A Double-Blind Randomized Controlled Trial of High Cutoff Versus Standard Hemofiltration in Critically Ill Patients With Acute Kidney Injury

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Objectives: In critically ill patients with acute kidney injury receiving vasopressors, high cytokine levels may sustain the shock state. High cutoff hemofiltration achieves greater cytokine removal in ex vivo and in animal models and may reduce the duration of shock but may also increase albumin losses.

Design: This was a single-center double-blind randomized controlled trial comparing continuous venovenous hemofiltration-high cutoff to continuous venovenous hemofiltration-standard.

Setting: Tertiary care hospital in Australia.

Patients: Vasopressor-dependent patients in acute kidney injury who were admitted to the ICU.

Interventions: Norepinephrine-free time were calculated in critically ill vasopressor-dependent patients in acute kidney injury, randomized to either continuous venovenous hemofiltration-high cutoff or continuous venovenous hemofiltration-standard.

Measurement and Main Results: A total of 76 patients were randomized with the following characteristics (continuous venovenous hemofiltration-high cutoff vs continuous venovenous hemofiltration-standard); median age of 65 versus 70 year, percentage of males 47% versus 68%, and median Acute Physiology and Chronic Health Evaluation scores of 25 versus 23.5. The median hours of norepinephrine-free time at day 7 were 32 (0–110.8) for continuous venovenous hemofiltration-high cutoff and 56 hours (0–109.3 hr) ($p = 0.520$) for continuous venovenous hemofiltration-standard. Inhospital mortality was 55.6% with continuous venovenous hemofiltration-high cutoff versus 34.2% with continuous venovenous hemofiltration-standard (adjusted odds ratio, 2.49; 95% CI, 0.81–7.66; $p = 0.191$). There was no significant difference in time to cessation of norepinephrine ($p = 0.358$), time to cessation of hemofiltration ($p = 0.563$), and filter life ($p = 0.21$). Serum albumin levels ($p = 0.192$) were similar and the median dose of IV albumin given was 90 grams (20–212 *g*) for continuous venovenous hemofiltration-high cutoff and 80 grams (15–132 *g*) for continuous venovenous hemofiltration-standard ($p = 0.252$).

Conclusions: In critically ill patients with acute kidney injury, continuous venovenous hemofiltration-high cutoff did not reduce the duration of vasopressor support or mortality or change albumin levels compared with continuous venovenous hemofiltration-standard. (*Crit Care Med* 2018; XX:00–00)

Key Words: acute kidney injury; blood purification; critical illness; hemofiltration; high cutoff filter; super high flux filter

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Shock states with accompanying acute kidney injury (AKI) are a leading cause of death in critically ill patients (1), with a mortality rate of approximately 60% (2). In this setting, high cytokine levels are believed to contribute to sustained vasodilatation, continued multiple organ dysfunction

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syndrome, and mortality (3, 4). They appear to do so through complex effects on inflammation, immunity, and coagulation pathways (5). Accordingly, they have been the target of therapeutic interventions for more than two decades.

For example, antibodies against key cytokines such as tumor necrosis factor (TNF)–alpha and interleukin (IL)–1 as well as analogs to cytokine antibodies such as IL-1ra have been studied as adjunctive treatment of septic shock (6). However, such treatments have been unsuccessful. This lack of success with the targeting of specific individual molecules has suggested the need to test broader approaches including nonspecific extracorporeal cytokine removal (7, 8). In this regard, the application of blood purification therapies has been proposed as a way of returning cytokines to more homeostatic levels (9). Various blood purification techniques aimed at cytokine clearance have been explored for such purposes over the last 20 years including standard hemofiltration, adsorption techniques, plasmapheresis, and hybrid techniques (10). Unfortunately, many of these techniques have also been unsuccessful. Such lack of success, however, may, at least in part, be related to the use of membranes that can only achieve low levels of cytokine removal due to their limited porosity.

