Journal of Critical Care 35 (2016) 51–56

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Renal

Can early initiation of continuous renal replacement therapy improve patient survival with septic acute kidney injury when enrolled in early goal-directed therapy?

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ARTICLE INFO

Keywords:
Sepsis
EGDT
AKI
Early CRRT
28-Day mortality

ABSTRACT

Purpose: The purpose of our study was to investigate the timing of continuous renal replacement therapy (CRRT) application, based on the interval between the start of early goal-directed therapy (EGDT) and CRRT initiation, to ascertain whether the timing was an independent predictor of mortality in patients with septic acute kidney injury (AKI).
Materials and methods: An observational retrospective cohort study was conducted of 60 patients (>18 years old) who had been admitted to the emergency department and received resuscitation according to the standard EGDT algorithm for severe sepsis and septic shock, and who were treated with CRRT due to septic AKI, between June 2008 and February 2013 at a tertiary hospital in Seoul, Korea. The patients were divided into 2 groups based on the median interval between the start of EGDT and the commencement of CRRT. The main outcome was 28-day all-cause mortality, and a multivariate Cox analysis for mortality was used to evaluate the independent impact of the early CRRT treatment.
Results: The mean patient age was 66.3 years, and 52 (86.7%) were male. The most common comorbid disease was diabetes mellitus (35.0%) followed by malignancy (26.7%). The median interval between the start of EGDT and commencement of CRRT was 26.4 hours. During the study period, 28-day mortality was 43.3% (26 of 60 patients). The 28-day all-cause mortality rate was significantly higher in the late CRRT group than in the early CRRT group (56.7 vs 30.0%, $P = .037$). Furthermore, the higher mortality risk in the late group remained significant even after adjusting for diabetes mellitus, liver failure, and Acute Physiology and Chronic Health Evaluation II scores (hazard ratio, 2.461; 95% confidence interval, 1.044-5.800; $P = .026$).
Conclusion: Early initiation of CRRT may be of benefit. Given the complex nature of this intervention and the ongoing controversy regarding early vs late initiation of therapy in acute and chronic situations, it is vital to develop accurate clinical trials to find definitive answers.

1. Introduction

Severe sepsis, defined as sepsis associated with multiple organ dysfunction, remains a leading cause of admission to the intensive care unit (ICU) and is associated with a high mortality rate despite advances in critical care management [1,2]. Acute kidney injury (AKI) frequently occurs during the course of ICU treatment, with sepsis being the cause of approximately 50% of new-onset AKI in patients in the ICU [3]. Moreover, evidence indicates that AKI accompanied by sepsis increases the risk of mortality in critically ill patients [4].

Although continuous renal replacement therapy (CRRT) is a well-known treatment for AKI and the technical advances for CRRT treatment have been performed [5–8], the mortality rate among these patients still remains extremely high. Until now, it has been considered to result from the difficulty in not only treating AKI patients but also managing the extracorporeal systems, such as effective management of the CRRT [6,9,10]. Recently, several studies showed that early CRRT treatment can be associated with improving clinical outcomes. Moreover, we checked the reference and corrected proper references [11–14]. However, the definition of *early* in terms of CRRT initiation has not been uniformly described [11,13], with some studies describing it as

All authors have contributed significantly, and they are in agreement with the content of the manuscript. Conception/design: HJO, NSK; provision of study materials: all authors; collection and/or assembly of data: all authors; data analysis and interpretation: all authors; manuscript writing: all authors; final approval of manuscript: all authors.

The authors have no conflicts of interest to disclose.

The authors declare no financial disclosures.

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http://dx.doi.org/10.1016/j.jcrc.2016.04.032
0883-9441/

commencing CRRT at the "risk" or "injury" stage of the Risk, Injury, Failure, Loss, and End-stage Kidney classification, others basing it on the time interval between the initiation of CRRT and admission to the ICU [15], and still others basing it on the median values of blood urea nitrogen (BUN) [11,16,17] or serum creatinine levels [18]. The effects of the timing of CRRT initiation on clinical outcomes of sepsis patients remain controversial. Therefore, we studied AKI patients with sepsis admitted to the emergency department (ED) who received resuscitation according to the standard early goal-directed therapy (EGDT) algorithm for severe sepsis and septic shock to clarify whether the timing of applying CRRT, based on the interval between the start time of EGDT and CRRT initiation, is an independent predictor of mortality in critically ill patients with septic AKI.

2. Materials and methods

2.1. Ethics statement

The study was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center. Because the study was retrospective and the study subjects were anonymized, the Institutional Review Board waived the requirement for written consent from the patients.

