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Continuous Renal Replacement Therapy Improves Septic Shock in Patients Unresponsive to Early Goal-Directed Therapy

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Abstract

Background: Early goal-directed therapy (EGDT) has been shown to improve patient outcomes. Treatment of patients unresponsive to the protocol, however, is difficult and the result is occasionally fatal. Recently, continuous renal replacement therapy (CRRT) has been used to treat acute kidney injury (AKI) to improve survival. We examined the effectiveness of CRRT in treating septic shock patients with concurrent AKI who are not amenable to EGDT.

Methods: We studied 17 patients who underwent emergency surgery for intra-abdominal infection; these patients experienced AKI complications and did not respond to EGDT within 6 hrs after intensive care unit (ICU) admission. We treated patients with continuous venovenous hemodiafiltration (CVVHDF; dialysis = 900 ml/hr, filtration = 900 ml/hr, total hemopurification = 1800 ml/hr). We measured mean arterial pressure (MAP), central venous pressure (CVP), central venous oxygen saturation ($ScvO_2$), catecholamine index (CAI), and determined serum concentrations of lactate, interleukin-6 (IL-6), and high mobility group box-1 protein (HMGB-1) immediately before and 3, 6, 12, 24, 48 hrs after CRRT initiation. We also evaluated 28-day survival, ICU survival, and hospital survival.

Results: CRRT duration was 6.5±4.2 days. MAP and $ScvO_2$ significantly increased with CRRT, while CAI and concentrations of lactate, IL-6, and HMGB-1 significantly decreased. After CRRT, no patients required intermittent hemodialysis in the ICU. Mean ICU stay was 15.1±10.4 days. ICU survival, 28-day survival, and hospital survival were 76.5%, 76.5%, and 70.6%, respectively.

Conclusions: CRRT may be an effective treatment for seriously ill patients who have complications of AKI and are unresponsive to EGDT.

Keywords: Early goal-directed therapy; Septic shock; Continuous renal replacement therapy (CRRT)

Introduction

Septic shock is associated with poor prognosis and can lead to multiple organ failure for reasons such as tissue hypoxia. To prevent progression to organ failure, aggressive treatment at an early stage is needed as soon as a diagnosis can be established [1]. To improve the efficacy of treatments for severe sepsis and septic shock, the Surviving Sepsis Campaign Guidelines (SSCG) were recently developed [2]. Among the treatments recommended by SSCG, early goal-directed therapy (EGDT) has been shown to improve survival rates of septic shock patients in a randomized study carried out at a single institution [3]. In EGDT, fluid resuscitation helps increase the central venous pressure (CVP) of patients. However, in some cases, maintaining mean arterial pressure (MAP) by vasoconstrictors is difficult, preventing use of the EDGT protocol. Moreover, some patients develop complications of acute kidney injury (AKI), which makes treatment of concurrent sepsis difficult. How can we save the lives of these patients [4]?

Hemopurification is used to treat AKI. SSCG suggests continuous renal replacement therapy (CRRT) to be used for patients with severe sepsis and acute renal failure to manage the body fluid balance of these unstable patients. Several studies have reported improved hemodynamics and prognosis by using a high flow rate for the hemopurification process [5-8]. However, other studies reported that increasing the flow rate did not influence prognosis [9,10].

Shock associated with sepsis and the onset of organ damage involves overexpression of inflammatory mediators [11]. The cytokine interleukin-6 (IL-6) and the nuclear protein high mobility group box 1 (HMGB-1) exacerbate organ damage as circulation suppressors or inflammation enhancers [12-15]. Controlling these mediators is an important part of treating sepsis.

In the present study, we performed CRRT in septic shock patients who had concurrent complications of AKI and were not responsive to EGDT. We also measured serum levels of IL-6 and HMGB-1 to evaluate their role in septic shock.

Materials and Methods

Patients

The subjects of this study were 17 patients who underwent emergency surgery for intra-abdominal infection at the Oita University Hospital Surgery Unit between April 2007 and March 2010. After surgery, these patients were admitted to the intensive care unit (ICU) with septic shock; however, the goals of EGDT were not met within 6 hours of entering the ICU and the patients developed complications of AKI. The definition of septic shock was based on that of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [16]. AKI was defined by the Risk Injury Failure Loss End-stage (RIFLE) kidney disease classification [17].

