Optimal stage of initiating continuous renal replacement therapy in the treatment of neonatal acute kidney injury

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Abstract. To explore the optimal stage of initiating continuous renal replacement therapy (CRRT) in the treatment of neonatal acute kidney injury (AKI), a total of 25 AKI neonates treated with CRRT were hospitalized at the Department of Neonatology of Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University (Shanghai, China) from November 2016 to June 2021. According to the renal function, the AKI neonates prior to CRRT were divided into two groups as follows: AKI stage 0-1 and AKI stage 2-3. The changes noted in specific indicators including renal function, electrolyte concentration, and acid-base balance index were analyzed at 0, 12, 24 and 48 h, and at the end of the CRRT treatment. Among the 25 neonates with AKI, serum potassium, urea nitrogen and creatinine levels were significantly decreased following 12 h of CRRT treatment and reached the normal range following 24 h of CRRT treatment with a significant increase in the volume of urine. The serum creatinine levels of the neonates in the AKI stage 0-1 group were significantly decreased following 24 h of CRRT treatment and urine output was significantly increased. At 24 h and following CRRT treatment, the levels of serum creatinine of AKI stage 2-3 neonates were higher than those of AKI stage 0-1 neonates ($F=3.013$, 5.005; $P<0.05$), and at all time-points, the urine output of AKI stage 0-1 was higher than that of AKI stage 2-3 ($F=13.785$, 4.008, 0.965; $P<0.05$). A total of four cases of thrombocytopenia, two cases of obstruction, and two cases of hypotension were noted in the course of CRRT treatment (the occurrence rate was 8/25). Therefore, it was concluded that CRRT could be an effective measure for the treatment of AKI neonates. Thus, ideally CRRT treatment of AKI neonates should be initiated in cases characterized as AKI stages 0-1.

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Introduction

Neonatal acute kidney injury (AKI) refers to the rapid decline of neonatal renal function caused by various etiologies, which is common in neonates admitted to the neonatal intensive care unit (NICU) and is associated with increased morbidity and mortality (1). The incidence of AKI in the NICU is estimated to be ~30% and those with AKI exhibit >4-fold higher independent odds of death (2). The main causes of neonatal AKI include perinatal asphyxia, followed by congenital kidney and urinary tract malformations, congenital heart disease, and sepsis. The clinical manifestations are oliguria or anuria, electrolyte disorder, imbalance of acid-base balance, and increased concentration of metabolites in plasma (3). At present, there are no effective prevention and treatment measures for neonatal AKI.

Continuous renal replacement therapy (CRRT), also known as continuous blood purification (CBP), removes harmful substances continuously, rapidly, and directly. In recent years, with the development of CBP technology, the application of CBP has been expanded from AKI in children to neonatal AKI (4). However, there is still a lack of large sample multicenter research data of CRRT regarding neonatal AKI treatment. A study conducted by The Children's Hospital of Ankara University in Turkey retrospectively evaluated NICU and PICU hospitalized patients who received CRRT from February 2010 to November 2015, proving that CRRT is a life-saving method, and an experienced team can be applied to critical children with AKI and fluid overload of any age and weight (5). In the present study, the clinical data of 25 AKI neonates treated with CRRT in the NICU were analyzed in order to explore the potential application of CRRT and its efficacy in the treatment of neonatal AKI.

Materials and methods

Ethics approval and consent to participate. All parents of the infants signed the informed consent for the study. The present study was approved (approval no. 2012C001-F01) by the Ethics Committee of Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University (Shanghai, China).

Subjects of the study. From November 2016 to June 2021, 41 critically ill neonates who received CRRT in the NICU of

Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University were included in the study. Among them, 25 AKI neonates were treated with CRRT as the subjects of the present study (cases treated with CRRT for other reasons, such as metabolic diseases were excluded). According to the diagnostic criteria of neonatal AKI (Table I), 25 cases were divided into two groups: AKI stage 0-1 (15 cases) and AKI stage 2-3 (10 cases). The gestational age (GA) of the 25 AKI neonates ranged from 33^{+4} to 40^{+1} weeks, the age of admission ranged from 2 to 28 days, and the birth weight range was 2,250-4,000 g. A total of 14 males, 11 females, 18 term infants, and 7 preterm infants were included. The primary diseases included 10 cases of severe asphyxia at birth, 8 cases of neonatal septicemia, and 7 cases of congenital metabolic diseases.

