Continuous Renal Replacement Therapy (CRRT) in children: 14 years' experience in a single center in Korea, retrospective and comprehensive study

Keum Hwa Lee

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Jae Il Shin

The Master's Thesis is submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

Keum Hwa Lee

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This certifies that the Master's Thesis of
Keum Hwa Lee is approved.

Thesis Supervisor: Jae Il Shin

Thesis Committee Member#1: Ji Hong Kim

Thesis Committee Member#2: Jung Tak Park

The Graduate School
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ABSTRACT

Continuous Renal Replacement Therapy (CRRT) in children: 14 years' experience in a single center in Korea, retrospective and comprehensive study

Keum Hwa Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Jae Il Shin)

Introduction: Continuous renal replacement therapy (CRRT) has been used as an important intervention in critically ill children with acute kidney injury (AKI). The objective of this study was to evaluate the clinical course of children receiving CRRT and to analyze the factors which lead to a need for CRRT or influence the outcome of CRRT.
Method: This study is a retrospective single-center analysis including all patients admitted to the intensive care unit (ICU) of Severance hospital in South Korea, who under the treatment of a pediatric nephrologist and received CRRT between 2003 and 2016. We obtained the data for gender, age, weight, diagnosis, blood flow rate or type of CRRT machine used, indication for CRRT, administration of inotropic agents or anticoagulants, hours to initiating CRRT, and survival rate following CRRT.
Result: Two hundred and ninety-one patients were identified and subsequently classified according to the primary disease. The mean age was 6.6 years (range 1.1 - 12.1 years) and the mean body weight was 23.2 kg (range 5.9 – 40.5 kg). The primary reasons for the initiation of CRRT were a combination of fluid overload, uremia, and oliguria

(20.6%), oliguria only (15.8%), and uremia only (12.0%). The diagnoses before CRRT in these patients were renal disease (e.g. focal segmental glomerulosclerosis (FSGS), nephrotic syndrome, and hemolytic uremic syndrome), pure sepsis, and drug intoxication-. 86.4% of the patients survived after undergoing CRRT. The CRRT modalities included continuous veno-venous hemodiafiltration (CVVHDF) in 55.9% and continuous veno-venous hemodialysis (CVVHD) in 43.4% of the patients; PRISMA® was the most commonly used machine (80.8%). Mean CRRT duration was 5.8 days and the mean blood flow rate was 72.7 ml/min. 25% of the patients received nafamostat mesilate (Futhan®) and 1.4 % were switched to systemic heparin. The most common site of insertion of the initial hemo-catheter was left femoral (33.0%) and right femoral vein (31.9%). Twenty-one patients (7.8%) received extracorporeal membrane oxygenation (ECMO) and CRRT simultaneously. The overall survival rate was 31.2 %. More than one inotropic agents were infused in 70% of the patients and the non-survivors group (n=196) required them more than the survivors' group did (n=93, $p<0.001$).

Conclusion: Based on the 14 years of comprehensive experience at our center, we concluded that CRRT is an effective intervention for critically ill children with AKI or those with an underlying renal disease without significant complications.

Key words: Continuous renal replacement therapy (CRRT), acute kidney injury (AKI), retrospective study

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Ⅰ. INTRODUCTION

Since continuous renal replacement therapy (CRRT) was first introduced by Kramer in 1977, it has been the most important renal replacement modality in critically ill patients.[1] Although both hemodialysis and peritoneal dialysis are established interventions for patients who require renal replacement, CRRT is known to be a more efficient tool in stabilizing circulatory, acid-base, and electrolyte balance especially when the patient has unstable vital parameters.[2] Despite these advantages, CRRT in children has been used only since 1985.[3]

In 2001, the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry started collecting and analyzing the in-depth data of pediatric patients in the United States (US).[4] The ppCRRT Registry analyzed the data of 350 patients from thirteen pediatric centers in the US for 4 years and 4 months (from January 1, 2001, to May 12, 2005).[5] Subsequent to this analysis, many papers have been published demonstrating that CRRT is a very important tool for critically ill children.[4-6]

However, there have been only four studies with detailed analyses of the patients treated with CRRT in recent years in Korea. In 2005, Lim et al. enrolled 23 patients for 4 years and reported that the survival rate was affected by the

PRISM III score and the number of vasopressors administered at the time of initiation of CRRT.[7] Two years later, our previous study reported that early initiation of CRRT prevented systemic worsening and progression of fluid overload.[8] Lee et al. suggested that nafamostat mesilate (Futhan®) could be a good optional anticoagulant in pediatric patients with a high risk of bleeding and receiving CRRT.[9] Oh et al reported that CRRT was effective in lowering the plasma ammonia level in neonates in the neonatal intensive care unit (NICU).[10]

However, the number of pediatric patients or the duration of these studies were too small or too short for a comprehensive present status, compared to the ppCRRT Registry (23 patients for 4 years,[7] 32 patients for 3 years,[8] 40 patients for 4 years,[9] and 17 neonates for 10 years,[10] respectively). Our center is the biggest tertiary care center in Korea with an experience of 14 years with CRRT. Therefore, the objective of this study was to evaluate the clinical course of children requiring CRRT and to analyze the factors which lead to a need for CRRT or influence the outcome of CRRT. with a large number of patients over a long duration.

