Netherlands Journal of Critical Care
Submitted: June 2016; Accepted: March 2017

ORIGINAL ARTICLE

Comparing CVVH with CVVHD during citrate anticoagulation in ICU patients

A. Dalhuisen[1], N. Vogtländer[2], A. Katinakis[1], H. Steenbergen[1], S. Kamphuis[3], P.E. Spronk[1]
Departments of [1]Intensive Care, [2]Clinical Nephrology and [3]Clinical Chemistry, Gelre Hospitals, Apeldoorn, the Netherlands

Correspondence
P.E. Spronk - p.spronk@gelre.nl

Keywords - **citrate, renal replacement therapy, CVVHD, CVVH, ICU**

Abstract

Introduction: We aimed to evaluate continuous venovenous haemofiltration (CVVH) versus continuous venovenous haemodialysis without filtration (CVVHD) - using citrate as regional anticoagulation - on solute clearance, nurse workload, and costs.

Methods: Prospective crossover study in a cohort of ICU patients with acute kidney injury. We compared urea, creatinine and β2-microglobulin clearance, filter lifespan and membrane performance over 72 hours (maximal filter runtime) during 15 CVVH and 15 CVVHD sessions. Anticoagulation was performed with tri-sodium citrate. Direct costs were calculated per 72 hours. Values indicate median and [P25-P75].

Results: Thirty filter runs were evaluated in 15 patients (9 male) with acute kidney injury (age 70 [59-76]). During CVVH, urea and creatinine clearances (34 [34-36] and 31 [27-33] ml/min) were comparable with CVVHD (32 [25-33] and 25[20-30] ml/min, respectively; p=0.117 and p=0.041). The clearance of β2-microglobulin was higher during CVVH (20 [16-22] ml/min) than during CVVHD (13 [12-14] ml/min; p=0.006). With a maximum allowed filter runtime of 72 hours, the filter survival time was longer during CVVHD (72 [4-73 h]) than during CVVH (43 [17-66 h]; p=0.004). CVVHD was considered less time-consuming and more user friendly than CVVH by most nurses, with less down time moments. Costs per 72 hours were lower during CVVHD: €1073 [€1072-€1146] than during CVVH €1427 [1225-1551]; p=0.002, with a cost saving of €354 [€153-€405].

Conclusion: During locoregional citrate anticoagulation, CVVHD is similarly effective, easier to handle and more cost-effective than standard CVVH.

Introduction

Acute kidney injury (AKI) occurs frequently in patients admitted to the intensive care unit (ICU) with critical illness.[1,2] AKI develops in 15-45% of all ICU admissions, while 2-6% require renal replacement therapy.[3,4] The underlying causes of AKI are multifactorial and include direct renal toxicity due to radiocontrast agents or medication, while hypovolaemic hypotension and shock may induce acute tubular necrosis. AKI frequently surfaces during the course of sepsis; the reported incidence varies from 20% in moderate sepsis to >50% in septic shock.[2,5] AKI is associated with a high mortality rate, in particular in sepsis, i.e. in patients with isolated AKI mortality is 45%, whereas patients with AKI during the course of sepsis may demonstrate mortality rates of up to 70%.[5]

The optimal way of performing continuous renal replacement therapy (CRRT) is not known. In haemodynamically unstable patients, intermittent haemodialysis is frequently not tolerated because of unwanted drops in blood pressure and risks of progressive shock or myocardial infarction. In practice, most patients with AKI are treated with CRRT.[6] The most frequently applied and efficient form of renal replacement therapy is continuous venovenous haemofiltration (CVVH) [6, 7]. This treatment modality, although effective, is not only expensive and laborious, but also associated with a number of important drawbacks, such as thrombosis, bleeding at line entry, sepsis due to line infection, as well as limitations in the patient's mobility. An additional set-back, a frequent off-time due to filter circuit clogging, may be addressed by newer techniques with lower blood flow rates such as CVVH with dialysis without filtration (CVVHD).[8,9] In addition, current views on the way the extracorporeal circuit should be anticoagulated move towards regional citrate anticoagulation with improved filter patency, safety, costs, and even mortality in surgical ICU patients with sepsis.[10-14]

We hypothesised that treatment with CVVHD using locoregional citrate anticoagulation is equally efficient to CVVH with respect to solute clearance, safety, costs and user friendliness.

