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Overview of Pediatric Continuous Renal Replacement Therapy in Acute Kidney Injury

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= **Abstract** =

Acute kidney injury (AKI) is associated with mortality and may lead to increased medical expense. A modified criteria (pediatric RIFLE [pRIFLE]: Risk, Injury, Failure, Loss, and End-stage renal disease) has been proposed to standardize the definition of AKI. The common causes of AKI are renal ischemia, nephrotoxic medications, and sepsis. A majority of critically ill children develop AKI by the pRIFLE criteria and need to receive intensive care early in the course of AKI. Factors influencing patient survival (pediatric intensive care unit discharge) are known to be low blood pressure at the onset of renal replacement therapy (RRT), the use of vasoactive pressors during RRT, and the degrees of fluid overload at the initiation of RRT. Early intervention of continuous RRT (CRRT) has been introduced to reduce mortality and fluid overload that affects poor prognosis in patients with AKI. Here, we briefly review the practical prescription of pediatric CRRT and literatures on the outcomes of patients with AKI receiving CRRT and associations among AKI, fluid overload, and CRRT. In conclusion, we suggest that an increased emphasis should be placed on the early initiation of CRRT and fluid overload in the management of pediatric AKI. (J Korean Soc Pediatr Nephrol 2011;15:107-115)

Key Words : Acute kidney injury, Continuous renal replacement therapy, Children

Introduction

Acute kidney injury (AKI), previously referred to as acute renal failure, is a complex renal disorder with multiple causes and is manifested by various clinical abnormalities from minimal serum creatinine (SCr) elevation to anuria [1]. The reported incidence rate of AKI was estimated to be 82% and 47-61% in critically ill patients in pediatric intensive care units (PICU) and neonate intensive care units, respectively [2-5]. However, the exact incidence rate might be higher because these values only represent the most severe cases

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of AKI. The common etiology of AKI in children includes hypoxia/ischemia, nephrotoxins, and sepsis [6].

Although no uniform strategies exist, there are three dialysis modalities for the treatment of AKI: intermittent hemodialysis (IHD), peritoneal dialysis (PD), and continuous renal replacement therapy (CRRT). Each has its own advantages and disadvantages, and the choice is guided by patient characteristics, goals of therapy, and availability at each hospital [7].

CRRT is defined as any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and is applied for 24 hours/day [8-10]. CRRT is becoming the preferred treatment of AKI in critically ill pediatric patients who are hemodynamically unstable and sometimes with multiple organ failure. CRRT allows gentle and gradual removal of solutes and fluid, thereby decreasing the episodes of hypotension and electrolyte disturbance [11]. In this review, we will focus on the use and outcome of CRRT in the treatment of AKI.

Modified pRIFLE criteria and AKIN staging

The creatinine-based pediatric modified RIFLE (pRIFLE) criteria for AKI are used to classify patients using the changes in estimated creatinine clearance (eCCr) from baseline eCCr [12]. The pRIFLE criteria divide the severities of AKI as risk, injury, failure, loss, and end stage renal disease [2]. Baseline kidney function is defined as the lowest known SCr value in the previous three months. The minimal diagnostic criterion for AKI is a 25% decrease in eCCr or urine output less than 0.5 mL/kg/hr for 8 hours [12].

AKI using the acute kidney injury network (AKIN) criteria differs from pRIFLE by inclusion of a serum creatinine rise of 0.3 mg/dL to qualify for AKIN Stage I (pRIFLE-Risk equivalent) and by the duration of less than 0.5 ml/kg per hour for more than 6 and 12 hours at Stage I and II (Table 1) [13, 14].

Indications for pediatric CRRT

CRRT has also been used successfully for

Table 1. Acute Kidney Injury Network (AKIN) Staging System [12].

