Optimizing continuous renal replacement therapy in the ICU

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Chapter 8

Continuous venovenous hemofiltration with or without predilution regional citrate anticoagulation: a prospective study

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Abstract

Background/aims. Continuous venovenous hemofiltration (CVVH) requires anticoagulation to prevent circuit clotting and its use is contraindicated in patients with high bleeding risk. The aim of this study was to compare CVVH with and without regional citrate anticoagulation (RCA) with respect to filter life, azotemic control and cost.

Methods. This was a prospective sequential cohort study. The first cohort of patients with a high bleeding risk and acute renal failure was treated by anticoagulant-free predilution CVVH (n=31). In the second cohort, CVVH was applied with RCA (n=20).

Results. The median filter life was 41h (interquartile range 20-62) with RCA and 12h (8-28) without RCA (P=0.001). The azotemic control was better in the group with RCA. The hourly cost was comparable between the two groups.

Conclusion. Regional anticoagulation with citrate-based replacement solution improved filter life compared to anticoagulant-free predilution CVVH. This regimen appeared safe, feasible and without metabolic complications or increased costs.

Keywords

- continuous venovenous hemofiltration – CVVH - trisodium citrate - regional anticoagulation - filter life

Introduction

Despite major improvements in dialysis and supportive therapy, the mortality rate for intensive care patients with acute renal failure remains 50% or higher.[1] Continuous renal replacement therapy (CRRT) is being used at ever increasing rates worldwide, because it offers several advantages compared to intermittent forms of dialysis, such as hemodynamic stability, avoidance of rapid fluid and electrolyte shift and better solute clearance. The main disadvantage, however, is the necessity of continuous anticoagulation for maintenance of the integrity of the extracorporeal circuit. The need for frequent filter change can be economically undesirable and excessive down-time can jeopardize azotemic control.[2] Anticoagulation however, may result in bleeding complications reported to occur in 5-26% of treatments.[3,4] Moreover, many critically ill patients have an identified risk for bleeding complications rendering systemic anticoagulation undesirable. The need for anticoagulation has to be balanced against the increased risk of bleeding in high-risk patients. Several methods of anticoagulation have been developed in patients with bleeding or increased risks, such as regional heparinisation, saline flush, low dose heparin or regional citrate.[5-13] There are many reports that CRRT can be safely managed without anticoagulation resulting in satisfactory filter life and azotemic control in these patients.[14,15]

Trisodium citrate (TSC) is an anticoagulant by its ability to chelate calcium. When given prefilter, it will allow complete regional anticoagulation of the entire circuit due to a low free calcium level. The anticoagulant effect is overwhelmed and neutralized when citrated blood from the extracorporeal circuit returns and mixes with central venous blood or replacement solution containing sufficient amounts of calcium; the calcium losses in the ultrafiltrate are replenished. Citrate has been widely used for conventional hemodialysis and has been successfully adopted for use in continuous arteriovenous hemo(dia)filtration and continuous venovenous hemo(dia)filtration.[10-17] RCA appears effective in prolonging filter survival. RCA can be achieved by two methods. The infusion of concentrated TSC is cumbersome and associated with potentially dangerous side effects such as extra sodium load and metabolic alkalosis.[18-20] Predilution CRRT with a citrate-based replacement solution as described by Palsson et al. is simple and relatively safe compared to the infusion of concentrated TSC.[21]

We prospectively studied two cohorts of critically ill patients with acute renal failure and high bleeding risk treated with either predilution anticoagulant-free CVVH or RCA using a custom-made citrate-based replacement solution and tested the hypothesis that treatment

with RCA prolongs filter life and improves azotemic control by less down-time without increasing costs.

Materials and methods

Study design and patient selection. This prospective observational sequential cohort study was conducted from August 2004 to February 2006 at the adult intensive care units of the VU University medical center in Amsterdam. The indication for renal replacement therapy was based on standard clinical indications that include renal failure accompanied by hemodynamic instability, ongoing hypercatabolism, diuretic resistant volume overload, respiratory distress, multi-organ failure, or some combinations of these factors. The study started one year prior to the availability of a custom-made citrate-based CVVH replacement fluid. Until that time all consecutive patients (n=31) with acute renal failure and high bleeding risk were treated by continuous venovenous hemofiltration (CVVH) without systemic anticoagulation and were prospectively observed. Since the availability of citrate-based solution in may 2005, the following 20 consecutive patients were treated with CVVH using RCA (fig. 1). A high bleeding risk was defined as a platelet count below 40 x 10^9 /L, or an activated partial thromboplastin time (aPTT) of more than 60 seconds or a prothrombin time test (PT-INR) of more than 2.0, a recent major bleeding or significant active bleeding. There were no exclusion criteria. The study has been performed in accordance with the ethical standards laid down in the declaration of Helsinki. The local ethics committee approved the study and waived the need for informed consent, since all patients were treated according to current local standards.

