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Original Investigation

High-Dose Versus Conventional-Dose Continuous Venovenous Hemodiafiltration and Patient and Kidney Survival and Cytokine Removal in Sepsis-Associated Acute Kidney Injury: A Randomized Controlled Trial

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Background: Soluble inflammatory mediators are known to exacerbate sepsis-induced acute kidney injury (AKI). Continuous renal replacement therapy (CRRT) has been suggested to play a part in immunomodulation by cytokine removal. However, the effect of continuous venovenous hemodiafiltration (CVVHDF) dose on inflammatory cytokine removal and its influence on patient outcomes are not yet clear.

Study Design: Prospective, randomized, controlled, open-label trial.

Setting & Participants: Septic patients with AKI receiving CVVHDF for AKI.

Intervention: Conventional (40 mL/kg/h) and high (80 mL/kg/h) doses of CVVHDF for the duration of CRRT.

Outcomes: Patient and kidney survival at 28 and 90 days, circulating cytokine levels.

Results: 212 patients were randomly assigned into 2 groups. Mean age was 62.1 years, and 138 (65.1%) were men. Mean intervention durations were 5.4 and 6.2 days for the conventional- and high-dose groups, respectively. There were no differences in 28-day mortality (HR, 1.02; 95% CI, 0.73-1.43; $P = 0.9$) or 28-day kidney survival (HR, 0.96; 95% CI, 0.48-1.93; $P = 0.9$) between groups. High-dose CVVHDF, but not the conventional dose, significantly reduced interleukin 6 (IL-6), IL-8, IL-1b, and IL-10 levels. There were no differences in the development of electrolyte disturbances between the conventional- and high-dose groups.

Limitations: Small sample size. Only the predilution CVVHDF method was used and initiation criteria were not controlled.

Conclusions: High CVVHDF dose did not improve patient outcomes despite its significant influence on inflammatory cytokine removal. CRRT-induced immunomodulation may not be sufficient to influence clinical end points.

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INDEX WORDS: Sepsis; acute kidney injury (AKI); sepsis-induced AKI; continuous renal replacement therapy (CRRT); CRRT intensity; continuous venovenous hemodiafiltration (CVVHDF); CVVHDF dose; cytokine removal; interleukins; inflammatory cytokines; immunomodulation; systemic inflammatory response syndrome; randomized controlled trial.

Acute kidney injury (AKI) is a common and serious complication in critically ill patients.[1,2] The presence of AKI has a poor prognostic impact on morbidity and mortality in these patients, increasing the mortality rate to approximately 60% to 80%.[3-5] Sepsis is the most common cause of AKI, especially in patients admitted to the intensive care unit (ICU), accounting for >50% of AKI cases.[6,7]

Sepsis-induced AKI has been known to occur as a result of acute tubular necrosis due to decreased kidney perfusion caused by septic shock.[8,9] However, recent investigations have revealed that in addition to ischemic acute tubular necrosis, circulating pro- and anti-inflammatory cytokines, such as tumor necrosis factor α, interleukin 6 (IL-6), IL-8, and IL-10, play a key role in the pathogenesis of sepsis-induced AKI

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through the recruitment of inflammatory cells and induction of apoptosis in tubular cells.[10-12]

Continuous renal replacement therapy (CRRT) is an established core treatment modality for patients with AKI in ICUs. In addition to its advantage in maintaining hemodynamic stability through slow continuous ultrafiltration, current studies have proposed a role in immunomodulation by efficiently removing proinflammatory cytokines of medium molecular size through convection or adsorption.[13-17] Animal experiments have shown that hemodynamic recovery is most evident with high-volume convective treatments through increased removal of soluble inflammatory mediators.[18-21]

Because higher CRRT doses are expected to achieve more effective cytokine removal, an increase in CRRT dose may benefit clinical outcomes in patients with sepsis-induced AKI. Therefore, based on this concept, several clinical trials have been performed to confirm better survival rates at higher CRRT doses.[22-26] However, the effect of CRRT dose on immunomodulation and its clinical impact are not yet clear.

By conducting a prospective randomized controlled investigation, this study aimed to examine the effect of high CRRT intensity on inflammatory cytokine removal in addition to its influence on clinical outcomes.

METHODS

Study Setting

We conducted a prospective, randomized, controlled, open-label trial that assessed high and conventional doses of continuous venovenous hemodiafiltration (CVVHDF) in patients with septic AKI requiring CRRT support in the medical ICU of 2 large academic hospitals (Seoul National University Hospital and Severance Hospital in Yonsei University, Seoul, Korea). The study was conducted from January 2011 through August 2014. The study was approved by the institutional review boards of each participating study site and conducted in accordance with provisions of the Declaration of Helsinki (institutional review board approval numbers: Seoul National University Hospital, H1006-096-322; Severance Hospital at Yonsei University, 4-2010-0440). All patients were informed about the study and participated voluntarily after providing written consent.

