Optimizing continuous renal replacement therapy in the ICU

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Chapter 4

Pre- versus postdilution continuous venovenous hemofiltration: no effect on filter life and azotemic control in critically ill patients on heparin

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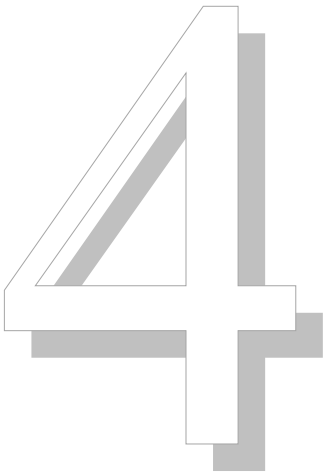

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Abstract

Background/aims. In continuous venovenous hemofiltration (CVVH) the delivery of replacement fluid in pre- or postdilution mode remains subject to controversy. We compared both modes in terms of filter life, dose and azotemic control.

Methods. All patients admitted to the intensive care units of a university hospital between November 2004 and December 2006 receiving CVVH and systemic anticoagulation with heparin were retrospectively studied.

Results. Thirty six patients treated by CVVH in predilution and 27 in postdilution mode were studied, with 132 filters in the former and 111 for the latter. The filter life (median ± interquartile range) was 24 ± 38 and 29 ± 46 h (P=0.58), respectively. Although the fall in creatinine and urea depended on dose, the 19% greater delivered dose in post- than predilution mode did not impact on azotemic control.

Conclusions. In critically ill, heparinised patients on CVVH, filter life and azotemic control are similar in pre- and postdilution modes and underscore the clinical applicability of the predilution mode.

Key words

- acute kidney injury – azotemic control - CVVH - dose – filter life - postdilution - predilution -

Introduction

Acute renal failure is common in critically ill patients and necessitates renal replacement therapy in about 5% of the total intensive care population.[1,2] Continuous venovenous hemofiltration (CVVH) is frequently used for that purpose, but the optimal infusion site for the replacement fluid remains controversial. In predilution mode, clearance may be limited because blood is diluted before it enters the filter; the latter, however, results in a lower blood viscosity which may retard coagulation, prolong filter life and thereby improve efficiency. Less clotting may thus render predilution preferable over postdilution when systemic anticoagulation is contraindicated.[3] Hemodilution may also facilitate removal of urea from red blood cells.[4-6] The argument against postdilution is that the increase in blood viscosity leads to early filter coagulation and to a shorter filter life but clearance, for a given blood flow and ultrafiltrate rate, may be higher as compared to predilution, in the absence of hemodilution.[7] Clinical evidence favouring one or the other concept is scarce, however. Postdilution infusion was associated with a reduced filter life without any beneficial effects on azotemic control according to one study on patients with highly variable anticoagulant regimens,[8] whereas filter life was longer on predilution in patients receiving intravenous nadroparin at the cost of lower creatinine clearances in another study.[9] Lack of differences in filter life and clearance were also observed when nadroparin was used as a systemic anticoagulant.[10] So, the available data concerning this issue are conflicting. Moreover, with 31 and 9 included patients respectively, some of these studies were rather small.[9,10]

In the current study, we evaluated a relatively large number of homogenous critically ill patients anticoagulated by heparin and filters used for CVVH in pre- and postdilution mode. We hypothesized equivalence of pre- and postdilution CVVH regarding filter life and azotemic control, in spite of a difference in delivered dose.

Patients and methods

Patients. This is a retrospective study. All patients admitted at the intensive care unit (ICU) of the Free University medical center between November 2004 and December 2006 treated by CVVH were studied. The ICU of the Free University Medical Center consists of two equally sized but separate units; one unit historically treated all patients with CVVH in the predilution mode, and the other unit in the postdilution mode. In the past both units were separate departments; in 2001 the units were merged with similar admission and discharge policies and rotating medical staff. The nursing personnel, however, remained fixed. The indication to start