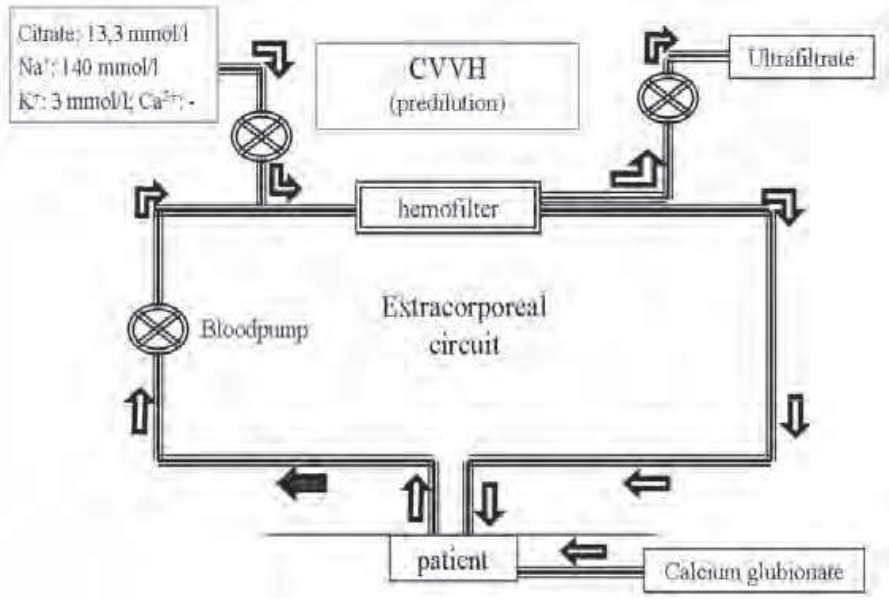

Fig 1. Continuous venovenous hemofiltration (CVVH) setting with regional anticoagulation with a custom-made citrate-based replacement solution. The calcium losses in the ultrafiltrate are replenished intravenously.

Data collection and clinical outcome measures. At baseline demographic data and clinical information were obtained. A severity of illness score at the time of ICU admission was generated by employing the Acute Physiology and Chronic Health Evaluation (APACHE II).[22] The Sequential Organ Failure Assessment (SOFA) score was evaluated at the time of admission.[23] CVVH parameters were also recorded including the survival time of the first filter used, the cause of filter termination, the number of filters used in the first 72 hours, the prescribed hours of CVVH in this period and the down-time. Clotting as a reason of filter termination is defined as spontaneous clotting or a persistently high trans-membrane pressure (TMP) (>200 mmHg) prohibiting the continuation of CVVH. A major cause of spontaneous circuit clotting is clotting of the bubble trap chamber, which is accompanied by an increase of the venous pressure (PV). Down-time is defined as the interval of time during the first 72 hours of observation that CVVH was not applied as a result of circuit clotting or as a result of transport to radiology/OR. An observation period of 72 hours is chosen because this was the predefined limit for filter use. Censored data for down-time are those cases in which more than one filter is used during the observation period of 72 hours and the cases with scheduled filter change. Azotemic control is determined by evaluating the decrease of daily determined creatinine and blood urea nitrogen (BUN) concentration in the first 72 hours in which CVVH was applied. Bleeding complications are also determined and significant bleeding is defined as the documentation of a newly onset acute bleeding at a primary or secondary site and/or the need for transfusion of more than two units of packed red blood cells within 48 hours. Hospital mortality and discharge were also evaluated. In the analysis of the costs per hour of CVVH the following formula is used: the hourly cost of the replacement solution used + (costs of the total number of filters used in the observation period + half hour wage for filter change) / (effective hours of CVVH) + hourly costs of calcium glubionate.

