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Continuous veno-venous hemofiltration without anticoagulation in high-risk patients

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Abstract *Objective*: To study the safety and operative efficacy of continuous veno-venous hemofiltration (CVVH) without anticoagulation in patients at high risk of bleeding.
Design: Prospective cohort study and comparison to control group.
Setting: Tertiary, multidisciplinary intensive care unit.
Patients: Forty hemofiltration circuits in 12 patients with severe acute renal failure (ARF) deemed at high risk of bleeding. Forty control circuits in 14 patients treated with low-dose pre-filter heparin infusion.
Interventions: CVVH at 2 l/h of pump-controlled ultrafiltration without anticoagulation or saline flush in patients at high risk of bleeding. Collection of data at the bedside.
Measurements and main results: Mean circuit life was 32 h (95 % CI: 20–44.4) in patients receiving CVVH without anticoagulation. Forty-three per cent of filters lasted longer than 30 h. Circuit lifespan did not correlate with international normalized ratio (INR), activated partial thromboplastin time (APTT) or platelet count. There were no bleeding complications and azotemic control was not compromised by lack of circuit anticoagulation with a mean serum urea of 16.0 mmol/l (95 % CI: 14.9–18.1) during treatment. A control group of consecutive similarly ill patients not at high risk of bleeding received low-dose pre-filter heparin (mean dose 716 IU; 95 % CI: 647–785). Their mean filter life was 19.5 h (95 % CI: 14.2–23.8), significantly shorter than in the study patients ($p = 0.017$).
Conclusions: Critically ill patients at high risk of bleeding who require continuous renal replacement therapy (CRRT) can be safely managed without circuit anticoagulation. This strategy minimizes bleeding risks and is associated with an acceptable filter life. CRRT without anticoagulation should be strongly considered in high-risk patients.

Key words Critical illness · Acute renal failure · Hemofiltration · Anticoagulation · Bleeding · Uremia · Heparin · Prostacyclin · Citrate · Liver failure · Multi-organ failure

Introduction

Severe acute renal failure (ARF) is a common complication in critically ill patients with multi-organ failure [1, 2]. Continuous renal replacement therapies (CRRT) such as continuous veno-venous hemofiltration (CVVH) are now accepted ways of managing such patients [3, 4]. Successful application of CRRT, however, depends on adequate extracorporeal circuit (EC) life. The duration of EC life in turn hinges on anticoagulation [5]. The need for anticoagulation has to be balanced against the increased risk of bleeding in high-risk patients. In these patients, performing CVVH without anticoagulation may be an acceptable strategy. The practicability of such an approach has, however, been questioned. Anticipated recurrent filter clotting and the need for frequent filter replacement would be economically undesirable. Furthermore, excessive " down time " could jeopardize azotemic

control. Only limited uncontrolled data exist to guide clinicians with regard to the safety and operative efficacy of CRRT without anticoagulation. Thus, in order to understand the clinical consequences of a no-anticoagulation approach to CVVH, we studied 40 hemofilters in 12 critically ill patients at high risk of bleeding. We tested the hypothesis that a "no-anticoagulation" strategy in high-risk patients yields an acceptable filter life by comparing this cohort of patients to a consecutive series of patients treated with low-dose pre-filter heparin and now report our findings.

Materials and methods

A total of 12 critically ill patients with severe ARF requiring CVVH without anticoagulation were prospectively identified and studied. ARF was defined by the presence of severe refractory oliguria (urine output < 200 ml/12 h) or anuria, despite adequate fluid resuscitation. Adequate fluid resuscitation was defined as a central venous pressure (CVP) above 10 mmHg or a pulmonary artery occlusion pressure (PAOP) above 12 mmHg. These 12 patients were compared to 14 consecutive patients who received pre-filter, low-dose heparin for circuit anticoagulation. This study was an audit of current practice in our institution and required no specific intervention other than documentation. Our institutional ethics committee waives the need for informed consent under such circumstances.