Patients and methods

Setting

We performed a single-centre prospective cross-over study in a 12-bed closed-format (intensivist led) mixed medical-surgical intensive care unit (ICU) of Gelre Hospitals, a 654-bed university-affiliated teaching hospital in Apeldoorn, the Netherlands. The study was approved by the local ethics committee of Gelre Hospitals Apeldoorn, which waived the necessity to obtain informed consent. Allocation was performed based on the availability of a CRRT machine with CVVHD capacity, i.e. when that machine was in use, the eligible patient was first treated with standard CVVH. If the machine was available, the patient started with CVVHD. In this way, the study was non-blinded. We aimed for 15 patients in line with a previous study on this subject.[15] Filter use was maximised at 72 hours, i.e. even if the filter was still functional, the modality was stopped and the patient was then crossed-over to the other mode in the study.

AKI criteria

We classified the patients with AKI according to the RIFLE system: Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease.[16]

Renal replacement therapies

CVVH procedure

CVVH was performed by using a Polysulfone filter, Ultraflux AV 600S (Fresenius Medical Care). A blood flow of 200 to 300 ml/min was used, and the substitution flow was set at 32 ml/kg/h. The blood flow was dictated partly by the machine software, which does not accept low blood flows with higher substitution rates because of an increased risk of filter coagulation. Anticoagulation was achieved by intravenous infusion of citrate into the afferent line of the CRRT machine with a separate volumetric pump (Alaris®) in accordance with a standard ICU protocol aiming at a citrate concentration between 4-7 mmol/l in the filter. Details of the protocol were described previously.[14] No anticoagulation bolus was given. Two kinds of substitution fluids were used, depending on base deficit: one bicarbonate-buffered (Multibic; MedicalCare, Homburg, Germany) and one buffer-free (HF281; Medical Care). The maximum filter runtime was set at 72 hours.

CVVHD procedure

CVVHD was performed by using Polysulfone Ultraflux AV1000S filters (Fresenius Medical Care). A blood flow of 100 to 120 ml/min was used, and the dialysate flow was set at 25 ml/kg/h according to the specific manufacturer's instructions. Anticoagulation was achieved by intravenous infusion of citrate into the afferent line of the CRRT machine with an integrated citrate-calcium (Ci-Ca) module in accordance with a standard ICU protocol based on the instructions of the manufacturer. No bolus of anticoagulation was given. Calcium-free dialysate fluid was used (Ci-Ca dialysate K2; Medical Care). The maximum filter runtime was set at 72 hours.

Properties of filters

Both the AV600S (1.4 m^2) and AV1000S (1.8 m^2) filters are steam sterilised polysulfone membrane filters.

Efficacy of renal replacement therapy

We compared creatinine, urea, and β_2-microglobulin clearance. Samples of blood, urine and ultrafiltration were withdrawn at the start of treatment. Blood samples were taken from the patient and from the ultrafiltration fluids. Urea, creatinine and β_2-microglobulin clearance were calculated using the formula U*V/P. For U we used the concentration of the solute measured in the ultrafiltrate; for V the substitution rate in case of haemofiltration was used and the dialysate dose in case haemodiafiltration was used; for P we entered systemically measured levels of the solute under calculation, obtained from an arterial line, not from the dialysis line. In that way we aimed to correct for recirculation, filter clotting and other effects, which might influence clearance from the circulation. For comparing efficacy between the two modalities, filtrate rates during CVVH were individually corrected to the same filtration dose (ml/kg/h) applied during CVVHD. This means that if a filtration dose of 2500 ml/h was used in a patient during CVVH, while during the subsequent CVVHD phase a dose of 1950 ml/h was used, the calculated solute clearance during CVVHD was mathematically corrected by a factor of 2500/1950.

Costs

Costs were calculated breaking down individual components, i.e. circuit costs, laboratory costs according to the protocol, substitution and dialysis fluids, required citrate and calcium infusion. Subsequently, cumulative costs were calculated in a period of 72 hours in both the CVVH period and the CVVHD period. For instance, with a filter life of 36 hours, the total circuit cost would be twice that of a filter life of 72 hours. We did not add labour costs of the nurses involved since nurses in the ICU are continuously present and this would not explain differences between the two modalities when evaluated at a departmental level.