Diagnostic criteria for neonatal AKI. According to the AKI clinical practice guidelines issued by the Global Committee for the Improvement of the Prognosis of Kidney Diseases: Improving Global Outcomes (KDIGO) in 2013 (6), the current diagnostic criteria of neonatal AKI mainly depend on the changes in the concentration of serum creatinine and the volume of urine (Table I). Since the serum creatinine levels of neonates are influenced by maternal factors, premature delivery, hyperbilirubinemia, and other factors and the majority of the neonatal cases with AKI are non-oliguric cases with AKI, the early diagnosis of neonatal AKI is considerably difficult (7).

CRRT treatment for AKI neonates. The indications for CRRT were as follows: CRRT treatment was initiated as long as the diagnostic criteria of AKI were met and irrespective of the factors causing AKI or its stage (8,9).

The following method of CRRT was used: i) Operating methods: The equipment used was Plasauto IQ21, which was a blood purifier instrument manufactured in Japan. Continuous veno-venous hemodialysis filtration (CVVHDF) mode was selected according to the molecular weight of solute removal. The CRRT instrument was divided into the external blood circulation and the filter. The specific operation process was as follows: External blood from the circulation was mixed with physiological saline containing heparin and filtered; 68 ml red cell suspension was used to pre-fill the external blood circulation sample and the new sample was filtered. The blood circulation volume of CRRT was 38 ml (arterial line + venous line). The CRRT instrument was purchased from Japan Lai Fuen Co., Ltd. and the filtering capacity was 30 ml. For CRRT, 4Fr, 5Fr, single-tube, and a double-chamber central venous catheter were used. The arterial foramen was located at the telecentric end and the venous foramen at the proximal end, 2 to 3 mm apart. The blood recirculation was <10%. The most common puncture sites were the femoral vein, the internal jugular vein, and the umbilical vein, which could be used for neonates with an age <7 days. The blood purifier pipeline was connected for bypass. ii) The following CBP parameters were used: The initial flow rate of the blood pump was 3 ml/(kg/min) which was increased to 5 ml/(kg/min) according to the blood pressure. The replacement fluid and the dialysate had the following volume range: 20-30 ml/(kg/h) for the replacement fluid, and 15-25 ml/(min/m^2) for the dialysate. The dehydration speed was calculated by the following formula: Filter pump - dialysis pump-rehydration pump, uninterrupted flow. iii) The following dialysis and replacement fluids were used: Baxter dialysate (Baxter International, Inc.). The replacement solution was prepared by NICU nurses in the unit. The Ports scheme was adopted to improve the formula; specifically, Ringer's solution (3,000 ml) was mixed with 5% glucose solution (100 ml), 10% calcium chloride solution (7.5 ml), 50% magnesium sulfate solution (1.6 ml) and 5% sodium bicarbonate solution (200 ml). The ionic concentrations of the formula components were the following: 130.0 mmol/l sodium ion, 4.0 mmol/l potassium ion, 28.0 mmol/l bicarbonate ion, 1.5 mmol/l calcium ion, 3.2 mmol/l magnesium ion and 109.0 mmol/l chloride ion. The final concentration of glucose was 0.2 g/l. The ion concentration was adjusted according to electrolyte monitoring.

The following maintenance of CRRT was used: i) Anticoagulation was achieved by filtering and pre-filling with heparin solution. Heparin anticoagulation was used to maintain prothrombin time at 25-40 sec; the activated partial thromboplastin time range was 80-120 sec. The dosage range of heparin was generally 5-40 U/(kg/h). ii) The replacement of the filter membranes was performed in case blockage was noted during treatment. The termination indications of the CRRT were as follows: A neonatal urine volume of AKI >2 ml/(kg/h), the presence of anhydrous solution, and an electrolyte acid-base balance disorder.

Plasma exchange (PE) treatment for AKI neonates. PE is a special support and treatment method, which is a part of blood purification technology. It refers to extracting the blood of a patient, separating and filtering out the pathogenic substances existing in the blood circulation of the body, such as poisons, pathogens, autoantibodies and metabolites, and then returning them to the patient and replenishing the same amount of replacement fluid, so as to achieve the purpose of treatment and support. Its technologies mainly include total plasma exchange (TPE) and double filtration plasma exchange (DFPP) (10).