Continuous veno-venous hemofiltration was performed as previously described [6]. In brief, it was carried out using either the BM-10/ BM-11 dual module (Baxter Healthcare, Sydney, Australia) or the AK-10 (Gambro, Lund, Sweden) machines. Veno-venous access was secured by inserting a 13.5 Fr double-lumen catheter (Niagra, Vascath, Ontario, Canada) into one of the central veins (internal jugular, femoral or subclavian). The polyacrylonitrile AN69 (Hospal, Lyon, France) hollow-fibre hemofilter was used in all patients. Blood pump speed was kept between 200–300 ml/min. Ultrafiltrate generation was volumetrically controlled by a pump at 2000 ml/h. Commercially prepared lactate-buffered hemofiltration replacement fluid (Viaflex, Baxter Hemofiltration Solution, Baxter Health Care, Sydney, Australia) was delivered pre-filter (pre-dilution mode) by intravenous volumetric pump at rates ranging from 1600 to 1900 ml/h, to allow for fluid losses as clinically indicated.

A lactate-free bicarbonate-buffered hemofiltration replacement fluid (Hemasol, Gambro, Lund, Sweden) was also used for severely acidotic and hyperlactatemic patients. Fluid replacement and ultrafiltration rates were controlled by the integrated pumps in the dual-module BM-10/ 11 machines while, with the AK-10, these were controlled with separate twin-channel intravenous volumetric pumps (Gemini pumps, IMED, San Diego, USA).

No anticoagulation or saline flushes were used in the study patients. However, in accordance with our CVVH operational protocol, all circuits received 5000 IU of heparin during the final stages of priming. Before connection of the circuit to the patients, the heparin prime was flushed out, thus avoiding anticoagulating these patients.

Patient selection

The intensivists in charge of patient care independently decided to perform CVVH without anticoagulation based on a clinical assessment of a high risk of bleeding. These physicians were not directly involved in the study. Our unit guidelines suggest that patients should receive CVVH without anticoagulation if a) there is ongoing bleeding, b) there has been a major hemorrhage in the last 48 h, c) they have had surgery in the last 24 h or d) they have either an international normalized ratio (INR) more than 2 or an activated partial thromboplastin time (APTT) greater than 60 s or a platelet count less than $60 \times 10^3/mm^3$. However, the final decision is left to the treating physician.

Control patients were treated with exactly the same CVVH protocol but, in addition, were given low-dose heparin delivered pre-filter at a dose between 5 and 10 IU of heparin·kg·h according to clinician judgement. In our institution, the administration of low-dose (10 IU heparin·kg·h) constitutes routine CVVH management and is given to the majority of patients. If the APTT appears to have been prolonged by such a dose, the amount of heparin is then adjusted down to 5 IU·kg·h and the APTT is rechecked. If the APTT is back to normal values, the patient is continued on that dose of heparin. The aim of low-dose heparin in our institution is to provide a degree of circuit anticoagulation without any systemic anticoagulant effects.

For the purpose of this study, the following criteria for diagnosing circuit failure were adopted: (1) the ultrafiltrate (UF) volumetric outflow pump was unable to deliver the prescribed (dialed-in) UF rate more than 3 times over a 5 min interval. Such failure to yield the prescribed 2000 ml/h of UF should be deemed secondary to loss of filtering membrane surface as a result of clotting. In addition, the pump should continue to fail in delivering prescribed UF even after reducing the UF effluent flow to 1500 ml/h, (2) presence of visible blood clot in the venous air-chamber of the EC associated with a steep and sustained rise in the venous pressure above 150 mmHg and a sudden/ rapid cessation of blood flow in the circuit, and (3) presence of visible blood clot in the hemofilter and a sudden/ rapid cessation of blood flow in the EC.

Elective CVVH cessation for activities such as surgery and radiological investigations were considered non-clotting events for which there were no hemofilter changes. In addition, the bedside nurse routinely recorded when the filter, EC lines and venous and arterial chambers were changed. Coagulation (APTT, INR), hematological (platelet count) and biochemical (serum urea, creatinine) indices were routinely measured at least once daily.