Immediately after entering the ICU, patients were treated with

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the EGDT protocol, and CVP increased due to fluid resuscitation. Total catecholamine dosage corresponded to a catecholamine index (CAI) [18] of 5 or more; CAI = (dopamine dose) + (dobutamine dose) + (epinephrine dose × 100) + (norepinephrine dose × 100) + (phenylephrine dose × 100). The subjects of this study were patients who did not respond to EGDT within 6 hrs, because of difficulties in maintaining MAP, and who met the diagnostic standard of AKI. We excluded patients younger than 18 years, pregnant women, patients with chronic renal damage, and patients using steroids or immunosuppressants. We obtained approval from the ethics committee of our institution. Written informed consent was obtained from each patient or his/her proxy prior to study enrollment.

Hemodynamic monitoring and initial management of circulation failure

Immediately after the patients entered the ICU, we initiated continuous monitoring of MAP, CVP, and central venous oxygen saturation ($ScvO_2$) using a 8.5-French central venous oximetry catheter (PreSep, Edwards Lifesciences, Irvine, CA, USA).

Treatment goals of the EGDT protocol were: CVP = 8–12 mm Hg, MAP = 65–90 mm Hg, and $ScvO_2$ >70%. First fluid therapy was conducted until CVP reached 8–12 mm Hg (500–1000 ml crystalloid fluid or 300–500 ml colloidal fluid for 30 min). If MAP did not reach the goal even with appropriate fluid therapy, we administered vasoconstrictors such as dopamine or norepinephrine. If $ScvO_2$ did not exceed 70%, we transfused red blood cells aiming at >30% hematocrit level or administered positive inotropic agonists such as dobutamine.

Continuous renal replacement therapy

Vascular access was obtained by cannulation with a 12-French triple-lumen catheter (Gentlecath, Nippon Sherwood, Shizuoka, Japan) into the femoral vein or internal jugular vein using the Seldinger method. The 2.1 m^2 hemofilter (UT-2100, Nipro, Osaka, Japan) was a cellulose triacetate membrane. We adjusted the dose of the anticoagulant nafamostat mesilate (Futhan, Torii Pharmaceutical, Tokyo, Japan) to achieve an activated coagulation time of 150–170 sec. The hemopurification system was a personal bedside consol (JUN-505, JUN-KEN Medical, Tokyo, Japan); patients received continuous venovenous hemodiafiltration (CVVHDF) with the following flow rates: blood = 100 ml/min, dialysis = 900 ml/hr, filtration = 900 ml/hr, and total hemopurification = 1,800 ml/hr. The path of the replacement fluid was post-dilution. Treatment was administered without water removal for the first 24 hrs. After 24 hrs, water removal was left to the discretion of the ICU doctors. Hemofilters were replaced every 24 hrs. Sublood-BS (Fuso Pharmaceutical, Osaka, Japan) was used as the dialysate as well as the replacement fluid. Criteria to terminate CRRT were: a) urine output ≥ 1ml/kg/hr for >24 hrs [19] and b) no increase in serum creatinine.

Measurements

When patients arrived in the ICU, disease severity was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [20], Simplified Acute Physiology Score (SAPS) II score [21], and Sequential Organ Failure Assessment (SOFA) score [22]. Before administering antibiotics, we obtained venous blood from two places. We measured MAP, $ScvO_2$, CVP, and CAI at six time points: immediately before CRRT (T1) and 3, 6, 12, 24, and 48 hrs after CRRT initiation (T2-T6). Blood was drawn at each time point to measure lactate (ABL 725, Radiometer, Copenhagen, Denmark), IL-6, and HMGB-1 levels. Commercial enzyme-linked immunosorbent assay (ELISA) kits were used to determine the concentrations of IL-6 (Invitrogen Corporation, Carlsbad, CA, USA) and HMGB-1 (Shino-Test Corporation, Tokyo, Japan) according to manufacturer protocols. Absorbance at 450 nm was measured on an ELISA reader (Bio-Rad Laboratories, Hercules, CA, USA).

