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Original Article

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Use of high-volume haemodiafiltration in patients with refractory septic shock and acute kidney injury

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Abstract

Background. High-volume haemofiltration (HVHF) has been used successfully in animal models with sepsis, and preliminary data have shown that this technique may improve the haemodynamics in patients with refractory septic shock. We used high-volume continuous venovenous haemodiafiltration (CVVHDF) in patients with acute kidney injury (AKI) and refractory septic shock to evaluate their outcome when compared with their prognosis predicted by scores of severity.

Methods. This is a cohort study in a Medical and Surgical Intensive Care Unit. Fifty-five patients with refractory septic shock and AKI were included in the study.

Results. High-volume CVVHDF was started in patients with AKI and septic shock requiring norepinephrine dose >0.2 μg/kg/min. AKI was classified according to the RIFLE criteria. Treatment was implemented within the first 24 h of refractory septic shock with a dialysis dose of 70 mL/kg/h until reversal of shock or death. Fifty-five patients were treated with high-volume CVVHDF with an observed mortality of 63%, similar to the mortality predicted by the APACHE II and SAPS II scores.

Conclusion. Survival rate in our patients with AKI and refractory septic shock treated with high-volume CVVHDF was identical to survival predicted by the severity scores. Treatment with high-volume haemodiafiltraton is applicable to severely ill patients with septic shock but does not confer any clear advantage in terms of survival. This therapy should not be implemented on a routine basis in patients with AKI and refractory septic shock.

Keywords: acute kidney injury; high-volume haemodiafiltration; septic shock

Introduction

Sepsis and septic shock are the most common causes of death in the intensive care unit (ICU) with a mortality rate ranging from 50 to 80%. Higher mortality rate is observed in patients with septic shock whose haemodynamic state is not improved by high doses of amines [1].

High-volume haemofiltration (HVHF) produces higher volumes of ultrafiltrate, and this technique has been coined 'renal support' rather than 'renal replacement' therapy. Some authors have employed the term 'septic dose' in contrast to the usual 'standard dose' [2]. Three main theories have been elaborated to support the use of this technique in patients with sepsis. First, removing the peak cytokine concentration from the blood circulation during the early phase of sepsis might stop the inflammatory cascade and prevent the accumulation of free cytokines [3]. Secondly, the 'so-called' threshold immunomodulation hypothesis states that pro-mediators as well as mediators are removed from the interstitium and tissues following removal from the blood compartment, until a new threshold point is reached [4]. Finally, the 'mediator delivery hypothesis', states that the lymphatic flow is increased by HVHF with concomitant substantial drag and displacement of mediators and cytokines to the blood compartment allowing them to be available for removal [5]. These theories are not mutually exclusive and form the rationale for using HVHF in the case of septic shock. The clinical foundations of the high-volume technique were laid in a randomized clinical trial examining different doses of haemofiltration in patients with AKI. The outcome of those with sepsis improved by increasing the dose from 35 to 45 mL/kg [6].

This technique has demonstrated its efficacy in experimental animal models of septic shock or severe inflammatory syndrome [7]. In humans, some studies showed that HVHF allowed reduction of epinephrine dose and improve haemodynamic parameters [8–11]. Two studies even suggest improved survival with this technique [8, 10].

Catecholamine-resistant septic shock, either hypo- or hyperdynamic, could be considered as an indication for

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HVHF in patients with AKI [12]. This technique was adapted in our centre as a 'rescue' therapy in patients with amine-resistant septic shock and AKI [13]. This report describes our 3-year experience using high-volume continuous venovenous haemodiafiltration (CVVHDF) in this subset of patients.

Materials and methods

High-volume CVVHDF was performed in the ICU of the University Hospitals of Geneva during 3 year, from July 2007 to July 2010 and data were analyzed, retrospectively.

Patients

Sepsis was diagnosed according to the Bone's criteria with clinical evidence of infection [14]. Refractory septic shock was defined locally in agreement with the intensive care team as a norepinephrine's dose >0.2 μg/kg/min. Severity of illness was determined on the first day starting the continuous renal replacement treatment (CRRT) using SAPS II and APACHE II scores. Acute kidney injury (AKI) was classified according to the RIFLE categories using creatinine and urine output criteria prior to high-volume CVVHDF. Patients were eligible for enrolment in the study if they were in refractory septic shock and presented AKI (categories R, I and F). Clinical management, high-volume CVVHDF implementation and treatment in these patients were supervised jointly by nephrologists and intensivists.