CVVH was based on clinical grounds. In order to warrant filter patency patients were treated per protocol by heparin in order to reach an activated partial thromboplastin time (aPTT) between 55-65 seconds. In our unit, patients with an increased bleeding risk are treated with regional anticoagulation with citrate-containing replacement solution and they do not form part of this study. Patients on the ICU for a minimum of three days and treated by heparin were included in this study only. Patients were excluded if only one filter was used with a filter life of less than 12 hours. CVVH was performed using a hemofiltration machine (Diapact, B.Braun, Melsungen, Germany). Vascular access was secured by inserting an 11-French double lumen catheter (GamCath, Gambro, Hechingen, Germany) into one of the three large veins (jugular, femoral or subclavian). In all patients, a 1.9 m^2 highly permeable cellulose triacetate hemofilter was used (Nipro UF205, Nissho corporation, Osaka, Japan). Filters were routinely changed after 72 hours. Blood flow and flow of lactate- or bicarbonate-based replacement fluid were routinely set at 180 ml/min and 2 l/h, respectively, with net ultrafiltrate determined by treating physicians. CVVH was discontinued at the discretion of treating physicians and patients were otherwise treated according to institutional guidelines. If not explicitly mentioned otherwise, the nurses were initially free to set the dilution mode in the way they were most comfortable with. Since December 2006 all patients are treated in predilution mode.

Data collection. We designed a predefined checklist for this retrospective study. Our ICU has an electronic patient file where patients' details are stored. Baseline characteristics were retrieved, including age, gender, weight, height, prior chronic intermittent hemodialysis, and date and reason of admission. A severity of illness score at the time of ICU admission was generated by the Acute Physiology and Chronic Health Evaluation (APACHE II).[11] The Sequential Organ Failure Assessment (SOFA) score was evaluated at admission.[12] Also recorded were the life of all filters used (up to number 12 per patient), the cause of filter termination, the prescribed hours of CVVH, downtime and last transmembranous pressure (TMP). Clotting as a reason of filter termination was defined as spontaneous clotting or a persistently high TMP (>200 mmHg) prohibiting continuation of CVVH. Downtime was defined as the interval that CVVH was prescribed but not applied as a result of circuit clotting or as a result of transport to radiology or operation room. Other collected data included the aPTT, platelet count and hematocrit (Ht), which were measured daily after start of CVVH. Azotemic control was determined by evaluating the daily serum creatinine and blood urea concentrations on the first 3-10 CVVH days. The daily net ultrafiltrate volume, urine production and fluid balance were registered. Delivered dose was defined as the ultrafiltration volume

(substitution volume + net ultrafiltrate) delivered per kilogram preadmission body weight per hour; it was averaged per day and thus included downtime. For predilution, the ultrafiltration flow per hour (Quf) was adjusted by the following formula: [13,14]

$$\frac{[Qb \times 60 \times (1-Ht)]}{[(Qb \times 60 \times (1-Ht)) + Qs]} \times Quf$$

where Qb = blood flow per minute and Qs = substitution flow per hour.

Creatinine clearance is identical to the adjusted ultrafiltrate but is expressed as millilitres per minute. The filtration fraction (FF) was calculated. For postdilution the following formula was used: FF = Quf/Qp x 100, where Qp = plasmaflow (Qb x (1-Ht) per minute. For predilution Qs was added to Qp (Quf/(Qp+Qs) x100). The length of stay in the ICU was recorded.

Statistical analysis. Values are summarized as mean ± standard deviation (SD) or median ± interquartile range (IQR), in case of non-normal distribution (Kolmogorov-Smirnov test $P<0.05$). Values were logarithmically transformed in the latter case. The Mann-Whitney U test was used for univariate analyses. For categorical variables, the X^2 and Fisher exact tests were used. Generalized estimating equations (GEE), taking repeated measurements in the same patients into account, were used to evaluate determinants, including dilution mode, of filter life and azotemic control, until filter number 12 at maximum per patient, or per CVVH day, from day 0 (start of CVVH) to 2 or 0 to 9. GEE is used to fit parameters of a generalized linear model where unknown correlation is present.[15] The focus of GEE is on estimating the average response over the population rather than the regression parameters that would enable prediction of the effect of changing one or more covariates on a given individual.The course of logarithmically transformed creatinine and urea was compared among dilution modes after entering baseline values as covariates for adjustment. Filter life in the two groups is presented graphically as Kaplan-Meier survival curves; the log-rank test was used to compare filter life among the two groups. Exact P values are given and considered statistically significant if <0.05.

Results

A total of 230 critically ill patients were treated by CVVH in the observation period. Sixty three patients fulfilled the inclusion criteria, 36 patients in predilution and 27 patients in postdilution mode. A total of 243 filters were analysed (up to 12 filters per patient), 132 in pre- and 111 in postdilution, so that between day 0-9 123 filters were used in pre- and 97 in postdilution mode. There was no difference in baseline patient characteristics between pre- and postdilution modes (Table 1).