To perform PE, 4.0 or 5.0Fr double lumen central venous catheters, and internal jugular vein, subclavian vein or femoral vein catheters were selected. The single exchange dose was: Plasma volume (L)=0.08 x weight (kg) x (1-hematocrit), and the general replacement plasma volume was 50-80 ml/kg per newborn. The replacement solution is usually: i) Plasma products, including fresh plasma, fresh frozen plasma and purified plasma protein. The main advantage is that these plasma products contain most coagulation factors, albumin and immunoglobulins, and are suitable for patients with deficiency of coagulation factors or other factors. ii) Human albumin: 5% human albumin is commonly used. Due to the low concentration of potassium, calcium and magnesium in human serum albumin, attention should be paid to adjusting the electrolyte balance during the treatment to avoid causing hypokalemia and hypocalcemia. iii) Crystal solution: Including normal saline, glucose normal saline, and Ringer's solution, used to supplement the loss of various electrolytes in plasma. The exchange rate, generally, is the amount of plasma exchanged and is 50-80 ml/kg each time, and the blood flow rate is 3-5 ml/kg. The displacement pump speed was 1/4-1/3 of the blood flow rate. The general treatment time was 2-3 h. The anticoagulant selected was unfractionated heparin continuously infused at

Table I. Neonatal KDIGO acute kidney injury definition.

Stage	SCr	Urine output over 24 h
0	No change in SCr or an increase of <0.3 mg/dl	>1 ml/kg/h
1	SCr increase of ≥0.3 mg/dl within 48 h or an SCr increase of ≥1.5 to 1.9 x reference SCr[a] within 7 days	>0.5 and ≤1 ml/kg/h
2	SCr increase of ≥2 to 2.9 x reference SCr[a]	>0.3 and ≤0.5 ml/kg/h
3	SCr increase of ≥3 x reference SCr[a] or an SCr increase of ≥2.5 mg/dl[a] or receipt of dialysis	≤0.3 ml/kg/h

[a]Reference SCr is the lowest prior to SCr measurement. KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine.

10-20 U/kg per hour during the replacement process, and the addition is expected to stop 30 min before the end of the process. Heparin dosage should be adjusted individually according to the coagulation status of patients. Attention should be paid to monitoring electrolyte, blood gas and fibrinogen levels while also monitoring vital signs. Calcium chloride or calcium gluconate can be continuously supplemented during blood replacement.

Observation indices. The observation indices included the following: i) The changes in the serum levels of potassium, sodium, urea nitrogen, and creatinine and the urine volume were assessed prior to CRRT treatment, at 12, 24 and 48 h and at the end of CRRT treatment; ii) the changes in the renal function prior to, 24 h after and at the end of the CRRT treatment in AKI neonates classified as stage 0-1 and 2-3; iii) the clinical outcome of 25 AKI neonates; iv) the occurrence of CRRT-related complications, such as pipeline blockage, hypothermia, hemorrhage, thrombosis, infection and thrombocytopenia.

Evaluation of efficacy. The curative effect was evaluated as follows: The changes in the renal function, urine volume, blood electrolyte levels, and acid-base balance prior to and following CRRT treatment were analyzed. In case the aforementioned indicators were apparently improved and/or no improvement was noted, the treatment was considered to be ineffective.

Evaluation of safety. In the present study, the failure rate of intravenous catheterization in neonates and the incidence rate of CRRT-related complications were used to evaluate the safety of CRRT in the application of AKI in neonates, both of which were expressed by the percentage of failure of catheterization and CRRT related complications.

Statistical analysis. SPSS 22.0 (IBM Corp.) was used to analyze the data. The measurement data in the present study followed a normal distribution and were expressed by the mean ± standard deviation (x±s). One way repeated measures ANOVA was used to test the effect of CRRT on serum sodium, potassium, blood urea nitrogen, blood creatinine and urine output of neonates with AKI at various time points of treatment, and Bonferroni's post hoc test was used for pairwise comparison between groups. Two-way repeated measures ANOVA was used to test the effect of CRRT on urine output and serum creatinine of neonates with AKI stage 0-1 and AKI stage 2-3. $P<0.05$ was considered to indicate a statistically significant difference.