CRRT procedures

A 13-French dual-lumen venous catheter was inserted through a central vein to maintain a blood flow above 250 mL/min. CRRT with a dose of 70 mL/kg/h was started within 24 h of refractory septic shock and continued until reversal of shock or death but for a maximum of 96 h. After 96 h of high-volume CVVHDF or reversal of shock, CRRT dose was decreased to 40 mL/kg/h.

Dialysis treatment was performed by pump-driven machines (Prismaflex®, Gambro®) with fluid balance systems and acrylonitrile 1.5 m^2 AN 69® membrane (Gambro®). Hemosol® (Gambro®), a bicarbonate-buffered solution, was the standard replacement fluid provided. We use CVVHDF with one-third of dialysis and two-thirds of haemofiltration [13]. The haemofiltration was divided into one-third post-dilution and two-thirds pre-dilution according to our unit protocol. Temperature and serum electrolytes were monitored several times a day and drug dosage was adapted to avoid infra-therapeutic blood levels [15].

Statistical analysis

Categorical variables were expressed as numbers and frequencies. Continuous variables were expressed as mean and standard deviation or median and interquartiles when distribution was abnormal. Normality was tested using Kolmogorov–Smirnov test. We compared survivors with non-survivors using Mann–Whitney test for continuous variables and χ^2 test for categorical variables. A $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 17.0 software (SPSS Inc. Chicago IL).

Results

During the study period, 297 patients with AKI were treated by CRRTs in our institution. Of these 297 patients, 55 patients (19%) met the diagnosis criteria of refractory septic shock and AKI and were treated with high-volume CVVHDF.

Baseline characteristics of the patients are shown in Table 1. Their main comorbidities were cancer (25%), diabetes (25%), hepatopathy (22%), alcoholism (18%), immunosuppression (16%) and chronic kidney disease (15%). Sepsis was microbiologically diagnosed in two thirds of the patients. The two main sources were pulmonary (44%) and digestive (22%). The most common bacteria found were *Escherichia coli* (22%), *Streptococcus* sp. (16%), mixed flora (16%) and Methicillin-resistant *Staphylococcus aureus* (9%). The most prescribed antibiotics and their dosage adjustment to high-volume CVVHDF are listed in Table 2 [15]. Thirty-one patients (56%) had thrombopoenia at the beginning of high-volume CVVHDF.

Table 1. Patient characteristics[a]

Age (years)	61.8 ± 12
Male sex no. (%)	34 (62)
Creatinine at high volume CVVHDF start(μmol/l)	272 (151–311)
RIFLE categories no. (%)	
Risk	11 (20)
Injury	11 (20)
Failure	33 (60)
Mechanical ventilation no. (%)	55 (100)
APACHE II score[b]	27 ± 7
SAPS II score[c]	59 ± 14
Weight (kg)	80 ± 16
Main comorbidities no. (%)	
Cancer	14 (25)
HIV	3 (5)
Hepatopathy	12 (22)
Chronic kidney disease	8 (15)
Immunosuppression	9 (16)
Alcoholism	10 (18)
Diabetes	14 (25)
Type of admission no. (%)	
Medical	36 (65)
Surgical	19 (35)
Sepsis source no (%)	
Pulmonary	24 (44)
Digestive	12 (22)
Urinary	4 (7)
Unknown	8 (15)
Others	7 (13)
Bacteriology no. (%)	
Methicillin-resistant *Staphyloccocus aureus*	5 (9)
Escherichia Coli	12 (22)
Streptococcus sp.	9 (16)
Proteus Mirabilis	2 (4)
Enterococcus faecalis	3 (5)
Klebsiella pneumonia	3 (5)
Mixed (more than one bacteria)	9 (16)
Others	5 (9)
Unknown	17 (31)
High-volume CVVHDF characteristics	
Length of high-volume CVVHDF (h)	37 ± 25
Dialysate fluid (ml/h)	1801 ± 375
Replacement fluid	
Pre-dilution (mL/h)	2684 ± 497
Post-dilution (mL/h)	974 ± 115
Platelet count (g/L)	147 ± 115

[a]Continuous variables are presented as means ± standard deviation. Only creatinine is expressed as median and interquartile range (25–75th).
[b]APACHE denotes acute physiology and chronic health evaluation. APACHE II scores range from 0 to 71, with higher scores indicating more severe illness.
[c]SAPS denotes simplified acute physiology score. SAPS II scores range from 0 to 163 and predicted mortality between 0 and 100%.

All patients were treated with hydrocortisone, as this is part of the standard management of septic shock in our centre. Two of the patients received activated protein C and none of them received selenium. Levels of serum phosphate were measured each day. Intravenous substitution was started in the case of hypophosphataemia. Despite this precaution, 30 patients (55%) still presented an hypophosphataemia during the time of the monitoring.