Study Population

Participants were eligible for enrollment if they were critically ill adults 20 years or older who had AKI due to sepsis and required CRRT. Each case of sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference criteria.[27] If a patient had a suspected infection and coincidentally had 2 consecutive measurements corresponding to systemic inflammatory response syndrome criteria (body temperature $>$ 38°C or $<$35°C, heart rate $>$90 beats/min, respiratory rate $>$20 breaths/min, $Paco_2 < 32$ mm Hg, white blood cell count $> 12.0 \times 10^3/\mu L$ or $<4.0 \times 10^3/\mu L$, or $>$10% immature white blood cells), we diagnosed sepsis. Infection was diagnosed if the causative organisms were confirmed by culture studies or clinically suspected as follows: (1) white blood cells in normally sterile fluid, (2) perforated viscus, or (3) obvious evidence of infection from imaging tests. We included patients with AKI at a level greater than the injury stage according to the RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria, which was consistent with urine output $<$ 0.5 mL/kg/h over 12 hours or a more than 2-fold increase in serum creatinine level compared with baseline. Patients older than 80 years; with life expectancy less than 3 months, terminal cancer, Child-Pugh class C liver cirrhosis, or history of dialysis; and those who were pregnant or lactating prior to randomization were excluded. Participants were not included in the final analysis if their severe hypophosphatemia (serum phosphorus $<$ 3.5 mg/dL) or hypokalemia (serum potassium $<$ 3.5 mEq/L) was not corrected within 12 hours after first detection. Those who were hemodynamically unstable due to CRRT performance and those who withdrew consent during the study were also excluded.

Treatment Assignments

CVVHDF was initiated at the discretion of the consulting nephrologists without consideration of the patient's eligibility for this study. In general, CVVHDF was applied in patients with AKI at a level greater than the injury stage according to RIFLE criteria with severe acidemia (pH $<$ 7.2), uncontrolled hyperkalemia (potassium $>$ 6.5 mEq/L), or the presence of significant organ edema. CVVHDF therapies were delivered by the Gambro Prisma or Prisma Flex machines using ST100 (surface area, 1.0 m^2) filter sets, which contain a polyacrylonitrile AN 69 membrane (Gambro). For cases that required flow rates $>$ 2,000 mL/h, the Prisma Flex RRT machine was preferred; in other cases, either the Prisma or Prisma Flex RRT machine was used. Vascular access for CVVHDF was obtained by the insertion of a 14F double-lumen catheter into the femoral or internal jugular vein. Blood flow rate was initiated at 100 mL/min and gradually increased to 150 mL/min. Effluent volume was set to achieve a clearance of 40 mL/kg/h (conventional-dose group) or 80 mL/kg/h (high-dose group). The replacement and dialysate volumes were set using the 1:1 balanced-predilution method. Half the calculated total effluent volume was given as replacement Hemosol (Gambro), and the other half was administrated as dialysate. Only the Hemosol replacement fluid was administered intravenously through the predialyzer replacement pump. The dialysate remained outside the dialyzer membrane and was not given intravenously. Decisions regarding circuit anticoagulation (no anticoagulation, heparin, or nafamostat mesilate) and volume control were made by an experienced nephrologist. Patients remained on CVVHDF treatment until death, withdrawal of CVVHDF therapy as part of withdrawal of life support, achievement of sustained hemodynamic stability, change to conventional hemodialysis therapy, or kidney function recovery. The decision to wean patients from CVVHDF was made by the nephrologists when the patient was transferred from the ICU to the general ward or had recovered hemodynamic stability with considerable urine output. If the patient needed transition to intermittent hemodialysis therapy, the timing and dose of hemodialysis were dependent on the treating nephrologist's decisions.

Patients eligible for inclusion were informed of the study, and those who gave written consent were randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups by means of a centralized computer-generated adaptive randomization scheme at the time of CRRT initiation. Patients remained on the allocated CVVHDF prescription until CRRT discontinuation.

Measurements

We collected baseline demographic, clinical, and biochemical characteristics at the time of randomization. Disease severity was determined by Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE) II score. At the time of CVVHDF initiation, we evaluated vital signs and laboratory test results, including those from liver function tests, blood gas analyses, and lactic acid assessments.

End Points

The primary end point was death from any cause within 28 days after randomization. Secondary end points included death from any cause within 90 days after randomization, ICU death, and in-hospital death; ICU death and in-hospital death were defined as death during the time in the ICU or hospital stay regardless of time point. Renal survival at 28 and 90 days was also included as a secondary end point. Renal survival was represented as the proportion of survivors who did not require RRT at the indicated time point. Inflammatory cytokine removal rates were assessed additionally.

Sample Collection

Blood samples were obtained from patients whose legal representative allowed sample donation. Blood samples were collected in nonheparinized tubes from each patient before and 24 hours after the initiation of CVVHDF from the inlet and outlet ports of the CRRT filter. Samples were centrifuged at 2,000 *g* for 10 minutes at 4°C, divided into aliquots, and stored at −80°C until assayed.

