in unselected patients, together with the addition a higher citrate concentration option for early filter loss, will achieve substantial better filter lifespans - although our particular case mix may remain challenging even with optimal anticoagulation.

Of note, in routine clinical practice filter lifespans are often poorer than those reported in patients recruited into controlled clinical trials even in very experienced hands [17]. In particular, other factors such as line position and length can affect filter lifespan independent of anticoagulation [18], in our pilot patients with catheter tips sited in the superior vena cava or right atrium had significantly longer lifespan

than those in the brachiocephalic vein or in the inferior vena-cava (data not shown) emphasising that while effective use of RCA does not obviate the need for other elements of best practice in CRRT delivery such as obtaining best vascular access.

Finally, this report focuses on the adoption of a novel therapy, not the performance of a fully developed protocol in a unit familiar with RCA therapy, in particular software modifications (in partnership with the manufacturer) were required to minimise low access pressure alarms associated with low blood flow rates through low resistance catheters that causes persistent interruption of therapy in some early patients, this was particularly relevant in the patients with end stage renal disease who were receiving intermittent haemodialysis through long, low-resistance tunnelled catheters.

On-going RCA development

The success of this pilot has allowed adoption of citrate regional anticoagulation as the anticoagulant of choice for CRRT at the Royal London Hospital with familiarization with the RCA protocol embedded into rolling programs of nurse training. Building on the confidence using RCA during protocol development we have modified a set of exclusions and cautions (Supplementary table 3) for the use of RCA-CVVH as well as extending to a 6 hourly minimum frequency of blood gas monitoring in stable patients. A final version of the current Royal London Hospital RCA-CVVH protocol is provided as a supplementary file incorporating these alterations.

In addition, while generally successful, the variation in filter lifespans observed in our pilot suggests there might potential to optimise anticoagulation by increasing citrate dose in some patients. Accordingly, we have subsequently introduced a protocol increasing the citrate dose to a target circuit citrate concentration of 3.5mmol/L, using a 25 ml/kg/h exchange rate (Supplementary table 1). This higher citrate dose, 25 ml/kg/h protocol provides a similar total citrate exposure to the basic 35 ml/kg/h protocol. As there can be considerable inter-individual variations in citrate concentration required to achieve post filter iCa of

0.25-0.35 prescription of citrate based on post filter iCa would be the ideal, however this requires accurate measurement low ionised calcium concentrations which may not be routinely available. We do not advocate routine monitoring of post-filter iCa to direct citrate dose with point of care analysers blood gas analysers as these measurements lie outside of the calibrated reference range and may be prone to inaccuracy [19]. We therefore recommend switching to the 3.5mmol/L citrate protocol in patients with clearly inadequate filter lifespan (<12h after optimisation of vascular access), as a pragmatic indicator of sub-optimal anticoagulation.

Strengths and Limitations

The principal strength of this service development project was our major focus on patient safety in a simple and reliable protocol. As a consequence, we did not observe any unexpected complications or major adverse events due to RCA. We provided 24-hour access to senior clinical staff (CK and JP) during the pilot period and developed a comprehensive audit tool that was able to rapidly detect biochemical changes. This cautious approach combined with close industry involvement during the development of this protocol allowed rapid technical support during early implementation and enabled successful clinical uptake.

As this was not a clinical trial, our study is limited by a lack of direct comparison between RCA and other forms of anti-coagulation in equivalent patients. However, filter lifespan was superior to that historically achieved in comparable patients and our focus was to demonstrate successful pragmatic implementation of RCA with acceptable filter lifespan and not to prove superiority to other forms of anticoagulation such as heparin which are less suitable for our case-mix. The control of alkalosis might be better monitored using the calculation of the strong ion difference (SID) instead of pH and plasma bicarbonate. However, we chose a practical solution to allow our 240+ nursing staff and 30+ residents and fellows to use the system without addition calculation. Finally, we accept that by basing prescription on whole blood filtration ratio, instead of using the filtration fraction

individualised to each patient's haematocrit, we may have missed the influence of a key factor in filter lifespan.