Table 1. Patient characteristics.

	Predilution n=36	Postdilution n=27	P
Age (years)	67 ± 16	66 ± 18	0.84
Weight (kg) *	74 ± 15	80 ± 14	0.15
Height (cm) *	175 ± 12	175 ± 12	0.32
APACHE II score *	22 ± 6	23 ± 5	0.28
SOFA score *	12 ± 4	11 ± 3	0.59
Previous hemodialysis	5 (14)	3 (11)	1.00
Reason for admission			0.88
Sepsis	14 (39)	11 (41)	
Cardiogenic shock	6 (17)	7 (26)	
Aneurysm repairPost	3 (8)	2 (7)	
CABG	9 (25)	5 (19)	
Other	4 (11)	2 (7)	
Mechanical ventilation	31 (86)	22 (81)	0.73
Days in ICU	17 ± 14	20 ± 13	0.37

Mean ± SD, median ± IQR (*), or number (percentage), where appropriate. APACHE II, acute physiology and chronic health evaluation; CABG, coronary artery bypass grafting; SOFA, sequential organ failure assessment. ICU, intensive care unit.

Filter life. The filter life in pre- and postdilution mode was comparable (Table 2, Fig. 1). Furthermore the filter life was inversely associated with TMP (P=0.001). Table 3 describes similar anticoagulation by heparin among dilution modes. Clotting was the leading cause of filter termination (Table 4) and again predicted by the TMP (P=0.007 by GEE) and not by pre- or postdilution mode, filtration fraction or aPTT. In the predilution group 19 (14%) filters were electively changed after 72 hours versus 20 (18%) in the postdilution group. After exclusion of these filters, the filter life was still comparable between the two dilution modes (data not shown).

Table 2. Patients, fluids and filters.

	Predilution	Postdilution	P
Patients	n = 36	n = 27	
CVVH days	5.4 ± 2.5	6.0 ± 3.1	0.43
Number of filters day 0-9 *	3.0 ± 2.7	3.0 ± 3.0	0.62
Urine (ml) *			
day 0	224 ± 333	145 ± 329	0.52
day 2	357 ± 451	175 ± 402	0.57
Fluid balance (ml)			
day 0	4391 ± 2983	3892 ± 2863	0.41
day 2	1410 ± 2355	2210 ± 2434	0.38
Fluids day 0-9	n = 194	n = 162 days	
Ultrafiltrate (ml/hr) *	2038 ± 98	2039 ± 108	0.85
Adjusted ultrafiltrate (ml/h) *	1618 ± 82	2039 ± 108	<0.001
Creatinine clearance (ml/min) *	27 ± 1	34 ± 2	<0.001
Delivered dose (ml/kg/h) *	22.4 ± 4.4	26.7 ± 9.6	0.01
Filters no. 1-12	n = 132	n = 111 filters	
Replacement fluid			
lactate/bicarbonate (%)	31/69	22/78	0.46
Filter life (h) *	24 ± 38	29 ± 46	0.58
Filter downtime (h/day) *	2 ± 3	2 ± 2	0.57
TMP (mmHg) *	103 ± 94	91 ± 83	0.25
Filtration Fraction (%) *	21 ± 0.02	27 ± 0.02	<0.001

Mean ± SD or median ± IQR (*), where appropriate. CVVH, continuous veno-venous hemofiltration. TMP, transmembranous pressure prior to filter termination.

