Original Paper

nephron Clinical Practice

Nephron Clin Pract 2003;94:c94–c98
DOI: 10.1159/000072492

Received: December 2, 2002
Accepted: May 7, 2003

Pre-Dilution vs. Post-Dilution during Continuous Veno-Venous Hemofiltration: Impact on Filter Life and Azotemic Control

Shigehiko Uchino Nigel Fealy Ian Baldwin Hiroshi Morimatsu
Rinaldo Bellomo

Department of Intensive Care and Department of Medicine, Austin & Repatriation Medical Centre, Melbourne, Vic., Australia

Key Words
Acute kidney failure · Critical illness · Renal replacement therapy · Hemofiltration · Clearance · Dilution

Abstract
Background/Aims: To determine the impact of replacement fluid infusion site on filter life and azotemic control during continuous veno-venous hemofiltration (CVVH). ***Methods:*** Pre-dilution CVVH was conducted from February 2001 to December 2001 and then practice was changed to post-dilution (from January 2002 to July 2002). Filter life was prospectively observed and the following data obtained for each filter: starting date and time, ending date and time, heparin use, heparin dose and protamine use. Daily creatinine, urea, INR, APTT and platelet count were also collected. ***Results:*** Forty-eight patients were studied (33 in pre-dilution and 15 in post-dilution) for a total of 309 filters (202 in pre-dilution and 107 in post-dilution). The median filter life was significantly shorter in the post-dilution period (18.0 vs. 13.0 h, p = 0.021). Multivariate linear regression analysis showed that pre-dilution was a significant independent predictor of increased filter life (p = 0.029), together with platelet count (p = 0.0035) and heparin dose (p = 0.046). There was no significant improvement in daily creatinine and/or urea reduction in the post-dilution period (% Δ creatinine: 7.9 vs. 10.2%/day, p = 0.99, urea: 5.4 vs. 9.7%/day, p = 0.78). ***Conclusions:*** Post-dilution was associated with reduced filter life without any beneficial effect on daily changes in urea and creatinine levels. Pre-dilution appears a preferable technical approach to CVVH.

Introduction

Continuous veno-venous hemofiltration (CVVH) is commonly applied to patients with acute renal failure (ARF) in critical illness [1, 2]. One of the controversies surrounding CVVH relates to the infusion site for the replacement fluid. Pre-dilution (administration of replacement fluid before the filter) should decrease the hemoconcentration associated with the removal of plasma water in the filter. Thus, theoretically, it should prevent filter clotting and increase filter life. However, it should also decrease plasma solute concentration as it enters the filter, thereby decreasing solute clearance and, theoretically, worsening uremic control. Previous studies, which compared pre- and post-dilution have either involved intermittent hemofiltration or have been statistically underpowered, lacking in suitable controls, not inclusive of the full treatment cycle for each patient and unable to provide comprehensive data on azotemic control [3–6]. Thus, both pre- and post-dilution remain widely practiced [7–10].

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1660–2110/03/0944–0094$19.50/0

Accessible online at:
www.karger.com/nec

Prof. Rinaldo Bellomo
Department of Intensive Care
Austin & Repatriation Medical Centre
Heidelberg, Vic 3084 (Australia)
Tel. +61 3 9496 5992, Fax +61 3 9496 3932, E-Mail rinaldo.bellomo@austin.org.au

Accordingly, we have prospectively studied the effect of a planned change in practice for CVVH from pre- to post-dilution on filter life and small solute control in a suitably large sample of filters and now report our findings.

Materials and Methods

This study was conducted between February 2001 and July 2002 in the ICU at a university-affiliated hospital. The prospective collection of data on filter life and solute control has been an ongoing quality assurance activity in our unit and its application existed and continued before and after the unit protocol change from pre- to post-dilution. Thus, the collection of data in relation to this change was classified as a quality improvement activity. In our institution, the Ethics Committee waives the need for informed consent under such circumstances.

All patients who had ARF treated with CVVH in the ICU and who did not die within 24 h were prospectively observed.