II. MATERIALS AND METHODS

A retrospective study was performed, including the medical records of 291 children (0-18 years) admitted to the intensive care unit (ICU) of Severance hospital in South Korea who were under the treatment of a pediatric nephrologist and received CRRT between January 1, 2003 and December 31, 2016 (Figure 1). Patients over 19 years old were excluded from this study. The study was approved by the local institutional review board (IRB).

During the study period, patients receiving CRRT (171 boys [58.8%] and 120 girls [41.2%], with a mean age of 6.6 years [range 1.1 - 12.1 years]) were included. Three different types of CRRT machines were used: MultiFiltrate™ CRRT device (Fresenius Medical Care (FMC), Germany), PRISMA® (Gambro Healthcare, Lakewood, CO, USA) and PRISMAFLEX® (Gambro Healthcare, Lakewood, CO, USA). Double-lumen catheters between 6.5 F and 13.5 F in diameter were inserted into the central veins (Gambro Healthcare) depending on

the age and weight of the child.

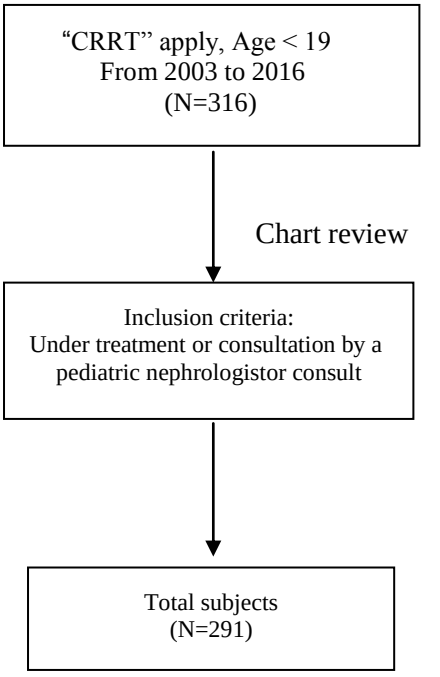


Figure 1. **Study design of patients who received CRRT**

Polyacrylonite or polysulfone hollow-fiber hemofilters (HF-20, ST- 60/100, Gambro/ multifilter number 4, multipaed, FMC) were used in all patients, depending on the patient's weight. HF-20 or multipaed filters were used in children weighing less than 10 kg; ST-60 were used in patients weighing 10 to 20 kg, and ST-100 or multifilter number 4 filters were used in children weighing more than 20 kg.

Commercially prepared bicarbonate-buffered hemofiltration replacement fluid (Hemosol B0, Gambro Healthcare, Seoul, Korea) was used as a dialysate and replacement fluid. The blood flow rate was determined as 5 mL/kg/min. The predilution replacement fluid rate or dialysate rate was determined at a rate of

2,000 mL/1.73 m^2/hour. The mode of CRRT was selected from one of the following, depending on the patient's status of solute imbalance: continuous venovenous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). These were determined by the pediatric nephrologists.

The time to initiate CRRT was decided by the intensivist depending on each patient's clinical condition such as anuria or oliguria (<0.5 mL/kg/h), positive fluid balance regardless of administration of high doses of diuretics (over furosemide 1 mg/kg/h). Each patient's fluid removal rate was also determined by the nephrologist depending on the patient's fluid status. Anticoagulation was not administered at the time of initiating CRRT; however, if the filter was blocked within 12 hours of initiation of the CRRT, anticoagulation agents such as continuous heparin or nafamostat mesilate infusion via the pre-blood pump port were used.

At the time of initiating CRRT, the following data were obtained for all patients: gender, age, weight, diagnosis, and underlying patient conditions, blood flow rate, severity scores (Pediatric Risk of Mortality Score [PRISM] III),[11] blood pressure, need for inotropic agents, diuretics or anticoagulants, results of the laboratory tests, hours to starting CRRT, and mortality or survival rate during CRRT. In this study, the estimated glomerular filtration rate (eGFR) was calculated using the Bedside Schwartz equation[12, 13] for children:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = (0.41 \times \text{Height in cm}) / \text{Creatinine in mg/dL}).$$

The percentage of fluid overload at CRRT initiation (%FO) was calculated using the following formula[14]:

$$\%FO = (\text{Fluid In} - \text{Fluid Out})/ (\text{ICU admission weight}) \times 100\%.$$

Statistical analysis

Statistical analyses were performed, using the SPSS for Windows version 18.0 (SPSS Inc., Chicago, Illinois, USA). The independent *t*-test was used for continuous variables and expressed as a mean ± standard deviation. Chi-square test, Fisher's exact test, and Mann–Whitney tests were used to analyze the categorical variables. Multiple logistic regression analysis was used to identify independent predictive factors for critically ill children treated with CRRT. Univariate and multivariate Cox regression analyses were performed to analyze the influence of each factor on mortality. In the multivariate model, we included the baseline factors that were found to be associated with mortality on univariate regression analysis. All differences were considered statistically significant at a *P* value< 0.05.