Stage	SCr criteria	UO criteria
1	Increase in SCr to ≥0.3 mg/dL (≥26.4 μmol/L) or to ≥150% to 200% (1.5- to 2-fold) from baseline	<0.5 mL/kg/h for >6 h
2	Increase in SCr to >200% to 300% (>2- to 3-fold) from baseline	<0.5 mL/kg/h for >12 h
3	Increase in SCr to >300% (>3-fold) from baseline (or SCr of ≥4.0 mg/dL [≥354 μmol/L] with an acute increase of at least 0.5 mg/dL [44 μmol/L])	<0.5 mL/kg/h for >12 h <0.3 mL/kg/h for >24 h or anuria for 12 h

Abbreviations : SCr, serum creatinine; UO, urine output; h, hours

renal support in the following patients [15-17]: 1) hemodynamically unstable AKI patients with reduction in urine output or elevated SCr; 2) patients with diuretics-resistant hypervolemia with pulmonary edema and respiratory failure; 3) patients with overwhelming sepsis; 4) patients with oliguria or anuria who require large volume of total parenteral fluids, blood products, and other fluids; 5) inborn errors of metabolism (often in conjunction with hemodialysis), e.g., in urea cycle defect, organic acidemia, and maple syrup urine disease; 6) tumor lysis syndrome and stem cell or solid organ transplantation; 7) progressive and uncontrolled electrolyte imbalance such as dysnatremia and hyperkalemia and acid-base derangements (e.g. severe lactic acidosis); 8) suspected end-organ uremia with pericarditis or encephalopathy; 9) drug intoxications with dialyzable toxins; 10) rhabdomyolysis.

Principles of CRRT

CRRT can involve any of the following four major transport mechanisms: diffusion, convection, adsorption, and ultrafiltration [18]. Diffusion is solute transport across a semi-permeable membrane; molecules move from an area of higher concentration to an area of lower concentration by a concentration gradient. Convection is a process where solutes pass across a semi-permeable membrane along with the solvent in response to a positive transmembrane pressure. Convection improves the removal of large particles. Adsorption is the removal of solutes from the blood because they cling to the membrane. High levels of adsorption can cause filters to clog and become ineffective. Ultrafiltration refers to the passage of water through a membrane under a pressure gradient. Higher pressures and faster flows increase the rate of ultrafiltration [9].

Different modalities of CRRT

There are four different modes of CRRT: 1) SCUF: Slow Continuous Ultrafiltration; 2) CVVH: Continuous Veno-Venous Hemofiltration; 3) CVVHD: Continuous Veno-Venous Hemodialysis; and 4) CVVHDF: Continuous Veno-Venous Hemodiafiltration. Replacement fluids can be given before or after the hemofilter (pre-or post-dilution) [11].

Significant advancements have taken place in the technology of CRRT. For example, many medical appliance companies offer CRRT machines such as Prisma® (Gambro, Sweden), Prismaflex® (Gambro, Sweden), Multifiltrate® (Fresenius Medical Care, USA), Diapact CRRT® (B. Braun, Germany), Acquarius® (Edwards Life Sciences, USA), Equa-Smart® (Medica, Italy), BM 25® (Edwards Life Sciences, USA), HF 400® (Infomed, Switzerland), Hygeia plus® (Kimal, UK), and Performer LRT® (Rand, Italy) [10]. Currently, Prisma®, Prismaflex®, and Multifiltrate® are available in the Korean market. A CRRT machine is usually placed in the CVVHDF mode for the addition of replacement solution. A bicarbonate buffer including Hemosol B zero®, Accusol®, Duosol®, Normocarb®, and PureFlow® is preferred to lactate buffer such as hemosol L zero®. This is because bicarbonate buffer is more biocompatible and has less risk of lactic acidosis than lactate buffer. Solute clearance

from small to large molecules is achieved by both convection and diffusion.

Vascular access for pediatric CRRT

The function of vascular access is crucial in the CRRT circuit. A double lumen venous hemodialysis catheter can be inserted into the femoral vein, internal jugular vein, or subclavian vein. The internal jugular site is preferable over the femoral route when clinical situation allows. If possible, the use of a 5 Fr. single lumen catheter should be avoided. Vascular access is usually determined by the patient weight: <3 kg, 6.5 Fr.; 3−10 kg, 7 Fr. dual lumen; 10−30 kg, 8−10 Fr. dual lumen; >30 kg, 10−12 Fr. dual lumen catheter [19]. The largest and shortest catheter would be best in allowing adequate blood flow for dose delivered and filter−circuit life.

