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Continuous renal replacement therapy for the treatment of acute kidney injury

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Background/Aims : Continuous renal replacement therapy (CRRT) has been widely used for treating critically ill patients with acute kidney injury (AKI). Whether CRRT is better than intermittent hemodialysis for the treatment of AKI remains controversial. We sought to identify the clinical features that can predict survival for the patients who are treated with CRRT.

Methods : We analyzed the data of 125 patients who received CRRT between 2005 and 2007. We identified the demographic variables, the underlying diagnoses, the duration of CRRT, the mean arterial blood pressure (ABP) and the Simplified Acute Physiology Score (SAPS) II. The classification/staging system for acute kidney injury (AKI) was applied to all the patients, who were then divided into stage 1-3 subgroups.

Results : The average age of the patients was 61.414.3 years and the mortality rate was 60% (75 of 125 patients). The survivors had a significantly higher mean ABP and a higher mean serum bicarbonate level, which were measured the day after CRRT, than the nonsurvivors (86.723.7 vs. 69.224.6 mm Hg, respectively, 21.43.5 vs. 16.45.4 mmol/L, respectively,; $p<0.05$ for each). The stage 3 AKI patients showed the worst parameters for the SAPS II score and the serum levels of creatinine and blood urea nitrogen. The mortality rate was higher for the stage 3 subgroup than the other groups (70.5%, $p<0.05$).

Conclusions : The patients with AKI and who require CRRT continue to have a high mortality rate. A higher mean ABP and a higher serum bicarbonate level measured the day after CRRT may predict a more favorable prognosis. The staging system for AKI can improve the ability to predict the outcomes of CRRT patients.

Key Words : Hemodiafiltration; Acute kidney injury

INTRODUCTION

Acute kidney injury (AKI) is a clinical disorder that has an extremely high mortality rate, and the cases that are induced by septicemia or multiorgan failure syndrome show poor outcomes. Although the mortality rate of AKI has been reduced since the use of renal replacement therapy (RRT) for patients with AKI, its mortality rate is still reported to be as high as 40~70%. Intermittent hemodialysis (IDH) has the disadvantage in that it cannot successfully treat AKI due to the hypotension that occurs during dialysis. Since continuous renal replacement therapy (CRRT) has the advantage of removing the solute slowly and continuously, it has been primarily used for treating AKI patients with an unstable hemodynamic status or the AKI is associated with multiorgan failure syndrome[1-4]. However, although CRRT has many advantages, previous studies have reported that

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CRRT has not reduced the mortality rate any more than intermittent RRT[5, 6]. Although AKI itself may contribute to its high mortality rate, there is the possibility that RRT can further increase the mortality rate.

Thus, the present study was conducted to determine the important factors that are related to the mortality rate of patients who undergo CRRT.

MATERIALS AND METHODS

Patients

This study included 125 patients who underwent CRRT at the Chonnam National University Hospital between October 2005 and May 2007. We retrospectively reviewed the patients' medical records in terms of age, gender, underlying diseases, treatment outcomes, accompanying diseases and the mortality rate. We also investigated differences in the aforementioned clinical variables between the study groups that were categorized according to the classification/staging system of AKI, as well as the severity of the accompanying diseases.