Observed mortality was 63% at 28 days. The mortality rates predicted by APACHE II and SAPS II scores were 60 and 66%, respectively. Mortality was not affected by the severity of AKI according to the RIFLE criteria (Table 3). The survivors were younger and had lower creatinine and severity scores than non-survivors. The average duration of dialysis was longer in the survivors. Except for the APACHE II score ($P = 0.04$), these differences were statistically non-significant (Table 3). Distribution in relation to RIFLE criteria was the same with 60% of patients presenting with Failure stage. The mortality during high-volume CVVHDF therapy is shown in Figure 1: 23 patients (66%) died during this treatment period and 12 (34%) died later (>96 h).

Table 2. Most commonly used antibiotics and their dosage during high-volume CVVHDF

Antibiotic	Dosage or level
Imipenem	500 mg TID or QID
Vancomycin	Trough levels 10–15 mg/l
Piperacillin/tazobactam	2.25 g TID
Ceftriaxon	2 g QD
Metronidazole	500 mg TID or QID
Clarithromycin	250–500 mg BID
Clindamycin	600 mg TID or QID
Meropenem	1–2 g BID
Ciprofloxacin	400 mg QD

Table 3. Characteristics of patients according to survival at 28 days[a]

Characteristic	Non survivors ($n = 35$)	Survivors ($n = 20$)	*P* Value
Age (years)	63 ± 12	59 ± 12	NS
Male sex no. (%)	22 (63)	12 (60)	NS
Mean creatinine at HVHF start (μmol/l)	281 ± 187	256 ± 189	NS
APACHE II score[b]	29 ± 6	24 ± 9	0.04
SAPS 2 score[c]	61 ± 13	56 ± 17	NS
RIFLE criteria no (%)			
Risk	7 (20)	4 (20)	NS
Injury	7 (20)	4 (20)	NS
Failure	21 (60)	12 (60)	NS
high-volume CVVHDF characteristics			
Length of high volume CVVHDF (h)	34 ± 25	44 ± 24	NS
Dialysate fluid (mL/h)	1837 ± 364	1740 ± 397	NS
Replacement fluid			
Pre-dilution (mL/h)	2724 ± 495	2613 ± 505	NS
Post-dilution (mL/h)	977 ± 231	968 ± 299	NS
Platelet count (g/L)	137 ± 113	165 ± 118	NS

[a]Continuous variables are expressed as means ± standard deviation. NS, non significant ($P > 0.05$).
[b]APACHE denotes acute physiology chronic health evaluation. APACHE II scores range from 0 to 71, with higher scores indicating more severe illness.
[c]SAPS denotes simplified acute physiology score. SAPS II scores range from 0 to 163 and predicted mortality between 0 and 100%.

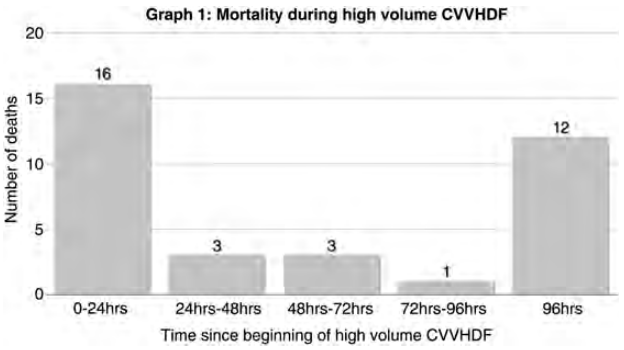

Fig. 1. Mortality during high volume CVVHDF.

Discussion

In patients with refractory septic shock and AKI treated by HVHF, we found no difference between observed versus expected mortality by clinical scores (63 versus 60% for APACHE II and 66% for SAPS II). Nevertheless, some clinically relevant findings emerged from our data. It appears that HVHF can be safely performed in critically ill patient with refractory septic shock. No serious adverse events were noted during this treatment. We had to use a 13-French catheter and that could be a problem in septic patients with clotting problems. We noted that the blood pressure did not drop further with the introduction of HVHF. With such large fluid volumes, the body temperature is lower and may be involved in the observed stability [16]. On the other hand, this requires a greater supply of fluid reinjection and consequently higher costs. An intermediate analysis of the cohort was done in 2008 with 25 patients and the decision was made to continue to use HVHF as the survival rate observed at that time was higher than what clinical scores predicted (50 versus 33% with scores).