Cytokine Measurement

Circulating serum cytokines and cytokines from the dialyzed inlet and outlet were measured. We measured IL-1b, IL-6, IL-8, and IL-10 with the Bio-Plex Pro system (Bio-Rad Laboratories), which essentially consists of immunoassays performed on magnetic beads. Samples were diluted 1:4 to measure IL-6 and IL-8, whereas samples were used undiluted to measure IL-1b and IL-10. The loading dose was 50 μL. Detection limits were 2.13 pg/mL for IL-1b, 1.23 pg/mL for IL-6, 1.89 pg/mL for IL-8, and 1.83 pg/mL for IL-10. Each sample was run in duplicate, and the mean cytokine concentration was calculated.

Sample Size Estimation

The sample size was selected on the basis of the following assumptions. Conventional-dose CVVHDF group mortality at 28 days was estimated to be 60%.[25] The study was designed to demonstrate a ≥ 20% reduction in mortality rate. For this purpose, we estimated that 88 participants would be required for each arm to detect a significant difference in primary outcome, with a 2-sided type I error of 0.05 and 80% power. We aimed to enroll at least 109 patients to allow for a dropout rate of 25%. A total of 212 incident CRRT patients were included in the final analysis (Fig 1).

Statistical Analysis

SAS software, version 9.1.3 (SAS Institute Inc), was used for statistical analysis. All data are expressed as mean ± standard deviation. A *t* test or Mann-Whitney *U* test was used for continuous variables, and χ^2 test was used for categorical variables. A univariate Cox proportional hazards analysis was performed to compare survival between the conventional- and high-dose CVVHDF groups at 28 and 90 days after randomization, as well as ICU death and in-hospital death. Survival among groups at 28 and 90 days was also compared using Kaplan-Meier analyses and Wilcoxon tests. To analyze renal survival at 28 and 90 days, χ^2 test was used. Linear mixed-model analyses were used to assess differences between time points, as well as between inlet and outlet data. Analyses of data were made by an independent statistician blinded to treatment assignment. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

From January 2011 through August 2014, a total of 212 patients were randomly assigned to a treatment group as follows: 107 to the conventional-dose CVVHDF group (effluent rate of 40 mL/kg/h) and 105 to the high-dose CRRT group (effluent rate of 80 mL/kg/h). As shown in Table 1, baseline characteristics were similar between the 2 groups. Mean age was 62.1 ± 13.1 (standard deviation) years, and 65.1% were men. More than one-quarter (27.4%) of the study sample had diabetes. Sepsis was attributed to gastrointestinal infections in 47.6% of patients. Mean APACHE II score was 28.7 ± 7.3, and mean

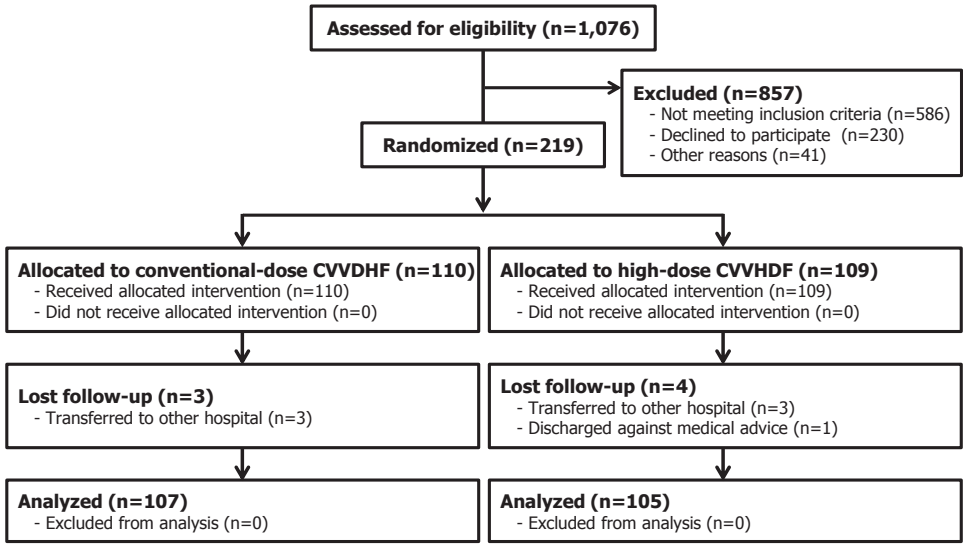

Figure 1. Flow diagram of study participants. From January 2011 to August 2014, a total of 1,076 patients who initiated continuous venovenous hemodiafiltration (CVVHDF) at Seoul National University Hospital or Severance Hospital in Yonsei University in Korea were initially recruited for this prospective, randomized, controlled, open-label trial. According to inclusion and exclusion criteria, 212 patients were included in the final analysis.