III. RESULTS

Demographics and clinical manifestations of the patients treated with CRRT are presented in Table 1. Of all children requiring CRRT, 58.8% were males. There were 55 patients (18.9%) aged less than 1 year, and 10% were aged less than 6 months. Fifty-five children (18.9%) weighed less than 10 kg, and 191 children (65.6%) weighed less than 30 kg. The mean age was 6.6 years (range 1.1 - 12.1 years) and the mean body weight was 23.2 kg (range 5.9– 40.5 kg).

Fifty-five patients received inotropic agents at CRRT initiation, and 30 of these patients required more than three kinds of inotropics. The mean duration in the ICU before CRRT initiation was 13.08 ± 5.86 hours.

Table 1. Characteristics of patients receiving CRRT

Variables	Total number of patients (n=291)
	Number of patients (%)
Age	
<1month	9(3.1%)
1-6 month	20(6.9%)
7-12month	26(8.9%)
1-3year	54(18.6%)
3-5year	45(15.5%)
5-10year	54(18.6%)
10-15year	59(20.3%)

15-20year	25(8.6%)
Sex	
Male	171(58.8%)
Female	120(41.2%)
Weight (kg)	
<10	55(18.9%)
10-19	98(33.7%)
20-29	38(13.1%)
30-49	72(24.7%)
50-69	25(8.6%)
>70	3(1.0%)
Vasopressors at CRRT initiation	
0	85(29.2%)
1	171(58.8%)
2	5(1.7%)
>3	30(10.3%)
ICU days before CRRT initiation (hours)	13.08± 5.86

CRRT: Continuous renal replacement therapy, ICU: intensive care unit

The details of the CRRT are shown in Table 2. Eighty-one patients received a combination of diffusion and convection (CVVHDF), 63 patients received the diffusion only CRRT modality (CVVHD), and only one patient received a convective modality (CVVH). In all 156 (55.9%) patients were initiated on CRRT without anticoagulants. Seventy-two (25.8%) patients were initiated on CRRT with a single infusion of nafamostat mesilate and 35 (12.5%) patients received a single dose of heparin. Twelve (4.3%) patients were switched from heparin to nafamostat mesilate and 4 (1.4%) patients were switched from nafamostat mesilate to heparin. The most common site of insertion of the initial hemo-catheter was left femoral (33.0%) and right femoral vein (31.9%), respectively. Twenty-one patients (7.8%) received extracorporeal membrane oxygenation (ECMO) and CRRT simultaneously. In such cases, the CRRT pump was cannulated into the ECMO circuit. The mean blood flow rate was 72.65±30.89 ml/min and the median PRISM III score was 5. The overall survival rate was 31.2 %. PRISMA® (80.8%) was the most commonly used equipment for CRRT (Table 3).

The indications for initiating CRRT are listed in Table 4. The most common indications for CRRT were a combination of fluid overload and uremia with

oliguria (60%), isolated oliguria refractory to diuretic treatment (46%), and isolated uremia (12.0%). Metabolic acidosis (7.6%) and isolated electrolyte imbalance (3.8%) were also marked as the cause for initiating CRRT in children.

Table 2. Technical characteristics of CRRT

Characteristics	Total number of patients (n=291)
	Number of patients (%)
Modality	**145(49.8%)**
CVVH	1(0.7%)
CVVHD	63(43.4%)
CVVHDF	81(55.9%)
Anticoagulation	**279(95.9%)**
No anticoagulation	156(55.9%)
Heparin	35(12.5%)
Nafamostat mesilate	72(25.8%)
Nafamostat mesilate→ heparin	4(1.4%)
Heparin→Nafamostat mesilate	12(4.3%)
Initial catheter position	**270(92.8%)**
Right femoral	86(31.9%)
Left femoral	89(33.0%)
Right internal jugular	31(11.5%)
Left internal jugular	22(8.1%)
Subclavian	20(7.4%)
PCPS(ECMO)	21(7.8%)
Other	1(0.4%)
Blood flow rate (ml/min)	
Range	15-180
Mean	72.65 ± 30.89
PRISM III score	**6(9.7%)**
Median	5(8.1%)
Survivors	**91(31.2%)**

