Review article

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Pediatric Hemodialysis

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Hemodialysis is rarely used in neonates and infants due to the risk of major complications in the very young. Nevertheless, there are clinical situations where hemodialysis is needed and may be helpful in small children. Recently, new developments in specialized hemodialysis equipment and specifically trained personnel have made it possible to implement hemodialysis in neonates and infants. In this review, we will discuss hemodialysis for the treatment of small children with renal replacement therapy-requiring conditions, and consider indications, prescriptions, complications, and ethical issues.

Key words: Hemodialysis, Children, Complications

Introduction

The history of dialysis treatment for children is closely related to the development of pediatric nephrology and to renal replacement therapy (RRT) in general, which both started soon after World War II[1]. The practice of pediatric hemodialysis (HD) was first restricted to a few pediatric centers, mainly for the treatment of acute intoxication although the application of peritoneal dialysis (PD) in acute kidney injury (AKI) has been institutionalized in many children's hospitals since the 1950s[2]. The first use of maintenance pediatric hemodialysis was reported in 1968 by Fine et al[3]. Until recently, PD was the preferred mode of RRT in infants with end-stage renal disease (ESRD), and HD is seldom used in neonates and infants due to the risk of major complications in the very young. Nevertheless, there are clinical situations where hemodialysis is needed and may be helpful in small children. Previously, it was difficult to implement in children due to their small weight and difficulty in vascular access, but recently, with the development of HD equipment, it has become possible to implement in children up to 2 kg[4]. However, well-trained personnel are essential to prevent dialysis complications in infants and small children under 2 years of age. In this review, we will discuss HD for the treatment of small children with RRT-requiring conditions, and consider indications, prescriptions, complications, and ethical issues.

Indications for hemodialysis

HD is preferred in certain conditions where a high rate of solute clearance

is required such as tumor lysis syndrome, inborn error of metabolism, hyperkalemia, ingestion of dialyzable toxins, severe fluid overload, and severe lactic acidosis[5,6]. Hyperammonemia is a common indication for acute HD in infants with inborn error of metabolism, and the reported time from diagnosis to HD ranged from 2 to 19 hours[7-9]. Hemodialysis is an indication even in patients who are unable to perform PD due to recent abdominal surgery, abdominal drainage, and severe respiratory disease[5].

However, there is a limit to the patient's capacity in intermittent HD, which removes a large amount of water in a short period of time. Therefore, a certain degree of water restriction is essential when intermittent HD is performed in AKI and ESRD children.

Access

For HD in small children, central venous catheters represent the sole initial vascular access for HD[10]. The recommended ideal initial vascular access point is the internal jugular vein, and the femoral vein provides the next best alternative site[5]. Appropriate vascular access should be selected according to the child's age and size (Table 1)[5,11,12]. Usually, a double lumen tunneled 7-Fr or 8-Fr catheter with short neonatal tubing with blood pump set at 2.6 mm Hg or pediatric tubing with blood pump set at 6.4 mm Hg are desirable[5]. In Korea, a 6.5-Fr or 8-Fr catheter is available for the acute HD in small infants. However, the smallest size as the permcath is 11.5-Fr, and it is difficult to fix the HD catheter in small children in Korea. Lopez et al., reported that in children weighing less than 15 kg, the preferred insertion site was the right internal jugular vein[10]. According to that study, the mean duration of HD was 312 days, and mean catheter survival was 110 days/catheter[10].

Table 1. Vascular Access for Hemodialysis

Patient size	Catheter size	Insertion site
Neonate	4–6 F single lumen Double-lumen 7F	Femoral artery or vein
3–6 kg	Double- or triple-lumen 7 F	Jugular, subclavian, or femoral
6–15 kg	Double-lumen 8 Fr	Jugular, subclavian, or femoral
15–30 kg	Double-lumen 9 Fr	Jugular, subclavian, or femoral
>30 kg	Double-lumen 10 F or triple-lumen 12 F	Jugular, subclavian, or femoral