Most cytokines have molecular sizes that range between 8 and 60 kDa, whereas standard hemofiltration membranes have nominal cutoff points of somewhere between 10 and 30 kD. These observations logically suggest the need of more targeted membrane characteristics to achieve greater levels of cytokine removal. In this regard, high cutoff (HCO) filters, also known as "super high flux filters," have been developed and tested. Such membranes have larger nominal pore sizes ranging between 60 and 150 kDa and offer better removal of cytokines ex vivo (11). In this regard, some early studies have shown promising results with these HCO filters in the treatment of sepsis and AKI and demonstrated a degree of safety (5, 12, 13).

In light of the above considerations, we designed and performed a phase II double-blind randomized study comparing continuous venovenous hemofiltration-standard (CVVH-Std) with continuous venovenous hemofiltration-HCO (CVVH-HCO) in critically ill patients with AKI requiring vasopressor support (ClinicalTrial.gov/NCT00912184). We hypothesized that there would be a difference in norepinephrine requirements expressed as hours of norepinephrine-free time within the first week of treatment.

METHODOLOGY

The study was approved by the Austin Hospital Human Research Ethics Committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

We randomized patients in a 1:1 ratio to receive either CVVH-Std or CVVH-HCO within 12 hours of a decision to commence hemofiltration. Randomization was achieved through random allocation generated by a computer program using permuted block sizes undisclosed to recruiting personnel. Concealment of allocation was achieved through opaque sealed envelopes labeled with sequential numbers.

We included patients on norepinephrine for hemodynamic support who required hemofiltration for AKI. The criteria for initiating hemofiltration included either oliguria (< 100 mL/6 hr) unresponsive to fluid resuscitation, hyperkalemia of more than 6.5 mmol/L, severe acidemia of less than pH of 7.2, serum urea of more than 25 mmol/L, serum creatinine of more than 300 µmol/L, or clinically significant organ edema in the setting of acute renal failure (e.g., pulmonary edema). Patients were recruited if the clinician anticipated that the patient would require hemofiltration for at least 72 hours.

We excluded patients who were less than 18 years old and those in whom the treating clinician believed that death was likely within 24 hours. We also excluded patients who had been treated with hemofiltration or other dialysis during the same hospital admission, were on maintenance dialysis prior to admission or were pregnant or breastfeeding. The study was conducted in a general ICU within a major tertiary hospital. Informed consent was obtained from the legally responsible person (next of kin or person with medical power of attorney).

Following enrolment, patients were randomly allocated to either continuous venovenous hemofiltration (CVVH) with custom manufactured polyethersulfone standard hemofilters (CVVH-Std) with nominal cutoff point of 30 kDa or CVVH with polyethersulfone HCO filters (CVVH-HCO) with nominal cutoff point of 100 kDa (P2SH filters, 1.12 m^2; Gambro, Hechingen, Germany). Patients, healthcare personnel, and researchers were blinded to treatment allocation. The two types of filters were indistinguishable in appearance.

For each treatment, the technical settings were the following: blood flow at 200 mL/min, ultrafiltration rate at 25 mL/kg/hr rounded to the nearest 100 mL with bicarbonate-buffered replacement fluids. The choice of anticoagulation was left to the discretion of the treating clinician. However, the mainstay of anticoagulation mode was low dose prefilter heparinization. Each treatment was applied until a maximum of 14 days or until cessation of continuous renal replacement therapy (CRRT) or death or discharge from ICU, whichever occurs earlier. Other aspects of treatment continued according to clinical needs and standard care. In patients with vasodilatory shock, the unit protocol calls for fluid resuscitation aimed to ensure a central venous pressure between 8 and 12 mm Hg, assessment of cardiac output by either echocardiography or other monitoring techniques (e.g., cardiac output monitors) and titration of norepinephrine to achieve a mean arterial pressure (MAP) of 65 mm Hg. Filters were changed only upon clotting or termination of renal replacement therapy. CRRT was discontinued based on standard indications for discontinuation of any standard CRRT, that is, normalization of any of the indications for initiation namely resolution of oliguria, acidosis, and hyperkalemia and normalization of urea and creatinine over a period of 24 hours without CRRT.