CVVH was conducted with either the AK-10 (Gambro, Lund, Sweden), BM-10/BM-11 (Edwards Life Sciences, Sydney, NSW, Australia) or Hygieia (Kimal, Sydney, NSW, Australia) machines. Veno-venous access was secured by inserting a 13.5-Fr double-lumen catheter (Niagara, Vascath, Ont., Canada) into one of the large veins (most commonly femoral veins). Either AN69 (Hospal, Lyon, France) or APS650 (Asahi Medical, Tokyo, Japan) hollow-fiber hemofilters were used. Blood flow was kept at 200 ml/min. Commercially prepared lactate-buffered hemofiltration replacement fluid (Hemofiltration Solution, Edwards Life Sciences) was infused pre- or post-filter at 2 l/h. When lactic acidosis (lactate >5 mmol/l) occurred, the replacement fluid was switched to a lactate-free bicarbonate-buffered fluid (Hemosol, Gambro, Lund, Sweden). In the pre-dilution period, replacement fluid was infused pre-filter (pre-dilution period: February 2001 to December 2001). Beginning on January 1, 2002, due to a change in our unit protocol, all patients were treated with post-dilution CVVH. Replacement fluid was infused post-filter (post-dilution period: January 2002 to July 2002). There was no other difference between the two periods. A comparison of the effect of the protocol change on filter life was planned after 6 months of operation.

Anticoagulation was conducted according to our protocol. 5 IU/kg/h of heparin were generally given. 10 IU/kg/h of heparin were administered if prothrombin time-international normalized ratio (PT-INR) was <1.5, activated partial thromboplastin time (APTT) <40 s and platelet counts $>150 \cdot 10^3/\mu l$. No anticoagulation was used if a patient had more than one of the following criteria: PT-INR >2.5, APTT >60 s, platelet $<60 \cdot 10^3/\mu l$, active bleeding or immediate post-surgery period. When a filter life was unacceptably short with no anticoagulation (e.g. <6 h for two consecutive filters), regional anticoagulation (heparin 1,000 IU/h pre-filter plus protamine 10 mg/h post-filter) was considered.

Age, gender, SAPS-II [11] and APACHE-II [12] scores were obtained at ICU admission, as is routine for our unit database. For each filter, the following data were also obtained: starting date and time, ending date and time, heparin usage, heparin dose and protamine usage. Biochemical tests were performed at 5 a.m. daily and results (platelet count, PT-INR, APTT, urea and creatinine) were collected, as is routine in our institution. Hospital mortality was also obtained. For each filter, platelet count, PT-INR and APTT were defined as the values measured in the morning of the same day as the filter was used. If a filter lasted more than 2 days, averaged values were used. Percentage daily Δ for creatinine and urea were calculated as:

$$\% \Delta = (C_{day\ N} - C_{day\ N+1})/C_{day\ N},$$

where $C_{day\ N}$ is a concentration of creatinine or urea on day N and $C_{day\ N+1}$ is on the next day. A positive value of % A indicates a daily reduction in creatinine or urea.

Data are expressed as medians with 25th–75th percentiles. The X^2 test and the Mann-Whitney test were used for nominal values and numerical variables, respectively, to compare the pre-dilution period and the post-dilution period (StatView, Abacus Concepts, Berkeley, Calif., USA). Because of significant differences in variables between the two groups, which might influence our findings, we also conducted multivariate analysis. Multivariate linear regression analysis was performed for filter life as the dependent variable. Because filter life, platelet count, INR and APTT were not normally distributed, they were log-transformed prior to analysis. A p value of <0.05 was considered statistically significant.

Results

Forty-eight patients were studied (33 in pre-dilution and 15 in post-dilution). The relevant demographic data are shown in table 1. There was no significant difference between the two periods.

