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Evaluation of urea and creatinine change during continuous renal replacement therapy: effect of blood flow rate

Nigel Fealy, Leanne Aitken, Eugene du Toit, Michael Bailey and Ian Baldwin

ABSTRACT

Objective: To determine if faster blood flow rate (BFR) has an effect on solute maintenance in continuous renal replacement therapy.

Design: Prospective randomised controlled trial.

Setting: 24-bed, single centre, tertiary level intensive care unit.

Participants: Critically ill adults requiring continuous renal replacement therapy (CRRT).

Interventions: Patients were randomised to receive one of two BFRs: 150 mL/min or 250 mL/min.

Main outcome measures: Changes in urea and creatinine concentrations (percentage change from baseline) and delivered treatment for each 12-hour period were used to assess solute maintenance.

Results: 100 patients were randomised, with 96 completing the study (49 patients, 150 mL/min; 47 patients, 250 mL/min). There were a total of 854 12-hour periods (421 periods, 150 mL/min; 433 periods, 250 mL/min). Mean hours of treatment per 12 hours was 6.3 hours (standard deviation [SD], 3.7) in the 150 mL/min group, and 6.7 hours (SD, 3.9) in the 250 mL/min group ($P = 0.6$). There was no difference between the two BFR groups for change in mean urea concentration (150 mL/min group, –0.06%; SD, 0.015; *v* 250 mL/min group, –0.07%; SD, 0.01; $P = 0.42$) or change in mean creatinine concentration (150 mL/min, –0.05%; SD, 0.01; *v* 250 mL/min, –0.08%; SD, 0.01; $P = 0.18$). Independent variables associated with a reduced percentage change in mean serum urea and creatinine concentrations were low haemoglobin levels (–0.01%; SD, 0.005; $P = 0.002$; and 0.01%; SD, 0.005; $P = 0.006$, respectively) and less hours treated (–0.023%; SD, 0.001; $P = 0.000$; and –0.02%; SD, 0.002; $P = 0.001$, respectively). No effect for bodyweight was found.

Conclusions: Faster BFR did not affect solute control in patients receiving CRRT; however, differences in urea and creatinine concentrations were influenced by serum haemoglobin and hours of treatment.

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Acute kidney injury (AKI) is a complication of critical illness that affects up to 50% of intensive care patients.[1-3] The use of renal replacement therapy has evolved as the treatment for severe AKI, and is required in up to 5–6% of all critically ill patients in intensive care units (ICUs).[4] Continuous renal replacement therapy (CRRT) is the most common dialytic therapy used to treat AKI worldwide.[5] CRRT techniques are instituted by clinicians with the aim of achieving homeostasis of water, electrolytes, acid base and removal of waste products in this group of patients.[6] Solute control and maintenance have long been key priorities in the provision of CRRT and has been an area of research and focus since the first Acute Dialysis Quality Initiative consensus meeting.[7,8] Subsequently, two large multicentre randomised controlled trials definitively showed that there was no survival benefit in increasing the dose of CRRT from the common dose of 25 mL/kg/h.[9,10]

While a greater CRRT dose does not lead to improved patient outcomes, solute removal (particularly small solutes, such as urea and creatinine) remains an important aim of the therapy. For prescribing CRRT, clinicians continue to target a prescription dose and best settings to achieve solute removal for each 24-hour period, to remove excessive toxins and maintain solute balance for each individual patient.[8] In addition to a prescribed effluent rate, other clinical variables may contribute to solute clearance in CRRT, including "down time", membrane composition, membrane fouling and frequent circuit clotting.[11] The Acute Dialysis Quality Initiative has recently recommended research objectives aimed at identifying optimal techniques and practical prescriptions for solute removal.[8] Blood flow rate (BFR) and a modality of CRRT — that is, continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD) or continuous venovenous haemodiafiltration (CVVHDF) — are two common bedside prescriptions that may have a direct impact on solute removal, but have not been assessed in any randomised controlled study. An increase in BFR in convective modes, such as CVVH, may directly assist solute removal by increasing transmembrane pressure, exposing additional plasma water to the dialyser per effluent dose and assisting solvent drag across the membrane. Indirectly, a faster BFR may decrease blood viscosity in the membrane,

increase filtration fraction and decrease membrane fouling with eventual clotting. In diffusive modes, such as CVVHD and CVVHDF, faster BFR may assist with solute removal by maximising concentration gradients between blood (plasma) flow and dialysate flow rates, decreasing dwell time and sustaining diffusive movement of solutes across the membrane.[12]

