Pediatr Nephrol (2014) 29:1869–1871
DOI 10.1007/s00467-014-2910-8

EDITORIAL COMMENTARY

Designing technology to meet the therapeutic demands of acute renal injury in neonates and small infants

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Received: 4 July 2014 / Accepted: 9 July 2014 / Published online: 16 August 2014

Abstract Within paediatric intensive care units (PICU), clinicians face an increasing demand to support neonates and small infants with acute renal injury or medication-resistant oedema. Of all PICU admissions, fluid overload or a requirement for renal replacement therapy (RRT) is a poor prognostic factor, resulting in death in 25–50 % of such babies. For those who survive, RRT is supportive until kidney recovery, but up to 30 % of babies may have chronic kidney sequelae. Owing to their size, neonates and small infants present specific challenges for dialysis. Dialysis technology was designed for use in adults and had to be adapted for pediatric use, creating a less than ideal treatment environment fraught with complications. Consequently, wherever possible, the vast majority of physicians default to peritoneal dialysis. Clinicians now have access to two new dialysis systems with technology specifically designed for use in babies ranging from 800 g to 8 kg: the CARPEDIEM and Nidus exhibit preliminary data that demonstrates both purification and ultrafiltration capability, with safety records that exceed any existing systems presently in practice. These are truly exciting times, as these systems have the potential to revolutionise how such babies in the PICU are treated.

Keywords Neonates · Continuous renal replacement therapy · Dialysis · Acute renal injury · CARPEDIEM · Nidus

Introduction

Owing to the highly evolving world of medical and surgical specialties, clinicians are in a very privileged position in which babies with complex medical and surgical challenges are expected to survive the neonatal period. However, this places huge demands on the babies themselves, pushing their physiological systems to the limit. Consequently, clinicians increasingly find themselves having to intervene to support vital organs struggling to cope within this intense medical environment.

The kidneys of newborn babies are physiologically immature and very sensitive to internal and external stresses, with a limited capacity to deal with extreme physiological demands. Nephrologists have seen an increasing requirement for renal support services to manage acute renal injury and/or oedema resistent to medical management. A collaborative study of children prospectively registered between 2000 and 2011 in the European Society for Paediatric Nephrology/European Renal Association–European Dialysis and Transplant (ESPN/ERA-EDTA) registries, the International Pediatric Peritoneal Dialysis Network (IPPN) Registry (since 2007), the Japanese Registry or the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry reported 264 patients from 32 countries started renal replacement therapy (RRT) in the first month of life; 242 of those neonates were started on peritoneal dialysis (PD), 21 on haemodialysis (HD) and one received a renal transplant. These babies were followed for a median of 29 months [interquartile range (IQR) 11–60 months]. Within 2 years after the start of RRT, dialysis modality was changed in 69 children, and 53 received a renal transplant. After a median of 7 months, 45 babies had died, mainly because of infection, resulting in an estimated 2-year survival of 81 % and 5-year survival of 76 % [1]. Askenazi et al. reported data on 84 babies ≤10 kg between January 2001 and August 2005 from 13 US tertiary care centres, indicating they had lower survival rates than babies>10 kg: 36/84 (43 %) vs 166/260 (64 %). Urine output and fluid overload at continuous renal replacement therapy (CRRT) initiation are independently associated with mortality. Acute kidney injury

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(AKI) in the short term is also associated with increased resource use and length of hospital stay [2].

Existing dialysis practices for neonates and small infants

Internationally, there are three established dialysis modalities for the intensive care setting: PD, intermittent HD and continuous venovenous hemofiltration (CVVH) or HD. When treating babies with renal disorders, none of those methods is practical and straightforward; each has its own set of complications or limitations. The final decision on the type of therapy is dependent on clinician expertise and patient characteristics and medical requirements.