Statistical analysis

Statistical analysis was performed using a statistical software package (StatView, Abacus Concepts, Berkeley, CA). Descriptive statistics were obtained and values presented as means with 95 % confidence intervals. Comparisons between means were performed using the Mann-Whitney test for unpaired non-parametric data. Comparisons within each group were performed using Wilcoxon's signed rank test. Correlations between coagulation variables, biochemical data and filter life were tested using Spearman's correlation test. Comparison of filter life in the study patients and controls was performed using the Mantel-Cox log rank test. In all cases, a p less than 0.05 was considered statistically significant.

Results

Forty hemofilters and circuits were studied in 12 critically ill patients (8 males and 4 females) with severe ARF admitted to the intensive care unit (ICU) between July 1998 and July 1999. They were compared to 40 consecutive filters in 14 patients treated with low-dose pre-

Table 1 Clinical characteristics of study and control patients (*APACHE II* Acute Physiology and Chronic Health Evaluation II, *SAPS II* Simplified Acute Physiology Score II, *CVVH* continuous veno-venous hemofiltration, *APTT* activated partial thromboplastin time, *INR* international normalized ratio)

	No anticoagulation ($n = 12$)	Low-dose heparin ($n = 14$)
Age (years)	57.7 (50.9–64.5)	61.1 (57.1–64.1)
Gender (M/F)	8/4	9/6
APACHE II score	28.1 (23.1–33.1)	26.7 (23.2–30.2)
SAPS II score	60.3 (54.1–66.5)	56.2 (50.9–61.5)
Duration of CVVH (days)	8.2 (4.1–12.3)	7.6 (5.4–9.8)
Mechanical ventilation	7 (58 %)	9 (64.2 %)
Inotropic drugs	9 (75 %)	11 (78.6 %)
Pre-CVVH urea (mmol/l)	19.6 (13.5–25.7)	22.3 (18.2–26.4)
Pre-CVVH creatinine (μmol/l)	264 (168–360)	354 (290–418)
Urea on CVVH (mmol/l)	16 (11.8–20.2)[b]	16.9 (12.3–21.5)[b]
Creatinine on CVVH (μmol/l)	198 (166–230)[b]	235 (192–278)[b]
APTT (s)	48 (42–54)	56 (43–69)
INR	1.81 (1.58–2.04)[a]	1.24 (1.15–1.33)
Platelets (x 10^3/mm^3)	72 (56–88)[a]	187 (154–220)
Liver failure	6	1
Ongoing blood loss	4	0
Severe coagulopathy	2	1
Survival	5 (42 %)	8 (57 %)

NB Numerical values indicate means with 95 % confidence intervals in brackets
[a] significant difference from controls at a $p < 0.0001$
[b] different from baseline value at a $p < 0.01$

Table 2 Clinical diagnoses, source of bleeding risk and hospital outcome for patients receiving continuous veno-venous hemofiltration without anticoagulation (*CAD* coronary artery disease, *CABG* coronary artery bypass grafting, *FHF* fulminant hepatic failure, *FFP* fresh frozen plasma, *U* units, *cryopr.* cryoprecipitate)

Patient	Age	Gender	Diagnosis	Source of bleeding	Blood products given	Outcome
1	64	Male	CAD	Post-CABG	10 U platelets, 10 U cryopr.	Survived
2	47	Male	Acute on chronic liver failure	Post liver transplant	10 U FFP, 15 U platelets	Survived
3	60	Male	FHF	Post liver transplant	12 U FFP, 15 U platelets	Survived
4	44	Female	FHF	Subdural hematoma	15 U FFP, 20 U platelets	Died
5	45	Male	Fungemia and renal transplant	Severe coagulopathy	8 U FFP, 25 U platelets	Died
6	49	Male	Cardiogenic shock	Cardiac tamponade	15 U platelets, 15 U FFP	Died
7	67	Female	FHF	Hemorrhagic gastritis	5 U FFP	Died
8	74	Female	Enterobacter sepsis with shock	Bleeding post-hip replacement	2 U FFP, 5 U platelets	Survived
9	66	Male	CAD	Post-CABG	5 U platelets	Survived
10	55	Female	CAD	Post-CABG	7 U platelets	Survived
11	79	Male	Biliary sepsis	Post-biliary surgery	–	Survived
12	43	male	Leukemia and septic shock	Severe coagulopathy	35 U platelets, 10 U FFP	Died