2.2. Study population

Eligible adult patients who were admitted to the ED and who had received CRRT treatment for septic AKI between June 2008 and February 2013 were assessed for possible enrollment according to the inclusion and exclusion criteria (Fig. 1). Since November 2007, EGDT has been implemented at the ICU and ED at our institute as part of a quality-improvement initiative. Patient eligibility for EGDT was assessed if they presented with 2 or more systemic inflammatory response syndrome (SIRS) criteria and were suspected of having an infection. One or both of the following triggered initiation of the EGDT protocol: initial systolic blood pressure less than 90 mm Hg despite a 20-mL/kg intravenous crystalloid fluid challenge and/or initial serum lactate level greater than or equal to 4 mmol/L. The criteria for exclusion included the following: age less than 18 years, any contraindication to central venous catheterization, and/or the presence of a do-not-resuscitate (DNR) order. The resuscitation team composed of emergency medicine specialist, physician, and anesthesiologist followed the protocol outlined in Surviving Sepsis Campaign management guidelines [19]. The team promptly placed central venous catheter to monitor pressure and central venous oxygen saturation and to administer intravenous fluids, vasopressor, or packed red cell transfusions. The protocol in our study specified crystalloid as resuscitative fluid and specified norepinephrine as vasopressor. We resuscitated patients up to 6 hours after enrollment and evaluated whether the goal was achieved (Supplemental Fig. 1 in the online version at http://dx.doi.org/10.1016/j.jcrc.2016.04.032). All other aspects of care were given at the discretion of treating physician.

For SIRS [20], at least 2 of the following criteria were required: a core temperature greater than or equal to 38°C or less than or equal to 36°C, heart rate greater than or equal to 90 beats per minute, respiratory rate greater than or equal to 20 breaths per minute, pco_2 less than or equal to 32 mm Hg or using a mechanical ventilator, and a peripheral leukocyte count greater than or equal to 12,000/mm^3 or less than or equal to 4000/mm^3. For renal dysfunction [20], the criterion was a urinary output less than or equal to 700 mL/d in a patient not previously undergoing hemodialysis for chronic renal failure. For septic AKI, the criteria were SIRS combined with an infectious episode and renal dysfunction. Moreover, *severe sepsis* was defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension. Hypoperfusion abnormalities included lactic acidosis, oliguria, and acute changes in mental status. *Septic shock* was defined as sepsis with hypotension despite adequate fluid resuscitation. *Hypotension* was defined as a systolic blood pressure of 90 mm Hg or less, or a reduction of greater than 40 mm Hg from the baseline in the absence of other causes of low blood pressure [21]. Furthermore, *liver failure* was defined as total bilirubin greater than 4 mg/dL and a 3-fold higher level of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) than the upper normal limit (35 IU/L) [22], and *heart failure* was defined as left ventricular systolic dysfunction (left ventricular ejection fraction of 40% or less) on a transthoracic echocardiography [23]. We prescribed empirical antibiotics to these patients within first 1 hour according to the EGDT protocol (Supplemental digital table in the online version at

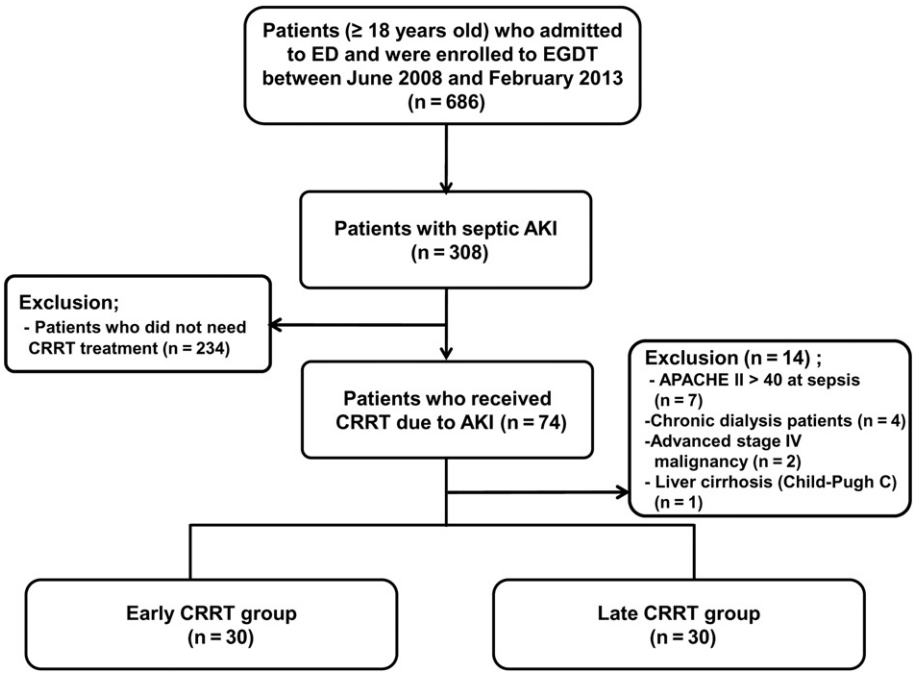

Fig. 1. Study selection diagram. From June 2008 to February 2013, 686 patients who were enrolled for EGDT were recruited, and 60 patients who received CRRT treatment for AKI were analyzed in the final results. These patients were divided into 2 groups based on the median value of the interval between the time of EGDT enrollment and the time of CRRT initiation.