Hemofiltration procedure. Vascular access was secured by inserting an 11F double lumen catheter (GamCath. Gambro, Germany) into the jugular, femoral or subclavian vein. CVVH was carried out using a hemofiltration machine (DIAPACT, B.Braun, Germany). In the group receiving no anticoagulation, commercially prepared lactate or bicarbonate-buffered replacement solution was used (BH504, HF 32 bic, Dirinco, Rosmalen, The Netherlands). The custom-made citrate-based replacement solution was supplied by Dirinco (table 1). The citrate containing solution were in bags with an obvious green label instead of black labels in order to minimize the chance of errors in switching solutions. In all patients a 1.9 m^2 highly

Table 1. Composition of the different replacement solutions.

	Lactate buffer BH 504®	Bicarbonate buffer HF 32 Bic®	Citrate buffer HF CitPre®
Sodium (mmol/l)	140	140.0	139.9
Potassium (mmol/l)	1.5	2.0	3.0
Magnesium (mmol/l)	0.5	0.5	0.5
Calcium (mmol/l)	1.5	1.75	---
Chloride (mmol/l)	103	111.5	104.0
Glucose (mmol/l)	11.1	1.0	5.0
Citrate (mmol/l)	---	---	13.3
Bicarbonate (mmol/l)	---	32.0	---
Lactate (mmol/l)	42.0	3.0	---

***** The ready mixed bicarbonate-buffered replacement solution is prepared in bags of special plastic sheeting to prevent evaporation of carbon dioxide.

permeable cellulose triacetate hemofilter was used (NIPRO UF205, Nissho corporation, Japan). Filters were routinely changed after 72 hours. In both groups the replacement solution was delivered prefilter. The blood flow was set at 180 ml/min. In the group of patients with anticoagulant-free CVVH, the replacement solution ran at a rate of 2000 ml/hr which was the standard setting at that point. With this blood flow, the citrate containing replacement solution ran at a rate of 2400 ml/hr, since the rate of infusion of the citrate-based solution was continuously coupled to the blood flow. The replacement solution is infused after the blood pump in order to prevent backflow to the patient. Patients on RCA had a separate intravenous calcium drip for which we used calcium glubionate (Calcium Sandoz® containing calcium 0.225 mmol/ml, Novartis Consumer Health, The Netherlands). The calcium administration depended on the systemic ionized calcium concentration (table 2). Our protocol precluded adaptations of citrate infusion rates to the ionized calcium level in the extracorporeal circuit, because it would unintendedly influence acid-base and sodium balance. For this reason calcium-levels in the extracorporeal circuit were not measured. With this regimen patient safety and protocol simplicity prevailed over possibly improved efficacy. However the citrate administration with our method was expected to yield an ionized calcium level in the extracorporeal circuit below 0.3 mmol/l.

Safety monitoring and criteria to stop CVVH with TSC. A low systemic ionized calcium, metabolic alkalosis and citrate accumulation are the main potential complications. In order to prevent these complications, the anion gap, total to ionized calcium ratio, pH, bicarbonate and base excess were measured at least four times daily in arterial blood samples, drawn from an arterial line. The first measurement was done 1 hour after initiation of CVVH. Serum citrate

Table 2. Algorithm of calcium infusion during TSC CVVH.

A. Initial pump settings

Blood pump (ml/min)	Citrate-substitution flow (ml/hr)	Calcium pump (ml/hr)
140	1900	9.5
160	2100	10.5
180	2400	12
200	2700	13.5
Everybody starts according to this chart. Furthermore, this chart regards every patient with a systemic ionised calcium of **1.0 – 1.1 mmol/l**.		

B. Low calcium: 0.9 – 1.0 mmol/l.

Blood pump (ml/min)	Citrate-substitution flow (ml/hr)	Calcium pump (ml/hr)
140	1900	11
160	2100	12.5
180	2400	14
200	2700	16
This chart regards every patient with a systemic ionised calcium of **0.9 – 1.0 mmol/l**.		

C. Low calcium: 0.8 – 0.9 mmol/l.

Blood pump (ml/min)	Citrate-substitution flow (ml/hr)	Calcium pump (ml/hr)
140	1900	15
160	2100	16.5
180	2400	18
200	2700	20
This chart regards every patient with a systemic ionised calcium of **0.8 – 0.9 mmol/l**.		

D. High calcium

Blood pump (ml/min)	Citrate-substitution flow (ml/hr)	Calcium pump (ml/hr)
140	1900	7.5
160	2100	8.5
180	2400	10
200	2700	11
This chart regards every patient with a systemic ionised calcium of **1.1 – 1.2 mmol/l**.		