Methods

The data on the vital signs and laboratory findings, including the serum levels of urea nitrogen, creatinine, albumin, electrolytes and C-reactive protein, the causes of AKI and the presence of oliguria were collected immediately before the start of CRRT. The disease severity of the patients undergoing CRRT was assessed using the Simplified Acute Physiology Score (SAPS) II system[7]. CRRT was performed with a computerized, automated hemodialyzer (Prisma, Gambro, Sweden). The venous route for RRT was established with a double-lumen catheter that was inserted through a venovenous access puncture through the femoral and interval jugular veins. Anticoagulant therapy was carried out with heparin and using an AN69 filter (a copolymer of acrylonitrile and an sodium methallylsulphonate fibrous membrane) in the patients with AKI, except for those who were contraindicated for the therapy. The indications, duration of admission until the initiation of RRT, the amount of ultrafiltrate, the blood flow rate, the duration of RRT, the use of heparin and the complications were analyzed. In cases where patients with AKI died during RRT, the time point of death was defined as the end point of RRT. Filters were replaced only when they were occluded and did not function properly. The patients were divided into 2 groups: the survivor and nonsurvivor groups. We compared the amount of electrolytes, the kidney functions, the mean arterial blood pressure (ABP), the SAPS II scores and the blood flow rate before and after continuous RRT between the 2 groups. We also analyzed the data on the serum levels of electrolytes, creatinine and bicarbonate, and the mean ABP that was measured on the day after continuous RRT. In addition, after excluding 7 patients who underwent RRT such as peritoneal dialysis or hemodialysis, 118 subjects were divided into 3 subgroups according to the serum creatinine and urine output: the stage 1 AKI subgroup that had an increase in serum creatinine of =0.3 mg/dL or an increase of 200~300% above baseline and a urine output of 〈0.5 mL/kg/h for 〉6 h, the stage 2 AKI subgroup that had an increase in serum creatinine of 〉200~300% above baseline and a urine output of 〈0.5 mL/kg/h for 〉12 h and the stage 3 AKI subgroup that had an increase of serum creatinine of 〉300% above baseline or a serum creatinine of =4 mg dL with an acute rise of =0.5 mg/dL and 0.3 mL/kg/h for 〉24 h or anuria for 〉12 h[8]. The mortality rates were compared between the 3 subgroups, and the serum electrolyte levels, the mean ABP and the outcomes of dialysis were assessed for the 3 subgroups.

Statistical analysis

The data was expressed as means SDs. Statistical comparisons were made between the survivor and nonsurvivor groups using the independent *t*-test, and statistical comparisons between the 3 subgroups were done using the chi-square test and the one-way ANOVA test. The contributory factors for the mortality rate were analyzed using logistic regression analysis. The survival rate was calculated using the Kaplan-Meier method. A p value of 〈0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows 12.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 125 patients received RRT. The mean age of the patients was 61.4 (14.3) years. There were 55 males (44.0%) and 70 females (56.0%). Medical diseases (n=91, 72.8%) were the most common cause of AKI, followed by surgical diseases (n=29, 23.2%) and trauma (n=5, 4.0%). Oliguria occurred in 84 (67.2%) patients and septicemia occurred in 48 (38.4%) patients who underwent RRT. The mean SAPS II score was 60.5±16.3 (Table 1).

The most common indication for CRRT was hemodynamic instability (n=88, 70.4%), followed by cardiogenic shock (n=23, 18.4%) and acute respiratory failure (n=13, 10.4%). The mean time lapse between admission and the start of RRT was 7.3±11.1 days and the mean duration of RRT was 4.8±4.5 days. The mean amount of ultrafiltrate was 956.8±180.7 mL/h and heparin was used in 29 (23.2%) patients. Complications occurred in 33 (23.2%) patients after RRT. The use of filters 2 or more times per day (n=26, 22.0%) was the most common complication, followed by bleeding (n=3, 2.5%) and catheter-

Table 1. Characteristics of the patients treated with continuous renal replacement therapy

Number	125
Demography	
Age (years)	61.4±14.3
Gender (F/M)	70 (56.0%)/55 (44.0%)
Causes of acute renal failure	
Surgical	29 (23.2%)
Medical	91 (72.8%)
Trauma	5 (4.0%)
Clinical characteristis	
SAPS score	60.5±16.3
Mean blood pressure(mmHg)	76.9±18.6
Presence of sepsis	48 (38.4%)
Oliguria	84 (67.2%)
BUN (mg/dL)	69.2±39.3
Creatinine(mg/dL)	4.5±2.6
Albumin (g/dL)	2.8±0.6
Hemoglobin (g/dL)	9.8±2.25
CRP (mg/dL)	13.6±10.2
HCO_3^- (mmol/L)	17.0±5.2

SAPS, simplified acute physiology score; BUN, blood urea nitrogen; CRP, C-reactive protein

related infections (n=3, 2.5%).