For clinical outcomes, we calculated ICU survival, 28-day survival, and hospital survival rates. Duration of ICU stay and CRRT were recorded. Urine output prior to CRRT initiation was measured, as well as the number of patients who were transferred to intermittent hemodialysis (IHD) while staying at the ICU.

Statistical analysis

Results are expressed as mean±standard deviation (SD). Data was compared by analysis of variance followed by Scheffe post hoc test using StatView (Abacus Concepts, Berkeley, CA, USA). A p-value >0.05 was considered statistically significant.

Results

Patient clinical data

Disease severity scores were 26.8±3.7, APACHE II; 60.7±12.6, SAPS II; and 13.1±2.4, SOFA. Urine output prior to CRRT was 21±13 ml/hr (0.4±0.2 ml/kg/hr). According to RIFLE classification, six patients were classified as risk, seven as injury, and four as failure. Venous blood culture revealed that 10 patients (58.8%) were positive for infection: gram-negative bacteria (n = 8), gram-positive bacteria (n =3), fungi (n =1), and mixed infections (n =2) (Table 1).

Changes in hemodynamic parameters and CAI

MAP increased significantly 3 hrs after CRRT began (Figure 1). Subsequently, we were able to maintain MAP at 65–90 mmHg. $ScvO_2$ began to increase significantly 6 hrs after CRRT started and was

Age (years)	68.6±11.9
Male:female	9:8
Weight (kg)	57.6±12.2
APACHE II	26.8±3.7
SAPS II	60.7±12.6
SOFA	13.1±2.4
Laboratory data before study	
pH	7.34±0.17
Base excess (mmol/L)	–7.8±7.2
Blood urea nitrogen (mg/dL)	44.8±12.9
Creatinine (mg/dL)	2.5±1.1
Urinary output pre-CRRT (mL/hr)	21±13
RIFLE classification	
Risk	6
Injury	7
Failure	4
Blood culture-positive cases, n (%)	10 (58.8)
Gram-negative	8
Gram-positive	3
Fungus	1
Mixed	2

APACHE: Acute Physiology and Chronic Health Evaluation
SAPS: Simplified Acute Physiology Score
SOFA: Sequential Organ Failure Assessment
CRRT: continuous renal replacement therapy
RIFLE: Risk, Injury, Failure, Loss, End-Stage Kidney Disease

Table 1: Baseline Characteristics of Study Patients.

maintained at >70% thereafter. CVP did not change significantly during treatment, but CAI decreased significantly after 3 hrs. Mean CAI was 17 before CRRT; 12 hrs after CRRT began it was possible to maintain CAI < 5.

Changes in serum lactate, IL-6, and HMGB-1 levels

As shown in Figure 2, serum lactate concentration was significantly lower 24 hrs after beginning CRRT compared with pretreatment levels (2.0±1.6 mmol/l vs. 4.1±2.9 mmol/l). Similarly, IL-6 concentration decreased from 987±540 pg/ml (immediately before CRRT) to 528±298 pg/ml (6 hrs later); HMGB-1 also decreased significantly from 6.5±4.0 ng/ml (before CRRT) to 3.0±1.8 ng/ml (12 hrs later).

CRRT data and clinical outcomes

Mean flow rate of hemopurification was 32.5±6.3 ml/kg/hr and duration of CRRT was 6.5±4.2 days. No patients required IHD during their ICU stay (15.1±10.4 days). Mean survival rates were ICU survival, 76.5%; 28-day survival, 76.5%; and hospital survival, 70.6%. The four deaths in the ICU were all caused by multiple organ failure; one death after release from the ICU was caused by acute myocardial infarction (Table 2).