User friendliness

The nurses who were working with CVVHD during the study were asked to answer a short questionnaire about workload, safety and user friendliness in comparison with the standard of care using CVVH. The following questions were asked: 1) Is the alarm incidence during CVVHD higher or lower than during CVVH?; 2) Was the post filter ionised calcium level lower than 0.25 mmol/l?; 3) In terms of protocol friendliness: is the required

change in calcium and citrate flow easy and clear?; 4) Did any difficulties occur preparing the machine for CVVHD compared with CVVH?; 5) Did problems occur while changing fluid bags? ; 6) Do you have comments about the treatment modality?

Statistical analysis

Statistical analysis was performed with the SPSS software package. Data are reported as median and interquartile range (IQR; P_{25}-P_{75}). Groups were compared with the non-parametric paired Wilcoxon's test. Filter survival for each modality was tested using log-rank Mantel-Cox analysis. A $p<0.05$ was considered to indicate statistical significance unless multiple comparisons were performed. In that case, Bonferroni's correction was applied.

Results

During the study period, 15 critically ill patients (9 male, 6 female) were treated with CVVH and CVVHD for AKI according to the RIFLE criteria (age 70 [59-76]). Eight patients (53.3%) were initially treated with CVVHD, the other 7 patients (46.7%) initially started with CVVH. Patient characteristics are shown in *table 1.*

Table 1. Patient characteristics

N	15
Age (years)	70 [59-76]
Male/female	9/6
Length (cm)	170 [162-175]
Weight (kg)	80 [75-89]
Diabetes	2 (13%)
APACHE-II score	26 [22-29]
SAPS-II score	58 [48-63]
RIFLE criteria	
Risk	0
Injury	4
Failure	10
Loss of function	0
ESRD	1
Location of central venous catheter	
Femoral vein	13
Jugular vein	2
Subclavian vein	0
Admission type	
Medical	11 (73%)
Surgical	4 (27%)
LOS-ICU (days)	21 [13-39]
Hospital death	4 (27%)

APACHE = Acute Physiology Age and Chronic Health Evaluation; SAPS = Simplified Acute Physiology Score; LOS-ICU = length of stay in the ICU; ESRD = end-stage renal disease

Filter characteristics, efficacy and survival

The blood flow used was higher during CVVH (250 [200-255]) than during CVVHD (100 [100-100]; $p<0.001$). Creatinine clearance (31[27-33]) was slightly higher during CVVH than during CVVHD (25 [20-30] ml/min, $p=0.041$). Clearance of urea was similar in the two modalities, while clearance of β2-microglobulin was higher during CVVH (20 [16-22] ml/min) than during CVVHD (13 [12-14] ml/min; $p=0.006$). Keeping in mind that the maximum allowed filter runtime was 72 hours, the survival time of the filters was longer during CVVHD (72 [43-73] hours) than during CVVH (43 [17-66] hours; $p=0.004$); *figure 1.*

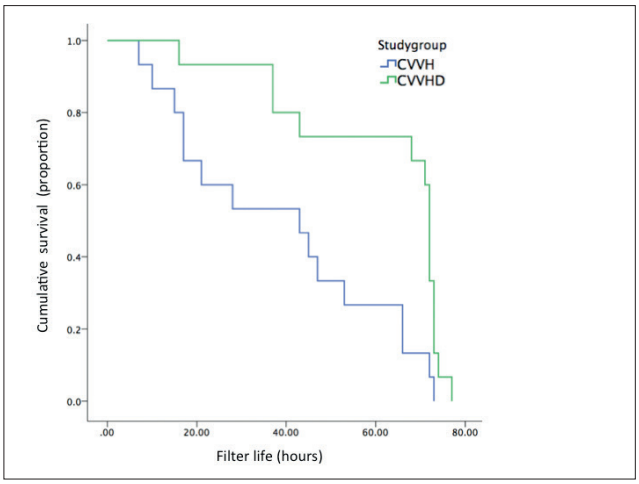

Figure 1. Filter survival during CVVH and CVVHD in 15 ICU patients. Maximum duration of filter use was 72 hours
Log Rank (Mantel-Cox analysis) p=0.004

Costs

Cumulative costs per 72 hours were lower during CVVHD (€1073 [€1072-€1146]) than during CVVH (€1427 [€1225-€1551]; $p=0.002$, *table 2*). The highest costs per 72 hours were laboratory analysis, followed by fluids used during renal replacement therapy, renal replacement kit, and citrate/calcium solutions used according to the protocol.