Of the patients who underwent CRRT, 50 (40%) survived. Table 2 shows the clinical characteristics, laboratory data and changes after RRT between the survivor (n=50) and nonsurvivor (n=75) groups. There was no significant differences in the causes of AKI between the 2 groups (p=0.875), including septicemia, hepatic failure, congestive heart failure and acute respiratory distress syndrome. The mean SAPS II score was higher for the nonsurvivor group (62.2±16.2) than for the survivor group (58.0±16.4), but the difference was statistically insignificant. Septicemia occurred in 19 (38%) patients of the survivor group and in 29 (38.7%) patients of the nonsurvivor group, but the difference was statistically insignificant. The mean ABP before the start of RRT was significantly lower for the nonsurvivor group than for the survivor group (73.0±17.4 mm Hg vs. 82.9±19.0 mm Hg, respectively; $p<0.05$). The mean ABP measured the day after RRT was significantly lower for the nonsurvivor group than for the survivor group (69.2±24.6 mm Hg vs 86.7±23.7 mm Hg, respectively; $p<0.05$). The serum albumin level was significantly lower for the nonsurvivor group than for the survivor group (2.7±0.6 g/dL vs. 3.0±0.5 g/dL, respectively; $p<0.05$). The serum C-reactive protein level was higher for the nonsurvivor group (14.6±9.7 mg/dL) than for the survivor group (12.1±10.8 mg/dL), but the difference was statistically insignificant.

There were no significant differences between the 2 groups for the blood flow rate, the amount of ultrafiltrate, the duration of dialysis and the use of heparin. The mean time lapse between admission and the start of RRT was 8.4±12.8 days for the nonsurvivor group and 5.8±7.7 days for the survivor group, but the difference was statistically insignificant. There was no significant difference for the changes of the serum levels of creatinine and urea after RRT between the 2 groups, but the serum bicarbonate level was significantly lower for the nonsurvivor group than for the survivor group (16.4±5.4 mmol/L vs. 21.4±3.5 mmol/L, respectively; $p<0.05$).

On the multivariate analysis of the contributory factors for the mortality rate, the serum albumin level and the mean ABP values measured before and the day after RRT and the serum bicarbonate level measured the day after RRT were significantly lower. However, on logistic regression analysis, the mean ABP and the serum bicarbonate level were the important factors for the mortality rate (Table 3).

For the stage 3 subgroup, the mortality rate, the SAPS II scores and the serum levels of urea and creatinine were significantly higher for the stage 3 subgroup, and the serum

Table 2. Comparisons between the survivors and nonsurvivors

	Survivors (n=50)	Nonsurvivors (n=75)	p-value
Age	61.1±13.2	61.7±15.0	NS
Gender (female)	25 (50%)	30 (40%)	NS
Presence of sepsis	19 (38%)	29 (38.7%)	NS
SAPS II score	58.0±16.4	62.2±16.2	NS
Mean blood pressure (mmHg)	82.9±19.0	73.0±17.4	$p<0.05$
Albumin (g/dL)	3.0±0.5	2.7±0.6	$p<0.05$
CRP (mg/dL)	12.1±10.8	14.6±9.7	NS
CRRT parameters			
Mean time from admission to CRRT	5.8±7.7	8.4±12.8	NS
Mean delivered ultrafiltration (mL/24hr)	943.4±166.3	966.0±190.6	NS
Mean duration of replacement (days)	4.6±3.6	4.8±5.0	NS
Mean blood pressure (mmHg) 1 day after CRRT	86.7±23.7	69.2±24.6	$p<0.05$
HCO_3^- (mmol/L) 1 day after CRRT	21.4±3.5	16.4±5.4	$p<0.05$

SAPS, simplified acute physiology score; CRP, C-reactive protein; CRRT, continuous renal replacement therapy