Conclusion

A simple post dilution regional citrate anticoagulation system is effective and simple to use on the Nikkiso Aquarius platform. The use of 'standard' calcium containing replacement fluid reduces the need for supplementary calcium. A median filter life span of 27 hours (censored for reasons other than clotting) in complex patients with a relative contraindication to heparin was demonstrated and we expect this to improve further as familiarity improves and RCA is used as first choice anticoagulation in our unit.

References

1. Mehta RL, McDonald BR, Aguilar MM, Ward DM, (1990) Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. Kidney Int 38: 976-981
2. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, (2012) KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter, Suppl 2: 1-138
3. Bai M, Zhou M, He L, Ma F, Li Y, Yu Y, Wang P, Li L, Jing R, Zhao L, Sun S, (2015) Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. Intensive Care Med 41: 2098-2110
4. Liu C, Mao Z, Kang H, Hu J, Zhou F, (2016) Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. Crit Care 20: 144
5. Gattas DJ, Rajbhandari D, Bradford C, Buhr H, Lo S, Bellomo R, (2015) A Randomized Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults. Crit Care Med 43: 1622-1629
6. Schilder L, Nurmohamed SA, Bosch FH, Purmer IM, den Boer SS, Kleppe CG, Vervloet MG, Beishuizen A, Girbes AR, Ter Wee PM, Groeneveld AB, group Cs, (2014) Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial. Crit Care 18: 472
7. Poply K, Shuaib FR, Bhamani AA, Saha S, (2013) Survey to determine the prevalence of regional citrate anticoagulation for renal replacement therapy (RRT) in intensive care units in the UK. Intensive Care Medicine 39: S318-S319

8. Davenport A, Tolwani A, (2009) Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. NDT Plus 2: 439-447
9. Oudemans-van Straaten HM, Ostermann M, (2012) Bench-to-bedside review: Citrate for continuous renal replacement therapy, from science to practice. Crit Care 16: 249
10. Ong SC, Wille KM, Speer R, Tolwani AJ, (2014) A continuous veno-venous hemofiltration protocol with anticoagulant citrate dextrose formula A and a calcium-containing replacement fluid. Int J Artif Organs 37: 499-502
11. Cointault O, Kamar N, Bories P, Lavayssiere L, Angles O, Rostaing L, Genestal M, Durand D, (2004) Regional citrate anticoagulation in continuous venovenous haemodiafiltration using commercial solutions. Nephrol Dial Transplant 19: 171-178
12. Tobe SW, Aujla P, Walele AA, Oliver MJ, Naimark DM, Perkins NJ, Beardsall M, (2003) A novel regional citrate anticoagulation protocol for CRRT using only commercially available solutions. J Crit Care 18: 121-129
13. Morabito S, Pistolesi V, Tritapepe L, Vitaliano E, Zeppilli L, Polistena F, Fiaccadori E, Pierucci A, (2013) Continuous venovenous hemodiafiltration with a low citrate dose regional anticoagulation protocol and a phosphate-containing solution: effects on acid-base status and phosphate supplementation needs. BMC Nephrol 14: 232
14. Slowinski T, Morgera S, Joannidis M, Henneberg T, Stocker R, Helset E, Andersson K, Wehner M, Kozik-Jaromin J, Brett S, Hasslacher J, Stover JF, Peters H, Neumayer HH, Kindgen-Milles D, (2015) Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study. Crit Care 19: 349
15. Oudemans-van Straaten HM, Bosman RJ, Koopmans M, van der Voort PH, Wester JP, van der Spoel JI, Dijksman LM, Zandstra DF, (2009) Citrate anticoagulation for continuous venovenous hemofiltration. Crit Care Med 37: 545-552
16. Poply K, Schwartz S, Lucena-Amaro S, Ramsey S, Robinson M, Kirwan C, Prowle J, (2014) Filter life and anticoagulation use in a mixed medical/surgical/trauma ICU: A baseline assessment. Intensive care medicine 40: S55-S55
17. Fealy N, Kim I, Baldwin I, Schneider A, Bellomo R, (2013) A comparison of the Niagara and Medcomp catheters for continuous renal replacement therapy. Ren Fail 35: 308-313
18. Baldwin I, Bellomo R, (2004) Relationship between blood flow, access catheter and circuit failure during CRRT: a practical review. Contrib Nephrol 144: 203-213
19. Kindgen-Milles D, Ostermann M, Slowinski T, (2015) Ionized calcium measurements during regional citrate anticoagulation in CRRT: we need better blood gas analyzers. Crit Care 19: 427

