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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.