CRRT: Continuous renal replacement therapy, CVVH: Continuous Veno-Venous Hemofiltration, CVVHD: Continuous veno-venous hemodialysis, CVVHDF: Continuous veno-venous hemodiafiltration
PCPS: percutaneous cardiopulmonary support, ECMO: Extracorporeal membrane oxygenation, PRISM: The Pediatric Risk of Mortality

Table 3. Distribution of CRRT machines which used to patients

CRRT machines	Total number of patients (n=291)
	Number of patients (%)

PRISMA ®	235(80.8%)
PRISMAFLEX ®	53(18.2%)
FMC ®	1(0.3%)
Unknown	2(0.6%)

CRRT: Continuous renal replacement therapy

The presumptive diagnoses of patients who received CRRT were renal disease (e.g. focal segmental glomerulosclerosis (FSGS), nephrotic syndrome and hemolytic uremic syndrome (HUS), pure sepsis and drug intoxication-. 86.4% of the renal disease patients and 100% of the patients with drug intoxication survived after CRRT. Although malignancy was the most common underlying disease (116 patients, 39.9%), only 19.0% survived following CRRT treatment (Table 5).

Table 6 shows a comparison of the variables between survivors and non-survivors after CRRT. There was no difference in the age, weight, duration of CRRT, blood flow rate, and urine output. However, the mortality was higher in males than in females (P= 0.028). Mortality was also higher in children who required inotropic agents, diuretics, and anticoagulation agents compared to those who did not require these therapies (P<0.001, 0.025 and 0.013, respectively). In addition, the non-survivors group had a statistically significant higher %FO than the survivors' group (P=0.041).

Table 4. Principal diagnosis and survival of CRRT patients

Indication	**Total number of patients (n=291)**
	Number of patients (%)
Fluid overload only	25(8.6%)
Uremia only	35(12.0%)
Oliguria	46(15.8%)
Fluid overload + uremia + oliguria	60(20.6%)
Uremia+oliguria	12(4.1%)
Electrolyte inbalace	11(3.8%)
Electrolyte inbalance+overload	1(0.3%)
Metabolic acidosis	22(7.6%)
Sepsis	11(3.8%)
Others	8(2.7%)

CRRT: Continuous renal replacement therapy

Table 5. Indications for CRRT initiation

Parameter	Numbers (n)	Survivors (n)	Survival (%)
Pure sepsis	15	5	33.3
Neurologic disease	40	20	50.0
Cardiac disease	32	8	25.0
Renal disease	22	19	86.4
FSGS	7	7	100.0
Nephrotic syndrome	2	2	100.0
Obstructive uropathy	1	1	100.0
HUS	4	3	75.0
Rhabdomyolysis	4	3	75.0
Others	4	3	75.0
Liver disease	29	10	34.4
Malignancy	116	22	19.0
No tumor lysis syndrome	108	15	13.9
Tumor lysis syndrome	8	7	87.5
Drug intoxication	1	1	100.0
Pulmonary disease	10	2	20.0
Metabolic disease	2	0	0.0
Immune deficiency	2	0	0.0
Other	22	3	13.6

CRRT: Continuous renal replacement therapy, FSGS: focal segmental glomerulosclerosis, HUSP: hemolytic uremic syndrome

Table 6. Comparison of variables in patients comparison of variables between the survivors and non-survivors groups in patients receiving CRRT

Valuables	Survivors (n=93)	Non-survivors (n=198)	*P value*
Age (years) ± SD	6.7±5.7	6.4±5.3	0.853
Male sex	46 (49.5%)	125 (63.1%)	0.028
Weight (kg)	21.2 ± 15.3	24.5±18.1	0.132
BSA (m^2)	0.9 ± 0.4	0.8 ± 1.0	0.091
Time until CRRT initiated† ± SD (hours)	4.4±8.4	2.8±3.9	0.256
Duration of CRRT ± SD (days)	8.1 ± 9.3	6.3 ± 7.3	0.095
Blood flow rate (ml/min)	70.3±30.0	74.4±31.7	0.298
Use of inotropics	50 (53.7%)	152 (76.8%)	<0.001

Use of diuretics	53 (57.0%)	142 (71.7%)	0.025
Use of anticoagulation	25 (26.9%)	29 (14.6%)	0.013
%FO at CRRT (%)	4.7±4.0	6.6±7.4	0.041
Urine output rate at CRRT(mL/kg/hr)	1.6±1.8	1.4±1.8	0.612
PRISM III score	15.0±7.8	12.7±7.0	0.207

CRRT: Continuous renal replacement therapy, %FO: percent of fluid overload, PRISM: The Pediatric Risk of Mortality, SD: Standard deviation
†Hours from admitting intensive care unit (ICU) to CRRT initiation

Table 7 demonstrates a comparison of the laboratory variables between the survivors and non-survivors following CRRT. There were statistically significant differences between the groups in platelet counts, BUN, and creatinine level. Other parameters including eGFR had no significant difference.