filter heparin. A summary of the clinical and demographic data for the two groups is presented in Table 1. In patients receiving no anticoagulation, mean circuit life was 32.0 h (95 % CI: 20–44.4) compared to 19.5 h (95 % CI: 14.2–23.8) in the controls ($p < 0.017$). Forty-three percent of hemofilters used in the study group lasted more than 30 h. A graphic representation of the lifespan of all the individual hemofilters in both groups is shown in Fig. 1. A degree of baseline pre-CVVH coagulopathy (APTT more than 1.5 normal or INR greater than 1.5 normal or platelet count lower than 100×10^3/mm^3) was seen in most of these patients. The mean APTT was 61 s (95 % CI: 45–77), the mean platelet count was 126×10^3 (95 % CI: 119–143)/ mm^3 and the mean INR was 1.9 (95 % CI: 1.7–2.1).

Sixty-seven percent of patients were post-operative cases with some degree of ongoing blood loss from surgical drains (> 50 ml/h) (Table 2). The coagulation findings during CVVH in the no-anticoagulation group differed from the control group because of a longer INR and a lower platelet count and are presented inTable 1. Hemofilter lifespan was not significantly correlated with INR, APTT or platelet count in either group.

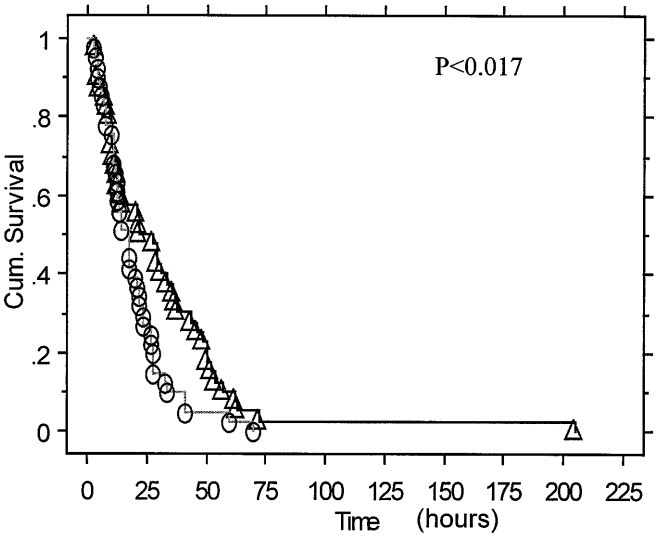

Fig. 1 Kaplan-Meier survival curves for all circuits. Circuits in patients receiving no anticoagulation are represented with *triangles*, and circuits in the control group with *circles*. The difference in filter survival is statistically significant ($p < 0.017$)

Discussion

Acute renal failure (ARF) is a relatively frequent and major complication of critical illness [7] and may require treatment with CRRT [8, 9]. The successful application of CRRT, however, depends on the maintenance of a patent extracorporeal circuit. Such patency depends on the prevention of circuit thrombosis by means of circuit anticoagulation [10]. Several agents and techniques can be used to achieve circuit anticoagulation [11]. However, heparin remains the most common, cheapest and simplest [12]. Unfortunately, most anticoagulation strategies are associated with an increased risk of bleeding. Systemic heparinization is particularly likely to increase the risk of hemorrhage [13]. Such an increased risk of bleeding may be unacceptable in some patients. Therefore, to decrease the risk of bleeding and still maintain a clinically acceptable circuit life, a variety of other strategies have been applied [14]. One such strategy is to administer pre-filter low-dose (5–10 IU·kg·h) heparin [15]. Although this approach is likely to decrease the risk of bleeding, it often induces a slight prolongation of the APTT and contributes to the development of thrombocytopenia [16]. In patients at very high risk of bleeding (recent hemorrhage, severe coagulopathy, liver failure, recent cardiac surgery or ongoing blood loss) even such effects may be clinically unacceptable [17].

