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Risk factors for mortality in patients with acute kidney injury and hypotension treated with continuous veno-venous hemodiafiltration

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Abstract

Background: Continuous veno-venous hemodiafiltration (CVVHDF) is a preferred treatment modality in hemodynamically unstable acute kidney injury (AKI) patients, because it has advantages over intermittent dialysis in terms of hemodynamic stability. However, this patient group still shows a significantly high mortality rate. To aid in the management of these high-risk patients, we evaluated the risk factors for mortality in CVVHDF-treated hypotensive AKI patients.

Methods: We studied 67 patients with AKI and hypotension who were treated with CVVHDF from February 2008 to August 2010. We reviewed patient characteristics and laboratory parameters to evaluate the risk factors for 90-day mortality.

Results: Of the 67 enrolled patients (male:female = 42:25; mean age = 69 ± 14 years), 18 (27%) survived until 90 days after the initiation of CVVHDF. There was no significant difference in survival rates according to the etiology of AKI [hypovolemic shock 2/10 (20%), cardiogenic shock 4/20 (20%), septic shock 12/37 (32%)]. Univariate analysis did show significant differences between survivors and non-survivors in the frequency of ventilator use (44% vs. 76%, respectively; $P=0.02$), APACHE II score (29 ± 7 vs. 34 ± 7, respectively; $P=0.01$), SOFA score (11 ± 4 vs. 13 ± 4, respectively; $P=0.03$), blood pH (7.3 ± 0.1 vs. 7.2 ± 0.1, respectively; $P=0.03$), and rate of urine output < 500 mL for 12 hours (50% vs. 80%, respectively; $P=0.03$). A multivariate Cox proportional hazards model showed that a urine output < 500 mL for 12 hours was the only significant risk factor for 90-day mortality following CVVHDF treatment (odds ratio = 2.1, confidence interval = 1.01–4.4, $P=0.048$).

Conclusion: A urine output < 500 mL for 12 hours before the initiation of CVVHDF is an independent risk factor for 90-day mortality in hypotensive AKI patients treated with CVVHDF.

Introduction

Renal replacement therapy (RRT) is required in 5–6% of critically ill patients, and acute kidney injury (AKI) requiring dialysis, is associated with especially high mortality rates of 50–80% [1]. AKI patients requiring RRT also have a high frequency of multiorgan failure or hemodynamic instability [2].

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Continuous renal replacement therapy (CRRT) was proposed as an alternative to intermittent dialysis in hemodynamically unstable patients, because it is better tolerated, due to the gradual removal of fluid and uremic toxins [3–5].

Although previous studies have identified several prognostic factors for mortality associated with CRRT, such as sepsis, higher APACHE II scores, oliguric AKI, the presence of coma, higher SOFA scores, and the need for mechanical ventilation in critically ill patients undergoing CRRT, each study found different results according to the indication for CRRT and the severity of the disease [6–11]. Therefore, the prognostic factors for patients requiring CRRT still remain somewhat obscure.

Confused classification of patients with regard to the severity and features of their disease, may lead to difficulties in identifying the factors affecting the prognosis of CRRT. Nevertheless, we attempted to assess the characteristics of patients undergoing CRRT treatment. Therefore, this study was focused on AKI patients with hemodynamic instability undergoing CRRT. We evaluated the risk factors for mortality within 90 days after the initiation of CRRT in patients with AKI and hypotension.

Methods

Study population

The inclusion criteria were a clinical diagnosis of AKI and hypotension. AKI was defined by a twofold increase in serum creatinine, a decrease in estimated glomerular filtration rate (GFR) of $>50\%$, or a reduction in urine output <0.5 mL/kg/hour for 12 hours [12]. Hypotension was defined by an initial mean arterial pressure <60 mmHg, or the use of vasopressors such as dopamine or norepinephrine, to maintain systolic blood pressure >100 mmHg when continuous veno-venous hemodiafiltration (CVVHDF) was started. A total of 108 patients were treated with CVVHDF in the medical-surgical intensive care unit from February 2008 to August 2010. Normotensive patients and those who had end-stage renal disease or malignancy were excluded. We identified 67 patients who had AKI and hypotension at the initiation of CVVHDF. All enrolled patients were followed for >90 days.