Multiple logistic regression analyses showed that sex, platelet count, and creatinine were predictive for the need of CRRT, survival or anything else (odds ratio [OR]: 2.074, 95% CI: 1.132-3.799, *P*=0.018; OR: 0.965, 95% CI: 0.945-0.985, *P*= 0.001; OR: 1.003, 95% CI: 0.870-1.156, *P*=0.036, respectively) (Table 8).

Kaplan-Meier survival curves for patients treated with CRRT indicate that there was no statistically significant difference in the combined cumulative survival of patients receiving diuretics in comparison to those who did not (P=0.760). However, patients receiving inotropics and anticoagulation agents showed an increased cumulative survival compared to patients who did not receive these agents (P=0.010, P=0.046, respectively). (Figure 2).

Table 7. Comparison of laboratory results between survivors and non-survivors among patients who received CRRT

Parameter	**Survivors (n=93)**	**Non-survivors (n=198)**	***P value***
Complete blood count			
WBC (/mm3)	13163.41 ± 11733.89	9585.59 ± 10826.74	0.015
Hemoglobin (g/L)	9.65 ± 2.70	9.87±2.78	0.538
Hematocrit (%)	28.92±8.03	29.63±8.90	0.531
Platelet count ($x10^3/\mu L$)	256.66±186.57	138.40±146.30	<0.001
Coagulation tests			

Prothrombin Time (sec)	24.81±30.76	24.60±26.33	0.955
aPTT (sec)	57.48±45.72	58.57±44.74	0.856
ABGA			
pH	7.32±0.15	7.32±0.17	0.849
pCO2 (mmHg)	38.75±17.57	43.04±25.27	0.165
pO2 (mmHg)	100.14±64.97	91.82±69.33	0.360
Lactate (mg/dL)	5.09±5.70	6.44±5.59	0.164
Routine chemistry			
Glucose (mg/dL)	129.39±83.01	152.85±99.37	0.062
Potassium (mg/dL)	4.35±1.12	4.14±1.24	0.178
tCO2 (mg/dL)	18.72±7.22	19.75±7.22	0.277
BUN(mg/dL)	40.21±44.46	26.14±26.87	0.008
Creatinine (mg/dL)	2.50±3.86	1.03±1.13	0.001
eGFR (mL/min/1.73 m^2)	83.56±60.25	77.85±46.12	0.670

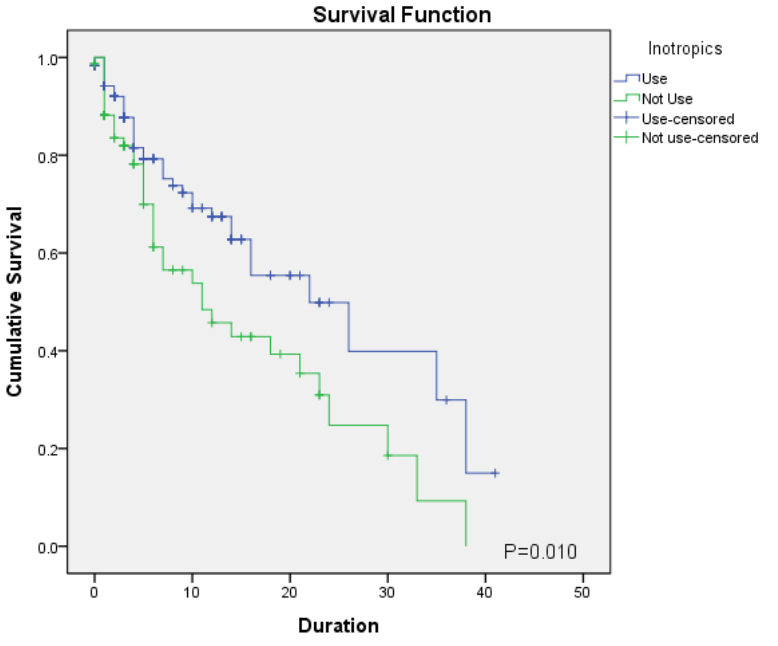
WBC: white blood cell, aPTT: activated Partial Thromboplastin Time, ABGA: arterial blood gas analysis, pH: acidity, pCO2: partial pressure of carbon dioxide, pO2: partial pressure of oxygen, tCO2: total carbon dioxide, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate

Table 8. Multiple logistic regression analysis of the risk for mortality in CRRT receiving patients

Variables	Mortality	
	OR (95% CI)	*P*-value
Sex	2.074 (1.132-3.799)	0.018
Use of inotropics	0.545 (0.283-1.050)	0.070
Use of diuretics	0.891 (0.431-1.841)	0.755
Use of anticoagulation	1.646 (0.712-3.803)	0.244
%FO at CRRT	1.030 (0.985-1.077)	0.193
WBC	0.998 (0.969-1.028)	0.910
Platelet count	0.965 (0.945-0.985)	0.001
BUN	1.004 (0.991-1.017)	0.557
Creatinine	1.003 (0.870-1.156)	0.036