Table 1. Baseline Clinical Characteristics and Biochemical Variables of Study Patients

Variables	Conventional Dose (n = 107)	High Dose (n = 105)	*P*
Age, y	61.9 ± 12.8	62.3 ± 13.4	0.8
Male sex	76 (71.0)	62 (59.0)	0.07
Body mass index, kg/m^2	23.6 ± 4.5	22.5 ± 3.9	0.06
Body weight, kg	62.4 ± 13.1	59.9 ± 11.1	0.09
Comorbid diseases			
Diabetes mellitus	31 (29.2)	27 (25.7)	0.6
Hypertension	46 (43.0)	54 (51.4)	0.2
COPD	7 (6.5)	5 (4.8)	0.6
Ischemic heart disease	8 (7.5)	5 (4.8)	0.4
Type of infection			0.8
Unknown	1 (0.9)	2 (1.9)	
Gastrointestinal	32 (34.6)	69 (30.5)	
Respiratory	47 (43.9)	44 (41.9)	
Genitourinary	3 (2.8)	7 (6.7)	
Neurologic	1 (0.9)	1 (1.0)	
Others	18 (16.8)	19 (18.1)	
Mechanical ventilation	88 (82.2)	89 (84.8)	0.6
Inotropic support	98 (91.6)	92 (87.6)	0.3
APACHE II score	28.9 ± 7.9	28.6 ± 6.6	0.7
SOFA score	14.2 ± 3.1	14.2 ± 3.1	0.9
eGFR, mL/min/1.73 m^2			
Preadmission	75.7 ± 52.8	71.4 ± 33.7	0.5
At randomization	25.8 ± 14.1	26.9 ± 28.4	0.7
Urine output for 2 h before CVVHDF initiation, mL	29.6 ± 56.0	26.5 ± 59.4	0.7
Mean arterial pressure, mm Hg	78.8 ± 14.5	79.1 ± 14.7	0.9
Biochemical parameters			
White blood cells, /μL	14,361 ± 12,689	12,807 ± 10,585	0.3
Hemoglobin, g/dL	9.4 ± 2.1	9.5 ± 1.8	0.6
Serum urea nitrogen, mg/dL	62.4 ± 31.3	62.3 ± 33.8	0.9
Creatinine, mg/dL	3.1 ± 1.8	3.1 ± 1.7	0.8
Albumin, g/dL	2.5 ± 0.5	2.4 ± 0.6	0.2
hs-CRP, mg/dL	20.1 [1.4-300.0]	19.1 [1.3-447.9]	0.9
pH	7.3 ± 0.1	7.3 ± 0.1	0.8
Lactate, mmol/L	4.2 ± 5.1	4.1 ± 5.2	0.9
Serum cytokine levels			
IL-6, pg/mL	4,666.2 ± 1,024.1	6,515.6 ± 1,091.7	0.2
IL-8, pg/mL	702.3 ± 209.4	1,117.6 ± 223.2	0.2
IL-1b, pg/mL	29.0 ± 13.5	40.3 ± 14.4	0.6
IL-10, pg/mL	859.2 ± 237.6	667.3 ± 253.3	0.6
CVVHDF dose and flow rates			
Blood flow rate, mL/min	125.6 ± 15.6	148.8 ± 5.9	<0.001
Dialysate rate, mL/h	1,327.1 ± 308.4	2,350.0 ± 320.9	<0.001
Replacement fluid rate, mL/h	1,272.9 ± 294.7	2,166.0 ± 311.4	<0.001
Observed effluent rate, mL/kg/h	34.3 ± 6.4	75.1 ± 12.4	<0.001
Total CVVHDF duration, d	5.4 ± 4.4	6.2 ± 4.5	0.4

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range]. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; serum urea nitrogen in mg/dL to mmol/L, ×0.357.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CVVHDF, continuous venovenous hemodiafiltration; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; SOFA, Sequential Organ Failure Assessment.

overall SOFA score was 14.2 ± 3.1. Overall, 83.5% of patients required mechanical ventilation. Mean serum creatinine level before AKI onset was 1.2 ± 0.8 mg/dL, and mean estimated glomerular filtration rate was 73.7 ± 44.6 mL/min/1.73 m^2. Serum IL-6, IL-8, IL-1b, and IL-10 concentrations were comparable between the groups (Table S1, available as online supplementary material).

Mean duration of the CVVHDF intervention was 5.4 (95% confidence interval [CI], 4.1-6.8) days for the conventional-dose CVVHDF group and 6.2 (95% CI, 4.9-7.6) days for the high-dose CVVHDF group ($P = 0.4$). Mean effluent rates measured during the first 24 hours of CVVHDF initiation were 34.3 ± 6.4 mL/kg/h for the conventional-dose group and 75.1 ± 12.4 mL/kg/h for the high-dose group ($P < 0.001$; Table 1).

CVVHDF Dosage and Patient Outcomes

Overall, 69 of the 107 (64.5%) patients in the conventional-dose group died within 28 days of randomization compared with 69 of 105 (65.7%) patients in the high-dose group. By day 90, a total of 80 (74.8%) patients died in the conventional-dose group compared with 82 (78.1%) in the high-dose group. Survival rates at 28 ($P = 0.5$) and 90 days ($P = 0.6$) after randomization did not significantly differ between the treatment groups (Fig 2).

