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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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Key Words

Citrate · Critical care · Hemofiltration · Haemofiltration · Renal replacement therapy · Regional citrate anticoagulation · Protocol

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 as a citrate source. Our objective was to demonstrate that the protocol was safe and effective. **Methods:** Prospective audit of consecutive patients receiving RCA for CRRT within intensive care unit, who were either contraindicated to heparin or had poor filter lifespan (<12 h 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 a duration of >27 h. Calcium supplementation was required for 30 (30%) filter circuits, in 17 of 29 (58%) patients. One patient discontinued the treatment due

to metabolic alkalosis, but there were 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.

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Published by S. Karger AG, Basel

Introduction

Regional citrate anticoagulation (RCA) has been used routinely for continuous renal replacement therapy (CRRT) in the treatment of critically ill patients for over 25 years [1] and is the recommended form of anticoagulation for both patients with and without contraindication to heparin in the international Kidney Disease Improving Global Outcomes Acute Kidney Injury guide-

This work was performed at the Royal London Hospital in the Adult Critical Care Unit, Barts Health NHS Trust, London, UK.

lines 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, the uptake of RCA has been limited in many countries, including in 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 being 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 contraindications to systemic anticoagulation are managed with no anticoagulation. Wide use of no anticoagulation 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, thus increasing the 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 contraindication to heparin anticoagulation, presenting a significant impetus to the development of alternative anticoagulant strategies locally.

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

Accusol 35 (mixed solution, no potassium), mmol/l		ACD-A, mmol/l	
Na ⁺	140	Na ⁺	224
Cl ⁻	109.3	H ⁺	115
HCO ₃ ⁻	35	Citrate ³⁻	113
Ca ²⁺	1.75	Glucose	139
Mg ²⁺	0.5		

Methodology

RCA Protocol Development

Development of the RCA protocol was constrained by availability of only a conventional hemofiltration replacement solution; Accusol (Nikkiso Europe GmbH, Hannover, Germany): a bicarbonate buffered solution, containing 1.75 mmol/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 extracorporeal circuits for apheresis and plasma exchange in the UK and for citrate anticoagulated CRRT in Europe and the USA [11, 12]. As an advantage over the widely used tri-sodium citrate (TSC) solution, 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 113 mmol/l citrate) was given to achieve a calculated pre-filter citrate concentration in blood of 2.8 mmol/l [10] (i.e., 2.8/113 = 1/40 of blood flow). This citrate dose, while being lower than in some RCA protocols, has been widely used for safe and effective RCA CRRT, achieving filter iCa²⁺ 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 (fig. 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 more sickly 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 the estimation of patient weight and programming of the indicated flow rates. Following the same process, a 25 ml/kg/h protocol was developed and stepped down of dose if required (table 2).

We aimed to maintain plasma ionized calcium in the range 0.9–1.2 [8]. Calcium replacement was principally by the post-dilution Accusol replacement solution, which contains 1.75 mmol/l calcium, equating the initial calcium replacement employed in many

Fig. 1. A schematic representation of the steps required to define flow rates in the RCA protocol. Step 1: an initial CRRT dose of 35 ml/kg/h. Step 2: blood pump speed (ml/min) is set to 5 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 2.8 mmol/l.