The use of prostacyclin, low-molecular weight heparin, heparinoids, serine proteinase inhibitors or dextran also exposes patients to an increased risk of bleeding [17]. Regional anticoagulation has been suggested in these cases and can be achieved by means of pre-filter heparin administration and post-filter protamine administration [18]. This approach, however, is often associated with a variable degree of heparin reversal, thus exposing the patient to its anticoagulant effects and increasing bleeding risk [18]. Further, protamine can induce life-threatening hypotension, if given as a bolus, or in allergic patients. Because of these problems, regional anticoagulation using pre-filter citrate-based calcium chelation and post-filter calcium administration has been proposed [19]. This strategy appears effective in prolonging filter life although no randomized controlled studies have been conducted [19]. However, it is associated with a relatively high incidence of metabolic alkalosis and requires the preparation of custom-made, calcium-free dialysate/ replacement fluid [19, 20]. Such preparation is costly, requires dedicated pharmacy personnel and can be cumbersome to set up. Thus, all strategies which expose patients to anticoagulants are associated with risks, costs and the potential to induce bleeding. In the light of such observations, the safest approach in patients at high risk of bleeding may be to perform CRRT without any anticoagulant at all.

Continuous renal replacement therapy without circuit anticoagulation has rarely and often only anecdotally been reported [21] because of the expectation that circuit life would be dramatically shortened by this approach. If circuit life were markedly shorter, the cost and labour-intensity of the procedure would become excessive and the "down time" of CRRT would be prolonged. Such increases in "down time" may lead to a deterioration in azotemic control. However, there has never been a study to prove that such concerns are justified. We, therefore, studied 40 circuits in 12 critically ill patients who were managed with anticoagulant-free CVVH and compared their duration to filters in a cohort of patients treated with low-dose pre-filter heparin, one of the most common approaches to filter anticoagulation worldwide. The aim of our investigation was to describe the safety, efficacy and feasibility of anticoagulant-free CVVH in high-risk patients.

Our patients were severely ill, as evidenced by their mean APACHE II and SAPS II. Sixty-seven percent of them were post-surgical patients with active bleeding from surgical drains. One of the post-cardiac surgery patients developed acute hemorrhagic cardiac tamponade in the immediate post-operative period and required emergency evacuation of blood clot and surgical hemostasis. Another patient with acute fulminant hepatic failure, coagulopathy and severe secondary cerebral edema had developed an acute, but small, iatrogenic subdural hematoma following elective insertion of an intracranial pressure probe. Before commencement of CVVH, most patients were thrombocytopenic and had a significant degree of coagulopathy, as evidenced by prolonged APTT and INR values. In all of these patients, therefore, it was felt that any further increase in the risk of

bleeding was unacceptable and that anticoagulation-free hemofiltration should be applied.

Despite the lack of any circuit anticoagulation, the mean circuit lifespan achieved in our study was 32 h. In addition, 43 % of circuits lasted more than 30 h. These data are all the more significant when one takes into account the results of other studies of filter/ circuit life during CVVH. Langenecker et al. [22], for instance, using pre-filter heparin at a dose of 6 IU·kg·h recently reported that the mean filter life was 14.3 h during CVVH. When prostacyclin at 6 ng·kg·min was used, the mean filter life increased to 17.8 h and when a combination of heparin and prostacyclin was used, it increased further to 22 h. In another study of CVVH [23], the mean hemofilter life was 69 h. In this study, however, ultrafiltration was not pump-controlled and heparin was administered to achieve levels just below systemic heparinization. Ponikvar et al. [24] studied the anticoagulant effects of prostacyclin at a dose of 5 ng·kg·min during CVVH. The mean hemofilter life here was 19.7 h. Thus the mean circuit life in our control patients is well within that reported in the literature for CVVH in patients receiving different forms of circuit anticoagulation. However, when compared to the control group, our high-risk patients achieved a longer duration of filter life.