For the calcium pump calciumglubionate (0.225 mmol/ml) is used.
If the ionised calcium level is < 0.8 mmol/l, administer 1 vial of calciumglubionate (0.225 mmol/ml) as a bolus (10 ml = 2.25 mmol) and adjust the calcium pump according to table 2C. If there is no satisfactory increase of ionised calcium level (less than 0.1 mmol/l), consider the administration of another bolus of caliumglubionate.
In case of decreasing ionised level (> 0.1 mmol/l per 6 hours) always exclude citrate-accumulation and monitor ionised calcium level three hours after pump adjustment.

concentration were not measured. Afterwards, these measurements were done at 6.00, 12.00, 18.00 and 24.00 hour. An electrocardiogram was made if hypocalcaemia (ionized calcium below 0.9 mmol/l) occurred. Blood samples were also taken to measure magnesium, sodium and potassium levels; APTT and PT-INR were also determined at least twice a day at 6.00 and 18.00 hour. White blood cell count, platelet count, haemoglobin and lactate levels were

measured at least once daily at 6.00 am. The safety monitoring lasted for the duration of CVVH requirement. CVVH was not stopped if there was a bleeding complication in either treatment protocol.

Citrate CVVH was stopped, if the patient fulfilled one of the following criteria: total to ionized calcium ratio of more than 2,5, persistent metabolic alkalosis with a base excess of more than 10 mmol/l, clinical signs of hypocalcaemia (tetanic symptoms or prolonged QT interval) or progressive non-lactic acidosis (pH<7.20) during CVVH combined with an increase in anion gap (>13 mmol/l) without the presence of endo- or exogenous acids other than citrate, suggesting citrate accumulation. If there were signs of citrate accumulation, predilution CVVH was continued without anticoagulation using bicarbonate-based replacement fluid.

Statistics. Statistical analysis was performed using a statistical software package (SPSS 12.0). Continuous data are presented as medians and interquartile range. Dichotomous data are presented as percentages. The Fisher's exact test was applied for dichotomous and categorical data. The Mann-Whitney test was used to compare numerical data of the two groups. Circuit life in the two groups is presented graphically as Kaplan Meier survival curves. The log rank test was used to compare circuit life among the two groups. A P-value < 0.05 was considered statistically significant. Exact p values are given.

Results

Fifty-one patients were included in the study. Among these, 31 were treated with no anticoagulation and 20 were treated by RCA. There were no differences between the two groups in baseline characteristics (table 3). In CVVH without RCA, the median circuit lifetime was 12 h (interquartile range 8-28) versus 41 h (interquartile range 20-62) with RCA (P=0.001, table 4). Fig.2 presents Kaplan-Meier curves of the time to failure of the hemofilters. The median filter life for filters terminated because of clotting or scheduled change was 12 h (interquartile range 8-28) and 48 h (interquartile range 27-72), for anticoagulant-free CVVH and CVVH with RCA (P=0.003) respectively.

Table 3. Baseline characteristics .

	No anticoagulation n=31	Regional citrate n=20	P
Sex, male/female	14/17 (45%/55%)	13/7 (65%/35%)	0.14
Age (y)	70 (59-75)	64 (55-75)	0.79
APACHE II	24 (18-30)	24 (22-28)	0.77
SOFA 0	13 (10-17)	13 (10-14)	0.69
Creatinine (μmol/l)	261 (230-324)	288 (216-340)	0.66
BUN (mmol/l)	17.8 (12.0-30.8)	21.2 (13.2-32.8)	0.40
Thrombocytopenia	9 (29%)	7 (35%)	0.76
Prolonged aPTT/PT-INR	13 (42%)	8 (40%)	0.77
Active recent bleeding	18 (58%)	15 (75%)	0.25
Diagnosis at admission			
Sepsis	14 (45%)	11 (55%)	
Trauma	0	1 (5%)	
Aortic aneurysm repair	4 (13%)	1 (5%)	
Pancreatitis	1 (3%)	0	
Glomerulopathy	1 (3%)	1 (5%)	
Cardiogenic shock	8 (26%)	2 (10%)	
Postoperative	3 (10%)	1 (5%)	
Others	0	3 (15%)	

Data presented as median (interquartile range) or number (%) where appropriate; Sofa: Sequential Organ Failure Assessment at admission (SOFA 0); APACHE II: the Acute Physiology and Chronic Health Evaluation; aPTT: activated partial thromboplastin time; PT-INR: prothrombin time test.