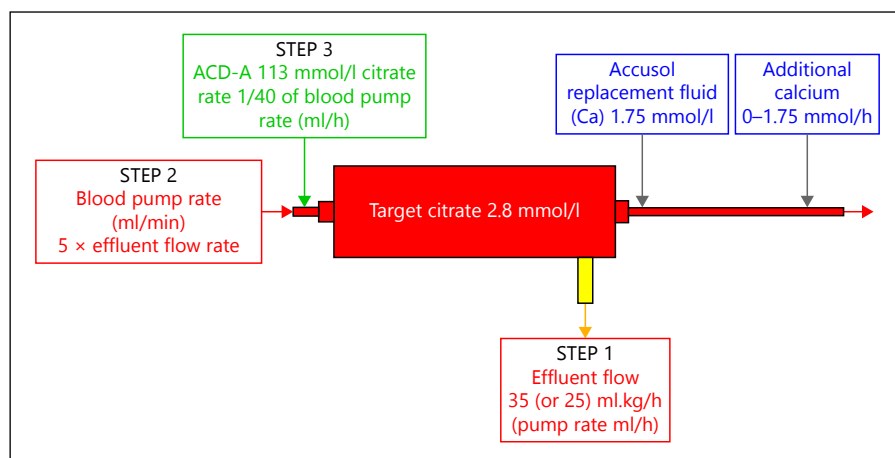


Table 2. Pump settings to deliver a CRRT dose of 35 or 25 ml/kg/h

IBW, kg	Post-dilution, ml/h		Blood pump, ml/min		ACD-A (citrate), ml/h	
<50	1,400	1,100	120	100	180	150
50–59	1,800	1,300	150	110	230	170
60–69	2,100	1,500	180	130	270	200
70–79	2,400	1,700	200	140	300	210
>80	2,700	1,900	230	160	350	240

other RCA protocols (3.5 mmol/h with a 2 liters 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 3 hourly 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 TSC) was chosen. Arterial pH and bicarbonate were monitored every 3 h. 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 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 hyperglycemia 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 ongoing treatment) and were considered by the treating physician to either have a contraindication to heparin anticoagulation, or had a filter lifespan of <12 h for >2 filter sets despite the use of heparin. Contraindications to commencement of RCA during the service implementation pilot that aimed at avoiding metabolic complications or citrate accumulation are set out in table 5. The first 30 consecutive CVVH-RCA treatments were evaluated.

Systemic arterial blood gas analysis including ionized calcium, pH, bicarbonate, sodium and glucose were performed before RCA, 1 h after initiation and then every 3 h or as dictated by the calcium replacement protocol. Central laboratory bloods for urea and electrolytes, calcium and magnesium levels were obtained before treatment and then every 12 h, allowing calculation of the total to ionized calcium ratio. We also recorded post-filter ionized 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.

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 and correct iCa	<0.8	<ul style="list-style-type: none"> - Doctor to give 5 ml, 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 and inform ICU Consultant immediately 	After 1 h
0.8–0.89	75 ml/h (0.75 mmol/h)	0.8–0.89	<ul style="list-style-type: none"> - Increase 1 CaCl infusion by 25 ml/h - If patient not on additional CaCl, start at 75 ml/kg - If CaCl infusion already at 175 ml/h, stop RCA and inform ICU Consultant immediately 	After 3 h
0.9–1	50 ml/h (0.5 mmol/h)	0.9–1.2	No change	After 6 h
>1	0 ml/h (0 mmol/h)	>1.2	<ul style="list-style-type: none"> - Decrease CaCl infusion by 25 ml/h - If CaCl infusion off, then check systemic [iCa] in 3 h - Inform Doctor if [iCa] rises to >1.5 	After 3 h

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/h	Blood pump, ml/min	ACD-A (citrate), ml/h
<50	Reached minimum blood flow rate – discontinue RCA		
50–59	Reached minimum blood flow rate – discontinue RCA		
60–69	1,500	100	150
70–79	1,700	120	180
>80	1,900	130	200

Table 5. Contraindications 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 >4 mmol/l
- Post-hepatic resection
- Severe shock with noradrenaline >0.5 µg/kg/min and/or lactate >4 mmol/l
- Arterial blood ionized calcium <0.8 µmol/l at commencement of RCA
- Arterial blood pH >7.5 or HCO₃⁻ >40 mmol/l at commencement of RCA
- Serum sodium <120 or >160 at commencement of RCA
- Uncontrolled hyperglycemia requiring >6 U/h insulin to maintain blood sugar <10

Results

The first 30 patients treated with CVVH-RCA received 112 RCA anticoagulated CRRT circuits in total (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000452755).

One patient, whose diagnosis was necrotizing pancreatitis due to a triglyceride level of 18.9 mmol/l, was excluded from final analysis (14 filters median lifespan 6.5 h range 4–12.5). The remaining 29 patients used 98 filters with a median (range)

filter lifespan of 21 h (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 a duration of greater than 27 h (fig. 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 of 29 (58%) patients. Only 3 patients (8 filters) required supplementary calcium throughout the whole time they were receiving RCA-CVVH, one of whom had necrotizing pancreatitis. Five patients (9 filters) developed a need for additional calcium during treatment, not having required it initially. In the remaining 9 patients (13 filters) who 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 used 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 minimizes the cost of addition of calcium solution. Our protocol was well tolerated; despite the use of bicarbonate-buffered replacement, only one of the 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