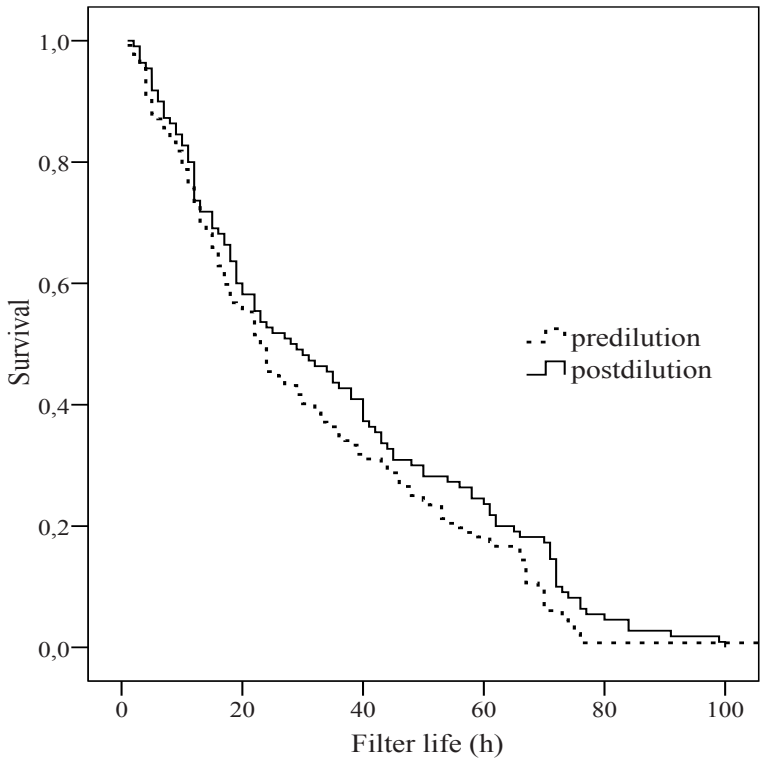

Fig. 1. Survival of filters in continuous venovenous hemofiltration in pre- and postdilution mode. There was no difference between dilution modes (P=0.150).

Table 3. Coagulation prior to and after heparinization during the study period.

	Predilution n=36	Postdilution n=27	P
aPTT (sec) (*)			
start	51 ± 25	50 ± 20	0.69
day 0	61 ± 28	66 ± 35	0.80
day 2	59 ± 23	56 ± 14	0.64
day 6	64 ± 32	50 ± 24	0.93
day 9	60 ± 32	64 ± 40	0.96
Platelets ($x10^9$/L) (*)			
start	134 ± 127	136 ± 102	0.93
day 0	109 ± 96	118 ± 128	0.61
day 2	90 ± 91	79 ± 77	0.90
day 6	114 ± 78	90 ± 41	0.80
day 9	150 ± 110	132 ± 118	0.61
Hematocrit (%)			
start	30 ± 5.5	29 ± 5.3	0.62
day 0	30 ± 5.5	30 ± 5.3	0.37
day 2	30 ± 5.0	30 ± 4.5	0.34
day 6	28 ± 3.0	26 ± 7.0	0.04
day 9	27 ± 4.0	27 ± 6.5	0.96

Mean ± SD or median ± IQR (*) where appropriate. aPTT: activated partial thromboplastin time.

Table 4. Causes of filter termination.

	Predilution n=132	Postdilution n=111	P
Coagulation of filter	98 (74)	72 (65)	0.17
Elective filter change	19 (14)	20 (18)	0.52
Catheter dysfunction	12 (9)	5 (5)	0.26
Renal function recovery	2 (1)	3 (3)	0.51
Transport	1 (1)	8 (7)	0.04
Technical problems	0	3 (3)	1.00

Data are number (percentage).

Delivered dose and azotemic control. Table 2 describes lower delivered dose per day, expressed as ml/kg/h and adjusted for baseline values, in pre- versus postdilution. Fig. 2 describes the daily course of creatinine and urea levels in the patients according to dilution mode, showing no differences. However, Table 5 shows that delivered dose had a direct effect on the fall of creatinine and urea levels in blood, between day 0-2 and 0-9.