The primary outcome measure for this study was cumulative hours of norepinephrine-free time within the first week after randomization. This was done to compensate for the competing risk of mortality (if a patient died while on norepinephrine, days after death contributed zero norepinephrine-free hours to the outcome).

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Assuming a SD for the primary outcome equal to 50% of the mean, we estimated that a sample of 36 patients in each group (total 72) would carry an 80% power of detecting a 25% difference in norepinephrine-free time in the first week at an alpha of 0.05. An additional four patients were recruited to account for possible loss to follow-up or protocol violations or technical failures.

A biological outcome study was also conducted as part of this assessment (change in the levels of each of three key cytokines; IL-1, IL-6, and IL-10) and has been previously reported (14).

Due to the potential loss of albumin with HCO hemofiltration, additional outcomes studied included the percentage change in serum albumin levels, and the total amount of albumin in grams administered IV for each patient over the first 7 days. If fresh frozen plasma was administered, its albumin concentration was estimated as 3.3 g/L (15).

We also measured filter life, maximum rate of vasopressor infusion per day in μg/min, and duration of hemofiltration. For maximum rate of vasopressor analysis, the highest rate recorded on the last day alive was carried forward to day 7. Three blinded interim analyses were conducted after 20, 40, and 50 patients, respectively, with the aim of stopping the trial if either group had a mortality rate of more than 60%.

STATISTICAL ANALYSIS

Analysis was performed according to a modified intention to treat principle which required both randomization and treatment initiation. Nonnormal data were log-transformed to enable the use of parametric statistics, and nonparametric tests were applied if the data remained nonparametric. Baseline characteristics were compared using the Mann-Whitney *U* test for continuous data or Fisher exact test for categorical data. Norepinephrine-free time in the first week, IV albumin administration, and filter life comparisons were performed using the Mann-Whitney *U* test. Changes in median serum albumin levels over time and maximum rate of vasopressor infusion per day comparisons were analyzed using repeated measures analysis of variance. Time to cessation of norepinephrine and time to cessation of hemofiltration were analyzed using the log-rank test with all patients contributing to the data; nonsurvivors were counted as "no event" and were right censored. As time to hospital discharge was variable for each patient, time to death was censored at 30 days; patients who survived to hospital discharge were assumed to have survived to 30 days. As a degree of imbalance in baseline characteristics is common in pilot studies such as this, post hoc outcome adjustments for ICU and hospital mortality using logistic regression analysis were performed and included key baseline variables (Acute Physiology and Chronic Health Evaluation [APACHE]–3) and those variables with greatest baseline imbalance.

RESULTS

We randomized 76 patients with 38 patients assigned to each group. Two patients were subsequently excluded; one patient had received prior hemofiltration during the same hospital admission and therefore fulfilled exclusion criteria, and another died shortly after recruitment and randomization but before treatment was commenced, leaving 74 patients for a modified intention to treat analysis.

Baseline Features and Process of Care

The baseline characteristics of the study patients are shown in **Table e1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D849). Indications for commencing norepinephrine were mainly septic shock and cardiogenic shock. One patient also had concurrent hypovolaemic shock. Patients recorded under "others" mainly had liver failure. The median noradrenaline rate at commencement in was 13 μg/min (6–29 μg/min) for CVVH-HCO and 13 μg/min (5–23.5 μg/min) for CVVH-Std ($p = 0.668$). Several variables differed at baseline including oliguria, international normalized ratio (INR), and blood lactate levels. However, APACHE II, APACHE III, and Sequential Organ Failure Assessment scores were similar between the two groups. Most patients were only on norepinephrine infusion. When patients were also on epinephrine, this was treated as just the same for norepinephrine, and the two values were added. Only a few patients were on vasopressin. Other vasoactive drugs involving a small number of patients included milrinone and dobutamine. One patient was on extracorporeal membrane oxygenation from the CVVH-HCO group, and another patient from CVVH-Std group was on intra-aortic balloon pump therapy. This breakdown has been added to **Table e2** (Supplemental Digital Content 2, http://links.lww.com/CCM/D850) for CVVH-HCO and **Table e3** (Supplemental Digital Content 3, http://links.lww.com/CCM/D851) for CVVH-Std and summarized in **Table e4** (Supplemental Digital Content 4, http://links.lww.com/CCM/D852). A total of 226 filters were used for CVVH-HCO group with a median filter life of 9 hours (4–17 hr) versus 269 filters for CVVH-Std group with a median filter life of 10 hours (5.5–19.8 hr) ($p = 0.21$). No anticoagulation was used for 119 (52.7%) CVVH-HCO filters and 118 (43.9%) CVVH-Std filters, mostly due to contraindications. Anticoagulation techniques, when applied, were unfractionated heparin, regional heparinization, citrate, low-molecular-weight heparin, and others (e.g., prostaglandin infusion) as shown in **Table e5** (Supplemental Digital Content 5, http://links.lww.com/CCM/D853).