Three hundred and nine filters were observed (202 in pre-dilution and 107 in post-dilution). The values for the relevant coagulation variables are shown in table 2. There were statistically significant but probably not clinically significant differences in INR (1.3 vs. 1.5, $p<0.0001$) and APTT (41 vs. 38 s, $p = 0.0025$) between the two periods. Approximately half the study filters were not anticoagulated during either period (48.7% vs. 57.9%, $p = 0.15$). Protamine was used more often in the pre-dilution period (15.3% vs. 0.0%, $p < 0.0001$). There was no significant difference in the platelet count. In 248 filters where the type of membrane was recorded, there was no difference in filter life (AN69: n = 121, 14.5 h, APS650: n = 127, 14.5 h, $p = 0.49$). However, filter life was significantly shorter in the post-dilution period (18.0 vs. 13.0 h, Mann-Whitney $p = 0.021$).

Because of the above differences in the values of likely determinants of filter life, we conducted multivariate linear regression analysis (table 3) using filter life as the dependent variable. We found that that pre-dilution was a significant independent predictor of increased filter life ($p = 0.029$). We also found that platelet count ($p = 0.0035$) and heparin dose ($p = 0.046$) were significant predictors of filter life.

Table 1. Demographics of patients with CVVH

	Total	Pre-dilution	Post-dilution	p value
Patients	48	33	15	
Age, years	65 (46–77)	67 (49–79)	57 (46–67)	0.24
Gender (male)	68.8%	72.3%	60.0%	0.50
SAPS-II score	41 (23–48)	38 (22–46)	46 (33–54)	0.083
APACHE-II score	22 (18–26)	22 (16–26)	22 (20–26)	0.70
Period of CVVH, h	114 (51–238)	101 (51–257)	129 (45–234)	0.60
Creatinine at start, μmol/l	267 (209–405)	308 (216–451)	225 (152–285)	0.062
Urea at start, mmol/l	19.5 (14.8–29.9)	23.1 (15.2–30.8)	18.2 (14.1–22.2)	0.23
Hospital mortality	54.2%	48.5%	66.7%	0.35

CVVH = Continuous veno-venous hemofiltration; SAPS-II = a new simplified acute physiology score; APACHE-II = acute physiology and chronic health evaluation; Period of CVVH = total period of time treated with CVVH.

Table 2. Clotting variables and filter life

	Total	Pre-dilution	Post-dilution	p value
Filters	309	202	107	
Platelets, $\times 10^3$/μl	78 (43–129)	78 (44–138)	88 (37–121)	0.45
INR	1.4 (1.2–1.8)	1.3 (1.1–1.7)	1.5 (1.3–1.9)	<0.0001
APTT, s	40 (33–51)	41 (33–54)	38 (32–44)	0.0025
Heparin usage	52.0%	48.7%	57.9%	0.15
Heparin dose, IU/h	400 (0–800)	0 (0–800)	500 (0–700)	0.36
Protamine usage	10.0%	15.3%	0.0%	<0.0001
Filter life, h	15.0 (8.9–26.1)	18.0 (9.5–27.5)	13.0 (7.1–23.4)	0.021

INR = Prothrombin time-international normalized ratio; APTT = activated partial thromboplastin time.

Table 3. Multivariate analysis for filter life

	Coefficient	Std Coeff	p value
Intercept	1.421	1.421	<0.0001
Log platelet	–0.191	–0.197	0.0035
Pre-dilution	0.097	0.14	0.029
Heparin dose	0.00012	0.146	0.046
Log PT-INR	–0.046	–0.021	0.78
Protamine usage	–0.01	–0.009	0.89
Log APTT	0.013	0.006	0.94

Std Coeff = Standard coefficient; Log = logarithm; PT-INR = prothrombin time-international normalized ratio; APTT = activated partial thromboplastin time.

Percentage Δ creatinine and urea are shown in table 4. There was no significant improvement in % Δ creatinine and urea in the post-dilution period (% Δ creatinine: 7.9 vs. 10.2%/day, p = 0.99, % Δ urea: 5.4 vs. 9.7%/day, p = 0.78).