The intensity or dose of CRRT was based initially on a prospective randomized control trial published in 2000 assuming that higher treatment doses in sepsis may improve survival [6]. The study compared prescribed CVVH doses of 20, 35 and 45 ml/kg/h and found improved survival in the 35 and 45 ml/kg/h group as compared with the 20 ml/kg/h group. In the subgroup of patients with sepsis, which accounted for 11–14% per randomization group, there was a trend towards an even further improved survival between the two higher treatment arms. In the same period, theories developed on immunomodulation provided by large doses of CRRT (see Introduction). However, only a few, mostly observational studies in humans, support this concept of providing HVHF [8–10, 17–21]. One of the largest studies, with 306 patients (roughly 30% with sepsis), started with a volume of 5 L/h (an average volume of 63 mL/min) in post-dilution CVVH with blood flow of 200 mL/min [8]. The mortality was lower than that expected by illness severity scores (APACHE II and SAPS II). Only two small randomized controlled trials investigated the effect of HVHF in septic shock. The first one by Cole *et al.* [9] enrolled 11 patients with septic shock and multiple organ failure in a crossover design. HVHF at 6 L/h versus CVVH at 1 L/h during eight hours resulted in a greater reduction of complement levels and IL-10, as well as more rapid decline of catecholamine requirements. This advantage disappeared after 24 h. The second study by Ghani *et al.* [21] enrolled 33 patients and compared 35 versus

100 mL/kg/h (maximum 6 L/h). The main finding in this study was a significant decline of IL-6 levels. Both studies are too small to show any difference in mortality. In order to clarify the role of HVHF in treatment of septic shock, a European multi-centre study (NCT00241228) was started in October 2005, the IVOIRE study (hIgh VOlume in Intensive caRE). The inclusion criteria included septic shock for <24 h, RIFLE criteria of Injury or worse and age over 18 years. Patients were randomized to receive either 35 or 70 mL/kg/h. This study should include 480 patients with an expected mortality of 49% in the 35 mL/kg/h and a reduction in mortality of 15% with HVHF. Recruitment appears to be difficult and intermediate results advanced by the investigator shows that the 28-day mortality of 139 patients included is 39% [22]. Recently, both the ATN and RENAL studies with 1124 and 1508 critically ill adult requiring RRT, failed to detect any survival benefit from more-intensive RRT [23, 24]. In addition, no significant difference in mortality rates were observed between high- and low-intensity treatment in pre-specified subgroups in either study. These subgroups included patients with sepsis and patients requiring vasopressors. These results provide evidence to recommend that escalation of CRRT intensity beyond conventional doses of 25 mL/kg/h is not beneficial for ICU patients with AKI [25].

Our data showed that even in septic shock, a higher dose of continuous haemodiafiltration does no't seem to change the prognosis. As this protocol was established on a routine basis in our ICU setting, all patients with refractory septic shock were included in the cohort according to the criteria defined above. No patient was excluded from our cohort as would have been the case in a randomized trial. Therefore, although not controlled, these data are representative for the entire activity of the ICU. Alternatively, the absence of effect of a higher dose of haemodiafiltration could be due to the improvement in the overall management of this kind of patient. The high mortality in our group does not confirm this hypothesis. Because of the HVHF, our patients may have had inadequate plasma antibiotic levels. Despite the fact that, we were careful to properly adjust the dose of the antibiotics based on current recommendations, it is possible that the doses are sometimes inappropriate [15, 26]. Pharmacology studies assessing this point in patients undergoing CRRT found that antibiotic levels were insufficient most of the time for the antibiotics tested [27]. Appropriate and adequate antibiotics are, however, the cornerstone of sepsis therapy [28]. Another possibility is that the treatment implementation was too late, as many of our patients were already in the Failure category (60%) at the time of inclusion. Timing of treatment in patients with AKI is still a matter of debate [25].

Our study has some important limitations. It is an uncontrolled, retrospective, small-scale and single-centre study. There was no control group and mortality must be compared with expected mortality predicted by clinical scores. Inclusion criteria include all RIFLE categories and therefore a wide range of AKI. It might be necessary to focus on one category and thus be more homogeneous, but then we would have lost one of the strengths of our study. Indeed, we have included a reasonable number of patients compared with other studies on HVHF.

In conclusion, HVHF is safe in patients with refractory septic shock and AKI. We are, however, unable to show an advantage in survival in patients with AKI and refractory septic shock treated with HVHF. Prior to recommending on a routine basis this therapeutic strategy in this subset of patients, we need more data coming from a randomized controlled trial.

Conflict of interest statement. No conflict of interest.

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