Results

General information. The GA of 25 AKI newborns ranged from 33^{+4} to 40^{+1} weeks; the age range of admission was 2-28 days; the birth weight range was 2,250~4,000 g, with an average weight of 3,090±550 g. A total of 15 cases with AKI were identified as stage 0-1 and 10 cases with AKI as stage 2-3. The primary diseases included 10 cases of severe asphyxia at birth (including 1 case of traumatic asphyxia), 8 cases of neonatal septicemia, 7 cases of congenital metabolic diseases, including 3 cases of urea circulation disorder, 1 case of pseudohypoaldosteronism, 1 case of midchain acyl coenzyme A dehydrogenase deficiency, 1 case of methylmalonate acidemia, and 1 case of liver failure. CVVHDF was used in 23 cases and PE was used in 2 cases combined with CRRT. The mean time of CRRT treatment was 90.1±32.6 h.

Changes in renal function and electrolyte indicator levels prior and following CRRT treatment. The results of one-way repeated measurement ANOVA showed that there were significant differences in creatinine levels, the blood urea nitrogen levels and urine output at each time-point of CRRT treatment (Table II and Fig. 1).

The results of Bonferroni multiple mean comparison showed that the level of serum creatinine and blood urea nitrogen prior to CRRT was significantly higher than that at 12 and 24 h as well as following treatment. In addition, the urine output was significantly increased at 12 and 24 h and following CRRT treatment than that prior to treatment (Table II and Fig. 1).

Comparison of urine output and serum creatinine levels prior to and following CRRT treatment for the AKI neonates of the two groups. The serum creatinine level of neonates with AKI stage 0-1 was significantly lower than that with AKI stage 2-3 following CRRT ($F=5.005$; $P=0.035$). At each time-point following CRRT treatment, the urine output level of neonates with AKI at any stage was significantly improved (Table III and Fig. 2).

Efficacy evaluation of CRRT treatment for AKI neonates. All 25 cases of AKI neonates were effectively treated, and the

Table II. Changes of renal function and electrolyte indexes of 25 neonates with AKI before and after CRRT therapy (x±s).

Time-points	Serum potassium (mmol/l)	Serum Sodium (mmol/l)	Blood urea nitrogen (mmol/l)	Serum creatinine (μmol/l)	Urine output (ml/kg/h)
Prior to treatment	4.41±1.54	128.74±38.98	14.8±17.6	144±94	0.6±0.8
12 h of treatment	4.31±0.74	134.45±29.50	10.1±14.0[a]	85±60[b]	1.4±1.4[a]
24 h of treatment	4.20±1.14	132.34±27.25	6.9±8.1[a]	57±38[a]	1.9±1.5[b]
Following treatment	4.27±0.97	132.60±27.27	7.5±7.2	46±31[b]	3.0±1.8[b]
F-value	0.198	0.490	7.201	28.648	22.581
P-value	0.897	0.508	0.008	<0.001	<0.001

[a]P<0.01 and [b]P<0.001, compared with prior to CRRT treatment. CRRT, continuous renal replacement therapy.