Outcomes

Median cumulative norepinephrine-free time over 7 days was 32 hours (0–110.8 hr) for CVVH-HCO and 56 hours (0–109.3 hr) for CVVH-Std after randomization ($p = 0.520$). **Figure 1** shows norepinephrine-free time (hr) per group per day for the first 7 days. The maximum noradrenaline rates of infusion per day (μg/min) were similar for both groups (**Fig. 2**) ($p = 0.750$). Tables showing median values and interquartile ranges for both Figure 1 and Figure 2 are provided in **Table e6** (Supplemental Digital Content 6, http://links.lww.com/CCM/D854) and **Table e7** (Supplemental Digital Content 7, http://links.lww.com/CCM/D855), respectively. Changes in

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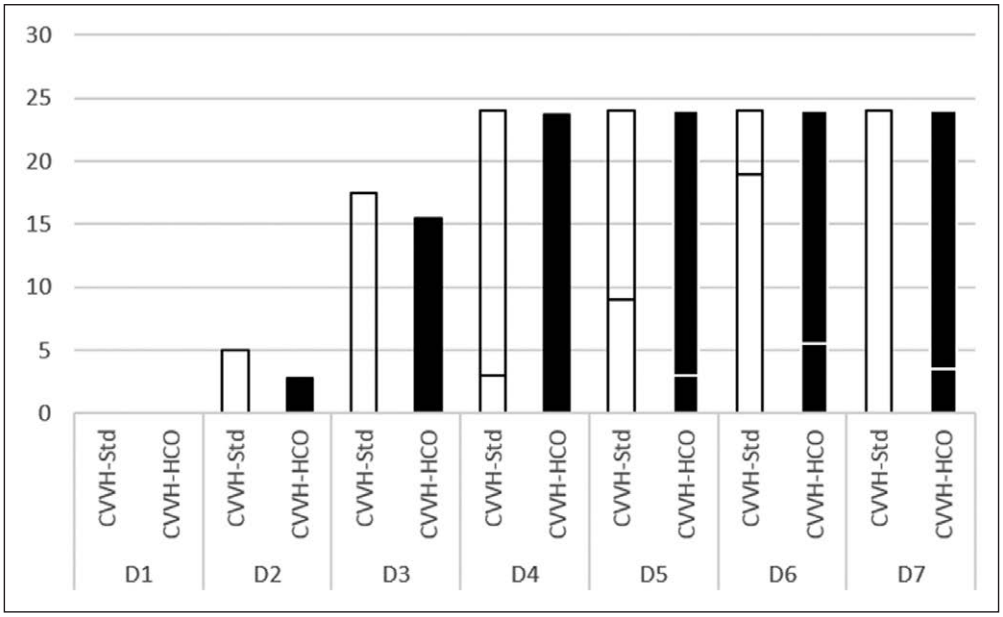

Figure 1. Norepinephrine-free time (hr) per day per group: day 1 to day 7. Values are median (*middle line*), Q1 (*lower margin*), and Q3 (*upper margin*). Continuous venovenous hemofiltration-high cutoff (CVVH-HCO): high cutoff group; continuous venovenous hemofiltration-standard (CVVH-Std): control/standard group. All patients contribute data. Nonsurvivors are recorded as having zero hours of norepinephrine-free time after death.