Figure 1: A schematic representation of the steps required to define flow rates in the RCA protocol: **Step 1:** An initial CRRT dose of 35ml/kg/h. **Step 2:** Blood Pump Speed (ml/min) is set to five times the post-dilution rate (ml/h) to achieve Filtration Ratio of 20%. **Step 3:** ACD-A solution rate (ml/h) was set to the hourly Blood Pump Speed ÷ 40 to achieve a calculated pre filter citrate concentration of 2.8mmol/L.

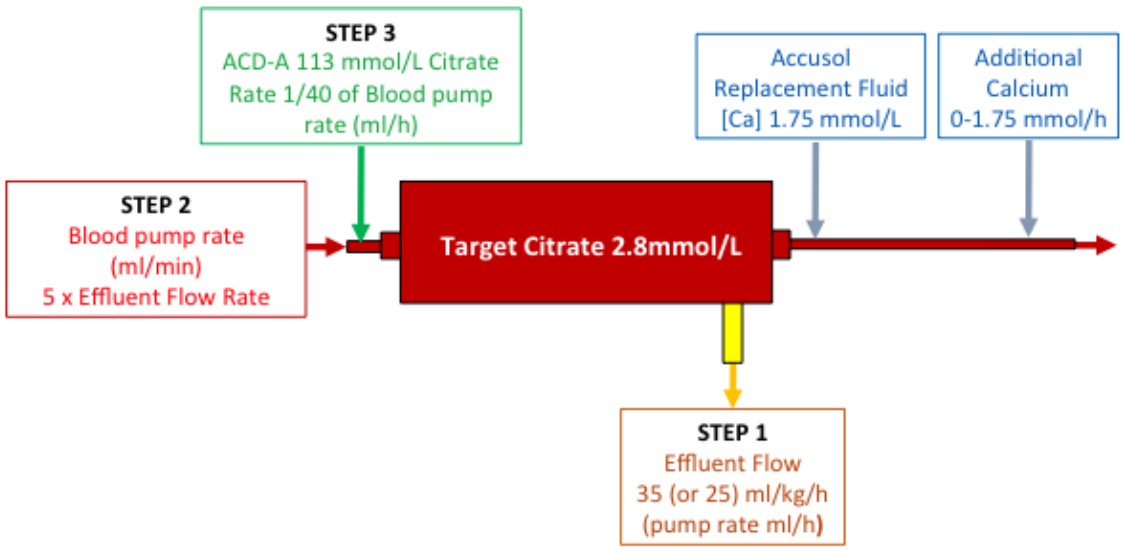

Figure 2: Kaplan Meier curve of filter survival censored for discontinuation due to technical (alarm or circuit errors) or medical reasons (discontinuation for procedures or imaging) – in this analysis median survival was 27 hours (dashed line)