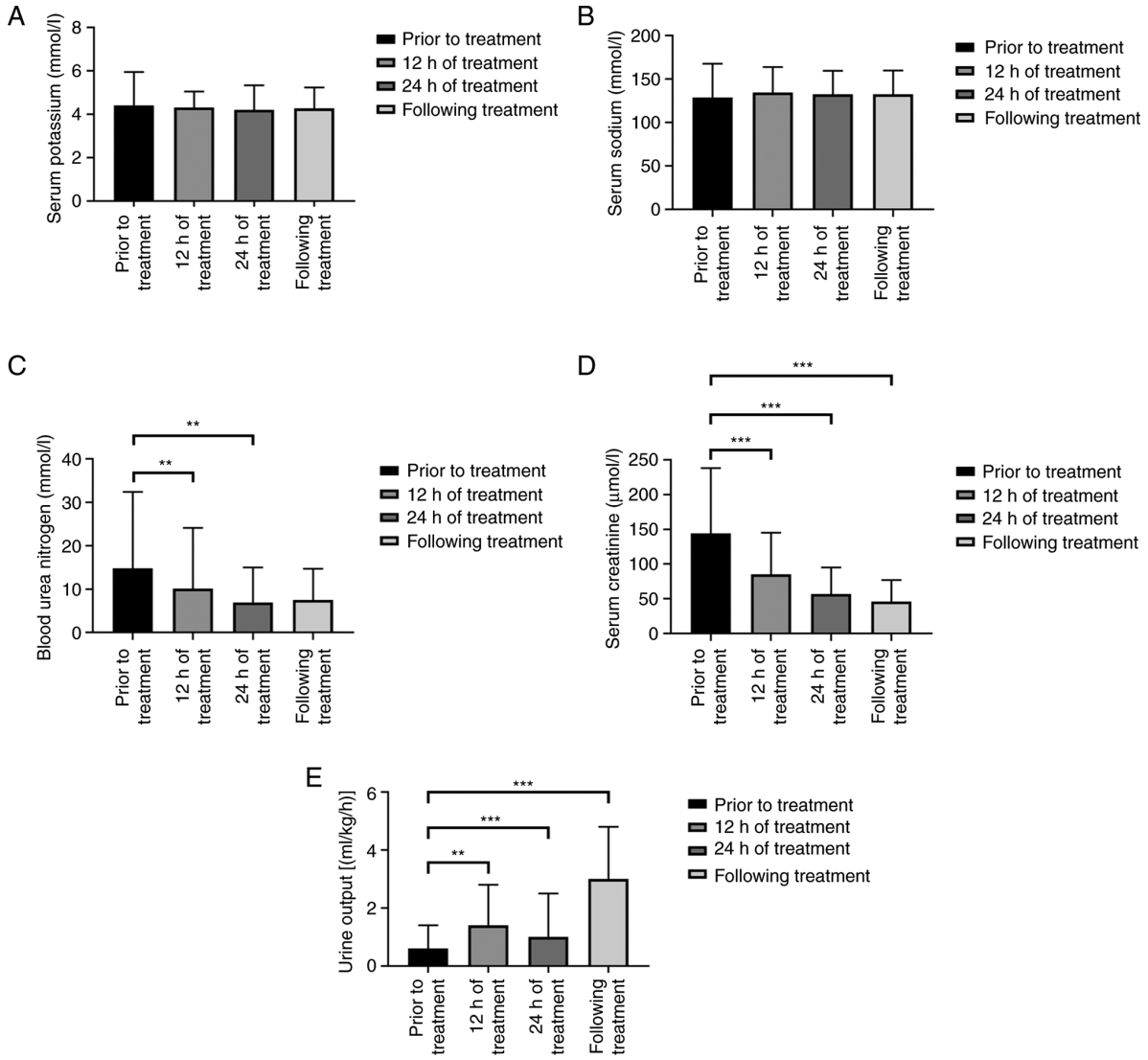

Figure 1. Changes in the renal function and electrolyte indexes of 25 children with acute kidney injury before and after continuous renal replacement therapy. (A) Serum potassium level in various groups. (B) Serum sodium level in various groups. (C) Changes in the blood urea nitrogen level among various groups. (D) Changes in the blood creatinine level among various groups. (E) Changes in the volume of urine. **P<0.01 and ***P<0.001.

indicators, such as renal function, urine volume, blood electrolyte, acid-base balance, and hemodynamics were significantly improved following CRRT treatment (Table II).

Safety evaluation of CRRT treatment for AKI neonates. Intravenous catheterization in 25 neonates with AKI was successfully completed. Thrombocytopenia was noted in

Table III. Comparison of urine output and serum creatinine levels prior to and following CRRT treatment of AKI neonates in 2 groups (x±s).

A, Urine output (ml/kg/h).

Group	n	Prior to CRRT treatment	CRRT treatment at 24 h	Following CRRT treatment
AKI stage 0-1 group	15	1.05±0.86	2.35±1.59[b]	3.26±1.84[c]
AKI stage 2-3 group	10	0.03±0.62	1.21±1.04[a]	2.56±1.61[c]
F-value		13.786	4.008	0.965
P-value		0.001	0.057	0.336

B, Serum creatinine (μmol/l)

Group	n	Prior to CRRT treatment	CRRT treatment at 24 h	Following CRRT treatment
AKI stage 0-1 group	15	122±71	46±21[b]	38±21[b]
AKI stage 2-3 group	10	177±117	72±52[c]	69±48[b]
F-value		2.215	3.013	5.005
P-value		0.150	0.096	0.035

[a]P<0.05, [b]P<0.01 and [c]P<0.001, compared with prior to CRRT treatment. CRRT, continuous renal replacement therapy; AKI, acute kidney injury.