Table 3. The unadjusted and adjusted predictors of survival

Variable	cOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Albumin	0.44 (0.23-0.83)	$p<0.05$	0.54 (0.23-1.26)	NS
Mean blood pressure (mmHg) 1 day after the initiation of CRRT	0.96 (0.94-0.98)	$p<0.05$	0.97 (0.95-1.00)	$p<0.05$
HCO_3^- (mmol/L) 1 day after the initiation of CRRT	0.80 (0.72-0.88)	$p<0.05$	0.83 (0.74-0.93)	$p<0.05$

CRRT, continuous renal replacement therapy

Table 4. The outcomes based on the acute kidney injury classification

	Tatal	Stage 1	Stage 2	Stage 3	*p*-value
No. of patients	118	11 (9.3%)	29 (24.6%)	78 (66.1%)	
No.of pateints (% mortality rate)	72/118 (61%)	1/11 (9.1%)	16/29 (55.2%)	55/78 (70.5%)	$p<0.05$
SAPS II score	61.1±16.1	50.0±12.4	61.3±19.1	62.7±14.9	$p<0.05$
Mean blood pressure (mmHg)	77.2±19.0	93.5±19.3	83.4±21.3	72.6±16.2	$p<0.05$
BUN (mg/dL)	70.2±39.9	45.0±19.1	58.5±31.9	78.0±42.4	NS
Creatiine (mg/dL)	4.5±2.6	3.0±1.8	3.0±1.2	5.2±2.8	$p<0.05$
Albumin (g/dL)	2.8±0.6	3.3±0.5	2.9±0.6	2.7±0.5	$p<0.05$
HCO3- (mmol/L) 1day after CRRT	18.3±5.3	21.7±4.4	18.8±5.4	17.8±5.2	NS
Mean blood pressure (mmHg) 1day after CRRT	75.6±25.9	97.5±7.4	71.8±30.5	73.9±24.5	$p<0.05$

SAPS, simplified acute physiology score; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy

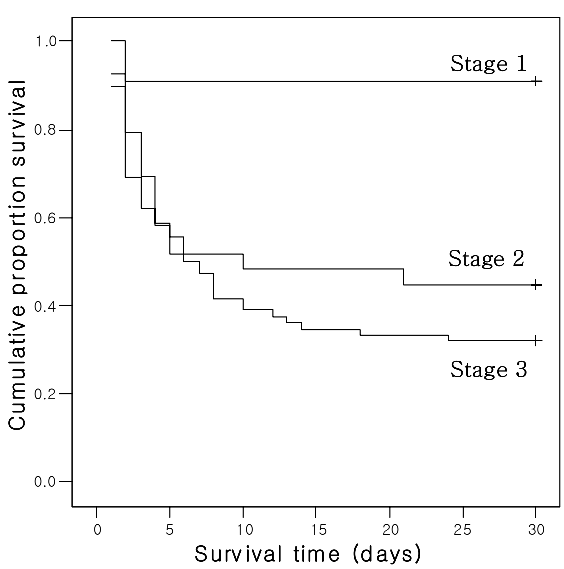

Figure. Kaplan Meier estimation of the survival rates for the three groups (Log-rank test: $p<0.05$).

levels of albumin and bicarbonate tended to be lower (Table 4).

The mortality rate was 90.9% for the stage 1 subgroup, 44.8% for the stage 2 subgroup and 29.5% for the stage 3 subgroup, and so the mortality rate was lowest for the stage 3 subgroup (Figure).

DISCUSSION

Although there is still no concordance between studies regarding the definition, treatment modalities and treatment outcomes of AKI, its mortality rate has been reduced because of the successful treatment of acute renal failure via dialysis[9]. Since Kramer et al.[10] first described continuous arteriovenous hemofiltration (CAVH) in 1977, CRRT such as continuous venovenous hemodiafiltration (CVVHDF) has been developed along with countermeasures for correcting its shortcomings and CRRT has been widely used in clinical settings. CRRT can lead to a normal equilibrium of electrolytes and a normal acid base balance, as well as hemodynamic stability, and it may be effective for the treatment of patients with brain edema. However, despite these therapeutic effects, it is controversial whether CRRT is better than intermittent hemodialysis for intensive care[11].