Table 4. Filter data, azotemic control and cost of CVVH.

	No anticoagulation n=31	regional citrate n=20	P
Filter run time (hr)	12 (8-28)	41 (20-62)	0.001
Prescribed hrs of CVVH in 72 hr	72 (23-72)	72 (65-72)	0.09
Down-time in first 72 hrs (hr)	3 (0-9)	2 (0-4)	0.15
Censored down-time (hr)	5 (3-13)	2 (0-4)	0.002
Filter use in 72 hr (n)*	3 (0-9)	2 (2-4)	0.27
Filter termination due to clotting	26 (84%)	8 (40%)	0.002
Filter life span > 24 hr	10 (32%)	14 (70%)	0.009
Filter life span > 36 hr	4 (13%)	11 (55%)	0.002
Filtration dose (ml/hr/kg)	27.8 (23.0-30.8)	30.0 (26.9-34.3)	0.04
Decrease in creatinine (μmol/l)	41 (20-146)	127 (54-153)	0.04
Decrease in BUN (mmol/l)	3.5 (0-9.3)	9.1 (3.5-13.4)	0.03
Cost per hour of CVVH ($)	12.85 (9.72–18.09)	14.33 (12.83–16.05)	0.40

Data presented as median (interquartile range or number (%) where appropriate). Azotemic control is defined as the decrease of serum levels of creatinine and BUN in the 72 hours after initiation of CVVH.

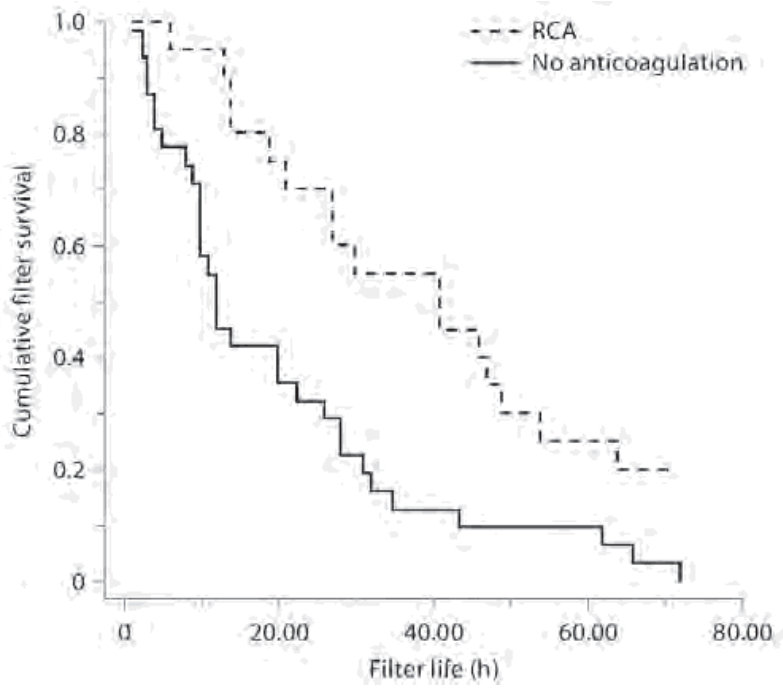

Fig.2. Kaplan-Meier curves for filter life of the first filter in CVVH with and without regional citrate anticoagulation (RCA) ($p < 0.005$); at 72 hours all filters were routinely changed.

The causes of filter termination are outlined in table 5. Filter termination due to clotting in the anticoagulant-free group was 84% (26/31) versus 40% (8/20) in the RCA group (P=0.002).

Table 5. Causes of filter termination.

	No anticoagulation n=31	Regional citrate n=20
Circuit clotting	26 (83.9%)	8 (40%)
Vascular access malfunction	1 (3.2%)	3 (9.7%)
Transport to radiology/OR	1 (3.2%)	1 (3.2%)
Renal function recovery	1 (3.2%)	2 (6.5%)
Citrate accumulation	--	1 (3.2%)
Death before filter termination	0	1 (3.2%)
Technical problems with CVVH machine	1 (3.2%)	1 (3.2%)
Scheduled filter change	1 (3.2%)	3 (9.7%)

Data are presented as numbers (%).