Anticoagulation

The degree of anticoagulation required will depend on the coagulation status of the patient, blood flow rate, and the vascular access [20]. In children at risk of bleeding due to sepsis and disseminated intravascular coagulation (DIC) and when the baseline activated clotting time (ACT) is >200 seconds, it is possible to provide CRRT without anticoagulation. However, with heparin or citrate is better than with no anticoagulation even in liver failure and DIC because circuit survival means less CRRT downtime and more therapy delivered. Citrate has fewer bleeding complications than heparin. The citrate−induced toxicities include hypocalcemia, alkalosis, and hypernatremia [9]. It is helpful to pick institutional strategy and learn to use it well. Nafamostat mesylate (Futhane®) can also be used as the anticoagulant of choice unless citrate or acrylonitrile 69 (AN69) membranes are used. The AN69 membranes interact with Nafamostat mesylate and cause adsorption of Nafamostat mesylate to the hemofilter. In addition, the diminished negative surface charge of the surface−treated AN69 membranes with polyethyleneimines decreases high molecular weight kininogen binding and bradykinin generation. Different filter options for CRRT are

Table 2. Different Filter Options for CRRT [10, 21]

Filter	Miniflow10	M60 (AN69)	M100 (AN69)	ST60 (AN69 ST)	ST 100 (AN100 ST)	HF20 (PAES)	HF1000 (PAES)
Surface area (m^2)	0.042	0.6	1.0	0.6	1.0	0.42	1.15
Blood volume in set (mL)	50	97	120	93	152	60	165
Priming volume (mL)	500	1,000	1,000	1,000	1,000	500	2,000
Blood flow rate (mL/min)	25−50	80−100	100−150	80−100	100−150	25−50	100−150
Application (kg)	<10	>10	>30	>10	>30	<10	>30

Abbreviations : AN69 ST, acrylonitrile 69 surface treated; PAES, polyarylethersulfone.

summarized in Table 2.

Prescribing pediatric CRRT [21]

An example of CRRT prescription is described for practical use: When a 30 kg (surface area 1.0 m^2) boy with AKI requires CRRT, the preferable vascular catheter is 12 Fr., which can be placed in the right internal jugular vein. The AN69 ST 100 hemofilter can be chosen. The mode of CRRT is CVVHDF. The blood flow rate is 120 mL/min (3–5 mL/kg/min). The dialysate and replacement flow rates are 1,200 ml/hr and 1,200 mL/hr (20–60 mL/kg/hr or 2 L/1.73m^2/hr). The loading dose of heparin is 10–20 units/kg prior to connecting the patient to CRRT and the maintenance dose is 10–20 units/kg/hr. The ACT needs to be checked every hour for two hours and then every four hours. The ACT should be between 170 and 220 seconds. No anticoagulation is recommended with the platelet count <50,000/mm^3, the international normalized ratio (INR) >2.0, the activated partial thromboplastin time (aPTT) >60 seconds, and an episode of active bleeding. Laboratory tests such as sodium, potassium, blood urea nitrogen, creatinine, phosphate, ionized calcium, aPTT, and INR should be monitored every 12 hours for a day and then every 24 hours.

Complications of CRRT

The complications of CRRT are as follows [22]: 1) hypotension due to excessive ultrafiltration; 2) hypothermia due to the use of unheated solutions in high volumes; 3) bradykinin release syndrome in acidotic patient or in patients who require a blood prime, which is associated with the use of AN69 membrane for blood prime and is reduced by using ST 60 or ST 100 membrane; 4) clotting in the circuit (especially the filter), which may cause a significant blood loss; 5) electrolyte imbalance such as hypophosphatemia and hypokalemia; 6) anticoagulation–related problems such as hypocalcemia due to citrate and hemorrhage from overusing heparin; 7) bleeding from vascular access; 8) infection due to contamination from extracorporeal circuit or central venous catheter; 9) nutritional deficiency; and 10) air embolism due to leaks or faulty connections in tubing or line separation.