There have been numerous studies on the indications and adequate timing of RRT and the clinical characteristics of AKI. Although there is controversy concerning the adequate timing of RRT, it is generally recommended that RRT should be initiated before the complications of AKI occur[12, 13]. In the present study, RRT was performed on the patients who were admitted to the intensive care unit due to AKI associated with hemodynamic instability, brain edema, a high catabolic state and a severe excess of body fluids, and their mortality rate was 61.0%, which was similar to the 62.0% mortality rate reported by a previous study. The previous study also reported that the mortality rate of CRRT increased for the cases where the duration of this treatment was long, oliguria was present and the renal functions were reduced[15]. There were no significant differences in the mortality rate in terms of the blood flow rate, the amount of ultrafiltrate, the duration of RRT and the use of heparin in the present study. However, since the mean amount of ultrafiltrate was relatively low (18.7 mL/kg/min), it is thought that the survival rate should have been compared with that of the patients with a higher amount of ultrafiltrate (35 mL/kg/min). In our study, there was no significant association between the mortality rate and oliguria, the RRT outcomes or renal functions. The mortality rate tended to become high for the cases where the serum C-reactive protein was increased, the mean ABP was decreased before the start of dialysis and the serum bicarbonate level was decreased the day after dialysis. The mortality rate was significantly higher for the cases where the mean ABP and the serum bicarbonate level decreased the day after RRT. It has been reported that there is a high mortality rate when the mean ABP before RRT is low and the blood pressure is low 2 hours after RRT[14]. In the present study, since the patients who were undergoing RRT were hemodynamically unstable, they showed remarkable changes in blood pressure on the day of RRT; however, their blood pressure was stabilized the day after RRT. Although the blood pressures before RRT, 2 hours after RRT and the day after RRT were related to the mortality rate, only the blood pressure measured the day after RRT showed a significant correlation with the mortality rate. The blood pressure and the serum bicarbonate level were significantly correlated with the mortality rate, which indicates that rapid restoration of hemodynamic stability and recovery from metabolic acidosis may be important factors for the mortality rate for patients with AKI. Wald et al[15] has reported that CRRT results in a low mortality rate through the restoration of hemodynamic stability and normal kidney functioning. The results of the present study indicate that the mortality rate is low for the cases where the mean ABP is high. This may be explained by the restoration of hemodynamic stability, which is one of the therapeutic effects of CRRT.

Since the prognosis of AKI is affected by numerous variables, its prediction and making precise comparisons of the accuracy between the prognostic factors are difficult. Various studies have compared prognostic factors with using the risk, injury, failure loss and end kidney disease (RIFLE) classification, the acute physiology and chronic health evaluation (APAHE) II scoring system, the SAPS II scoring system, the mortality prediction model (MPM), the sepsis-related organ assessment (SOFA) and the logistic organ dysfunction system (LODS)[16, 17].

In particular, since a review of the literature does not yield a consensus about the definition and classification of AKI, there remain some difficulties for conducting research and improving the prognosis. In the present study, the usefulness of the SAPS II scoring system and the classification proposed in 2007 by the Acute Dialysis Quality Initiative (ADQI) group[8] was evaluated for the patients who underwent CRRT. The stage 3 AKI subgroup showed the highest mortality rate (70.5%) and the highest SAPS II score (62.7±14.9), which was similar to the results of a previous study that the renal failure group according to the RIFLE classification showed the highest mortality rate (74.4%) and the highest SAPS II score (55.9±2.7)[16]. Based on the results that the stage 3 AKI subgroup, which was the most severe group and it exhibited the highest mortality rate, we think that the severity of AKI may affect the prognosis of AKI patients. Kresse et al[18] have reported that for patients with AKI, the mortality rate increases as the severity of the underlying diseases become more severe. It has been demonstrated that the APACHE II scores sensitively reflect the mortality rate for the injury group, whereas the SAPS II scores sensitively reflect the mortality rate for the high risk and severe injury groups. For these reasons, we evaluated the severity of the patients with AKI by using the SAPS II scoring system. Although there was no significant difference of the SAPS II scores between the survivor and nonsurvivor groups, the SAPS II scores were significantly increased for the stage 3 AKI subgroup, suggesting that the SAPS II scoring system can be used along with the AKI classification system for evaluating the severity of AKI.