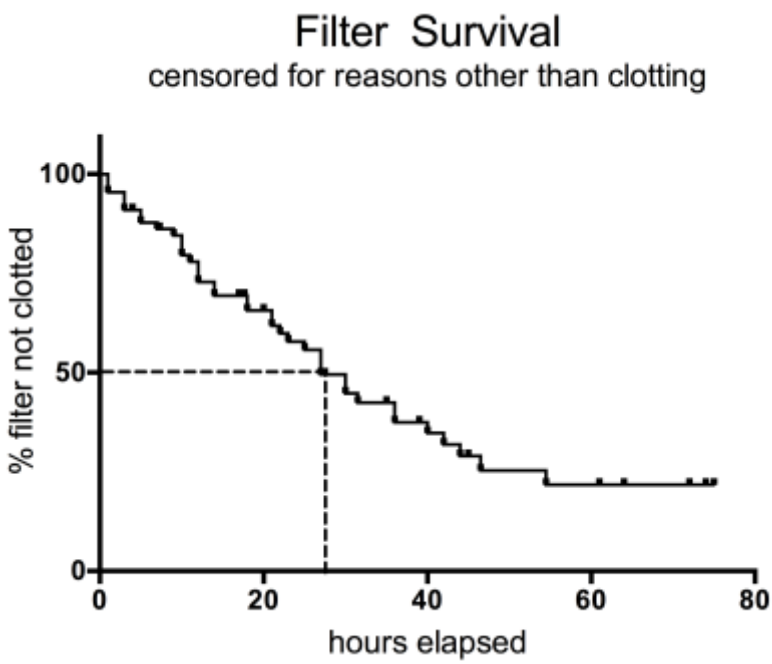

Table 1: Composition of fluids used in CVVH-RCA protocol

Accusol 35 (Mixed Solution, No Potassium)			**ACD-A (Acid Citrate Dextrose Solution A)**	
Na^+	140	mmol/L	**Na^+**	224 mmol/L
Cl^-	109.3	mmol/L	**H^+**	115 mmol/L
HCO_3^-	35	mmol/L	**$Citrate^{3-}$**	113 mmol/L
Ca^{2+}	1.75	mmol/L	**Glucose**	139 mmol/L
Mg^{2+}	0.5	mmol/L		

Table 2: Pump settings to deliver a CRRT dose of 35 or 25 ml/kg/h

	Post – dilution (ml/h)		Blood Pump (ml/min)		ACD-A (Citrate) (ml/h)	
IBW (kg)	DOSE (ml/kg/h)					
	35	25	35	25	35	25
<50	1400	1100	120	100	180	150
50-59	1800	1300	150	110	230	170
60-69	2100	1500	180	130	270	200
70-79	2400	1700	200	140	300	210
>80	2700	1900	230	160	350	240

Table 3: Guidance to calcium infusion monitoring and adjustment before and during RCA treatment

PRE-TREATMENT CALCIUM ADJUSTMENT		DURING TREATMENT CALCIUM ADJUSTMENT		
ABG [iCa]	Initial rate of additional CaCl solution	ABG [iCa]	CaCl infusion adjustment during RCA treatment (MAXIMUM RATE = 175 ml/h)	Repeat ABG
< 0.8	Medical review & Correct iCa	< 0.8	• Doctor to give 5ml, 10% CaCl (3.4 mmol) 'minijet' by slow IV bolus via a central line **immediately** • Increase CaCl infusion rate by 50 mL/h • If patient not on additional CaCl start at **100 ml/kg** ***If CaCl infusion already at 175 ml/h stop RCA & inform ICU Consultant immediately***	**After 1 hour**
0.8 – 0.89	75 mL/h (0.75 mmol/h)	0.8 – 0.89	• Increase 1CaCl infusion by 25ml/h • If patient not on additional CaCl and start at **75 ml/kg** ***If CaCl infusion already at 175 ml/h stop RCA & inform ICU Consultant immediately***	**After 3 hours**
0.9 – 1	50 mL/h (0.5 mmol/h)	0.9 – 1.2	No change	**After 6 hours**
> 1	0 mL/h (0 mmol/h)	> 1.2	• Decrease CaCl infusion by 25ml/h • If CaCl infusion off, then check systemic [iCa] in 3 hours **Inform Doctor if [iCa] rises to >1.5**	**After 3 hours**

Table 4: Reducing the blood flow (whilst adjusting the citrate rate to maintain a 1/40 concentration in the blood) increases the filtration ratio thus reducing the citrate delivery

IBW (kg)	Post – dilution (mL/hr)	Blood Pump (mL/min)	ACD-A (Citrate) (mL/hr)
<50	*Reached minimum blood flow rate – DISCONTINUE RCA*		
50-59	*Reached minimum blood flow rate – DISCONTINUE RCA*		
60-69	1500	100	150
70-79	1700	120	180
>80	1900	130	200