Outcomes of CRRT in children with AKI

There was a retrospective evaluation of 226 children who received RRT for AKI from 1992 to 1998 [23]. Factors influencing patient survival (PICU discharge) included the following factors: 1) low blood pressure at the onset of RRT (P<0.05), 2) the use of vasoactive pressors during RRT (P<0.01), 3) the diagnosis of the patients (primary renal failure with a high likelihood of survival vs. secondary renal failure with a poor outcome) (P<0.05), and 4) the modality of RRT (HF, PD, and HD) (P<0.01) [23]. Among these, the study concluded that the use of vasoactive pressor was a surrogate marker for the severity of illness and had the greatest prediction of survival. In a study by Lim et al. [24], patient survival was affected by the number of vasopressors the patients were taking at the initiation of CRRT and the Pediatric Risk of Mortality III scores.

Recently, pediatric nephrologists have focused on the importance of fluid overload (FO) in patients with AKI receiving CRRT [24-27]. Goldstein et al. [25] reported that lesser degrees of FO at the CVVH/D initiation was associated with improved outcomes (P=0.03) and improved outcomes were also observed when samples were adjusted for severity of illness (P=0.03). The median percent FO (%FO), calculated by [(fluid in)-(fluid out)/(ICU admission weight)]×100, was significantly lower in survivors than in non-survivors (P=0.02) and was also lower in survivors with multiple organ dysfunction syndrome (MODS) than in non-survivors with MODS (P=0.01) [26]. Percent FO was independently associated with CVVH survival in critically ill children with ≥three organ MODS [26]. Gillespie et al. [27] showed that children with high fluid overload (>10% over baseline) at CRRT initiation were at 3.02 times greater risk of mortality than those with low or no fluid overload (P=0.002). Hayes et al. [28] also reported that FO greater than 20% at the time of CRRT initiation was significantly associated with higher mortality for patients with AKI requiring CRRT. According to a study by Park et al. [29], FO was the only independent factor that reduced the survival rate, and CRRT was successful in treating critically-ill children Korean with AKI.

Collaboratively, a prospective pediatric CRRT (ppCRRT) registry has been collecting data from 13 pediatric centers over 5 years in America [30]. In a seven-center study from the ppCRRT registry, the percent FO at CRRT initiation was significantly lower in survivors than in non-survivors (P<0.03) [31]. Similarly, a positive fluid balance was an important risk factor associated with increased 60-day mortality in a European multicenter study [32].

The treatment outcomes of AKI were much better in children (70% at overall hospital survival, 79.9% at 3-5 year survival) [33, 34] than in adults in whom the mortality at 90 days was 44.7% despite higher-intensity treatment [35, 36]. Cerda et al. [37] suggested if FO develops and the patient does not respond to diuretics, which will lead to an increased risk of negative patient outcomes, an early initiation of CRRT might be preferable.

Conclusions

The outcomes among AKI children treated with CRRT were better than those treated without CRRT when RRT was started early in the course of AKI. Therefore, an early detection of AKI and rapid initiation of CRRT to critically ill pediatric patients will lead to better outcomes in terms of morbidity and mortality. Also, excessive volume overload was strongly correlated with poor outcomes in the previous studies, and an increased emphasis should be placed on the early initiation of CRRT in the management of pediatric AKI before excessive FO occurs.

한 글 요 약

급성 신손상을 가진 소아의 지속적 신대체 요법

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소아에서 급성 신손상의 흔한 원인들로는 신허혈, 신독성 약물들, 그리고 패혈증 등이 있으며, 신대체 요법 시작시의 저혈압, 신대체 요법 동안 승압제의 사용, 그리고 신대체 요법 시작시의 수액 과부하 정도가 환자의 생존(소아 중환자실 퇴원)에 영향을 미치는 요인들로 알려져 있다. 지속적 신대체 요법의 빠른 시작은 급성 신손상을 가진 환자들에게서 사망률과 예후에 나쁜 영향을 미치는 수액 과부하를 감소시키는 것으로 보고되었다. 이에 저자들은 소아 환자에게서 지속적 신대체 요법의 실제 처방과 급성 신손상, 수액 과부하, 그리고 지속적 신대체 요법간의 연관성 및 치료결과를 살펴보고자 한다. 결론적으로, 급성 신손상을 가진 소아의 치료에 있어서 과도한 수액 과부하가 발생하기 전에 빠른 지속적 신대체 요법의 시작이 필요하다고 제시하는 바이다.

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