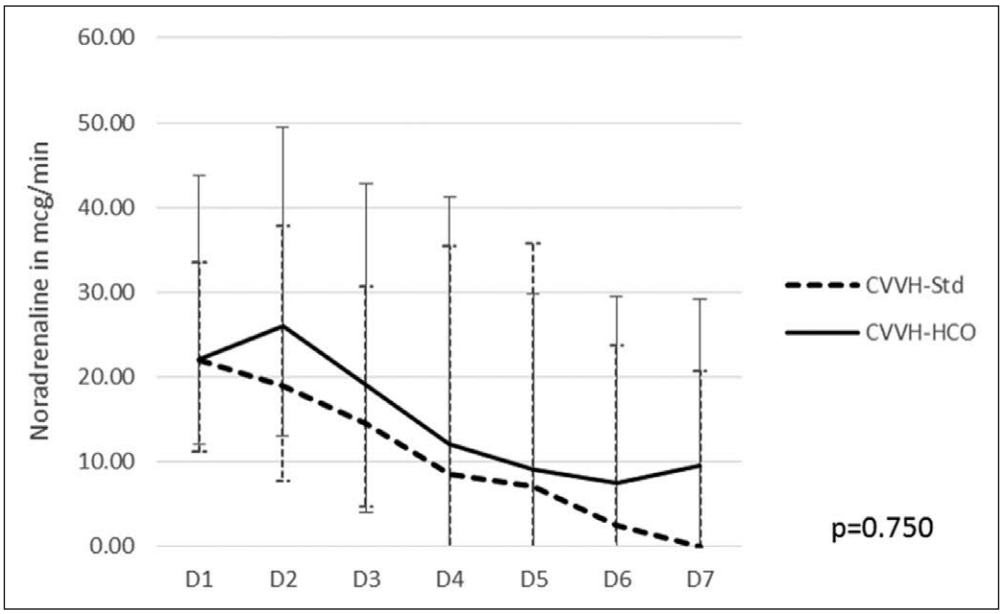

Figure 2. Median highest norepinephrine infusion rates per day. *Error bars* indicate interquartile ranges. Continuous venovenous hemofiltration-high cutoff (CVVH-HCO): high cutoff group; continuous venovenous hemofiltration-standard (CVVH-Std): control/standard group. *n* = 36 (CVVH-HCO); 38 (CVVH-Std).

serum albumin levels within the first 7 days were not significantly different between the two groups (p = 0.192) (**Fig. 3**). The median dose of IV albumin given over the first 7 days were 90 grams (20–212 *g*) for CVVH-HCO and 80 grams (15–132 *g*) for CVVH-Std (p = 0.252).

There was no difference in time to permanent cessation of noradrenaline (**Fig. 4**) (p = 0.358)) and time to permanent cessation of hemofiltration (p = 0.563) (**Fig. e1**, Supplemental Digital Content 8, http://links.lww.com/CCM/D856; **legend**, Supplemental Digital Content 10, http://links.lww.com/CCM/D858) within the full 14 days of treatment period. Median time to permanent cessation of noradrenaline could not be calculated as less than 50% of subjects achieved this event in both groups.

The unadjusted odds ratio for ICU mortality with HCO hemofiltration was 2.17 (95% CI, 0.84–5.58; p = 0.109) for ICU mortality and 2.40 (95% CI, 0.94–6.15; p = 0.067) for inhospital mortality. The adjusted odds ratio (lactate, INR, serum albumin, and APACHE 3) was 2.13 (95% CI, 0.69–6.65; p = 0.191) for ICU mortality and 2.49 (95% CI, 0.81–7.66; p = 0.112) for inhospital mortality (**Table 1**). There was no significant difference in time to death, but the trend was in favor of standard CVVH (p = 0.052) (**Fig. e2**, Supplemental Digital Content 9, http://links.lww.com/CCM/D857; legend, Supplemental Digital Content 10, http://links.lww.com/CCM/D858) within 30 days of commencing treatment.