The courses of the TMP and PV at initiation and at the end of the first filter are outlined in table 6. In the group treated without anticoagulation there was a important increase in PV, whereas the PV remained stable in the group treated with RCA.

In one case RCA was discontinued because of citrate accumulation. This was a patient with a rapidly progressive post renal transplantation lymphoproliferative disorder and fulminant sepsis and liver dysfunction. Citrate accumulation was recognized with the safety monitoring and the treatment was converted to anticoagulant-free predilution bicarbonate

Table 6. Pressure regimen over time.

	No anticoagulation n=31	Regional Citrate n=20	P
TMP (mmHg)			
at initiation of CVVH	41 (37-51)	40 (32-45)	0.31
at end of first filter	98 (68-155)	145 (111-200)	0.05
increase per hour	3.3 (1.6-5.5)	2.4 (1.6-3.9)	0.31
PV (mmHg)			
at initiation of CVVH	102 (82-121)	85 (75-98)	0.04
at end of first filter	110 (86-174)	80 (68-96)	0.002
increase per hour	1.1 (-0.2-5.2)	-0.3 (-0.4-0.3)	0.01

TMP: transmembranous pressure; PV: venous pressure. Data presented as median (interquartile range)

CVVH. There were no cases of hypernatremia or metabolic alkalosis and acidosis due to trisodium citrate. The transfusion requirements in the first 48 hours were equal in both groups: 2 packed cells (0-3) in the anticoagulant-free group and 1 packed cells (0-3) in the RCA group (P=0.35). With the longer circuit lifetime there were less filter changes in patients treated with RCA. In the anticoagulant-free group there were 10 cases in which only one filter was used (median filter life: 10 h (3 -30)) versus 4 cases in the RCA group (median filter life: 47 h (16-49)); in these cases there was no down-time. After excluding the latter, the down time in the anticoagulant-free group and the RCA group was respectively 5 h (3-13) and 2 h (0-4) (P=0.002) per 72 hours. In the observation period the decrease in plasma BUN and creatinine was 3.5 mmol/l (interquartile range: 0-9.3) and 41 mmol/l (interquartile range: 20-146) in the anticoagulant-free group versus 9.1 mmol/l (interquartile range: 3.5-13.4) and 127 mmol/l (interquartile range: 54-153) in the RCA group (P<0.05), respectively. The costs per hour of CVVH were comparable between the two groups: $14.33 (12.83–16.05) in CVVH with TSC versus $12.85 (9.72–18.09) in anticoagulant-free CVVH (P=0.40). The results are summarized in table 4. There were no major differences between the groups in biochemistry parameters such as calcium, sodium, potassium, bicarbonate and pH (data not shown).. Hospital mortality did also not differ between the groups: 61% and 40% in the anticoagulant-free and RCA group (P=0.20), respectively.

Discussion

In this study, CVVH with RCA proved superior to predilution anticoagulant-free CVVH in critically ill patients in which systemic anticoagulation was contra-indicated. To our knowledge this is the first prospective trial of regional anticoagulation with trisodium citrate

versus no anticoagulant in CVVH in patients at high risk for bleeding. In 2002 Hofmann et al. demonstrated an improved filter patency of a citrate CVVH system compared to historical anticoagulant-free CVVH systems.[24] In 2005 Brophy et al. made a comparison between three anticoagulation methods, citrate, heparin and no anticoagulation, in paediatric CRRT.[25] The mean circuit life in this prospective multi-center study was 42.1 h ± 27.1, 44.7 h ± 35.9 and 27.2 h ± 21.5 hours for heparin, citrate and no anticoagulation respectively; patients at high risk for bleeding were not studied separately.

Mortita et al. first described the use of citrate for anticoagulation during intermittent haemodialysis in 1961,[26] but it was not until 1990 Mehta described this technique of regional anticoagulation in CRRT.[17] Nowadays, RCA in CRRT is rapidly gaining popularity worldwide. In the vast majority RCA is accomplished with the technique as described by Mehta et al. with the infusion of concentrated TSC prefilter; the loss of calcium is replenished by substitution of calcium containing replacement solution postfilter or by intravenous administration of calcium chloride. Despite accumulating evidence in favour of citrate-based anticoagulant regime in patients at high risk for bleeding, in most ICU's anticoagulant-free CVVH is performed, as current protocols with RCA are complex. Moreover, there are serious concerns about potential metabolic complications and the bedside presence of concentrated TSC carries the risk of fatal errors, when erroroneously infused intravenously. The technique described by Palsson et al. overcomes these problems as it is characterized by its simplicity without concerns about metabolic complications and less susceptibility for potentially fatal errors.[21] The main drawback however, is the cost of citrate-based replacement solution which is not commercially available yet. Its effectiveness and safety has already been suggested previously.[13,21]