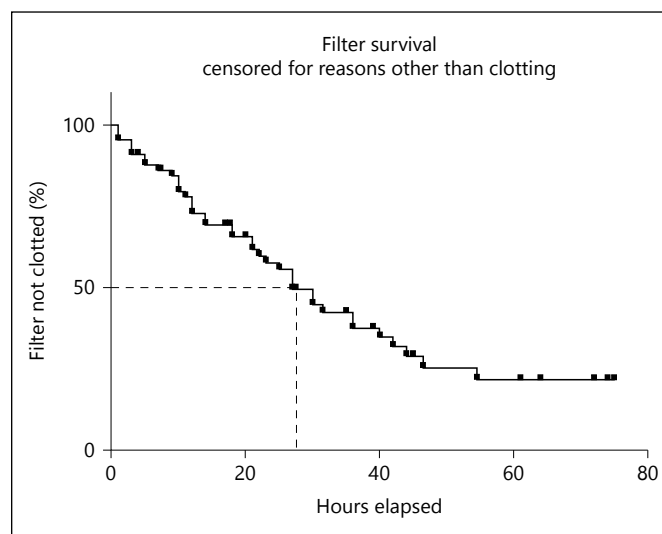


Fig. 2. Kaplan–Meier curve of filter survival censored for discontinuation due to technical (alarm or circuit errors) or medical reasons (discontinuation for procedures or imaging) – in this analysis, median survival was 27 h (dashed line).

Table 6. Reason for CRRT cessation in patients receiving RCA

	Number (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 (n = 3) and inadequate de-airing (n = 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:ionized 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 (27–2,640)
Patient total additional calcium delivered, mmol	7.5 (0.25–62.5)

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 h) reported in recent randomized trials 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 suggest typical filter lifespans using no anticoagulation in our unit were three-fold worse than those achieved with citrate in this pilot [16]. Based on our experience from this pilot, we expect that the 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) emphasizing that the 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 minimize low access pressure alarms associated with low blood flow rates through low resistance catheters that cause persistent interruption of therapy in some early patients, this was particularly relevant in the patients with end-stage renal disease who were receiving intermittent hemodialysis through long, low-resistance tunneled catheters.

On-Going RCA Development

The success of this pilot has allowed the adoption of citrate regional anticoagulation as the anticoagulant of choice for CRRT at the Royal London Hospital with familiarization of 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 (online suppl. table 2) 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 an online supplementary file incorporating these alterations.

In addition, while generally successful, the variation in filter lifespans observed in our pilot suggests there might be the potential to optimize 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 3.5 mmol/l, using a 25 ml/kg/h exchange rate (online suppl. table 3). This higher citrate dose, 25 ml/kg/h protocol, provides a similar total citrate exposure as that of 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, the prescription of citrate based on post-filter iCa would be the ideal; however, this requires accurate measurement low ionized 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 analyzers of blood gas as these measurements lie outside of the calibrated reference range and may be prone to inaccuracy [19]. We therefore recommend switching to the 3.5 mmol/l citrate protocol in patients with clearly inadequate filter lifespan (<12 h after optimization of vascular access), as a pragmatic indicator of suboptimal 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 (C.J.K. and J.R.P.) 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 the lack of direct comparison between RCA and other forms of anticoagulation 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 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 the prescription on whole blood filtration ratio, instead of using the filtration fraction individualized to each patient's hematocrit, we may have missed the influence of a key factor in filter lifespan.

Conclusion

A simple post-dilution RCA 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 lifespan of 27 h (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 the first choice anticoagulation in our unit.

Disclosure Statement

This service development program and open access publication of this manuscript have been supported by an unrestricted education grant from Nikkiso Europe GmbH, Hannover, Germany.

Ethics Statement

As this was a clinical service improvement project combined with data collection and analysis as part of a prospective audit, the Barts Health/QMUL joint research office waived the need for full Research Ethics Committee approval.

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In the article by Kirwan et al., entitled “Implementation of a simplified regional citrate anticoagulation protocol for post-dilution continuous hemofiltration using a bicarbonate buffered, calcium containing replacement solution” [Blood Purif 2016;42:349–355, DOI: 10.1159/000452755], the correct affiliation of Edward Thompson is Nikkiso UK Co. Ltd., Thatcham, UK. In the section Methodology, the manufacturer of Accusol should read Nikkiso Belgium bvba, Tienen, Belgium. In the Disclosure Statement, the unrestricted educational grant is from Nikkiso America Inc., San Diego, CA, USA.