We aimed to test our hypothesis that faster BFR increases small solute removal (eg, urea and creatinine) in critically ill patients receiving CRRT. To address this question, we report additional findings from our recently published randomised controlled trial comparing two BFRs and the effect on circuit life in patients treated with CRRT.[13]

Methods

Trial design and setting

This study was a prospective, parallel group randomised controlled trial conducted in a 24-bed, adult, tertiary referral ICU in Melbourne, Victoria, Australia. The study was registered at the Australian New Zealand Clinical Trials Registry (ACTRN: 12615001353583) and approved by Austin Health Human Research Ethics Committee (HREC project no. H2012/04772). Written informed consent from the patient or their next of kin was obtained before or soon after enrolment.

Eligibility criteria

Critically ill patients in ICU were eligible for the study if they fulfilled the following criteria:

- age ≥ 18 years; and
- AKI (RIFLE [risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease] classification = F)[14] requiring CRRT.
- Patients were considered ineligible for the study if they fulfilled any exclusion criterion:
- required citrate anticoagulation (citrate protocol requires a set BFR of 150 mL/min); or
- expected to stay in the ICU for < 24 hours.

Interventions

The study compared two BFR settings and the effect on small solute control in CRRT. BFR was either 250 mL/min or 150 mL/min using CVVH and CVVHDF modes. Vascular access was either Niagara 13.5 Fr catheter (24 cm) (Bard, Murray Hill, NJ, USA) or GamCath Dolphin Protect 13.0 Fr catheter (25 cm) (Gambro, Hechingen, Germany) dual lumen catheters. Machines used were Prismaflex with AN69 ST (ST100) 1.0 m^2 membrane (Gambro Nephral TM, Lund, Sweden) or Infomed HF440 with DF140 Polyethersulfone 1.4 m^2 membrane (Infomed, Geneva, Switzerland) for all treatments respectively. We used bicarbonate buffered replacement and dialysis fluid (Baxter, Castlebar, Co. Mayo, Ireland). In CVVH, the replacement fluid was delivered into the extracorporeal circuit before and after the filter (pre- and post-dilution), with a ratio of 50% pre-dilution and 50% post-dilution. The dose in CVVH was standardised at 2000 mL/h. In CVVHDF, the replacement fluid was delivered 100% post-dilution. The dose in CVVHDF was standardised at 1000 mL/h replacement and 1000 mL/h dialysate. CRRT was prescribed by the treating intensivist and provided by ICU nurses.

Data collection

We collected baseline data regarding age, gender, weight, body mass index (BMI), source of admission, severity of illness (APACHE [Acute Physiology and Chronic Health Evaluation] II and III score; SAPS [Simplified Acute Physiology Score] II), diagnostic group, presence of sepsis, mechanical ventilation, inotropes and vasopressors, and basic laboratory variables pertaining to renal function.