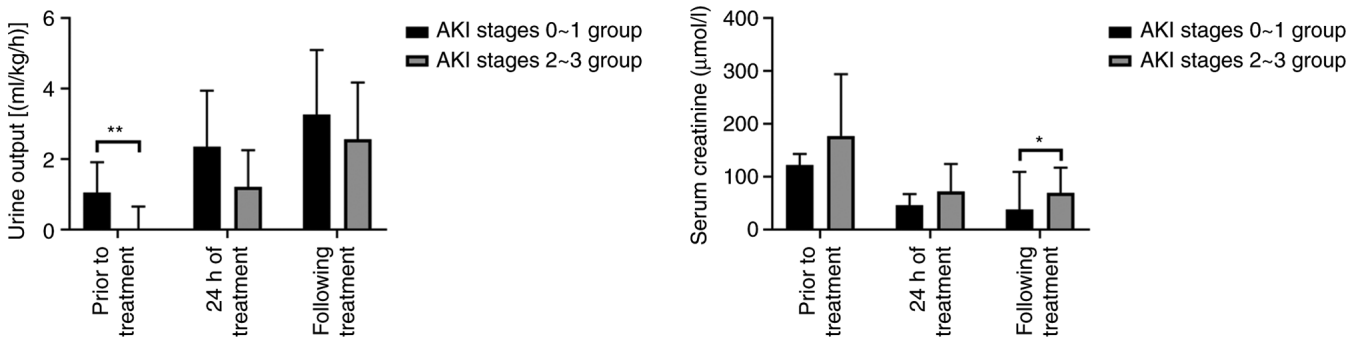

Figure 2. Comparison of serum creatinine and urine output levels between two groups of AKI newborns before and after CRRT. The serum creatinine level of neonates with AKI stage 0-1 was significantly lower compared with that with AKI stage 2-3 following CRRT. At each time-point following CRRT treatment, the urine output level of neonates with AKI at any stage was improved. *P<0.05 and **P<0.01. AKI, acute kidney image; CRRT, continuous renal replacement therapy.

4 cases, obstruction in 2 cases and hypotension in 2 cases. No hypothermia, bleeding, thrombosis or infection occurred (data not shown).

Clinical outcomes of 25 neonates with AKI. Among the 25 AKI newborns, 16 cases (14 cases of AKI stage 0-1 and 2 cases of AKI stage 2-3) were cured and discharged. The remaining 9 AKI neonates (3 cases of AKI stage 0-1 and 6 cases of AKI stage 2-3) exhibited functional dysfunction in ≥4 organs, deep coma, and multiple organ dysfunction syndrome (MODS) prior to CRRT treatment (data not shown). These neonates survived the AKI oliguria stage following CRRT treatment; however, they could not recover due to neurological injury. Therefore, their families consented to treatment discontinuation and these neonates succumbed to AKI.

Discussion

AKI is a common and life-threatening complication in critically ill neonates. Neonatal AKI is a clinical syndrome characterized by an acute decrease of glomerular filtration rate in a short time period caused by various factors, leading to the disturbance of acid-base balance, disrupted electrolyte levels, and accumulation of metabolic waste (11). Neonatal AKI can be caused by various pathogenic factors prior to, during, and following delivery (12). According to the nature and location of kidney injury, the etiology of AKI can be divided into three major categories including pre-renal AKI, renal AKI, and post-renal AKI (13,14). The risk factors for neonatal AKI include neonatal asphyxia, low Apgar score at birth, very low to extremely low birth weight of neonates, cardiac

arrest, endotracheal intubation, maternal and prenatal medications, sepsis, septic shock, nephrotoxic agents, extracorporeal membrane pulmonary oxygenation, and cardiac surgery (15,16).

CRRT, also known as continuous blood purification (CBP), is a method of continuous and slow removal of water and solute (17). In recent years, with the rapid development of the CRRT methodology, this treatment has become an important type of critical care medicine, playing a key role in the treatment of neonatal AKI and critically ill neonates; this type of treatment can significantly improve the efficacy and prognosis of neonatal AKI (18). In 1995, at the first international academic conference of CRRT held in San Diego (USA), CRRT was formally defined as 'all blood purification technologies that can continuously remove solutes and support the functions of organs' (19).