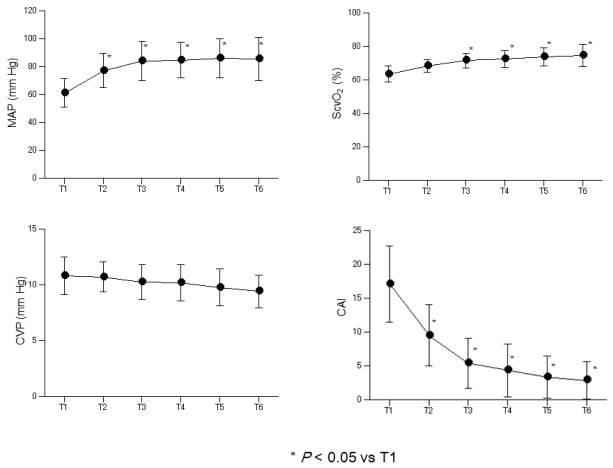

Figure 1:

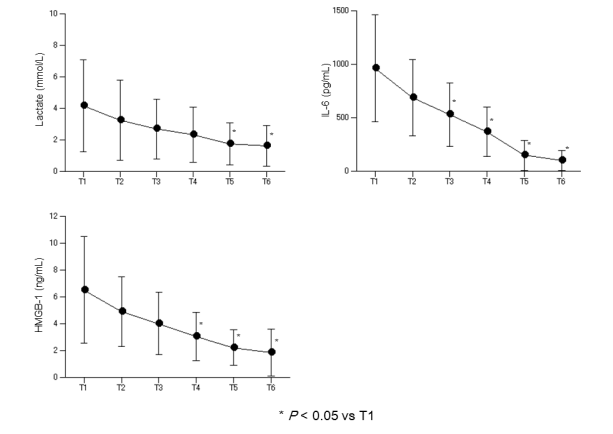

Figure 2:

Hemopurification flow rate (mL/kg/hr)	32.5±6.3
CRRT (days)	6.5±4.2
Patients treated with IHD in ICU, n (%)	0 (0)
ICU stay (days)	15.1±10.4
ICU survival, n (%)	13 (76.5)
28-day survival, n (%)	13 (76.5)
Hospital survival, n (%)	12 (70.6)

CRRT: continuous renal replacement therapy
IHD: intermittent hemodialysis

Table 2: CRRT Data and Clinical Outcomes.

During the course of this study, there were no cases in which it was necessary to exchange the CRRT circuit within 24 hrs because of blood clotting, nor any cases in which CRRT was aborted because of adverse side effects.

Discussion

In the present study, we showed that early CRRT intervention for patients with septic shock and AKI improves serum lactate concentration, stabilizes hemodynamics, and improves renal function. Severe sepsis and septic shock are associated with poor prognosis; these conditions can lead to multiple organ failure due to drop in blood pressure, tissue hypoperfusion, and tissue dysoxia. Occurrence of severe sepsis and septic shock is increasing [1]. Many studies have been conducted to elucidate the pathology, diagnosis, and treatment of severe sepsis and septic shock; however, satisfactory results have so far been elusive. Accordingly, the Surviving Sepsis Campaign Guidelines (SSCG) have recently been developed [2]. These guidelines mention that EGDT as proposed by Rivers et al. [3] reduces mortality rates of septic patients. However, the goals of EGDT can be difficult to achieve due to the difficulty of maintaining MAP with vasoconstrictors. Moreover, some patients develop complications of AKI, which has been reported to worsen prognosis [4]. Early intervention with CRRT has been proposed to improve the clinical condition of these patients.

In the present study, CRRT (mean hemopurification flow rate, 32.5±6.3 ml/kg/hr) clearly improved patient hemodynamics. This flow rate is higher than the rates normally suggested for CRRT, which are a subject of debate [23]. Following a study by Ronco et al. [5], higher hemopurification flow rates have been reported to improve hemodynamics and reduce mortality [6-8]. In contrast, Tolwani et al. [9] found that hemopurification flow rate had no effect on prognosis. However, CRRT was initiated extremely late in the Tolwani study—8 days after ICU admission. This timing of CRRT initiation drastically differs from our study in which CRRT began only 6 hrs after patients entered the ICU. These results suggest that early CRRT with a high flow rate may improve patient outcomes.