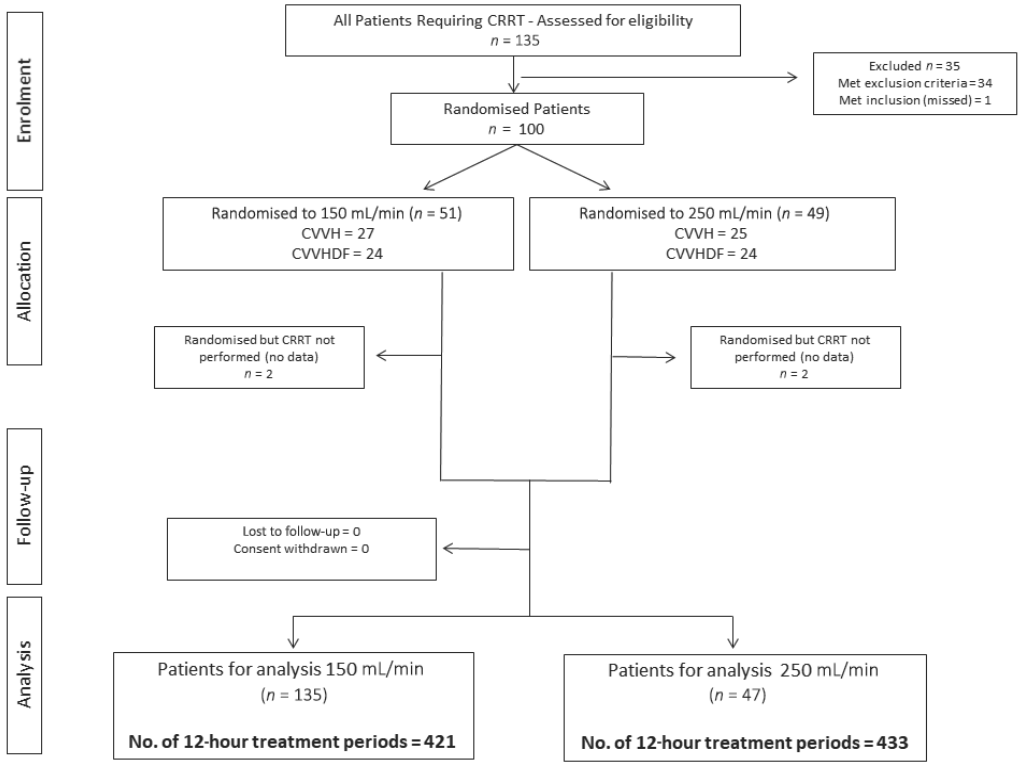
Outcome measurements

For all patients, twice-daily (0500 and 1700 hours) measurement of haemoglobin and biochemistry (serum creatinine and urea) was performed. The primary outcome was small solute maintenance estimated by the change in urea and creatinine concentrations over these two predefined 12-hour periods each day (percentage of change in serum levels over time). Circuit life was documented for each CRRT circuit as cumulative hours, so that delivered treatment hours could be calculated for each 12-hour period (T1, 0500–1700 hours; and T2, 1700–0500 hours).

Randomisation

Patients were screened and entered into the study by ICU clinical staff. Patients were assigned randomly with stratification for modality. Once the treating physician prescribed CRRT and the mode of therapy, patients were randomised using a web-based central randomisation service (Griffith University Clinical Trial Coordinating Centre). A variable block randomisation with parallel allocation was software-generated, with inbuilt concealment to allocate participants to each study group (150 mL/min *v* 250 mL/min). Patients stayed in the treatment group allocated at randomisation and modality (CVVH or CVVHDF) for treatment throughout their ICU stay. The sample size was without power calculation, was of convenience and was associated with the primary investigation.[13]

Figure 1. CONSORT diagram for patient enrolment



CONSORT = Consolidated Standards of Reporting Trials. CRRT = continuous renal replacement therapy. CVVH = continuous venovenous haemofiltration. CVVHDF = continuous venovenous haemodiafiltration.

Data analysis

Linear regression analysis was performed to identify independent variables that may be associated with change in small solute serum levels. Independent variables included modality of CRRT, gender, BMI, weight, haemoglobin level and number of hours treated in each 12-hr period. Repeated measures analysis of variance (ANOVA) was used on the independent variables showing significance. The advantage of this model is that it considers within-subject measures over multiple time points. In this study, patients contributed multiple 12-hour periods measuring solute percentage change over these periods. Data lacking normality of distribution are presented as median with interquartile range (IQR) (25% and 75%), using the Wilcoxon rank sum test or mean with standard deviation (SD) when normally distributed, and using the Student *t* test, χ^2 test and the Fisher exact test. A $P < 0.5$ was considered significant. SPSS Statistics 21.0 (IBM, Chicago IL, USA) software was used for all data analysis.

Results

Participants and recruitment

All patients receiving CRRT in the study ICU ($n = 135$) were screened for eligibility between June 2013 and August, 2014. From this screening, 100 patients were considered eligible and randomised to the study; and two patients from each group were randomised but did not receive CRRT. Figure 1 shows the CONSORT diagram for patient enrolment. Overall, 96 patients (49 in the 150 mL/min group, and 47 in the 250 mL/min group) contributed a total of 854 12-hour treatment interval periods (421 in the 150 mL/min group, and 433 in the 250 mL/min group). Of the patients studied, 50 received CVVH compared with 46 treated with CVVHDF.

At randomisation, patients were similar with respect to age, sex, severity of illness scores (APACHE II and III; SAPS II), admission source and diagnosis (Table 1). There was a slight weight difference, with patients in the 150 mL/min group being heavier ($P = 0.03$); however, BMI was similar for both groups. Pre-randomisation renal function was also similar for both groups.