Equipment

The rate of solute removal from the blood is determined by the blood flow rate, the dialysate flow rate, and the efficiency of the dialyzer. In dialysis, the urea clearance rate is important, and in order to obtain an adequate urea clearance rate without complications during dialysis, it is important to select a dialyzer suitable for the child's size (Table 2)[11,12]. Since the urea clearance rate reaches a plateau at a lower blood flow rate in a smaller dialyzer, a large dialyzer is needed to obtain a large urea clearance rate in large children. In small children, any dialyzer can be used if only the urea clearance rate is considered, but in small children, the volume of extracorporeal circulating blood must be small, so a dialyzer with the smallest volume among dialyzers that can obtain the necessary urea clearance should be selected. A dialyzer with a surface area similar to that of the patient's body should be selected, and the total amount of extracorporeal blood circulation should not exceed 10% of the patient's blood volume[12]. The dialyzer and blood line are selected according to the child's size and intravascular volume. Currently, dialyzers with a surface area as small as 0.2 m^2 are available[11,12]. High-flux dialyzers are difficult to use in small children, but if a high-flux dialyzer is used, blood flow rates and dialysis times should be reduced[12].

Table 2. Dialyzer for Children®

Dialyzer	Membrane	Surface area (m^2)	Prime volume (mL)
Polyflux® 6H*	Polyflux (polyarylethersulfone, polyvinylpyrrolidone, polyamide)	0.6	52
CA50*	Cellulose acetate	0.5	35
CA70*	Cellulose acetate	0.7	45
B 190*	Polyethersulfone	1.9	114
B 150*	Cellulose triacetate	1.5	95
F3+	Polysulfone	0.4	28
F4+	Polysulfone	0.7	42
F5+	Polysulfone	1.0	63
F6+	Polysulfone	1.3	82
FX paed+	Helixone®	0.2	18
FX 40+	Helixone®	0.6	32
F40S+	Polysulfone High flux	0.7	42
F160+	Polysulfone	1.5	83
F180+	Polysulfone	1.8	99

Manufacturer: *Baxter, +Fresenius.

For pediatric HD, a dialysis machine with a pump that can accurately control blood flow rate according to the child's size is required.

Prescription

Conventional HD provides rapid solute clearance by allowing for high blood and dialysate flow rates[5]. In infants, if the amount of extracorporeal blood volume exceeds 10 % of the patient's blood volume, there is a risk of complications, so red blood cells, or 5% albumin could be used to fill the line as priming[12]. A blood flow rate of 3–5 ml/kg/min is adequate to achieve the proper solute removal with the hemodynamic stability[12]. The dialysate flow rate is fixed at 500 mL/min on most dialysis machines and can be increased to 800–1,000 mL/min, but 500 mL/min is sufficient for children[12]. There is a risk of hypokalemia during dialysis in patients with AKI, due to the transfer of potassium into the cells resulting from the correction of severe acidosis. If the plasma potassium concentration before dialysis is more than 5.5 mEq/L, the potassium concentration in a dialysate of 2.0 mEq/L is adequate, but if the plasma potassium concentration before dialysis is 3.5–4.5 mEq/L, a potassium concentration in the dialysate of 4.0 mEq/L is recommended[12].

At low blood flow rates of less than 100 mL/min, it should be taken into account that the blood flow rate affects the ultrafiltration rate[13]. The ultrafiltration rate is determined by the transmembrane pressure and the ultrafiltration coefficient of the dialyzer. To maintain hemodynamic stability, the ultrafiltration rate should not exceed 0.2 mL/kg/min [4]. It is recommended to use a dialyzer with a small ultrafiltration coefficient to prevent excess water removal. Because hypoalbuminemia can reduce water removal, in patients with hypoalbuminemia, it is recommended to give intravenous albumin at the start of dialysis to increase the ultrafiltration rate by moving interstitial fluid to the intravascular compartment and to reduce the occurrence of hypotension[12]. Dialysis is usually performed in adults for about 4 hours, but HD is performed in children for a shorter period of time. In pediatric patients, solute removal can be effectively and safely removed, but it may be difficult to remove water while maintaining hemodynamic stability for a given period of time in children with severe excess water[12]. Therefore, it might be necessary to perform ultrafiltration first, followed by dialysis to prevent dialysis dysequilibrium syndrome[12]. Ultrafiltration is recommended before hemodialysis because high serum osmotic pressure can move water from interstitial fluid into the intravascular compartment to maintain effective circulation[12].