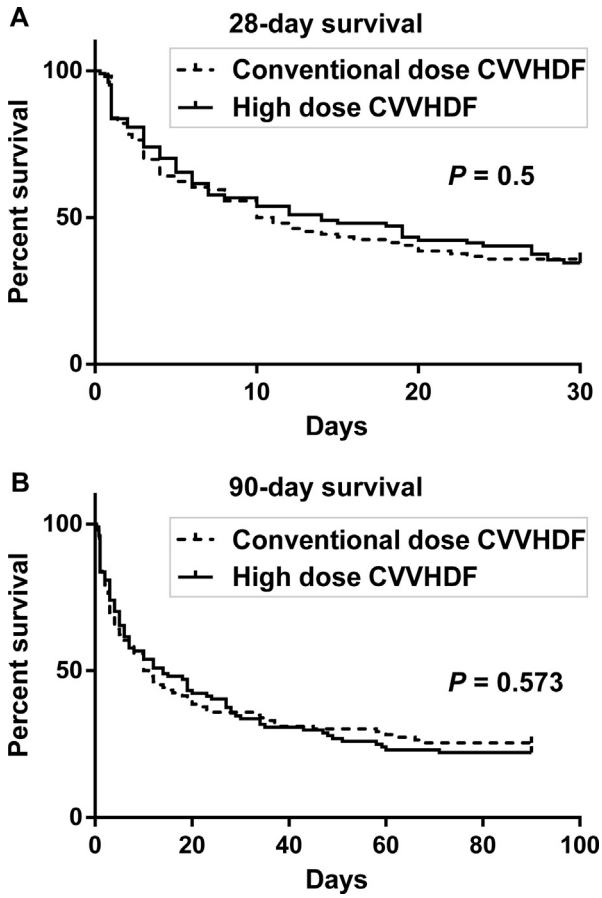

Figure 2. Kaplan-Meier curves showing patient survival according to continuous venovenous hemodiafiltration (CVVHDF) dose. The (A) 28-day ($P = 0.5$) and (B) 90-day ($P = 0.6$) survival rates were comparable between patients randomly assigned to receive conventional- and high-dose CVVHDF. Wilcoxon tests were used for comparison between groups. Abbreviation: IL-6, interleukin 6.

High-dose CVVHDF application did not significantly improve 28-day (hazard ratio [HR], 1.02; 95% CI, 0.73-1.43; $P = 0.9$) or 90-day (HR, 0.98; 95% CI, 0.72-1.34; $P = 0.9$) survival. Similarly, the high-dose group did not show a difference in ICU death (HR, 1.18; 95% CI, 0.85-1.65; $P = 0.3$) or in-hospital death (HR, 1.06; 95% CI, 0.78-1.44; $P = 0.7$) compared with patients in the conventional-dose CVVHDF group (Table 2).

Lengths of the ICU stay or total hospital stay among survivors were not statistically significant between the conventional- and high-dose groups. There were no differences in recovery of kidney function at 28 or 90 days after randomization between treatment arms (Table 3).

Adverse Events

There were no differences in the occurrence of severe adverse events regarding electrolyte balances. Serum potassium ($P = 0.5$), phosphate ($P = 0.2$), and magnesium ($P = 0.1$) levels were comparable between the conventional- and high-dose groups after 24 hours of CVVHDF. There was a higher trend of patients who had hypokalemia or hypophosphatemia. However, the number of patients requiring potassium or phosphate supplementation did not significantly differ between study groups (Table 4).

Effect of CRRT Dose on Cytokine Removal

To evaluate the effect of CVVHDF dose on the amount of cytokine removal, cytokines were measured from the dialyzer inlet and outlet at the time of CVVHDF initiation. IL-6, IL-8, IL-1b, and IL-10 levels measured at the dialyzer inlet or outlet did not differ between the conventional- and high-dose CVVHDF groups. However, when cytokine levels were compared between dialyzer inlet and outlet, outlet IL-6, IL-8, IL-1b, and IL-10 concentrations

Table 2. Univariate Cox Regression Analysis of CVVHDF Doses on Patient Survival at 28 and 90 Days

	HR (95% CI)	*P*
Patient survival		
28-d mortality	1.02 (0.73-1.43)	0.9
90-d mortality	0.98 (0.72-1.34)	0.9
ICU death	1.18 (0.85-1.65)	0.3
In-hospital death	1.06 (0.78-1.44)	0.7
Kidney survival		
28-d	0.96 (0.48-1.93)	0.9
90-d	0.94 (0.46-1.90)	0.9

Note: HRs are for high-dose versus conventional-dose CVVHDF.

Abbreviations: CI, confidence interval; CVVHDF, continuous venovenous hemodiafiltration; HR, hazard ratio; ICU, intensive care unit.

Table 3. Effect of CVVHDF Doses on Patient and Kidney Disease Outcomes

Variables	Conventional Dose (n = 107)	High Dose (n = 105)	*P*
Length of ICU stay, d	11.5 ± 10.9	18.2 ± 16.6	0.05
Length of hospital stay, d	38.8 ± 32.7	59.3 ± 45.2	0.08
Non-dialysis-dependent at day 28	13/38 (34.2)	13/36 (36.1)	0.9
Non-dialysis-dependent at day 90	2/27 (7.4)	0/23 (0.0)	0.1

Note: Values are given as n/N (percentage) or as mean ± standard deviation.

Abbreviations: CVVHDF, continuous venovenous hemodiafiltration; ICU, intensive care unit.

were significantly lower than inlet concentrations in the high-dose CVVHDF group. This decrease in outlet cytokine level was not observed in the conventional CVVHDF dose group (Fig 3).