DISCUSSION

Key Findings

We conducted a pilot, phase II, double-blind, randomized, controlled trial of CVVH-HCO compared with CVVH-Std in critically ill patients with AKI, using the primary outcome of norepinephrine-free time (hr) within the first week of treatment. We found no difference in median norepinephrine-free time between the two groups. There were also no differences between the two groups in terms of mortality, serum albumin levels, IV albumin administration, duration of hemofiltration, duration of norepinephrine infusion, and filter life. Finally, the adjusted odds ratio for ICU and inhospital mortality was not lowered by CVVH-HCO.

Relationship to Previous Studies

Previous clinical studies involving HCO filters suggested benefits from their use in terms of increased cytokine clearance

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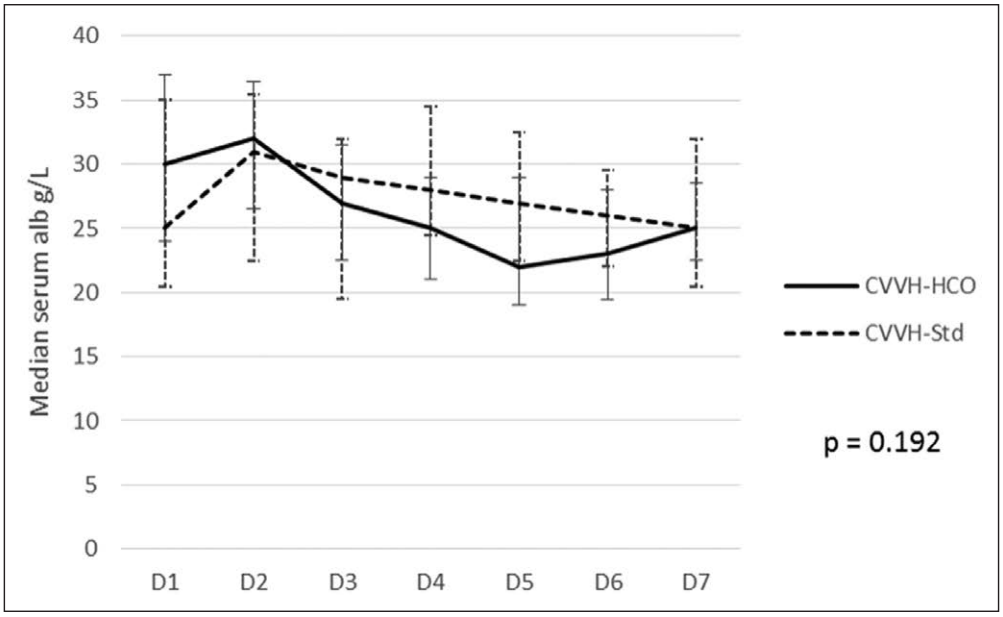

Figure 3. Median serum albumin (g/L): day 1 to day 7. *Error bars* indicate interquartile ranges. Continuous venovenous hemofiltration-high cutoff (CVVH-HCO): high cutoff group; continuous venovenous hemofiltration-standard (CVVH-Std): control/standard group.