Primary outcomes: solute maintenance

A total of 7745.5 treatment hours were recorded from both groups (3840.7 hours in the 150 mL/min group, and 3904.8 hours in the 250 mL/min group) (Table 2). The mean treatment hours for each 12-hour period was similar (150 mL/min group; 6.3 hours; SD, 3.7; 52.5%, *v* 250 mL/min group; 6.7 hours; SD, 3.9; 55.8%; $P = 0.6$) as well as total number of 12-hour periods for each BFR group (Table

Table 1. Baseline demographic and clinical characteristics*

Admission variables	150 mL/min (*n* = 49)	250 mL/min (*n* = 47)	*P*
Age	61.08 ± 15.96	60.77 ± 18.31	0.93
Gender (male/female)	34/49 (69%)	24/47 (51%)	0.10
BMI	29.01 ± 5.48	27.59 ± 6.85	0.26
Weight	85.19 ± 20.39	75.85 ± 20.30	0.03
APACHE II	22.16 ± 6.47	23.13 ± 6.55	0.47
APACHE III	85.65 ± 23.17	87.21 ± 26.28	0.76
SAPS II	56.22 ± 14.19	55.55 ± 15.21	0.82
Source of admission			
ED	13 (27.7%)	12 (25.5%)	
Ward	17 (34.7%)	17 (36.2%)	
Post-operative (elective)	7 (14.3%)	6 (12.8%)	
Post-operative (emergency)	5 (10.2%)	4 (8.5%)	
Transfer from other ICU	5 (10.2%)	5 (10.6%)	
Transfer from other hospital	2 (4.1%)	3 (6.4%)	
Admission diagnosis			
Cardiovascular	6 (12.2%)	5 (10.6%)	
Cardiac surgery	11 (22.4%)	8 (17.0%)	
Respiratory	0	1 (2.1%)	
Gastrointestinal	6 (12.2%)	6 (12.8%)	
Liver failure	5 (10.2%)	6 (12.8%)	
Liver transplant	10 (20.4%)	13 (27.7%)	
Acute renal failure/ genitourinary disorder	5 (10.2%)	5 (10.6%)	
Haematological	4 (8.2%)	1 (2.1%)	
Infection/abscess	2 (4.1%)	2 (4.3%)	
Mechanical ventilation	41 (83.7%)	36 (76.6%)	0.44
Vasopressor/inotrope	41 (83.7%)	41 (87.2%)	0.77
Severe sepsis	24/49 (49.0%)	26/47 (55.3%)	0.55
Laboratory data before randomisation			
Serum creatinine	317.20 ± 171.61	297 ± 181.54	0.16
Serum urea	23.62 ± 14.94	21.19 ± 10.03	0.33

APACHE = Acute Physiology and Chronic Health Evaluation. BMI = body mass index. ED = emergency department. ICU = intensive care unit. SAPS = Simplified Acute Physiology Score. * Independent *t* test and χ^2 test.

2). The median number of 12-hour periods per patient was also similar for both groups (150 mL/min; 6; IQR, 4–12; *v* 250 mL/min; 7; IQR, 4.5–12; *P* = 0.4).

Blood plasma concentrations of urea and creatinine were similar for time interval (T1 and T2), BFR and modality (Table 2). Linear regression analysis showed no difference in the change in urea and creatinine concentrations for BFR groups, modality of CRRT, gender, BMI and weight. Repeated measures analysis of variance (ANOVA) revealed no difference between the two BFR groups for change in mean urea concentration (150 mL/min; –0.06%; SD, 0.015; *v* 250 mL/min; –0.07%; SD, 0.01; *P* = 0.42) (Figure 2) or change in mean creatinine concentration (150 mL/min; –0.05%; SD, 0.01; *v* 250 mL/min; –0.08%; SD, 0.01; *P* = 0.18) (Figure 3) There was a significant correlation between the 12-hourly percentage change in the serum concentration of these two small solutes, with decreased haemoglobin levels (150 mL/min; –0.01%; SD, 0.005; *P* = 0.002; *v* 250 mL/min; 0.01%; SD, 0.005; *P* = 0.006) and less hours of CRRT during the 12-hour period (eg, more down time) (150 mL/min; –0.023%; SD, 0.001; *P* = 0.000; *v* 250 mL/min; –0.02%; SD, 0.002; *P* = 0.001).

Discussion

Key findings

In a cohort of 96 patients requiring CRRT, three key findings have been identified. First, analysis of the data from this study failed to support the hypothesis that faster BFR would improve small solute clearance. Second, there was an association with number of hours treated with CRRT and change in serum solute levels. Third, lower serum haemoglobin levels are an independent factor associated with difference in urea and creatinine levels.