Circulating cytokines were measured at the time of CVVHDF initiation and after 24 hours to investigate whether CRRT-induced cytokine removal has an influence on systemic cytokine concentrations. Serum cytokine levels measured at baseline or 24 hours after CVVHDF initiation did not differ between patients receiving conventional- or high-dose CVVHDF. However, when serum cytokine levels were compared between baseline and after 24 hours of CVVHDF treatment, IL-6 and IL-8 levels were significantly decreased at 24 hours compared to baseline in the high-dose group. These declines in IL-6 and IL-8 levels were not observed in the conventional-dose group (Fig 4).

Changes in cytokine levels between the inlet and outlet were significantly larger in the high-dose group compared to the conventional-dose group for IL-6 ($P < 0.001$), IL-8 ($P = 0.03$), and IL-10 ($P = 0.04$). However, when changes in cytokine levels between baseline and 24 hours after CVVHDF initiation were compared, only IL-6 levels ($P = 0.03$) showed a clear difference in the amount of cytokine change between groups. The change in IL-8 levels ($P = 0.05$) tended to be larger in the high-dose CVVHDF group (Fig S1).

Table 4. Comparison of Adverse Events Between Study Patients

Variables	Conventional Dose (n = 107)	High Dose (n = 105)	*P*
Baseline serum levels			
Potassium, mEq/L	4.4 ± 1.0	4.5 ± 0.9	0.5
Phosphate, mg/dL	5.6 ± 2.8	5.4 ± 2.2	0.5
Magnesium, mg/dL[a]	1.4 ± 0.3	1.4 ± 0.3	0.9
Serum levels after 24-h CVVHDF			
Potassium, mEq/L	3.9 ± 0.7	3.8 ± 0.8	0.5
Phosphate, mg/dL	4.1 ± 1.5	3.8 ± 1.9	0.2
Magnesium, mg/dL[a]	1.5 ± 0.4	1.4 ± 0.3	0.1
Patients with complications after 24-h CVVHDF			
Potassium < 3.0 mEq/L	4 (4.3)	9 (9.9)	0.1
Phosphate < 2.5 mg/dL	14 (15.1)	21 (23.3)	0.2
Patients requiring replacement			
Potassium	76 (81.7)	76 (84.4)	0.8
Phosphate	9 (9.7)	15 (16.7)	0.2

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation.

Abbreviation: CVVHDF, continuous venovenous hemodiafiltration.

[a]Magnesium levels were evaluated in 90 patients for whom data were available.

DISCUSSION

In the present study, high-dose CVVHDF (80 mL/kg/h) improved removal of some serum cytokines compared with conventional-dose CVVHDF (40 mL/kg/h) in ICU patients with sepsis-induced AKI. However, a high dose did not result in a survival advantage over the conventional dose.

Recent clinical trials have proposed optimal doses for CRRT. However, most of these prior investigations have been performed in patients with AKI of mixed causes.[22,23,25,28] In this study, the impact of CRRT dose on serum cytokine modulation and patient outcomes was evaluated in a population exclusively composed of patients with sepsis-induced AKI. Although Ronco et al[25] reported an increase in survival when the CRRT dose was increased from 20 to 45 mL/kg/h in patients with AKI requiring RRT, recent large-scale randomized controlled trials did not show an improvement in patient outcomes with higher CRRT doses.[22,23] Experimental models have proposed possible benefits associated with higher CRRT dose by increasing the removal of soluble inflammatory mediators, including cytokines that are increased under septic conditions.[29-32] Accordingly, CRRT dose would more likely benefit patients with sepsis-induced AKI. Although subgroup analyses of patients with sepsis have not shown benefit of an increased RRT dose in recent trials, a recent post hoc analysis of the RENAL (Randomized Evaluation of Normal Versus Augmented Level) Replacement Therapy Study showed that mean arterial pressure and vasopressor requirement were improved with higher intensity RRT in patients with metabolic acidosis, suggesting a possibility of high-dose RRT benefit in selected populations.[33]

The possibilities of increasing the clearance of soluble inflammatory mediators through higher RRT intensity have been proposed previously.[13-17] However, the effect of CRRT dose on cytokine removal