Treatment modality

CVVHDF was performed with the multiFiltrate (Fresenius Medical Care, Fürth, Germany) and the Ultraflux AV600S dialyzer (surface area $=1.4\ m^2$) (Fresenius Medical Care, St. Wendel, Germany) through double-lumen catheters inserted into the internal jugular or femoral vein. Blood flow rates were maintained between 100 and 150 mL/minute and the predilution replacement method was used. Anticoagulation was performed with heparin or nafamostat.

Investigated parameters

Demographic data including age, sex, diabetes mellitus, and hypertension, and clinical parameters such as duration of hospitalization, ventilator use, cause of hypotension, urine output before the initiation of CVVHDF, previous surgical intervention, and type of anticoagulation, were collected. Laboratory parameters, including C-reactive protein, blood urea nitrogen, serum creatinine, white blood cell count, hemoglobin, blood pH and chest radiographic information were also gathered at the initiation of CVVHDF.

SOFA scores and APACHE II scores were employed to evaluate the severity of disease.

Patients were assigned to two groups [RIFLE-I (injury) and RIFLE-F (failure)] with increasing severity of RIFLE stage. We compared demographic, clinical, and laboratory parameters as well as mortality between these two groups.

We also compared demographic, clinical, and laboratory parameters between the survivors and non-survivors to identify the risk factors for mortality in hypotensive AKI patients treated with CVVHDF.

Statistics

Data are presented as mean (standard deviation) or median and range. Between-group analyses were made using unpaired Student *t* tests. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Cox regression analysis was used to show the adjusted odds ratio of investigated parameters. Variables with a $P<0.10$ in univariate analyses were included for multivariate analysis. Hazard ratios with their corresponding 95% confidence intervals are reported. A $P<0.05$ was considered statistically significant.

Results

Baseline data and severity of illness

Basic demographic data are shown in Table 1.

A total of 67 patients were included in this study. The mean age of the patients was 69 ± 14 years, and 42/67 (62%) were male. The most common comorbidity was hypertension (47%), followed by diabetes mellitus (31%). The median length of hospital stay was 13 ± 18 days. Twenty-two out of 67 (32%) patients had undergone surgical intervention within the previous month. Forty-five out of 67 (66%) patients received ventilator care and 36/67 (53%) patients showed pulmonary edema on chest radiography before the initiation of CVVHDF. Oliguria, defined by a urine output <500 mL within 12 hours before the initiation of CVVHDF, occurred in 48/67 (71%) patients. Thirty-four out of 67 (51%) patients received loop diuretics.

The most common cause of hypotension was septic shock (37/67, 55%), followed by cardiogenic shock (20/67, 30%) and hypovolemic shock (10/67, 15%). The mean APACHE II score was 32 ± 7 and mean SOFA score was 13 ± 4. Mean values for blood urea nitrogen and serum creatinine were 62 ± 34 mg/dL and 3 ± 4 mg/dL, respectively.

In univariate analysis, the rate of oliguria before the initiation of CVVHDF was significantly higher in the RIFLE-F group than in the RIFLE-I group (81% vs. 58%, respectively; $P=0.04$). There was no difference in 90-day mortality between the two groups (73% vs. 73%, respectively; $P=0.99$).

Outcomes and predictors of survival

The mortality rate of the hypotensive AKI patients who received CVVHDF was 73% (49/67).

Table 2 shows univariate comparisons of clinical characteristics and laboratory findings between survivors and nonsurvivors.

There were no significant differences in survival rates according to the cause of shock; septic shock (12/37, 32%), cardiogenic shock (4/20, 20%), hypovolemic shock (2/10, 20%).

Table 1. Baseline characteristics of hypotensive acute kidney injury patients treated with continuous veno-venous hemodiafiltration (CVVHDF)