In conclusion, the most important prognostic factor for AKI patients may be the hemodynamic status, and especially the blood pressure or the serum bicarbonate level after undergoing CRRT. The AKI classification and the SAPS II scoring system can help evaluate the severity of AKI, which suggests that the general status of patients and the severity of AKI may be more important for the prognosis than the CRRT itself.

REFERENCES

1) Hyman A, Mendelssohn DC. *Current Canadian approaches to dialysis for acute renal failure in the ICU. Am J Nephrol 22:29-34, 2002*
2) Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, Paganini EP, Chertow GM. *Spectrum of acute renal failure in the intensive care unit. Kindey Int 66:1613-1621, 2004*

3) Silvester W, Bellomo R, Cole L. *Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. Crit Care Med 29:1910-1915, 2001*
4) Metnitz PG, krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W. *Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 30:2051-2058, 2002*
5) Swartz RD, Messana JM, Orzol S, Port FK. *Comparing continuous hemofiltration with hemodialysis in patients with severe acute renal failure. Am J Kidney Dis 34:424-432, 1999*
6) Bellomo R, Ronco C. *Continuous versus intermittent renal replacement therapy in the intensive care unit. Kidney Int Suppl 66:S125-S128, 1998*
7) Le Gall JR, Lemeshow S, Saulnier F. *A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957-2963, 1993*
8) Levin A, Warnock DG, Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C. *Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis 50:1-4, 2007*
9) Gillum DM, Dixon BS, Yanover MJ, Kelleher SP, Shapiro MD, Benedetti RG, Dillingham MA, Paller MS, Goldberg JP, Tomford RC. *The role of intensive dialysis in acute renal failure. Clin Nephrol 25:249-255, 1986*
10) Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F. *Arteriovenous haemofiltration: a new and simple method for treatment of over-hydrated patients resistant to diuretics. Klin Wochenschr 55:1121-1122, 1977*
11) Abramson S, Singh AK. *Continuous renal replacement therapy compared with intermittent hemodialysis in intensive care: which is better? Curr Opin Nephrol Hypertens 8:537-541, 1999*
12) Bellomo R, Ronco C. *Indications and criteria for initiating renal replacement therapy in the intensive care unit. Kidney Int Suppl 66:S106-S109, 1998*
13) Bellomo R, Angus D, Star RA. *The Acute Dialysis Quality Initiative: part II. patient selection for CRRT. Adv Ren Replace Ther 9:255-259, 2002*
14) Kang YS, Lee SY, Han SY, Jo SK, Shin JH, Cha DR, Kwon YJ, Cho WY, Pyo HJ, Kim HY. *The clinical characteristics of patients treated with continuous renal replacement therapy. Korean J Nephrol 21:93-101, 2002*
15) Wald R, Deshpande R, Bell CM, Bargman JM. *Survival to discharge among patients treated with continuous renal replacement therapy. Hemodial Int 10:82-87, 2006*
16) Abosaif NY, Tolba YA, Heap M, Russell J, El Nahas AM. *The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. Am J Kidney Dis 46:1038-1048, 2005*
17) Bouman CS, Oudemans-van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. *Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med 30:2205-2211, 2002*
18) Kresse S, Schlee H, Deuber HJ, Koall W, Osten B. *Influence of renal replacement therapy on outcome of patients with acute renal failure. Kidney Int Suppl 72:S75-S78, 1999*