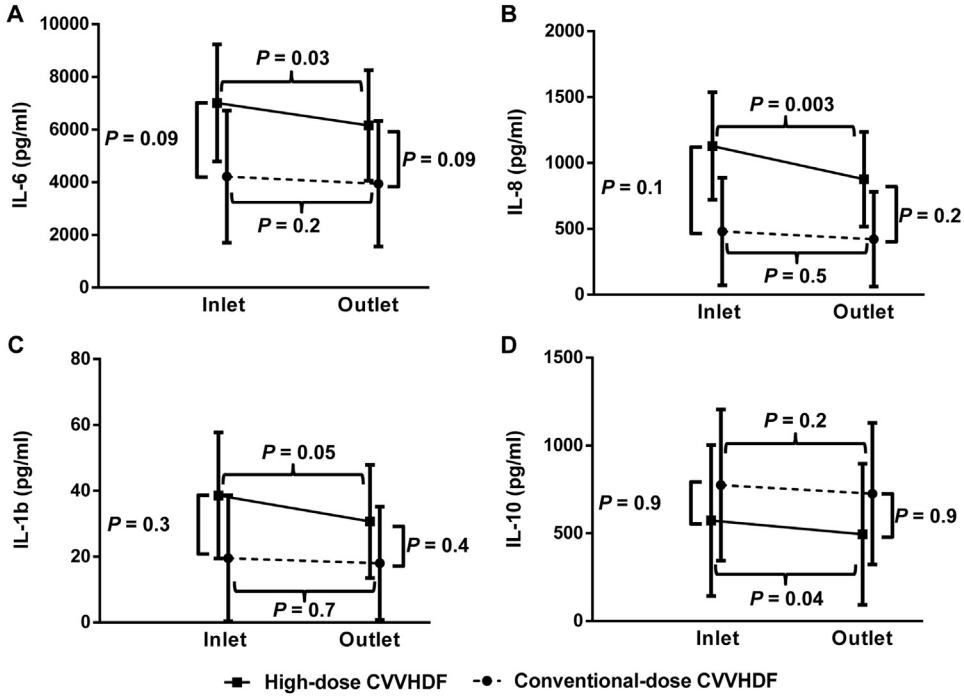

Figure 3. Circulating cytokine levels measured at the dialyzer inlet and outlet at the time of continuous venovenous hemodiafiltration (CVVHDF) initiation. Circulating mean (A) interleukin 6 (IL-6; $P = 0.03$), (B) IL-8 ($P = 0.003$), (C) IL-1b ($P = 0.05$), and (D) IL-10 ($P = 0.04$) levels were significantly reduced in the outlet compared with the inlet in patients treated with high-dose CVVHDF. However, these reductions in cytokine levels were not found in patients treated with conventional-dose CVVHDF. Circulating mean levels of (A) IL-6, (B) IL-8, (C) IL-1b, and (D) IL-10 measured at the dialyzer inlet and outlet at the time of CVVHDF initiation did not differ between the arms. Error bars denote standard errors.

has not been evaluated through randomized clinical trials. In this study, circulating IL-6, IL-8, IL-1b, and IL-10 levels from the dialyzer outlet showed a significant decrease compared with those from inlet samples in patients treated with high-dose CVVHDF. This may imply that circulating cytokines were more efficiently removed when CVVHDF was applied at a dose higher than that administered under standard care. The serum inflammatory cytokine levels evaluated in this study were somewhat higher compared with recent reports investigating cytokine levels in septic patients with AKI.[34,35] These findings could suggest that patients enrolled in the current study were more severely ill compared with previous investigations. The facts that the survival rate was lower and hospital stay durations were longer in this study further support this possibility.

Although high-dose CVVHDF seemed to be more efficient in removing some inflammatory cytokines, it did not show an advantage in improving patient outcomes in this study. One explanation for these results could be that CRRT-dependent cytokine clearance could have been trivial compared to the amount endogenously generated. Another could be that results of the cytokine level reductions were only for the initial 24 hours of CVVHDF and the effect of persistent cytokine production thereafter was not taken into account. The clinical outcome of the patients would have been more likely dependent on the progress of infection affecting the duration and amount of cytokine production than the brief attenuation of several cytokines. The possibility that the 2 study groups were not identical regarding inflammatory status may be worth considering also. Although not statistically significant, several inflammatory cytokines had nominally higher concentrations at baseline in the high-dose CVVHDF group, which is consistent with trends found in lengths of ICU and hospital stays. The possible difference in baseline characteristics, which may have been attributed to the relatively small sample size of the study, could have affected results of the primary outcome.

The conventional dose of the present study was prescribed based on results of recent trials.[22,23] However, adjustments were made for predilution, assuming the clearance would be 70% to 80% based on a previous report.[36] In addition, modifications were made for filter downtime resulting in a prescribed CVVHDF dose of 40 mL/kg/h for the conventional-dose group. Accordingly, the observed effluent rate for the conventional-dose group was 34.3 ± 6.4 mL/kg/h, which met the target dose of 25 mL/kg/h after adjusting for predilution-related efficiency reduction.