	All patients (n=67)	RIFLE-I (n=26, 39%)	RIFLE-F (n=41, 61%)	P
Demographic characteristics				
Age (y)	69 ± 14	66 ± 17	71 ± 12	NS
Male, n (%)	42 (62%)	16 (62%)	26 (62%)	NS
Death, n (%)	49 (73%)	19 (73%)	30 (73%)	NS
Diabetes mellitus, n (%)	21 (31%)	5 (19.2%)	16 (39%)	NS
Hypertension, n (%)	32 (47%)	11 (42%)	21 (51%)	NS
Clinical parameters				
Duration of hospitalization (d)	13 ± 18	13 ± 15	14 ± 21	NS
Previous surgical intervention, n (%)	22 (32%)	13 (50%)	9 (22%)	NS
Ventilator use, n (%)	45 (66%)	16 (62%)	29 (73%)	NS
Pulmonary edema on chest x-ray	36 (53%)	15 (58%)	21 (51%)	NS
Urine output < 500 mL for 12 h before initiation of CVVHDF, n (%)	48 (71%)	15 (58%)	33 (81%)	0.04
Loop diuretic therapy, n (%)	34 (51%)	17 (65%)	17 (41%)	NS
Cause of shock				NS
Septic shock, n (%)	37 (55%)	14 (54%)	25 (61%)	
Cardiogenic shock, n (%)	20 (30%)	8 (31%)	10 (24%)	
Hypovolemic shock, n (%)	10 (15%)	4 (15%)	6 (15%)	
Anticoagulation				NS
Nafamostat, n (%)	21 (31%)	10 (39%)	13 (32%)	
Heparin, n (%)	26 (39%)	9 (35%)	17 (42%)	
No anticoagulation, n (%)	20 (30%)	7 (27%)	11 (27%)	
Severity score				
APACHE II score	32 ± 7	32 ± 7	33 ± 7	NS
SOFA score	13 ± 4	14 ± 3	12 ± 4	NS
Laboratory findings on initiation of CVVHDF				
BUN (mg/dL)	62 ± 34	55 ± 31	67 ± 35	NS
Serum creatinine (mg/dL)	3 ± 4	3 ± 1	4 ± 4	0.02
C-reactive protein (mg/dL)	9 ± 7	10 ± 8	8 ± 7	NS
pH	7.3 ± 0.1	7.3 ± 0.1	7.2 ± 0.1	NS
WBC (/mm^3)	14,000 ± 7,000	16,000 ± 8,000	13,000 ± 7,000	NS
Hemoglobin (g/dL)	11 ± 3	11 ± 2	10 ± 3	NS
Platelets (× 10^3/mm^3)	140 ± 70	130 ± 70	150 ± 110	NS

Table 2. Univariate comparisons of demographic and laboratory findings between survivors and non-survivors in hypotensive acute kidney injury patients treated with continuous veno-venous hemodiafiltration (CVVHDF)

	Survivors (n=18)	Non-survivors (n=49)	P
Demographic characteristics			
Age (y)	65 ± 17	70 ± 13	NS
Male, n (%)	12 (67%)	30 (63%)	NS
Diabetes mellitus, n (%)	7 (39%)	14 (29%)	NS
Hypertension, n (%)	9 (50%)	23 (47%)	NS
Clinical parameters			
Duration of hospitalization, (d)	10 ± 15	15 ± 19	NS
Previous surgical intervention, n (%)	4 (22%)	18 (38%)	NS
Ventilator use, n (%)	8 (44%)	37 (76%)	0.02
Pulmonary edema on chest x-ray, n (%)	6 (33%)	30 (61%)	0.06
Urine output < 500 mL for 12 h before initiation of CVVHDF, n (%)	9 (50%)	39 (80%)	0.03
Loop diuretic therapy, n (%)	8 (44%)	26 (53%)	NS
Cause of shock			
Septic shock, n (%)	12 (67%)	25 (51%)	NS
Cardiogenic shock, n (%)	4 (22%)	16 (33%)	NS
Hypovolemic shock, n (%)	2 (11%)	8 (16%)	NS
Anticoagulation			
Nafamostat, n (%)	3 (17%)	18 (37%)	NS
Heparin, n (%)	6 (33%)	20 (41%)	NS
No anticoagulation, n (%)	9 (50%)	11 (22%)	NS
Severity score			
APACHE II score	29 ± 7	34 ± 7	0.01
SOFA score	11 ± 4	13 ± 4	0.03
Laboratory findings on initiation of CVVHDF			
BUN (mg/dL)	64 ± 31	62 ± 35	NS
Creatinine (mg/dL)	4 ± 2	3 ± 3	NS
C-reactive protein (mg/dL)	6 ± 7	9 ± 7	0.1
pH	7.3 ± 0.1	7.2 ± 0.1	0.03
WBC (/mm^3)	14,000 ± 7,000	14,000 ± 7,000	NS
Hemoglobin (g/dL)	11 ± 3	10 ± 3	NS
Platelets (× 10^3/mm^3)	160 ± 120	120 ± 80	NS