Discussion

Our investigation revealed several clinically relevant findings. Firstly, post-dilution was associated with reduced filter life. Secondly, post-dilution was not associated with improved azotemic control. Thirdly, platelet count and heparin dose were significant independent determinants of filter life, but INR and APTT were not.

The impact of the replacement fluid dilution site on filter life during CVVH has not been previously studied in a large sample of filters. Honore et al. [6] found a similar

Table 4. Percent daily reduction of creatinine and urea

	Total	Pre-dilution	Post-dilution	p value
Measurements	266	181	85	
% Δ creatinine, %/day	8.5 (–5.6 to 18.4)	7.9 (–4.0 to 17.9)	10.2 (–7.9 to 18.7)	0.99
% Δ urea, %/day	6.4 (–5.7 to 19.3)	5.4 (–5.5 to 19.3)	9.7 (–8.2 to 19.4)	0.78

% Δ = Percentage of daily reduction.

filter life in pre- and post-dilution but the post-dilution group required more heparin resulting in more bleeding. In their study the sample size was too small to detect anything but a large difference. Using a sample of >300 filters, we found a median difference of 5 h in filter life in favor of pre-dilution, approximately equivalent to one filter saved for every four used. Our findings are consistent with expectations. Pre-dilution should reduce the concentration of coagulation factors, proteins and platelets as they enter the filter and prevent intra-filter increases in hematocrit. These effects should attenuate clot formation.

A theoretical shortcoming of pre-dilution, however, is that it might reduce solute clearance and adversely affects azotemic control. For this reason, post-dilution continues to be used [7–10]. This theoretical argument in favor of post-dilution, however, has not been tested in vivo in terms of its practical clinical impact. We found that, in the clinical setting, post-dilution did not achieve any improvement in azotemic control. This unexpected finding could be explained by two possibilities. One is that pre-dilution might reduce so-called 'concentration polarization' and might improve the efficiency of solute movement across the membrane [13]. Because blood viscosity decreases with pre-dilution, the thickness of the protein layer at the blood-membrane interface might decrease, which would then improve membrane permeability and facilitate solute movement. The other possibility is that the shorter median filter life in the post-dilution period led to the need to change filters more frequently [14]. In this setting, the time a patient would spend without treatment would inevitably increase and solute clearance decrease.

We found that the platelet count was an independent predictor of filter life, which is consistent with previous studies [8, 15]. Platelets are an important factor for clot formation in the filter [16]. They adhere to the artificial surface, aggregate, release chemical substances, activate the coagulation cascade and provide phospholipids for the cascade to continue. We also found that heparin dose was an independent variable but that APTT and PT-INR were not, at least for normal or nearly normal values. These results are also consistent with previous studies [15, 17] and APTT has previously been shown to correlate poorly with serum heparin concentration [18]. Although frequent APTT measurements are often recommended for the monitoring or adjustment of heparin dosage to improve the efficacy of heparin-based filter anticoagulation [19], our findings do not support this recommendation. Nonetheless, measurement of the APTT is important to avoid systemic over-anticoagulation and its attendant risks.

There are some limitations in our study. Firstly, our results may not apply to other operative conditions for CVVH, i.e. different blood flow rates or replacement fluid rates. Secondly, this is not a randomized controlled study. Therefore, the results we found might have been due to unrecognized differences between the both groups (e.g. the post-dilution group had slightly higher SAPS-II and mortality and might have been more hypercoagulable). However, the observational period was relatively short (totally 19 months) and there were no other practice changes in the conduct of CVVH. Moreover, we observed more than 300 filters, which is more than any other published studies of filter life [8–10, 15, 17, 20, 21]. Thirdly, we did not measure small solute control (e.g. creatinine clearance) with the two methods. We focused instead on daily changes in azotemic control, which we considered a more relevant clinical outcome. Unfortunately, pre-treatment creatinine and urea were different between the two periods and we could not compare them directly. Although 'Δ%' is not a common method to assess solute control, we found this variable to be a useful surrogate marker of daily solute control. As patient weights were not measured, such a relative change in uremic state was also a way of partially correcting for possible differences in body weight.