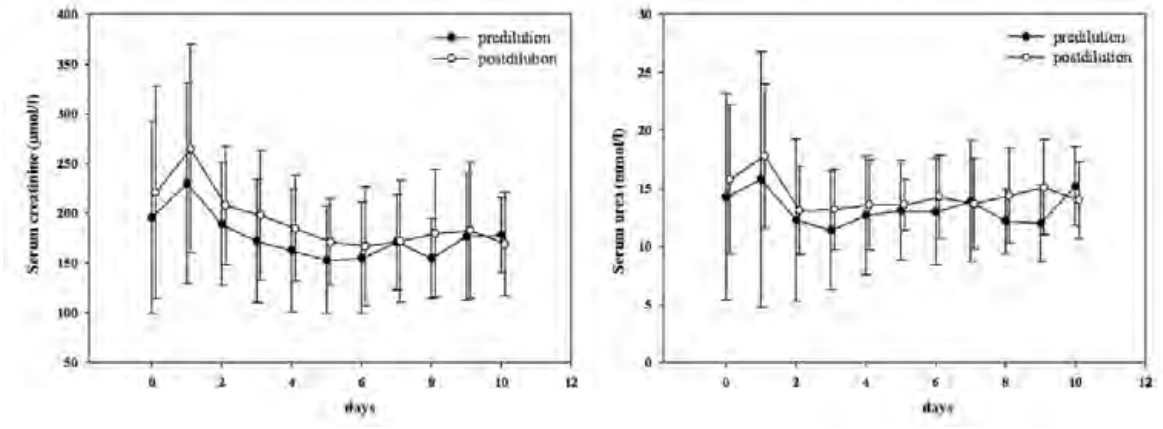

Fig. 2. The course of serum creatinine and urea in patients (day 0-9) treated by continuous venovenous hemofiltration in pre- and postdilution mode. Predilution resulted in similar azotemic control as postdilution (P=0.755 for creatinine and P=0.262 for urea).

Table 5. Generalized estimating equations considering effect of delivered dose on fall of creatinine and urea concentration in blood.

Dependent	ß	P
Log creatinine day 0-2	-0.10	0.003
Log urea day 0-2	-0.10	0.012
Log creatinine day 0-9	-0.26	<0.001
Log urea day 0-9	-0.21	0.004

ß=standardized regression coefficient; adjusted for baseline creatinine/urea.

Discussion

Our study shows similar filter life for pre- and postdilution CVVH in critically ill patients on heparin. Even though azotemic control depended on delivered dose, the 19% higher dose in post- than in predilution was insufficient to result in a difference in the course of serum creatinine and urea levels in our patients.

It is generally believed that hemodilution by prefilter administered replacement fluid prolongs filter life in CVVH in studies on patients with highly variable and thus presumably suboptimal anticoagulant regimens.[8,9] Our findings of a similar filter life when heparin is used systemically, however, confirm those by others in pre- (n=8) and postdilution CVVH (n=9) in patients all receiving anticoagulation by intravenous nadroparin.[10] Apparently, the effect of heparin overwhelmed that of predilution in inhibiting filter coagulation. Moreover, it is debatable if hemodilution has an inhibitory effect on coagulation as a hematocrit below 30% may more strongly activate coagulation when compared to those with a higher hematocrit.[16] Furthermore, in an analysis on extracorporeal circuit thrombogenesis no difference was found

between pre- and postdilution regarding parameters on thrombin generation or platelet activation.[10]

The predilution mode carries the potential drawback of diluting blood before it enters the filter and thereby decreasing clearance, as compared to the postdilution mode, for a given blood flow and ultrafiltrate flow rate. In a small study on patients with and without anticoagulants, however, the azotemic control was comparable.[8] One explanation is the loss of efficiency in the postdilution mode when filter life is shorter leading to frequent filter changes and increased downtimes. In the aforementioned study comparing patients on systemic anticoagulation with nadroparin treated by either pre- or postdilution CVVH no difference was observed in both filter life and azotemic control.[10] A major drawback of the latter study, however, was its small sample size with only 15 filters being analyzed. Our larger study on 243 filters is nevertheless in line with these data. Indeed, we observed that azotemic control depended on delivered dose, but the hemodilution-associated fall in delivered dose with predilution, for a given flow rate, was apparently too small to result in a difference in azotemic control between the dilution modes. In contrast to prior suggestions,[4-6] the data also argue against predilution facilitating urea clearance. As recent studies showed no survival benefit of delivered doses above 20 ml/kg/h or urea-targeted dialysis, it is doubtful whether the somewhat smaller clearance in the predilution mode is really a clinically important drawback.[17-21]

This study had several limitations. We have no detailed information concerning residual renal function. We used the urine production as derivative of residual function, which was comparable between the two CVVH modes. This was a retrospective single-centre study with all inherent drawbacks and therefore our result should be interpreted with caution. The organization of the ICU, however, with two identical units except for the mode of CVVH applied, created a unique opportunity to compare pre- and postdilution mode and patients were comparable among the units. In order to achieve complete uniformity between the ICU, all patients are treated in the predilution mode since December 2006. The choice for the predilution mode was predominantly based on our decision to adopt a regimen with regional anticoagulation with citrate-based replacement fluid in the predilution mode. The results of this study support that policy as there are no clear advantages of postdilution CVVH.

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Conflict of interest statement

The results presented in this paper have not been published previously in whole or part except in abstract.

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