User friendliness

The results of the questionnaire *(figure 2)* showed that the nurses felt comfortable with the CVVHD treatment when compared with the routinely used CVVH (5% reported some problems). Importantly, it was considered less time consuming than CVVH, particularly related to a longer runtime, lower frequency of changing fluid bags, as well as a lower frequency of equipment alarms. During CVVHD in patients with low measured post filter ionised calcium and normal systemic ionised calcium, no problems with bleeding occurred. Post filter ionised calcium below 0.25 mmol/l was measured in 21% of the patients during the treatments. Measuring calcium ratio and targeting citrate dose and calcium infusion rate during CVVHD proved to be easy and safe. Because of the lower blood flow and

Table 2. Comparison CVVH vs CVVHD in the first hour of RRT

	CVVH	CVVHD	P-value
Blood flow(ml/min)	250[200-255]	100[100-100]	<0.001
Dialysate flow/substitution flow (ml/kg/hr)	32 [29-35]	25 [24-27]	0.002
Creatinine clearance (ml/min)	31 [27-33]	25 [20-30]]	0.041
Urea clearance (ml/min)	34 [34-36]	32 [25-33]	0.117
B2M clearance (ml/min)	20 [16-22]	13 [12-14]	0.006
Platelets (x10^9/l)	146 [92-214]	96 [75-229]	0.570
Haematocrit (%)	26 [22-28]	23 [22-28]	0.779
APTT	39 [32-42]	34 [29-39]	0.814
Ca/Ca++ ratio	1.87 [1.83-1.93]	1.84 [1.73-1.87]	0.181
Ca++ (mmol/l)	1.03 [0.87-1.13]	1.19 [1.11-1.22]	0.143
Costs per 72 hours			
RRT kit	168 [119-414]	121 [120-184]	0.05
Lab costs (protocol)	586	415	0.002
Citrate/calcium solutions	151	241	0.001
Fluids (substitution/ dialysis)	413 [336-486]	295 [295-295]	0.002
Total costs	1427 [1225-1551]	1073 [1072-1146]	0.002

B2M = β2-microglobulin; CVVH = continuous venovenous haemofiltration; CVVHD = continuous venovenous haemofiltration with dialysis without filtration; RRT = renal replacement therapy; aPTT = activated partial thrombin time; iCa = ionised calcium; Ca/Ca++ ratio = calcium vs ionised calcium ratio. Due to multiple comparisons, the statistical significance level was set at 0.005 after Bonferoni's correction
For CVVHD, a Fresenius Multifiltrate machine was used with integrated pumps for calcium and citrate infusion, which pumps were not present on the machines used for CVVH. Details are described in the methods section.

lower alarm frequency, patients were more easily mobilised during CVVHD when compared with routine CVVH. Using the passive mobiliser, the patient could be moved to a chair, even if the catheter was placed in the femoral vein.

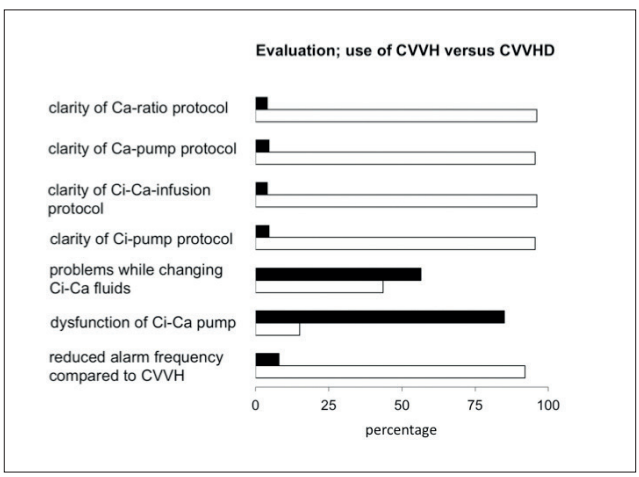

Figure 2. User satisfaction as perceived by ICU nurses working with CVVHD renal replacement therapy
CVVHD = continuous venovenous haemofiltration with dialysis; Ci-Ca = citrate – calcium; RRT = renal replacement therapy; CVVH = continuous venovenous haemofiltration

Discussion

This study directly compared CVVH and CVVHD during citrate anticoagulation in the same patients. We demonstrated that locoregional citrate anticoagulation in CVVHD is easy, user friendly, and cost-effective when compared with standard CVVH using citrate.