Table 5: Contra-indications to commencement of RCA CRRT during pilot phase

- Requirement for systemic anticoagulant (other than prophylaxis)
- Chronic Liver Disease - Childs B or C
- Acute Liver Injury with INR >2 or Lactate >4mmol/L
- Post-hepatic resection
- Severe shock with Noradrenaline >0.5mcg/kg/min and/or Lactate >4mmol/L
- Arterial Blood ionized calcium <0.8µmol/L at commencement of RCA
- Arterial Blood pH>7.5 or HCO_3^->40mmol/L at commencement of RCA
- Serum Sodium <120 or >160 at commencement of RCA
- Uncontrolled hyperglycaemia requiring >6U/h Insulin to maintain blood sugars <10

Table 6: Reason for CRRT cessation in patients receiving RCA

	N (filters)	**Median (range) hours of therapy**
Coagulation related	61	13
Clot in filter	*39*	*18 (1-54.5)*
Pressure alarm	*22*	*10 (1-44)*
Access issue	5	27 (5-44)
Technical issue*	6	13 (3-22)
Medical reason	11	27.5 (7-64)
Set expired	5	72 (45-75)
Reason not recorded	10	23 (6-66)

***Persistent low access pressure alarms (3) and inadequate de-airing (3)

Table 7: A summary of patients' biochemistry and need for calcium supplementation during treatment with RCA

	Median (Range) or Range
Post filter iCa (mmol/L)	0.39 (0.28-0.64)
Total:Ionised Ca Ratio	1.9 (1.01-2.59)
pH	7.11-7.53
Bicarbonate (mmol/L)	28.3-33.2
Sodium (mmol/L)	130-155
Patient time on additional calcium (min)	540 (27 – 2640)
Patient total additional calcium delivered (mmol)	7.5 (0.25 - 62.5)

Supplementary Material: *Implementation of a simplified regional citrate anticoagulation protocol for post-dilution continuous hemofiltration using a bicarbonate buffered, calcium containing replacement solution*. Christopher J Kirwan, Ross Hutchison, Sherif Ghabina, Stephaine Schwarze, Abigail Beane, Susan Ramsay, Edward Thompson, John R Prowle

Supplementary Table 1: An increased dose of Citrate with a delivered dose of 25 mL/kg/hr and filtration ratio of 20%

IBW (kg)	Post – dilution (mL/hr)	Blood Pump (mL/min)	ACD-A (Citrate) (mL/hr)
<50	1100	100	180
50-59	1300	110	200
60-69	1500	130	230
70-79	1700	140	260
>80	1900	160	300

Supplementary Table 2: Demographics of the first 30 patients who received RCA for CRRT (Median, Range or Number, %)

Age	**65 (20-87)**
Male	17 (57%)
Number of filters per patient	2 (1-13)
Ideal body weight	66 (40-81)
Ethnicity	
- White	12
- Black	8
- South Asian	2
- Mixed Race	8
Primary cause of admission to critical care	
- Single organ AKI	1
- Congestive cardiac failure	1
- Lupus	1
- Multi-organ failure	1
- Ruptured Aortic Aneurysm	1
- Sickle cell crisis	1
- Post Cardiac Arrest	2
- CVA	2
- Pancreatitis	2
- Pulmonary-renal vasculitis	2
- Poly-trauma	2
- Traumatic brain injury	3
- Upper GI bleed	3
- Septic shock	7

Supplementary Table 3: Updated cautions and contraindications for RCA post dilution CRRT following the successful pilot programme

EXCLUSIONS	**CAUTIONS -** *Monitor closely*
• Acute Liver Failure with INR>3 • Serum Sodium < 120 or > 160 mmol/L • pH > 7.5 or HCO3 > 40 mmol/L	• Chronic liver disease • Post hepatic Resection • Requiring >6 u/h insulin infusion • IBW> 90 kg (Use protocol 1 only) • Lactate >5 mmol/L