At the end of dialysis, the extracorporeal blood volume could be replenished using normal saline. When normal saline is used, an amount of about 100–200 mL can be given to the patient at the end of dialysis, which can reduce the effect of ultrafiltration. If the patient's blood pressure is low at the end of dialysis, this can help increase blood pressure. In the case of priming with blood, it is usual to discard the blood in the blood line when dialysis is finished. When priming with red blood cells, the hematocrit level is high, so even if the blood in the line is discarded after dialysis, the hemoglobin level rises in infants.

Adequacy

The concept of adequate dialysis refers to a minimum HD below which a clinically unacceptable rate of negative outcomes occur. "Optimal" dialysis refers to an HD dose above which no significant reduction in negative outcomes or improvement in positive outcomes occurs[13].

All methods of HD adequacy measurement is based on the assessment of dialysis dose reflecting the fractional urea reduction. The two fundamental clinical variables assessed by HD adequacy measurement are HD treatment urea clearance and patient nutrition status[13]. Fractional urea clearance can be described in terms of Kt/V[13]. The fractional urea mass removed during HD is affected by the following factors: dialyzer urea clearance coefficient (K in ml/min), pre-and post-treatment blood urea nitrogen (BUN) (mg/dL), treatment duration (t in minutes), patient total body water (V in mL), the amount of plasma water removed during dialysis (ultrafiltrate), and the intradialytic urea generation rate (G in mg/min)[13]. Patient nutrition status can be described by protein catabolic rate (PCR), which can be calculated by urea generation rate and V[13]. G can be calculated using the modified Borah equation and reflects patient protein intake. PCR is divided by post-di-

alysis patient weight in kg to yield a normalized protein catabolic rate (nPCR), which reflects the nutrition status of a patient receiving HD[14]. In a simple way, the urea reduction rate uses only the pre- and post-dialysis BUN samples to calculate the fractional reduction of urea caused by dialysis, which does not account for intradialytic urea generation or urea mass removed by ultrafiltration, and does not yield any information regarding nutrition status[13].

According to Kidney Disease Outcome Quality Initiative (KDOQI) guidelines, for the measurement of HD adequacy, single pool Kt/V (spKt/V), calculated by either formal urea kinetic modeling or the second-generation natural logarithm formula, should be used for month-to-month assessment of delivered HD dose[15]. Assessment of nutrition status is an essential component of HD adequacy measurement. nPCR should be measured monthly by using either formal urea kinetic modeling or algebraic approximation[15]. For the prescription of adequate HD, children should receive at least the delivered dialysis dose as recommended for the adult population[15]. For younger pediatric patients, prescription of higher dialysis doses and higher protein intakes at 150% of the recommended nutrient intake by age may be important[15].

Complications of hemodialysis

1. Catheter-related complications

Pneumothorax, hemothorax, artery injury, pulmonary embolism, central vein rupture, and pericardial tamponade can occur during catheter insertion[12]. Recurrent central venous catheter placements are frequently required, resulting in increased risk of central vein thrombosis and stenosis. An evidence-based effective preventive strategy is necessary[16]. The central venous catheter-related factors associated with increased risk of venous thromboembolism include multi-lumen catheters, polyurethane material, peripherally inserted central catheters, the subclavian site, tip positions in the superior vena cava, and left-sided upper limb insertion[16]. To maintain the patency of an HD central venous catheter, most pediatric centers use intraluminal heparin as a central venous catheter-locking solution with a wide variation of concentrations. In children, the use of altepase 1 mg/ml was more effective compared to heparin at 5,000 units/ml in reducing intraluminal clot formation between HD sessions[17].

Central venous catheter infection was a common complication. According to the report by Pollack S et al., the infection rate per 1,000 central venous catheter days was 0.30 and the infection rate was higher in the group in whom HD initiated <1 month of age than those in whom HD initiated 1–12 months of age[18].