There are several possible explanations for the circuit duration achieved in our study patients. Firstly, they suffered from coagulopathy and/or thrombocytopenia and thus experienced a degree of "auto-anticoagulation". In most of our patients, such coagulopathies required ongoing active treatment with repeated infusions of platelets and fresh frozen plasma. Secondly, CVVH was performed in the "pre-dilution" mode. Such pre-filter replacement fluid administration reduces the hemoconcentration associated with the removal of plasma water, thus decreasing the likelihood of circuit clotting [25, 26]. Thirdly, we routinely used blood flows equal to or greater than 200 ml/min. Such relatively high blood flows may increase shear forces on the capillary fibres, diminish protein layering and retard membrane clotting. In order to achieve and maintain such blood flows, we perform CVVH with large bore (size 13.5 Fr) double lumen catheters. Catheters of this size may minimize post-filter pressures, diminish the risk of mechanical problems and reduce the number and intensity of flow fluctuations within the circuit during CVVH. These effects are likely to retard circuit thrombosis. Whatever, the mechanisms at work, a mean filter life longer than 30 h is clinically satisfactory. In fact, it remains controversial whether a filter life longer than 24 h should be aggressively pursued. Several studies indicate that high flux membranes adsorb immunologically active molecules, which participate in the pathogenesis of the pro-inflammatory response to sepsis [27]. Membrane saturation occurs over a period of time and is usually complete before 24 h [27]. Maintaining filter life beyond such time exposes the patient to the release of such pro-inflammatory molecules back into the circulation and decreases the potential anti-inflammatory effect of CRRT [27, 28].

There was no correlation between filter lifespan and measured laboratory indices of coagulation such as APTT, platelet count and INR. This lack of correlation between standard clinical measures of anticoagulation and circuit lifespan has been a common finding in patients receiving therapeutic anticoagulation during CRRT [29, 30]. Such data suggest that factors other than the coagulation system, such as physical factors (for example, the blood-air interface in the venous air-chamber) and rheological components of the system may be more important in determining the lifespan of extracorporeal circuits [31]. There were no bleeding complications during CVVH in our patients.

It is worth mentioning that the coagulation profile and risk of bleeding in these patients is highly dynamic. The administration of clotting factors often occurs when the risk of bleeding is considered very high, removal of fluid by means of CVVH affects the platelet count and hemoglobin concentration with a secondary effect on bleeding time, and the correction of uremia improves platelet function. All these factors may affect filter life independently and require consideration by the clinician, especially with regard to the decision to switch from CVVH without anticoagulation to CVVH with low-dose heparin. In our unit, this decision is currently not subject to specific guidelines due to the lack of data. In general, our clinicians prefer to delay the resumption of circuit anticoagulation as long as possible.

A mean serum urea of 16 mmol/l and mean serum creatinine of 198 μmol/l were achieved during the course of anticoagulant-free CVVH, confirming adequate azotemic control. In fact, anticoagulation-free CVVH allowed clinicians to start therapy under any circumstances and very early in the course of a patient's illness. Thus anticoagulation-free CVVH has no adverse effect on uremic control and facilitates the early start of therapy.

Other strategies aimed at minimizing bleeding risk while maintaining circuit life might have been equally safe and effective. It is hard, however, to conceive of any therapy that would be safer than giving no anticoagulant at all. Nonetheless, interval circuit saline flushing has been proposed as an inexpensive, albeit time-consuming, method of overcoming build-up of cellular and macromolecular constituents, thereby prolonging circuit lifespan. No data have been published using this method in patients receiving CRRT.

Our study suffers from several limitations. It is not randomized. However, the control group is representative of typical ICU patients receiving CRRT and, in our opinion, sufficient for meaningful comparison. Due to the episodic nature of bleeding complications, a very large population of patients would have to be studied to demonstrate a significant reduction in bleeding episodes with antico-

agulant-free CVVH. Finally, we cannot provide a strict definition of which patients should receive anticoagulation-free CRRT. However, we have described the patients' clinical circumstances and coagulation profile and thus hope that this information conveys a useful impression of which patients may benefit from this approach. Furthermore, we have reported the guidelines for circuit anticoagulation under which clinicians operated during the study period. The data provided should enable other clinicians to reproduce our approach.

In summary, we have described a cohort of patients at high risk of bleeding in whom we have conducted CVVH without the use of anticoagulants and have compared it to a control group treated with low-dose heparin. Anticoagulant-free CVVH was associated with a satisfactory circuit life, no bleeding complications and excellent uremic control. Our findings suggest that anticoagulation-free CRRT should be strongly considered in patients at high risk of bleeding.

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