Many potential users of locoregional citrate anticoagulation are hesitant because of the risk of hypocalcaemia. Indeed, citrate has a history of being used as a local anticoagulant in patients with liver failure and inherent coagulation abnormalities where the use of heparin was regarded unsafe. Unfortunately, due to unwanted citrate accumulation in those patients, severe hypocalcaemia occurred.[17] These authors already warned to monitor Ca/Ca++ ratios, especially in patients with liver failure. Nevertheless, even in patients with liver failure citrate CVVHD may be used safely if strict monitoring of clotting factors and Ca/Ca++ ratios is practised.[18] This is most likely also true for standard CVVH, since during both modalities a similar citrate concentration is targeted in the filter, with inherent similar metabolic effects. In particular, protocols must take into account that calcium infusion is always linked to citrate use, which is specifically important when CRRT is temporarily stopped, or calcium infusion is inadvertently paused or not started when CRRT is resumed. However, even if strict protocols are in place, net calcium balance may prove to be negative warranting titration of local protocols.[19] We showed in our study that (ionised) calcium levels were stable during citrate anticoagulation, although the integration of citrate and calcium infusion pumps in the renal replacement machine may reduce errors.

We showed that filter survival time was at least 72 hours in most patients during CVVHD inherent to predefined stopping criteria. Filter survival during citrate renal replacement treatment was variable in previous studies. Using CVVHD and citrate anticoagulation, filter survival was 26 hours using low blood flows of 75 ml/min in a small study,[20] while others reported median filter survival times of 60 hours using higher blood flows up to 200 ml/min, dialysate flow 2000 ml/h in CVVHD.[21] Similar findings were reported in CVVHDF with an average filter survival of 64 hours using calcium containing dialysate fluids in 38 patients, with blood flow set at 150 ml/min and dialysate flow at 750 ml/h.[22] Indeed, filter survival seems to be considerably longer using citrate than during heparin anticoagulation in those settings.[23-25] Others confirmed that finding during CVVH with filter life spans of up to 157 hours.[26] Also during CVVHD, the filter life span was longer;[15] in this study, median filter survival time was 37 hours, while it was 72 hours in our study, limited by an arbitrarily and predefined maximum filter use time of 72 hours. Blood flow and anticoagulation strategies were similar, which suggests that the difference in filters (they used AN69) may account for that difference. In fact, the difference in filter type may partially

explain our results in that filter survival was much longer in the CVVHD group, although a markedly lower required blood flow may be the most important factor in explaining the long filter life span. In contrast to these findings, no difference in filter survival time was shown using locoregional citrate coagulation in a small study comparing heparin and citrate in burn patients.[27] Similar findings were reported in a retrospective dataset in a larger group of patients.[28] Moreover, no difference in filter survival time was found when citrate and nadroparin anticoagulation were compared.[14] In this study, filtration rates were high (4000 ml/h) with blood flow rates of 200 ml/min, which may partly explain these results. In this study the AN69 filter was used as well. Most interestingly, however, they found that the use of citrate proved to be independently related to better survival, a factor that remains to be elucidated. Filter survival seems to be related to several factors mainly blood flow, the filter used, locoregional anticoagulation or systemic anticoagulant, although citrate seems a useful and effective way to increase the time of filter patency.