Table 3. Multivariate Cox proportional hazards ratio of 90-day mortality after the initiation of continuous veno-venous hemodiafiltration (CVVHDF)

	Odds ratio	95% Confidence interval	*P*
SOFA score	1.1	0.99–1.18	0.1
Urine output < 500 mL for 12 h before initiation of CVVHDF	2.1	1.01–4.4	0.048

In univariate analysis, the rate of use of mechanical ventilation was significantly higher for the non-survivor group than the survivor group (76% vs. 44%, respectively; $P=0.02$). Oliguria before the initiation of CVVHDF occurred significantly more often in the non-survivor group than in the survivor group (80% vs. 50%, respectively; $P=0.03$). The mean APACHE II score was significantly higher for the non-survivor group than for the survivor group (34 ± 7 vs. 29 ± 7, respectively; $P=0.01$), as well as the SOFA score (13 ± 4 vs. 11 ± 4, respectively; $P=0.03$).

Multivariate Cox proportional hazards analysis showed that a urine output < 500 mL for 12 hours before the initiation of CVVHDF was the only significant risk factor for 90-day mortality (odds ratio=2.1, confidence interval=1.01–4.4, $P=0.048$) (Table 3). Comorbidities, cause of shock, clinical severity scores, degree of metabolic acidosis, and type of anticoagulation were not found to contribute to the mortality rate.

Discussion

This study shows that a decreased urine output < 500 mL for 12 h before the initiation of CVVHDF, is an independent risk factor for 90-day mortality. This result suggests that early initiation of CVVHDF may be associated with improved survival and that a decrease in urine output could be a parameter used to determine the time of CVVHDF initiation in hemodynamically unstable patients.

Several previous trials have investigated the prognostic factors for mortality of patients undergoing CRRT; these studies found different prognostic factors [8,10,11]. One study showed that metabolic acidosis and earlier initiation of CRRT were associated with the survival of patients with AKI receiving CRRT [10]. In another study, the independent prognostic factor for mortality in AKI patients treated with CRRT was found to be the APACHE II score [7]. In the current study, univariate analysis showed that arterial pH and APACHE II score were significantly different between survivors and non-survivors. However, multivariate analysis did not show that these factors were significant predictors of mortality.

Bouman et al. [13] defined early hemofiltration as treatment started when urine output is decreased < 30 mL/hour for over 6 hours and reported that early dialysis did not affect mortality. Bae et al. [11] reported that lower mean arterial blood pressure and lower serum bicarbonate levels measured the day after CRRT may predict a poor prognosis. These conflicting results might be caused by differences in disease severity and study populations, because we examined prognostic factors in a group with more severe disease and hemodynamic instability.

Our study indicates that urine output may be an important parameter for the determination of the optimal time for CRRT. Fluctuations in blood pressure affect renal blood flow and GFR due to renal autoregulation [14]. A marked reduction in renal perfusion may overwhelm autoregulation and precipitate an acute fall in GFR.

After Bellomo et al. [12] first suggested the RIFLE criteria for the classification of the severity of AKI and patient prognosis, many attempts have been made to prove the usefulness of these criteria. Studies report that when CRRT is applied at the "injury stage" when severity is relatively low, the mortality of patients decreases [15–19]. In addition, a recent domestic study also showed that the 90-day mortality rate was significantly lower in patients who received CRRT in the injury stage of the RIFLE criteria, when compared with those in the failure or loss stages [20]. However, the current study showed that there was no difference in 90-day mortality between the RIFLE-I group and the RIFLE-F group. Our results suggest that starting treatment prior to the RIFLE-I stage may represent the optimal timing for CRRT. Further studies using the RIFLE criteria as a prognostic factor are needed to support this idea.

There are some limitations to our study. Firstly, it is a retrospective, observational, single-center study, with all the inherent limitations of such investigations. Further, our study could not rule out the selection bias included in variable clinical conditions and the size of the study group was relatively small. Therefore, further prospective, multiple-center, large-group studies will be needed to clarify the factors affecting prognosis in hemodynamically unstable AKI patients receiving CRRT.

In conclusion, a decreased urine output < 500 mL for 12 h before the initiation of CVVHDF, is an independent prognostic factor for mortality in AKI patients with hemodynamic instability treated with CVVHDF. This result suggests that early initiation of CRRT before a decrease in urine output is beneficial.

Conflict of interest

The authors declare there is no conflict of interest.

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