CRRT: Continuous renal replacement therapy, %FO: percent of fluid overload, WBC: white blood cell, BUN: blood urea nitrogen, OR: odds ratio, CI: confidence interval

(A)



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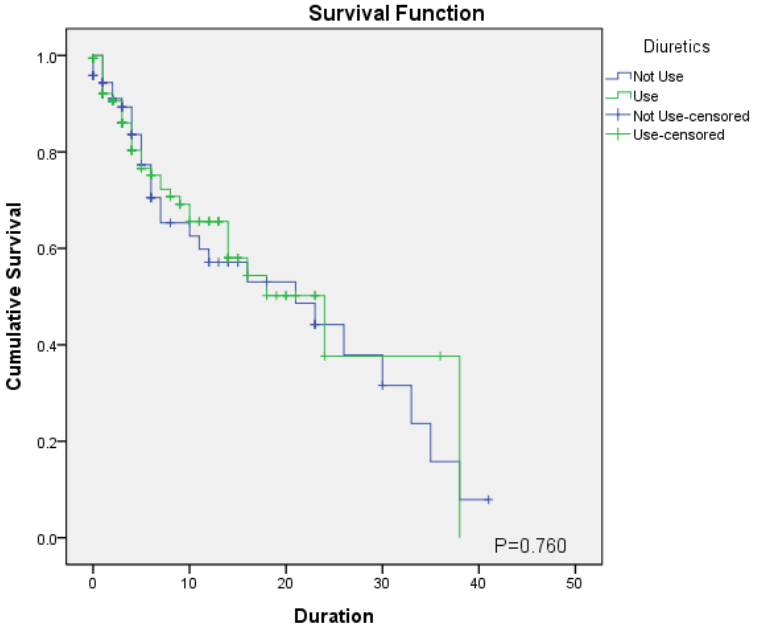

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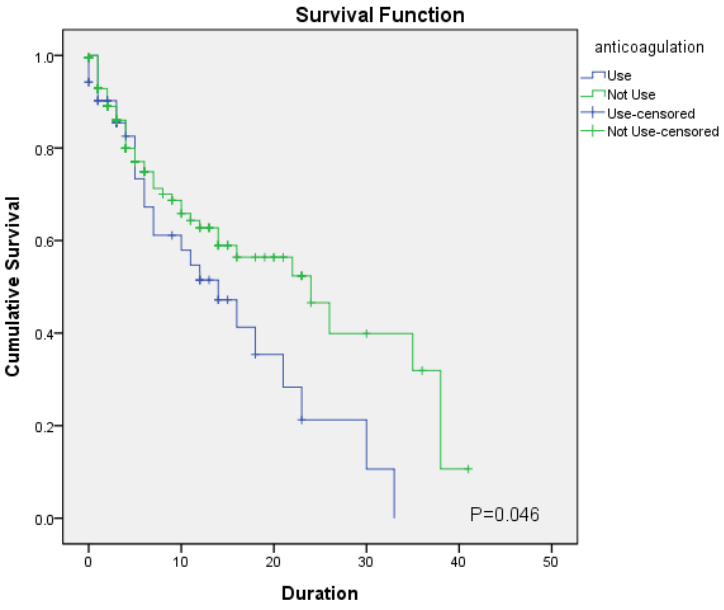

Figure 2. Kaplan-Meier survival curves for patients receiving CRRT (A) Survival comparison depending on sexes (B) Survival comparison between anticoagulation used group and not-used group (C) Survival comparison between diuretics used group and not-used group

IV. DISCUSSION

CRRT is an important treatment modality in the field of intensive care. In critically ill children, appropriate treatment has a significant impact on their future survival or prognosis. However, research on CRRT has been delayed compared to those on hemodialysis or peritoneal dialysis, because 1) CRRT must be administered for 24 hours a day, 2) almost all CRRT machines can only be used in the ICU, and 3) a skilled physician is necessary to operate these machines. In Korea, the number of skilled pediatric nephrologists and well-trained CRRT nurses is very small and the number of pediatric patients is much smaller than that of adults. These factors make research on pediatric CRRT difficult in Korea.

According to our results, most patients receiving CRRT were less than 10 years

of age (71.1%) and weighed less than 30 kg (65.7%). Small patients develop AKI in the early stage and AKI might progress rapidly, and thus, requiring renal replacement. If children develop AKI, they should be carefully monitored in the ICU and early initiation of CRRT should be considered. As seen in Table 5, patients with an underlying renal disease showed a better recovery and survival rate, indicating that CRRT should be considered promptly when these patients present with AKI.

Similar to other studies[4,5], continuous veno-venous hemodiafiltration (CVVHDF) mode was the most common modality used in our study. CVVHDF effectively resolves fluid retention and improves the electrolyte imbalance at the same time. The commonest catheter insertion position was the femoral vein (64.9%). Probably, the femoral site is more easily accessible without an ultrasonography.