At our institution, patients at high risk for bleeding were historically treated with anticoagulant-free predilution CVVH. We decided to adopt a citrate-based regimen in CVVH featuring safety and simplicity modified from the method of Palsson et al..[21] While awaiting the production and delivery of the citrate-based replacement fluid, we started including all patients at high risk for bleeding who were treated with CVVH without anticoagulation. In the same period we conducted a thorough educational program for intensive care medical and nursing staff. Once the solution was available CVVH with RCA became the standard method of treatment in patients carrying a high bleeding risk and the following 20 patients treated with this technique were included in the trial. In this prospective trial we demonstrated that RCA is superior to anticoagulant-free predilution CVVH, in accordance with previous suggestions in patients without bleeding risk.[10,12,13,17] The filter life increased more than

threefold, predominantly caused by decreased spontaneous circuit - and filter clotting. In the group treated with no anticoagulation, spontaneous circuit clotting due to clot formation in the bubble trap chamber, as demonstrated by the increased venous pressure, was a major cause of termination of the first filter.

Furthermore, we showed that in the RCA cohort, the azotemic control is better, maybe due to the prolonged filter life and hence shorter down time, while the transfusion requirement were comparable between the two groups. In one patient RCA had to be discontinued because of citrate accumulation; this was a patient with a rapidly progressive post renal transplantation lymphoproliferative disorder with severe liver dysfunction. After conversion to predilution bicarbonate-based CVVH the total to ionized calcium ratio normalized within one hour. Patients with liver failure were not excluded in this trial though it is known that liver cirrhosis is associated with a higher level of metabolic complications as a result of a decreased citrate clearance. There is however a substantial inter-individual variation in citrate clearance making it difficult to predict which patient will accumulate. Moreover, Kramer et al. demonstrated the feasibility of citrate anticoagulation in patients with advanced liver cirrhosis.[27] When the safety monitoring is performed according the protocol, citrate accumulation can be recognized timely.

In our population, no metabolic complications associated with the administration of TSC were observed. TSC is metabolized by the liver, muscle cells and renal cortex and each TSC molecule yields 3 molecules of bicarbonate releasing 3 molecules of sodium. Metabolic alkalosis and hypernatremia are the main metabolic complications which can occur with hypertonic TSC infusion. Mehta et al. reported a high incidence of metabolic alkalosis (4%) when using concentrated TSC infusion.[17] These problems can be avoided by using specially preformed solutions with a modified concentration of sodium and buffer or by using a isotonic citrate-based replacement solution. An often mentioned limitation of the latter technique is the cost of the solution. We have demonstrated that, although the solution is more expensive than lactate or bicarbonate buffered replacement solution, the cost per hour of CVVH is comparable, a finding which can be attributed to lower costs of filters and extracorporeal circuit lines and less cost of labour during treatment with RCA.

Our study has some drawbacks. This is not a randomised trial, but the patient groups are comparable. The substitution flow rate was different in both groups which might partly explain the difference found in filter survival or azotemic control. However, it is obvious that the significantly shorter off-time in the TSC-cohort adds to better azotemic control. Though theoretically the substitution flow rate can influence filter patency, it is unlikely that a 20%

increase in substitution flow rate in predilution mode can explain a more than 300% increase in filter life. Moreover, a study demonstrating the influence of substitution flow rate on filter life has not been performed yet.

In conclusion, our data suggest that CVVH with regional anticoagulation using a citrate-based replacement solution is superior to anticoagulant-free predilution CVVH regarding filter life and azotemic control. It is a safe and simple technique with no metabolic and bleeding complications at costs comparable to CVVH with lactate- or bicarbonate-buffered solution. In patients with a contraindication for systemic anticoagulation warranting CVVH, treatment with TSC should be the first choice modality for anticoagulation.