In summary, we have found that post-dilution was associated with reduced filter life without any beneficial effect on azotemic control. Pre-dilution appears a preferable technical approach to the conduct of CVVH.

References

1 Silvester W, Bellomo R, Cole L: Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. Crit Care Med 2001;29:1910–1915.

2 Ronco C, Zanella M, Brendolan A, et al: Management of severe acute renal failure in critically ill patients: An international survey in 345 centers. Nephrol Dial Transplant 2001;16: 230–237.

3 Schetz M: Anticoagulation in continuous renal replacement therapy. Contrib Nephrol. Basel, Karger, 2001, vol 132, pp 283–303.

4 Kaplan AA: Predilution versus postdilution for continuous arteriovenous hemofiltration. Trans Am Soc Artif Intern Organs 1985;31:28–32.

5 David S, Cambi V: Hemofiltration: Predilution versus postdilution. Contrib Nephrol. Basel, Karger, 1992, vol 96, pp 77–85.

6 Honore PM, Wittebolle X, Lozano A: Evaluation of the predilution technique in reducing the occurrence of bleeding during CRRT in critically ill patients. Efficacy of predilution in reducing the amount of anticoagulation during CVVH (abstract). Crit Care 1997;1(suppl 1): 97.

7 Ronco C, Bellomo R, Homel P, et al: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomized trial. Lancet 2000; 356:26–30.

8 De Pont AC, Oudemans-van Straaten HM, Roozendaal KJ, et al: Nadroparin versus dalteparin anticoagulation in high-volume, continuous venovenous hemofiltration: A double-blind, randomized, crossover study. Crit Care Med 2000;28:421–425.

9 Fiaccadori E, Maggiore U, Rotelli C, et al: Continuous haemofiltration in acute renal failure with prostacyclin as the sole anti-haemostatic agent. Intensive Care Med 2002;28:586–593.

10 Gabutti L, Marene C, Colucci G, et al: Citrate anticoagulation in continuous venovenous hemodiafiltration: A metabolic challenge. Intensive Care Med 2002;28:1419–1425.

11 Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE-II: A severity of disease classification system. Crit Care Med 1985;13: 818–829.

12 Le Gall JR, Lemeshow S, Saulnier F: A new simplified acute physiology score (SAPS-II) based on an European/North American multicenter study. JAMA 1993;270:2957–2963.

13 Ronco C, Bellomo R: Principles of solute clearance during continuous renal replacement therapy; in Ronco C, Bellomo R (eds): Critical Care Nephrology. Dordrecht, Kluwer Academic, 1998, pp 1213–1223.

14 Uchino S, Fealy N, Baldwin I, et al: 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.

15 Martin PY, Chevrolet JC, Suter P, et al: Anticoagulation in patients treated by continuous venovenous hemofiltration: A retrospective study. Am J Kidney Dis 1994;24:806–812.

16 Davenport A: The coagulation system in the critically ill patients with acute renal failure and the effect of an extracorporeal circuit. Am J Kidney Dis 1997;30(suppl 4):20–27.

17 Baldwin I, Tan HK, Bridge N, Bellomo R: A prospective study of thromboelastography and filter life during continuous veno-venous hemofiltration. Ren Fail 2000;22:297–306.

18 Baker BA, Adelman MD, Smith PA, Osborn JC: Inability of the activated partial thromboplastin time to predict heparin levels. Time to reassess guidelines for heparin assays. Arch Intern Med 1997;157:2475–2479.

19 Mehta RL: Anticoagulation for continuous renal replacement therapy; in Ronco C, Bellomo R (eds): Critical Care Nephrology. Dordrecht, Kluwer Academic, 1998, pp 1199–1211.

20 Van de Wetering J, Wesendorp 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.

21 Leslie GD, Jacobs IG, Clarke GM: Proximally delivered dilute heparin does not improve circuit life in continuous venovenous haemofiltration. Intensive Care Med 1996;22:1261–1264.