2. Hypotension

Hypotension is the most common complication during HD[12]. Excessive ultrafiltration, too fast ultrafiltration rate, improperly low sodium concentration in the dialysate, use of antihypertensive medications, and bio-incompatibility of the dialyzer membrane can be causes[12]. Since symptoms may be severe in children receiving vasodilators for treatment of hypertension, these drugs should be administered after dialysis. If hypotension occurs during dialysis, an intervention such as stopping ultrafiltration, putting the child in a Trendelenburg position, and injection of normal saline are necessary. In some cases, blood pressure rises suddenly due to the secretion of catecholamines and renin during rapid removal of intravascular volume[12]. In this case, blood pressure may drop if intravascular volume deficit is resolved by supplying fluids intravenously[12]. Picca et al., reported that HD-treated neonates with hyperammonemia showed severe hypotension requiring repeated plasma and blood transfusions, increase of inotropic support and suspension of dialysis[7]. In the study by Sadowski RH et al., 64% of patients weighing less than five kilograms showed hypertension that required saline and albumin infusion during HD[8].

3. Muscle spasms

Muscle spasms occur in about 20% of patients[12]. Excessive water removal, low blood pressure, and low sodium dialysate are known triggers[12].

4. Dialysis dysequilibrium syndrome

Dialysis dysequilibrium syndrome is caused by sudden osmotic pressure changes during HD. Children develop this more often than adults, and brain edema causes consciousness changes and convulsions. To prevent this during acute dialysis, it is recommended that the urea clearance

rate does not exceed 3 ml/kg/min and 20% mannitol is injected at the start of dialysis[12]. It is also helpful to shorten the dialysis time during initial dialysis.

5. Elimination of drugs and nutrients

When patients are being administered other drugs such as antibiotics, which can be removed during dialysis, dose adjustment is necessary. If the clearance rate of the drug during dialysis is more than 30% of total clearance, an additional dose is required after dialysis[12]. In the case of intermittent HD, the nutritional supply may be slightly limited, but protein 1–1.5g/kg/day can be safely supplied[12].

6. Long-term complications

Early recognition of long-term dialysis complications including hypertension, neurocognitive/neurodevelopmental delay, and psychological stress should be addressed to prevent morbidity[5,18].

Long-term outcome of pediatric hemodialysis

There are a few reports on long-term HD therapy in children. HD was reported in patients with chronic renal disorders including congenital anomalies of the kidney and urinary tract, cystic kidney diseases, hemolytic uremic syndrome, renal vein thrombosis, and congenital nephrotic syndrome[5]. For patients who were administered chronic dialysis before the age of 1 year, the main factors determining poor dialysis outcomes were extremely young age at dialysis initiation (1 month of age) in patients who had severe co-morbidities[19].

Pollack S et al., reported that long-term HD in neonates and infants with ESRD is technically feasible, can be implemented without major complications, carries a very low rate of central venous catheter infection and malfunction, and results in adequate nutrition, good growth, as well as good kidney graft and patient survival[18]. Shroff et al., reported that HD in infants and small children is an effective and safe form of RRT, but problems with vascular access limit its long-term use[20].

Some studies report that overall infant survival in those treated with HD varies from 50% to 100%, and this reported mortality was mainly due to complications such as infection, hemorrhage, cardiac arrest, and complications following transplantation rather than complications related to the HD procedure[5].

Further consideration of pediatric hemodialysis

1. Pediatric home HD

In 1971, home HD in children was first reported by Jones B et al[21]. Although there are limited data in children, pediatric patients and their families feel the greatest impact of ESRD and treatment on normal growth and development, quality of life, and social functioning due to pediatric intensified home HD[22]. However, clinical guidelines and dialysis equipment for implementing home HD are still limited. For home HD, appropriate patient selection, dialysis equipment such as systems that require home water conversions, and HD systems require a multidisciplinary team to support the family, as infrastructure, and financing are needed[22].

2. Ethical issues

HD in neonates and infants is challenging, and ethical conflicts could arise. There are a few recommendations for small children requiring RRT. According to the European Pediatric Dialysis Working Group, pediatric nephrology centers advocate multi-professional team discussion guided by a clinical ethics committee for starting RRT in neonates and infants[23]. The issues include short and long-term prognoses, medical care issues, and predicted quality of life for children and their family which should be discussed with members of the medical and paramedical team[23].

Conclusion

Small children requiring HD pose many challenges that include hypovolemia and catheter complications, and consensus guidelines and published data are lacking. While PD is widely used in small children, there are cases where only HD is possible and cases where HD is more helpful. Precise practices such as minimizing extracorporeal circuit volume and preventing catheter-related complications

could improve patient outcomes.

Conflict of interests

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