Table 2. Continuous renal replacement therapy treatment times and solute levels

	150 mL/min		250 mL/min	
	CVVH	CVVHDF	CVVH	CVVHDF
12-hour time periods	169	252	261	172
Total treatment time (hours)	1527.7	2313	2331.3	1573.5
Hours of treatment (12-hour periods); mean (SD)	6.3 (3.7)		6.7 (3.9)	
Urea level, mmol/L				
T1 (0500–1700); mean (SD)	15.7 (7.6)	16.7 (8.7)	13.2 (5.9)	13.1 (6.2)
T2 (1700–0500); mean (SD)	15.2 (7.5)	16.4 (7.7)	12.7 (5.2)	13.4 (6.1)
Creatinine level, µmol/L				
T1 (0500–1700); mean (SD)	217.0 (127.3)	226.7 (152.7)	167.8 (82.8)	209.1 (126.2)
T2 (1700–0500); mean (SD)	218.3 (144.9)	216.6 (118.8)	165.0 (87.1)	202.3 (102.9)

CVVH = continuous venovenous haemofiltration. CVVHDF = continuous venovenous haemodiafiltration. min = minute. SD = standard deviation

Figure 2. Urea change by grouping (repeated measures analysis of variance [ANOVA])

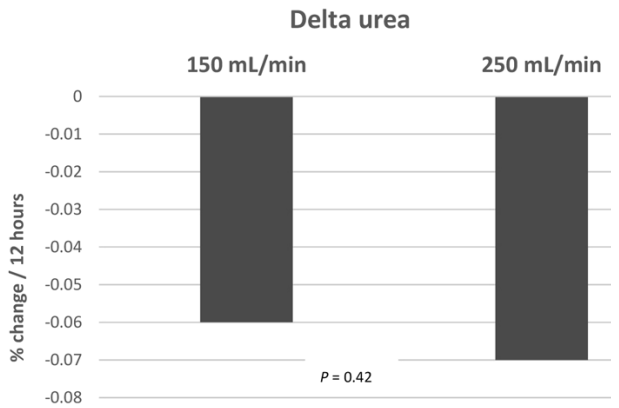
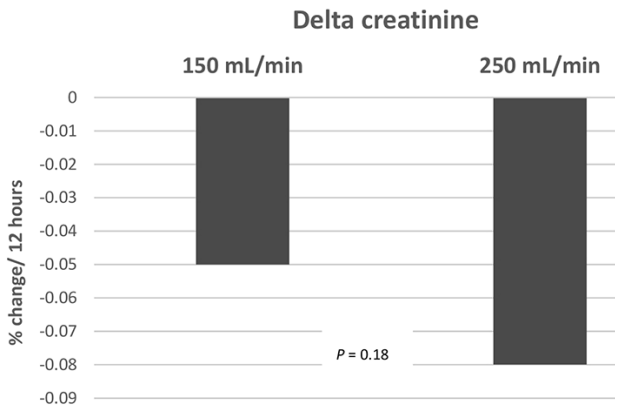


Figure 3. Creatinine change by grouping (repeated measures analysis of variance [ANOVA])



Relationship to previous studies

The efficiency of solute removal in CRRT has been a key focus since it started to be used for treating critically ill patients with AKI.[15,16] Foundation studies for small solute removal in CRRT were often unable to report BFR, as this was determined by arterial blood pressure in continuous arteriovenous circuits or as a low fixed rate (100 mL/min) determined by primitive blood pumps in the first venovenous circuits. These early reports identified that effluent rates (dialysate or ultrafiltration rates) were the most important determinants of small solute removal, as the volume of effluent would approximate the clearance.[15,16] Today, despite significant advances in CRRT technology, dosing or solute clearance in CRRT is still expressed as total effluent volume per weight and unit of time (mL/kg/h),[11] indicating that other factors may be less important in the clearance of solutes across the semi-permeable membrane.