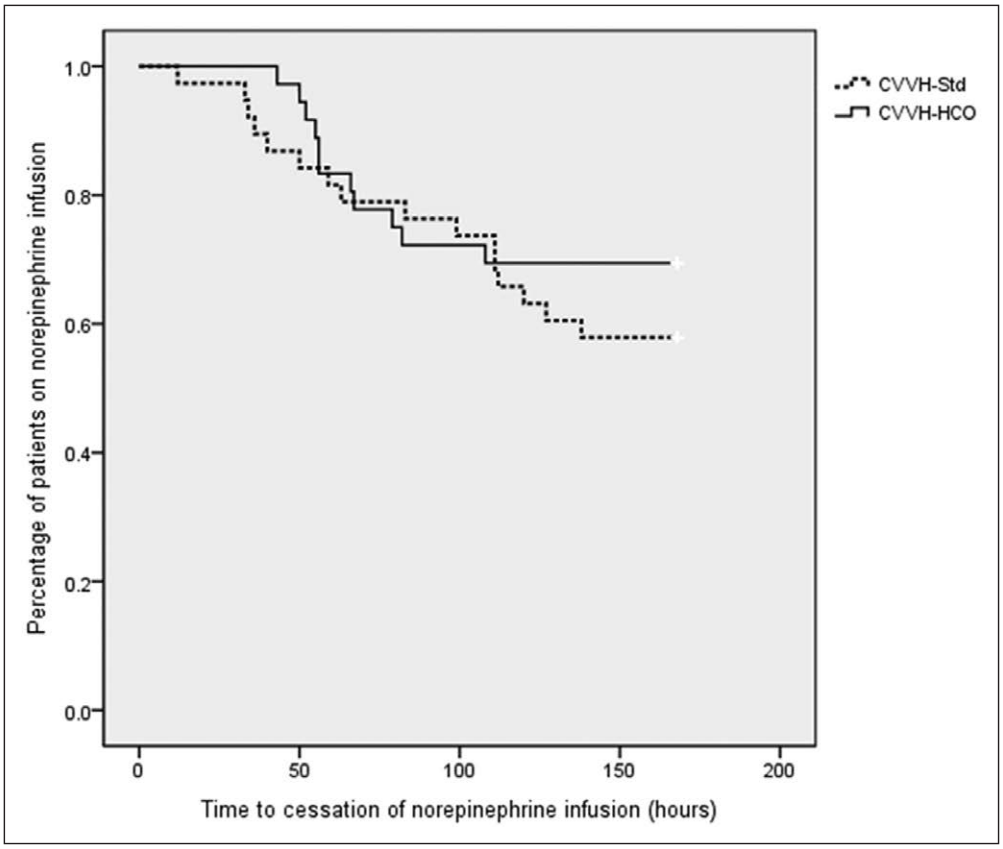

Figure 4. Time to permanent cessation of norepinephrine infusion within 7 days. Event = permanent cessation of norepinephrine infusion. Median time cannot be computed as the curve did not drop to 0.5 and below. Continuous venovenous hemofiltration-high cutoff (CVVH-HCO): high cutoff group; continuous venovenous hemofiltration-standard (CVVH-Std): control/standard group.

and attenuation of the inflammatory response (12, 13, 16, 17). Morgera et al (5) studied hemodynamic effects of HCO hemofiltration by comparing rates of norepinephrine infusion and found greater reduction in norepinephrine requirements in the HCO group following adjusted analysis. This study, however, was limited to a 48-hour period and was an open-label randomized trial. These investigators reported some changes in two selected cytokines.

In a previous publication involving this same cohort of patients (14), plasma and post-filter levels of IL-6, TNF-alpha, IL-8, IL-1 beta, regulated on activation, normal T cell expressed and secreted; CCL5, C-C motif chemokine ligand 5, IL-10, interferon (IFN)–gamma, and IFN-alpha were compared. Sieving coefficients and clearances were also calculated. There were few differences between the two groups with no distinct advantages were offered by CVVH-HCO. By 72 hours of treatment, IL-6 had significantly decreased with both techniques, and IL-10 had decreased with CVVH-Std, but not CVVH-HCO. There were also no significant between-group differences in plasma levels for each cytokine over the 72-hour treatment period.

Implications of Study Findings

This is a study involving off-label use for the HCO filter and as such is still investigational. Our study implies that there is no beneficial effect of CVVH-HCO on vasopressor therapy in critically ill patients with AKI. Furthermore, it implies that HCO does not lead to significant differences in serum albumin levels or albumin requirement compared with standard CVVH. In addition, it implies that there are no advantages in other important outcomes such as the level of vasopressor support, time to cessation of vasopressor therapy, time to cessation of hemofiltration, and filter life. Finally, our study

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TABLE 1. ICU and Hospital Mortality in the Study Groups

Outcomes	Continuous Venovenous Hemofiltration-High Cutoff, *n* (%)	Continuous Venovenous Hemofiltration-Standard, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
ICU mortality	18 (50)	12 (31.6)	2.17 (0.84–5.58); $p = 0.109$	2.13 (0.69–6.65); $p = 0.191$
Hospital mortality	20 (55.6)	13 (34.2)	2.40 (0.94–6.15); $p = 0.067$	2.49 (0.81–7.66); $p = 0.112$

OR = odds ratio.
[a]Adjusted to international normalized ratio, albumin, lactate, and Acute Physiology and Chronic Health Evaluation 3.

implies that there are no mortality advantages with CVVH-HCO. In their aggregate, these findings do not support a role for HCO hemofiltration in critically ill patients in the presence of AKI.