Univariate analysis also showed that platelet counts, blood urea nitrogen (BUN), and creatinine level were different between the surviving and non-surviving groups. On multivariate analysis, it was found that a lower platelet count and higher creatinine level at the initiation of CRRT, were indicators of a higher mortality rate.

However, in contrast to the ppCRRT, the Pediatric Risk of Mortality (PRISM) score itself was not significant in predicting mortality in our study. The PRISM score indicates the patient's condition and severity at the time of ICU admission; however, it takes about 2.8-4.4 hours to initiate the CRRT. In addition, some patients were initiated on CRRT in the emergency room or in the ward rather than in the ICU; hence, the PRISM score may not be an accurate predictor of mortality.

Fluid overload or oliguria accounted for 45% of all cases, and fluid retention was an important indication for initiating CRRT in this study. %FO was significant in the univariate analysis; however, the significance was borderline (P= 0.041). Although %FO was an important factor to initiate CRRT in the ppCRRT study, it was not very significant in this study. This could be because the %FO was not accurately measured before and after CRRT. In addition, the

patients' weight at the time of admission to the ICU and at the time of CRRT initiation might be also different. Changes in the chest x-ray and in the weight of patients are not reflected in this parameter. %FO might be an indicator of simple fluid retention.

There were limitations in the mortality predictors used in previous studies and we conducted several analyses to identify additional useful indicators. We also found that the use of inotropic agents and anticoagulants were important factors in predicting mortality. These are new indicators, which were not included in the parameters used for calculating the PRISM score or %FO in the existing study.

There were 21 patients (7.8%) with percutaneous cardiopulmonary support (PCPS) or extracorporeal membrane oxygenation (ECMO) connected to CRRT. The methods of CRRT connection to ECMO, duration of use, and the difference in survival rate were not separately analyzed in this study. Additional studies can be undertaken if plasmapheresis is performed simultaneously with CRRT in patients with liver disease.

The major difference in the use of anticoagulants is that citrate was used in patients with a bleeding tendency in the US study, but nafamostat mesilate is used in Korea because citrate is not licensed in Korea. In some studies, nafamostat mesilate has been known to have fewer complications such as hypocalcemia, compared to citrate.[15, 16]

The limitations of our study are as follows: Since this was a single-center study, it might have some bias compared to the ppCRRT registry, in which many institutes were enrolled. Moreover, this is a retrospective study compared to the prospective ppCRRT registry. However, in contrast to the ppCRRT, which had a similar number of patients but was conducted only for 5 years, our study was conducted in a single institution for 14 years. During the 14 years of the study period, there were significant changes in the development of machines, changes in technique, and the proficiency of doctors and nurses dealing with CRRT. The difference in survival rates might be greater at the end of the study period than at the initial period. These factors could affect the results; however, we could not accurately identify them. In addition, both univariate and multivariate analysis of

gender showed statistical significance (P=0.028 and P=0.018), but no accurate reason could be identified. This could be due to a bias in the process of collecting data and selecting patients.

Nevertheless, Severance Hospital is one of the five major hospitals in Korea and the number of patients who received CRRT in this single center is almost similar to the number of patients in 13 major hospitals in the US. In addition, the study period was relatively longer than the ppCRRT (14 years vs 5 years) reflecting almost all the cases of pediatric CRRT in Korea. Moreover, since this is a study in Korean children, it also reflects specific ethnic and national characteristics compared to the US studies.

There have been no multicentric CRRT studies in pediatric patients worldwide, apart from the US ppCRRT. Since the year 2005 when ppCRRT was implemented, there have been no significant researches about pediatric CRRT. Based on this study, an effort should be made in Korea to design an index to predict the mortality and to increase the survival of patients. Our study is significant in that it was the first study on pediatric CRRT in a large number of patients in a single institution.

V. CONCLUSION

In conclusion, this is the first study that identified the potential predictors of prognosis in critically ill children treated with CRRT. Based on our 14 years of experience, we conclude that CRRT is an effective method for critically ill children with AKI or those with an underlying renal disease without significant complications. Further multicenter or large prospective studies will be necessary to evaluate the methods for increasing the survival rates in children who require CRRT in the future.