In a study by Payen et al. [24], patients with severe sepsis were treated with CRRT at a relatively early stage, using the flow rate of 25 ml/kg/hr, but prognosis was not improved. However, Payen et al. [24] carried out CRRT in patients with and without concurrent AKI. When performed on septic patients showing no sign of AKI, CRRT may actually increase renal damage. In the present study, CRRT was performed only in patients with septic shock and concurrent AKI, which is the more serious clinical condition. We effectively treated these patients, thus it may be important to consider whether patients have concurrent AKI when considering CRRT for sepsis.

In the present study, we used a relatively high hemopurification flow rate with which we stabilized hemodynamics, attenuated inflammatory reactions, and improved renal function. However, high-

flow hemopurification also removes antibiotics [25], electrolytes [26], and nutrients [27]. According to the RENAL study [10], flow rates higher than 25 ml/kg/hr did not improve survival rates. Our study did not evaluate hemopurification rates lower than 25 ml/kg/hr. Thus, determining the optimal CRRT requires comparison of flow rates.

In this study, we did not monitor serum concentrations of antibiotics during CRRT. The Surviving Sepsis Campaign Guidelines (SSCG) [2] note that antibiotic therapy is critical for treating patients with sepsis and septic shock, and recommend empirical antibiotic therapy combined with sufficient doses of antibiotics. However, the pharmacokinetics of antibiotics are significantly different during CRRT than when CRRT is not used [28]. Antibiotics therapy can cause organ injury in cases of overdose administration; however, low doses are not always sufficient to yield a therapeutic effect. In particular, inadequate administration of antibiotics has been linked to death in patients with septic shock. As such, adequate (within therapeutic range) administration of antibiotics is critical. Antibiotics elimination during CRRT has been associated with molecular weight, protein binding, and distribution volume [29,30]. In general, antibiotics of low molecular weights can remove large amounts of drugs during CRRT. In addition, we have found that Doripenem (carbapenem antibiotics) can increase clearance in proportion to hemofiltration rate. Thus, we recommend that antibiotics administration is increased during high flow CRRT [31,32]. These results suggest that adequate administration of antibiotics during CRRT is extremely difficult. If at all possible, serum concentrations of antibiotics should be monitored closely during CRRT. If monitoring is not an option, then antibiotics should be administered with the consideration of clearance during high flow CRRT.

Using CRRT, we were able to reduce the serum concentrations of IL-6 and HMGB-1. Various inflammatory mediators are involved in shock associated with sepsis or onset of organ damage [33]. Among these mediators, IL-6 is considered a good indicator of cytokine cascade activities in sepsis [12]. In contrast, HMGB-1 is a mediator of late-stage inflammation and death [14]. Removal of these inflammation mediators by CRRT may have suppressed systemic inflammation, which in turn may have stabilized hemodynamics and improved renal function.

The EUPHAS trial [18] demonstrated the utility of direct hemoperfusion with polymyxin-B immobilized fiber (PMX-DHP) for severe sepsis and septic shock. Because our patients had concurrent AKI complications, we chose CRRT instead of PMX-DHP. We obtained clinical results equal to or better than those reported by the EUPHAS trial. The EUPHAS trial involved 34 patients with mean APACHE II score of 21 and SOFA score of 11; the 28-day survival rate was 68%. In the present study, the mean APACHE II score was 27 and SOFA score was 13, which was more severe than in the EUPHAS trial, but our 28-day survival rate was 77%. In all cases, AKI was improved and no patient required IHD after CRRT ended. It may be useful to compare CRRT with PMX-DHP for patients unresponsive to EGDT and evaluate the concurrent use of PMX-DHP and CRRT.

Limitations of the present study include lack of controls, the small number of patients, and use of a single institution. To further assess the usefulness of CRRT for septic shock, collaborative research among multiple institutions is desirable.

In conclusion, our study suggests that, for patients with septic shock and concurrent AKI who are not responsive to EGDT, a high-flow CRRT mitigates organ damage by controlling serum inflammatory mediators. CRRT may be an effective treatment for patients with septic shock.

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