Strengths and Limitations

Our study has several strengths. To our knowledge, it is the first trial of blood purification for the treatment of critically ill patients on vasopressor support and in AKI conducted in a double-blind fashion. This design attenuated the risk of performance and ascertainment bias. The risk of selection bias was further attenuated by concealed allocation. The inclusion and exclusion criteria were reflective of the population of interest for possible larger studies making our findings relevant to similar patients elsewhere and thus providing a degree of external validity. Patients were enrolled within 12 hours of a decision to start hemofiltration, a target that is clinically realistic and feasible and enabled an early effect if one was present. We included patients requiring vasopressor therapy due to various presumed etiologies, which reflects actual clinical practice as the treatment of shock states in critically ill patients remains similar irrespective of etiology, and there may be difficulty in differentiating etiology and mechanisms at the start of the critical illness (18). As such, although our patients had a degree of heterogeneity, this may be an advantage, as our findings have broad clinical relevance to critically ill patients requiring vasopressor therapy. We did not use physiologic variables such as MAP to compare the two groups as all patients received norepinephrine titrated to achieve a target MAP (e.g., 65 mm Hg). Our outcome measure reflects a comparison of the dose required to achieve this target between the two groups. We chose norepinephrine-free time rather than rate of norepinephrine infusion to effectively differentiate between patients who had norepinephrine ceased due to death from those who had norepinephrine ceased due to recovery. Our study carries some limitations. Sample size was small, although adequately powered for our primary outcome of interest and the largest sample size so far for the assessment of HCO filters. Thus, we cannot definitively comment on any possible mortality effects. However, within the limitations of a phase II study, the signal available is in favor of standard CVVH and does not support any beneficial effect of HCO-therapy on mortality and even suggests a potential for harm. We included a heterogeneous population of patients with vasoplegia, and not all patients had septic shock. However, a recent extensive review indicates that the biological high cytokine response to sepsis is likely similar to that associated with noninfective insults because damage-associated molecular patterns trigger essentially identical cellular responses as pathogen-associated molecular patterns (1). The baseline characteristics were not fully balanced, as is common with pilot studies, and this may have affected the results. Statistical adjustments, however, showed no differences in favor of HCO filtration. We did not use high volume exchanges. However, the recent hIgh VOlume in Intensive Care (IVOIRE) study (19) showed that such increased levels of dose intensity did not affect the outcomes of sepsis-associated vasodilatory shock. We did not collect data on fluid losses or other potential causes of differences in this regard; however, as this was a double-blind trial and treating physicians treated both cohorts according to standard management protocols in all other aspects of management, we believe there would not have been differences between the two study groups. The filter life for both groups was rather short. However, many of these patients were dramatically ill and had coagulopathies, whereas others had liver disease, both factors contributing to short filter life. Finally, we did not compare the effects of the two interventions on antibiotic levels. However, antibiotics are all relatively small molecules that will move freely across both filter types and would not be affected differently by CVVH-HCO versus CVVH-Std.

CONCLUSIONS

In conclusion, we found that treatment of critically ill patients with severe AKI receiving vasopressor support with HCO hemofiltration did not result in higher norepinephrine-free time at 1 week compared with patients treated with standard hemofiltration. Other secondary outcomes also showed no beneficial effects of HCO hemofiltration including the findings in our previous publication on the effects of HCO hemofiltration on cytokines level. Within the limitations of a pilot phase II trial, our study does not support further investigation of CVVH-HCO in critically patients in AKI who are on vasopressor therapy.

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