REFERENCES

1. 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 1977;55:1121–2.
2. Riegel W, Habicht A, Ulrich C, Kohler H. Hepatoactive substances eliminated by continuous venovenous hemofiltration in acute renal failure patients. Kidney Int Suppl 1999;72:S67–70.
3. Ronco C, Brendolan A, Bragantini L, Chiaramonte S, Fabris A, Feriani M, et al. Treatment of acute renal failure in the newborn by continuous arteriovenous hemofiltration. Trans Am Soc Artif Intern Organs. 1985;31:634-8.
4. Goldstein SL, Somers MJ, Brophy PD, Bunchman TE, Baum M, Blowey D, et al. The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry: Design, development and data assessed. Int J Artif Organs 20054;27:9–14.
5. Symons JM, Chua AN, Somers MJ, Baum MA, Bunchman TE, Benfield MR, Brophy PD, Blowey D, Fortenberry JD, Chand D, Flores FX, Hackbarth R, Alexander SR, Mahan J, McBryde KD, Goldstein SL. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol 2007;2:732-8.
6. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int 2005;67:653-8.
7. Lim YJ, Jin HS, Hahn HW, Oh SH, Park SJ, Park YS. Outcome of Continuous Renal Replacement Therapy in Children. Korean J Pediatr 2005;48:68-74.
8. Park KS, Son KY, Hwang YS, Kim JA, Cheung IC, Shin JI, et al. Outcome and Prognosis in Critically III Children Receiving Continuous Renal Replacement Therapy. Child Kid Dis 2007;11:247-54.

9. Lee ST, Cho HY. The Use of Nafamostat Mesilate as an Anticoagulant during Continuous Renal Replacement Therapy for Children with a High Risk of Bleeding. Child Kid Dis 2014;18:98-105.
10. Oh MY, Lee BS, Oh SH, Jang HJ, Do HJ, Kim AR, et al. Continuous Renal Replacement Therapy in the Neonatal Intensive Care Unit: A Single Center Study. Neonatal Med 2014;21:244-50.
11. Pollack MM, Ruttimann UE, Getson PR. The pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
12. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-37.
13. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol 2009;4:1832-43.
14. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics 2001;107:1309-12.
15. Chadha V, Garg U, Warady BA, Alon US. Citrate clearance in children receiving continuous venovenous renal replacement therapy. Pediatr Nephrol 2002;16:819–24.
16. Choi JY, Kang YJ, Jang HM, Jung HY, Cho JH, Park SH, et al. Nafamostat Mesilate as an Anticoagulant During Continuous Renal Replacement Therapy in Patients With High Bleeding Risk: A Randomized Clinical Trial. Medicine (Baltimore) 2015;94:e2392.

ABSTRACT(IN KOREAN)

소아에서의 지속적 신대체요법(CRRT)에 대한 후향적 연구 : 단일기관에서의 14년의 경험

<지도교수 신 재 일 >

연세대학교 대학원 의학과

이 금 화

지속적 신 대체 요법 (Continuous renal replacement therapy, CRRT) 은 급성 신장 손상을 가진 중환자 어린이의 신장 대체 요법의 중요한 치료법이다. 본 연구의 목적은 CRRT가 필요한 아동의 임상 경과를 평가하고 CRRT와 관련된 인자를 분석하는 것이다. 본 연구는 2003 년과 2016 년 사이에 CRRT 치료를 받은 세브란스 병원의 중환자 실에 입원한 19세 미만 모든 소아 환자들 중에서 소아 신장과 협진을 진행한 환자들을 대상으로 후향적 연구를 진행하였다. 성별, 연령, 체중, 진단, CRRT에 대한 적응증, 혈류 속도, CRRT 기계의 종류, 항응고제에 대한 필요성, CRRT 사용 일수 및 환자 생존율에 대하여 조사를 하였다. 그 결과 291 명의 환자가 확인되었고 환자들은 기저 질환에 따라 먼저 분류되었다. 평균 연령은 6.6 세 (1.1-12.1 세)였고 평균 체중은 23.2kg (5.9-40.5kg) 였다. CRRT를 시작하게 된 초기 원인은 대사성 산증 (24 %), 체액 과다, 핍뇨가 동반된 요독증 (24 %), 요독증 (17 %), 체액 과다 (11 %) 및 전해질 불균형 (8 %) 순이었다. CRRT 양상은 지속적 정정맥 혈액투석여과법 (CVVHDF, 27.6 %) 및 지속적 정정맥 혈액 투석법 (CVVHD, 22 %) 를 포함하였고 평균 CRRT 적용 기간은 5.8 일이었다. 34 %는 Nafamostat mesilate를 사용하였고 7 %는 전신 헤파린으로 바뀌었다. 12 %는 전신 헤파린만 사용하였고,

항응고제를 사용하지 않은 환자는 54 %였다. 27 명의 환자 (9.2 %) 가 체외 막형 산소화 요법 (Extracorporeal membrane oxygenation, ECMO)과 CRRT를 동시에 받았다. 전체 생존율은 32.1 % 였다. 이에 따라 우리 센터의 14 년간의 포괄적 경험을 바탕으로 CRRT는 심각한 합병증 없이 급성 신부전 또는 불안정한 생체 징후를 가진 중환자 어린이에게 가장 좋은 방법이라는 결론을 얻었다.

핵심되는 말: 지속적 신 대체 요법, 급성 신부전, 후향적 연구