Our findings with respect to the efficacy of CVVHD were in line with those obtained in a heparin anticoagulated CVVH versus CVVHD study, i.e. clearances of urea and creatinine were similar in both modalities, while clearance of β2-microglobulin was lower using CVVHD.[15] The actual clearance of solutes may be related to filter survival time with an inherently higher down-time of the circuit during CRRT. Indeed, median down-time for CVVH was three hours in a 160 patient observational study, mean down-time even being longer than five hours, which proved to affect azotaemic control.[29]

Although intermittent haemodialysis may be cheaper in the ICU,[30] modalities of choice in the ICU will predominantly be continuous modes, particularly due to haemodynamic intolerance. Few studies have described the effects on costs when comparing citrate and heparin anticoagulation during CRRT. In a prospective analysis in CVVHDF treatments, total CVVHDF costs were higher during heparin (€ 5580/72 hours) than during citrate anticoagulation (€921/72 hours).[24] This was partly explained due to a higher incidence of intestinal bleeding episodes in the heparin group with inherent frequent assessment of haemoglobin levels. A switch from standard CVVH to CVVHD will also decrease the requirements for fluid use. Indeed, this was shown to impact CRRT-related costs in the UK.[31] Although these findings illustrate that the choice of modality and filter life are strongly related to total costs, absolute values are difficult to compare due to differences in local reimbursement policies.

Prescribing CRRT requires knowledge and experience by the attending ICU nurses, which will put demands on the number of nurses that need to be trained, considering that educated nurses should staff all shifts. Since many factors should be taught, intensive training programs and e-learning modules have been proposed.[32] Others proposed to shift this specific workload to pharmacy technicians.[33] Most importantly, this illustrates that relative simplicity and safety are important factors to consider when implementing a new CRRT modality in the ICU. Although our questionnaire was not rigorously validated, we showed that the citrate CVVHD method was considered safe and user friendly by regular ICU nurses, leading to continuity of knowledge in all ICU nurses, not only in a smaller working group.

The strength of this study is its cross-over design. However, several serious study limitations should be acknowledged. Firstly, dosages of filtration and dialysis, and also the filters used, were not the same in the two study arms. Although we tried to mathematically correct for this factor, it is difficult to perform this correction when considering the clearance of creatinine, urea and β2-microglobulin during haemofiltration combined with dialysis. One has also to keep in mind that solute saturation in the filter is affected by the blood flow/dialysate flow during CVVHD. However, treatment was standardised in the CVVHD group, so we do not think this seriously affected the results. Secondly, this is a small single-centre study from the Netherlands. However, due to the study design and in view of the results, we think the data reflect daily critical care in the ICU. Thirdly, we used local costs in our hospital setting. Although costs may differ in other settings, the difference between CVVH and CVVHD was predominantly due to the difference in filter survival time. Hence, it is likely that the cost benefit in favour of CVVHD would also be present in other settings. Finally, separate infusion pumps for citrate were used during CVVH. Although one may suggest that this will lead to more labour time for the nurses, we consider the sole presence of one more pump not relevant in the ICU setting.

Conclusions

Using CVVH in a standard dose is similar to CVVHD with respect to creatinine and urea clearance, although CVVH is more effective in removing middle molecular weight molecules. During locoregional citrate anticoagulation, CVVHD is safe, easier to handle and more cost-effective than standard CVVH.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

References

1. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med. 1996;334:1448-60.
2. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet. 2005;365:417-30.
3. Block CA, Manning HL: Prevention of acute renal failure in the critically ill. Am J Respir Crit Care Med. 2002;165:320-4.
4. Hoste EA, Kellum JA, Katz NM, Rosner MH, Haase M, Ronco C. Epidemiology of acute kidney injury. Contrib Nephrol. 2010;165:1-8.
5. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol. 2003;14:1022-30.
6. Hoste EA, Dhondt A. Clinical review: use of renal replacement therapies in special groups of ICU patients. Crit Care. 2012;16:201.