The main principles of CRRT are dispersion, convection, adhesion and adsorption. Dispersion can remove small molecules, such as water, electrolytes, urea nitrogen, and creatinine. Convection can clear the molecular materials found in the serum, such as cytokines and inflammatory mediators (20). The successful application of blood purification techniques in adult patients with AKI was first reported in 1977. Following several years of investigation of the application of CRRT in the treatment of AKI in adults and children, Ronco *et al* (21) reported the application of continuous arteriovenous hemofiltration (CAVH) in 1985. CAVH is one of the models of CRRT. CAVH mainly uses the difference in arterial venous pressure of the human body as the driving force of extracorporeal circulation. Although it exhibits the characteristics of self-limited ultrafiltration, it can effectively reduce the risk of excessive ultrafiltration, overspeed, and result in hypotension. Following these studies, a new starting point for the treatment of neonatal AKI with CRRT was highlighted.

At present, the application of CRRT in children's diseases has been developed, and includes uremia, refractory hyperkalemia, volume overload, severe or metabolic acidosis with volume overload, some dialysis poisoning, some serious electrolyte disorders and anuria AKI (22). Studies have shown that there is an independent association between the degree of fluid overload at the beginning of CRRT and adverse outcomes, including increased mortality and duration of ECMO support. Intervention before significant fluid overload may be a clinical treatment target (23).

CRRT can accurately control neonatal blood volume via continuous, slow, and gradual control, which maintains fluid balance and hemodynamic stability (24). Neonates, notably premature infants, exhibit reduced blood volume and difficulty in vascular catheterization (25). Therefore, the developers of the blood purification equipment had limited power to develop specific CRRT filters for neonates, and the CRRT method was restricted from newborns for a long time period (26). With the development of catheterization technology and the research and development of an instrument suitable for neonatal CRRT, CRRT is more and more widely used in neonatal diseases. A study has shown that CRRT is safe and effective in the treatment of neonatal hereditary metabolic diseases and hyperammonemia (27). Successful treatment of neonatal AKI with CRRT has been reported, and CRRT has been gradually applied to premature infants and infants with low birth weight (28). In the present study, it was found that the serum urea nitrogen and creatinine levels were significantly decreased following 24 h of CRRT treatment in neonates with AKI stage 0-1. At each time-point in the study (prior to CBP treatment, 24 h following CBP treatment and following CRRT treatment), serum creatinine levels of stage 2-3 newborns with AKI were still significantly higher than those with stage 0-1 AKI, but urine output was lower than those with stages 0-1 AKI. Therefore, it was considered that the treatment time required to significantly reduce serum creatinine levels and improved urine output in AKI stage 2-3 neonates was significantly higher compared with that of the AKI stage 0-1 group. If CRRT treatment is provided promptly in cases with AKI stage 0-1, it can improve the kidney function avoiding more persistent damage to the kidney. In the present study, the efficacy of CRRT treatment in cases with AKI stage 0-1 was improved compared with that noted in the cases of AKI stage 2-3. Therefore, the present study demonstrated that the optimal selection for the application of the CRRT treatment is to treat neonates with AKI stage 0-1.

Lee and Cho (29) retrospectively analyzed the neonatal cases treated by CRRT at the Samsung Medical Center (Seoul, South Korea) from 2007 to 2014. The medical center treated 34 AKI neonates with CRRT, with a birth weight of 800-4,100 g. A total of 15 premature infants (GA 25-36 $^{+6}$ weeks) and 19 full-term infants were included in that study. The results indicated that CRRT was effective in treating AKI caused by fluid overload. Following treatment, 20 patients (58.8%) survived and 14 (41.2%) succumbed to AKI. The total number of patient was 14 and included 12 premature infants and 2 full-term infants. Therefore, neonatal or low birth weight should not be contraindicated for CRRT. CRRT is feasible and effective for neonates or infants with low birth weight; however, there are still apparent risks for premature infants.