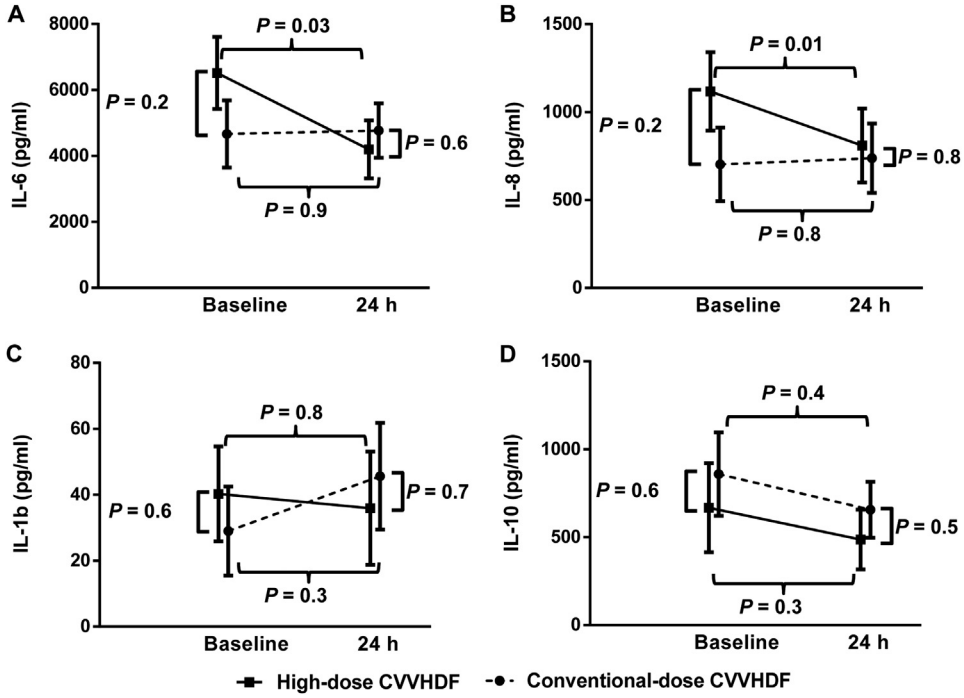

Figure 4. Serum cytokine levels measured at the time of continuous venovenous hemodiafiltration (CVVHDF) initiation and after 24 hours. Mean serum (A) interleukin 6 (IL-6; $P = 0.03$) and (B) IL-8 ($P = 0.01$) levels were significantly reduced 24 hours after CVVHDF initiation compared to baseline in patients treated with high-dose CVVHDF. However, these reductions in IL-6 and IL-8 levels were not found in patients who received conventional-dose CVVHDF. (C) IL-1b and (D) IL-10 levels were comparable between baseline and 24 hours after CVVHDF initiation in both the conventional- and high-dose CVVHDF groups. Mean serum (A) IL-6, (B) IL-8, (C) IL-1b, and (D) IL-10 measured at baseline or 24 hours after CVVHDF initiation did not differ between patients receiving conventional- and high-dose CVVHDF. Error bars denote standard errors.

Although the consulting nephrologists' decisions for initiating CVVHDF were fairly similar, the exact timing of CVVHDF therapy initiation could have varied among patients because CVVHDF initiation criteria were relatively broad. However, considering that urine output at the time of CVVHDF initiation was comparable between the study groups, CVVHDF therapy initiation timing did not differ between the study groups. In addition, because baseline disease severity scores and high-sensitivity C-reactive protein levels were also comparable between the study groups, it could be surmised that CVVHDF therapy was initiated at a similar state of sepsis progression. Although the timing of CVVHDF therapy initiation did not differ between study groups, it seemed to have an effect on patient outcome. When the relationship between urine output at the time of CVVHDF therapy initiation and patient outcome was evaluated, patients who initiated CVVHDF therapy with more urine volume were more likely to survive at 28 and 90 days after CVVHDF therapy initiation (Table S2). This could imply that the benefit of CRRT-induced immunomodulation could be related more to timing of initiation than dose.

Complications such as hypokalemia and hypophosphatemia are common concerns regarding higher CRRT dose applications. In this study, a protocolized replacement method was applied for the management of CRRT-related hypokalemia and hypophosphatemia. Although patients in the high-dose CVVHDF group tended to have hypokalemia and hypophosphatemia more frequently, the incidence of severe electrolyte-related complications did not increase in patients treated with a higher CVVHDF dose. The concern regarding underdosing of antibiotics in higher dose CRRT patients should also be recognized. Studies have identified increased antibiotic clearance in higher CRRT doses and have suggested possibilities of higher mortality due to antimicrobial treatment failure.[26,37] However, empirical antibiotic prescriptions that have taken CRRT clearance into account have been found to be complicated.[38] Nonetheless, antibiotic compounds having sieving coefficients close to 1.0 were encouraged to be used at a higher than usual dose in the high-dose CVVHDF group in this study in order to lessen the possibilities of underdosing.

There are several limitations to this study. The predilution method used in these patients could have lowered the clearance rate. However, because postdilution has its own disadvantages, such as shortening the filter life and increasing CRRT downtime,[39] the fact that both

treatment arms were given the same CVVHDF regimen enables direct comparison of the effect of the CVVHDF dose. In addition, the study could have been underpowered for the clinical outcomes due to the relatively small number of participants.

In conclusion, a high CVVHDF dose increases the clearance of some inflammatory cytokines, but does not improve patient outcomes compared with the conventional CVVHDF dose in patients with sepsis-induced AKI requiring RRT.

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Contributions: Research idea and study design: DKK, T-HY; data acquisition: JTP, HL, YKK, SP; data analysis/interpretation: JTP, HL, DKK, T-HY; statistical analysis: HJO; supervision or mentorship: SHH, KWJ, C-SL, YSK, S-WK. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. DKK and THY take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Comparison of baseline serum cytokine levels of study patients.

Table S2: Cox regression analysis of urine output for 2 h before CVVHDF initiation on 28- and 90-d survival.

Figure S1: Comparison of changes in cytokine levels between conventional- and high-dose CVVHDF.

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