7. Davenport A. Renal replacement therapy in acute kidney injury: which method to use in the intensive care unit? Saudi J Kidney Dis Transplant. 2008;19:529-36.
8. AlEnezi F, Alhazzani W, Ma J, et al. Continuous venovenous hemofiltration versus continuous venovenous hemodiafiltration in critically ill patients: a retrospective cohort study from a Canadian tertiary centre. Can Respir J. 2014;21:176-80.
9. Ho KM, Morgan DJ. Patient factors associated with frequent clotting of dialysers during haemodiafiltration in critically ill patients: a post hoc analysis of a randomised controlled study. Anaesth Intens Care. 2014;42:59-64.
10. Oudemans-van Straaten HM, Ostermann M. Bench-to-bedside review: Citrate for continuous renal replacement therapy, from science to practice. Crit Care. 2012;16:249.
11. Schilder L, Nurmohamed SA, Bosch FH, et al. 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. 2014;18:472.
12. Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. Am J Kidney Dis. 2012;59:810-8.
13. Lanckohr C, Hahnenkamp K, Boschin M. Continuous renal replacement therapy with regional citrate anticoagulation: do we really know the details? Curr Opin Anaesthesiol. 2013;26:428-37.
14. Oudemans-van Straaten HM, Bosman RJ, Koopmans M, et al. Citrate anticoagulation for continuous venovenous hemofiltration. Crit Care Med. 2009;37:545-52.
15. Ricci Z, Ronco C, Bachetoni A, D'Amico G, et al. Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion. Crit Care. 2006;10:R67.
16. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative w: Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204-12.
17. Meier-Kriesche HU, Gitomer J, Finkel K, DuBose T. Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. Crit Care. Med. 2001;29:748-52.
18. Schultheiss C, Saugel B, Phillip V, et al. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. Crit Care. 2012;16:R162.
19. Brain M, Parkes S, Fowler P, Robertson I, Brown A. Calcium flux in continuous venovenous haemodiafiltration with heparin and citrate anticoagulation. Crit Care Resusc. 2011;13:72-81.
20. Mitchell A, Daul AE, Beiderlinden M, et al. A new system for regional citrate anticoagulation in continuous venovenous hemodialysis (CVVHD). Clin Nephrol. 2003;59:106-14.
21. Swartz R, Pasko D, O'Toole J, Starmann B. Improving the delivery of continuous renal replacement therapy using regional citrate anticoagulation. Clin Nephrol. 2004;61:134-43.
22. Gupta M, Wadhwa NK, Bukovsky R. Regional citrate anticoagulation for continuous venovenous hemodiafiltration using calcium-containing dialysate. Am J Kidney Dis. 2004;43:67-73.
23. Bagshaw SM, Laupland KB, Boiteau PJ, Godinez-Luna T. Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement therapy? A prospective observational study in an adult regional critical care system. J Crit Care. 2005;20:155-61.
24. Park JS, Kim GH, Kang CM, Lee CH. Regional anticoagulation with citrate is superior to systemic anticoagulation with heparin in critically ill patients undergoing continuous venovenous hemodiafiltration. Korean J Intern Med. 2011;26:68-75.
25. Sponholz C, Bayer O, Kabisch B, et al. Anticoagulation strategies in venovenous hemodialysis in critically ill patients: a five-year evaluation in a surgical intensive care unit. Sci World J. 2014, 2014:808320.
26. Kutsogiannis DJ, Gibney RT, Stollery D, Gao J. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. Kidney Int. 2005;67:2361-7.
27. Mariano F, Tetta C, Stella M, Biolino P, Miletto A, Triolo G. Regional citrate anticoagulation in critically ill patients treated with plasma filtration and adsorption. Blood Purif. 2004;22:313-9.
28. Spronk PE, Steenbergen H, ten Kleij M, Rommes JH. Regional citrate anticoagulation does not prolong filter survival during CVVH. J Crit Care. 2006;21:291-2; author reply 290-1.
29. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. Intens Care Med. 2003;29:575-8.
30. Farese S, Jakob SM, Kalicki R, Frey FJ, Uehlinger DE. Treatment of acute renal failure in the intensive care unit: lower costs by intermittent dialysis than continuous venovenous hemodiafiltration. Artif Organs. 2009;33:634-40.
31. Paterson AL, Johnston AJ, Kingston D, Mahroof R. Clinical and economic impact of a switch from high- to low-volume renal replacement therapy in patients with acute kidney injury. Anaesthesia. 2014;69:977-82.
32. Graham P, Lischer E. Nursing issues in renal replacement therapy: organization, manpower assessment, competency evaluation and quality improvement processes. Sem Dial. 2011;24:183-7.
33. Benfield CB, Brummond P, Lucarotti A, et al. Applying lean principles to continuous renal replacement therapy processes. Am J Health System Pharm. 2015;72:218-23.