In 2016, a 'precise CRRT consensus meta-analysis' study clearly proposed that CRRT therapy should be initiated as soon as possible when the metabolic and fluid management requirements of the body exceed the capacity of the kidney (30). This indicates that as long as the body's metabolism and the fluid management exceed the capacity of the kidneys, CRRT should be treated quickly even in case of lack of renal injury. According to the neonatal KDIGO AKI definition, AKI stage 0-1 includes the early-stage cases with AKI and reversible renal injury, while AKI stage 2-3 corresponds to the state of renal failure. The complications of CRRT are important indices for safety evaluation. Certain complications in the treatment of AKI neonates have been identified following CRRT treatment, such as difficulty or failure of catheterization, hypothermia, hypotension, pipe blockage, thrombosis, bleeding, thrombocytopenia and bloodstream infection (31). In the present study, CRRT was used to treat 4 patients complicated with thrombocytopenia, 2 patients with pipe obstruction, and 2 patients with hypotension. No hypothermia, bleeding, thrombosis, or bloodstream infection occurred. The reason for hypotension may be volume-related factors, such as extremely rapid dehydration. The causes of pipeline blockage may be the slow blood flow rate and unsatisfactory anticoagulation control. The causes of thrombocytopenia may include sepsis, anticoagulants, disseminated intravascular coagulation, bleeding, and the effects of the filter membranes. Adequate puncture technique, timely and close monitoring, and strict aseptic operation are the key factors required to reduce or prevent CRRT complications (4).

During the treatment of CRRT, the coagulation function, blood gas analysis and trace blood glucose were strictly monitored every 2-4 h. In addition, liver and kidney function and blood electrolyte levels were detected every 6-12 h. Therefore, it is suggested that during treatment, children should be monitored, their vital signs closely observed, and various indicators timely detected, such as the balance of access volume, coagulation function, hemodynamics, blood electrolytes, and blood glucose. The monitoring of these indices, aims to avoid or reduce the complications of CRRT.

In the present study, 10 cases of severe asphyxia, 8 cases of neonatal septicemia and 7 cases of metabolic crisis of genetic metabolic disease were found in 25 cases of AKI neonates (15 of cases AKI stage 0-1 and 10 of cases AKI stage 2-3). A total of 9 neonates (3 neonates of AKI stage 0-1 and 6 neonates of AKI stages 2-3) had been in a deep coma prior to CRRT treatment. Although they had passed the oliguria stage following CRRT treatment, they could not recover due to neurological injury. Their families consented in treatment discontinuation and consequently, these neonates succumbed to AKI. Symons *et al* (32) retrospectively studied the CRRT data of 85 children with a body weight <10 kg in 5 hospitals in the United States. Their study included 13 cases with MODS and 12 cases of sepsis. Among 16 cases, the lowest weight was 1.5 kg. The results of their study indicated that the CRRT treatment effect and prognosis of children with a weight of 3.0-10.0 kg were similar to those of older children. Therefore, it was suggested, that the initiation of CRRT treatment at the early stage of AKI may significantly improve the clinical outcome and prognosis of AKI infants with low body weight.

The present study contains certain limitations. A relatively small sample number was included with only 25 neonatal cases with AKI treated with CRRT. Moreover, the present study was a single-center retrospective clinical study and provided insufficient information in assessing the types of CRRT treatment for their application in neonatal diseases and individualized CRRT treatment. In the future, a large sample and multi-center clinical study of CRRT treatment should be carried out to further explore the application of individualized and precise CRRT treatment for critically ill neonates.

In conclusion, CRRT is considered to be safe and effective in the treatment of neonatal AKI. This method should be an effective measure for the treatment of neonatal AKI. The optimal stage of initiation of CRRT to treat newborns with AKI should be in cases with AKI stage 0-1.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XZ, XG and CC made substantial contributions to the conception and design of the study, acquisition of data, and analysis and interpretation of data. WH and NL participated in data collection and analysis. CC and XG were involved in drafting the manuscript and revising it critically for important intellectual content. WH, NL, XG and CC revised the manuscript and provided final approval of the version to be published. XG and CC confirm the authenticity of all the raw data. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The study protocol and amendments were reviewed and approved by the Institutional Review Board, in accordance with the ethical principles of the Declaration of Helsinki. This study was approved (approval no. 2012C001-F01) by the Ethics Committee of Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University. All parents of AKI neonates provided written informed consent before enrollment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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