Disclosure

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References

1. Kellum JA, Angus DC, Johnson JP et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Med 2002; 28: 29-37.
2. 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. Intensive Care Med 2003; 29: 575-578.
3. Ward DM, Mehta RL. Extracorporeal management of acute renal failure patients at high risk of bleeding. Kidney Int Suppl 1993; 41: S237-244.
4. Van de Wetering J, Westendorp RG, Van der Hoeven JG, Stolk B, Feuth JD, Chang PC. Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage. J Am Soc Nephrol 1996: 7: 145-150.
5. Vos P, Speelberg B. Survival of the artificial kidney during systemic versus regional anticoagulation with heparin for continuous veno-venous hemofiltration in the intensive care unit. NTvIC 2001; 16: 266-272.
6. Morabito S, Guzzo I, Solazzo A, Muzi L, Luciano R, Pierucci R. Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding. J Nephrol 2003; 16: 566-571.
7. Kaplan AA, Petrillo R. Regional heparinization for continuous arteriovenous hemofiltration (CAVH). ASAIO Trans 1987; 33: 312-315.
8. Schwartz R, Port F. Preventing hemorrhage in high-risk hemodialysis; regional versus low-dose heparin. Kidney Int 1997; 16: 513-518.
9. Paganini EP. Slow continuous hemofiltration and slow continuous ultrafiltration. ASAIO Trans 1988; 34: 63-66.
10. Monchi M, Berghmans D, Ledoux D, Canivet JL, Dubois B, Damas P. Citrate vs heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. Intensive Care Med 2004; 30: 260-265.
11. Gabutti L, Marone C, Colucci G, Duchini F, Schonholzer C. Citrate anticoagulation in continuous venovenous hemodiafiltration : a metabolic challenge. Intensive Care Med 2002; 28: 1419-1425.
12. Kutsogiannis DJ, Mayers I, Chin WDN, Gibney RTN. Regional citrate anticoagulation in continuous venovenous hemodiafiltration. Am J Kidney Dis 2000; 35: 802-811.
13. Thoenen M, Schmid ER, Binswanger U, Schuepbach R, Aerne D, Schmidlin D. Regional citrate anticoagulation using a citrate-based substitution solution for continuous venovenous hemofiltration in cardiac surgery patients. Wien Klin Wochenschr 2002; 114: 108-114.
14. Uchino S, Fealy N, Baldwin I, Morimatsu I, Bellomo R. Continuous venovenous hemofiltration without anticoagulation. ASAOI Journal 2004; 50: 76-80.
15. Tan HK, Baldwin I, Bellomo R. Continuous venovenous hemofiltration without anticoagulation in high-risk patients. Intensive Care Med 2000; 26: 1652-1657.
16. Mehta RL, McDonald BR, Ward DM. Regional Citrate Anticoagulation for Continuous Arteriovenous Hemodialysis; An Update after 12 Months. Contrib Nephrol 1991; 93: 210-214.
17. Mehta RL, McDonald BR, Aguilar MM, Ward DM. Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. Kidney Int 1990; 38: 976-981.
18. Silverstein FJ, Oster JR, Perez GO, Materson BJ, Lopez RA, Al-Reshaid K. Metabolic Alkalosis Induced by Regional Citrate Hemodialysis. ASAIO Transactions 1989; 35:22-25.

19. Meier-Kriesche HU, Finkel KW, Gitomer JJ, DuBose TD. Unexpected Severe Hypocalcemia During Continuous Venovenous Hemodialysis With Regional Citrate Anticoagulation. Am J Kidney Dis 1999; 33:1-4.
20. Morgera S, Scholle C, Voss G et al. Metabolic Complications during Regional Citrate Anticoagulation in Continuous Venovenous Hemodialysis: Single-Center Experience. Nephron Clin Pract 2004; 97:c131-136.
21. Palsson R, Niles JL. Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding. Kidney Int 1999; 55: 1991-1997.
22. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13; 818-829.
23. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial Evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001; 286: 1754-1758.
24. Hofmann RM, Maloney C, Ward DM, Becker BN. A novel method for regional citrate anticoagulation in continuous venovenous hemofiltration (CVVHF). Ren Fail 2002; 24: 325-335.
25. Brophy PD, Somers MJG, Baum MA et al. Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). Nephrol Dial Transplant 2005; 20: 1416-1421.
26. Morita Y, Johnson RW, Dorn RE, Hall DS. Regional anticoagulation during hemodialysis using citrate. Am J Med Sci 1961; 42: 32-43.
27. Kramer L, Bauer E, Joukhadar C et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. Crit Care Med 2003; 31: 2450-2455.