One aspect of CRRT technology that has changed over time is clinicians prescribing a faster BFR. A recent survey of Australian and New Zealand ICUs indicated a BFR of 150–200 mL/min was the dominant setting; however, faster rates of 200–250 mL/min were now commonplace in the ICUs surveyed.[17] Observational studies and recent worldwide practice surveys of CRRT also show great variability in practice, from 80 mL/min[18] to 350 mL/min.[19,20] The prescription of BFR in intermittent haemodialysis (IHD) has long been seen as integral to therapy prescription for dosing (solute removal) in direct relation to dialysate flow rates, and is well established and standardised for the treatment of chronic kidney disease with dialysis.[21] Blood flow rates of ≥ 300 mL/min are prescribed typically with matching or higher dialysate flow rates (300–500 mL/min) to achieve azotemic control in this group of patients.[22,23] One key important difference between IHD and CRRT is the ability to achieve higher BFR during IHD with the use of long term large bore vascular access catheters and arteriovenous shunts, which both allow high BFR prescriptions aimed at targeted dosing regimens accordingly.

Historically, the prescription of BFR in CRRT has been based on the experience gained from IHD therapies, and a BFR of 200 mL/min has been common without any evidence for this.[24,25] However, limiting factors for blood flow in CRRT have been the use of short term small bore catheters in haemodynamically unstable patients[26] and the machine technology used to pump venous blood through the extracorporeal circuit. Unlike IHD, the setting of BFR in CRRT has been focused towards extracorporeal circuit patency and prevention of premature clotting (eg, < 6 hours) of the circuit.[13,19,27] The prescription of faster BFR in recent times may be attributed to improvements in vascular access catheters and machine capability rather than concern for solute clearance.

One retrospective review of 15 patients has examined any association with blood flow rates and clearances of urea and creatinine concentrations in CVVHDF.[28] Four BFR groupings were audited, with a mean rate of 125 mL/min that ranged between 35 mL/min and 175 mL/min. A comparative finding was that a BFR of 135–145 mL/min showed a difference in urea and creatinine concentrations compared with lower BFR ranges in this mode of CRRT. Consistent with our findings, Gilbert and colleagues[28] report that differences in change in urea and creatinine concentrations were best predicted by number of hours treated.

The acronym CRRT suggests that therapy is continuous and without interruption; however, down time and failure occurs frequently.[29] Reasons for interruptions to treatment are clotting, or when the patient requires procedures outside the ICU, or when native assessment of kidney function is trialled.[30] In this study, we identified an effective treatment time approximating 50% (6.3 hours and 6.7 hours/12 hours). The delivery therapy time is similar, with previously reported prescription versus delivery data.[24-33]

Similar to this study, it has also been shown that there is a direct correlation between reduction in hours of treatment and loss of small solute control in critically ill patients.[11,29,31] While there has been comparative prescribed versus actual delivered dose and therapy reports, it remains unclear which is the optimal number of CRRT hours per day to maintain small solute control in this group of patients. However, there is recent acknowledgement that clinicians who prescribe CRRT should be aware of the effect of delivery time in comparison to prescribed treatment, and should form an integral quality indicator measure in process reassessment, monitoring, reporting and benchmarking for CRRT.[34]

Based on the results identified in this study, we suggest that the number of hours of active treatment should be routinely reviewed as a component of practice. This information should be reviewed twice daily and then be considered in the context of solute levels and planned activities that might lead to down time, with CRRT prescriptions altered accordingly.

In this study, we report that low serum haemoglobin levels are an independent variable that affects small solute removal. Patients with lower serum haemoglobin count showed a smaller reduction in serum urea and creatinine levels over a 12-hour period. To our knowledge, this is the first study to report such finding.

Strengths and limitations

This randomised controlled trial of 100 patients presents, for the first time, an investigation into the effect of BFR on solute maintenance in two commonly used modes of CRRT. The analysis is based on 7745 hours (> 300 days) of treatment time. This number of patients and treatment time is representative of a tertiary level ICU and provides important findings for current CRRT practice. The study has some limitations. Solute clearance was reported as the percentage change in serum level over time. A direct measurement of serum solute levels and effluent solute levels would provide a more precise indication of control and represent a closer assessment for clearance. However, we did not measure effluent biochemistry.

The study was conducted in a single tertiary level ICU, where training and expertise among nurses for their ability to troubleshoot alarm conditions may influence delivered time (12 hours) compared with other centres, where circuits may terminate prematurely due to low skill level, or where the delays in reinstitution of therapy may be due to poor training. One further limitation may be the defined BFR used in this study. We chose 150 mL/min and 250 mL/min as a result of current intensive care practices. BFRs < 150 mL/min or > 250 mL/min may have yielded a different finding.

Conclusions

A BFR of 250 mL/min does not improve solute clearance compared with a BFR of 150 mL/min in CVVH or CVVHDF. Independent factors that affect solute removal include hours of effective treatment and haemoglobin levels.

Competing interests

None declared.

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