Peritoneal dialysis

PD is generally the preferred treatment option for neonates and young children. It is the least technically challenging and bypasses the requirement for vascular access; however, clearance is slow compared with other dialysis modalities, and ultrafiltration (UF) can be unreliable. PD in preterm or severely oedematous babies can be very challenging due to the high risk of fluid leak from the catheter exit site and malposition or obstruction of the PD catheter. This can severely limit the dialysis dose delivered. There is also a group of infants in whom PD is contraindicated, such as those with a history of abdominal surgery or abdominal-wall defects. In patients requiring rapid clearance, such as those with severe hyperammonaemia, PD may not be optimal for rapid therapy [3].

Intermittent hemodialysis

Intermittent HD is the least used therapy for babies with acute and chronic kidney failure, as it requires a large lumen vascular access to provide adequate blood flow rates for the dialysis procedure. This is practically challenging and on occasions unachievable with smaller babies. Larger catheters relative to vessel size also have the additional risk of causing central vessel stenosis, and this can have devastating consequences in planning life-long care in children with congenital heart disease or renal disease. Existing commercially available neonatal HD circuits require that in all infants weighing < 8 kg the circuit be primed with blood to prevent haemodilution and a decrease in extracellular fluid volume, which results in life-threatening hypotension. Priming the HD unit with blood, however, exposes the baby to a potassium and citrate overload. Citrate chelates calcium (and magnesium) ions, and the resultant hypocalcaemia may cause arrhythmias and thus must be monitored and may need correction. Blood priming also carries the risk of sensitisation, with implications in reducing the donor pool at the time of renal transplantation. Finally, dialysis treatments are physiologically demanding, causing rapid fluid, electrolyte and solute shifts, which are not well tolerated in infants. As a result, on the whole, intermittent HD has largely been replaced by CVVH/HD in the intensive care setting.

Continuous venovenous haemofiltration/continuous venovenous hemodialysis

CVVH/CVVHD is a gentler, extracorporeal treatment option, with superior UF and purification capability compared with other dialysis modalities in babies. However, existing circuits are dependent on large, double-lumen, central-vessel catheters and in babies require blood priming. Worldwide, existing CRRT systems are designed for adults and are adapted for pediatric use by software modifications to alter operational parameters and by using extracorporeal circuits with lower priming volumes. The US Food and Drug Administration (FDA) published a public health notification in 2004 and 2006 on the Gambro Prisma® CRRT System emphasising that "special caution must be used when operating the Prisma® System" to prevent excessive fluid removal, "paying particular attention to the incorrect weight-change-detected alarms". To date, the FDA has reported nine deaths and 11 serious injuries associated with excessive fluid removal. The cause for these concerns is the UF accuracy of these adult CRRT systems. For example, with the Prisma®, the displayed value of the amount of fluid removed may be inaccurate by ±60 ml/h from the actual value, even when the fluid removal rate is set to 0 ml/h. In babies with disproportionately lower intravascular volumes, such inaccuracies can be catastrophic, and thus a real safety concern.

New dialysis systems specifically designed for babies

Despite the compelling argument for a neonatal-specific extracorporeal circuit, an infant neonatal system was not forthcoming. Pediatric experts took the initiative, and there are now two new systems: the Cardiorenal Pediatric Dialysis Emergency Machine (CARPEDIEM) and the Nidus, which is being reported for the first time in this edition of *Pediatric Nephrology*.

CARPEDIEM

The CARPEDIEM is a CRRT machine designed specifically for infants weighing 2.5–10 kg and has the capability for various treatment modalities, including CVVH, predilution or postdilution, plasma exchange, blood exchange, CVV haemodiafiltration (HDF) and single-pass albumin dialysis with minimal, insignificant blood microhaemolysis as it

passes through the circuit. The extracorporeal circuit volume is miniaturized to 27 ml, minus the filter, and thus the requirement for blood prime is reduced. It can house three different-sized filters: 0·075, 0.15 and 0.25 m^2. Miniature roller pumps provide the capacity to run continuously at flow rates of 5–50 ml/min. As a result, babies have been successfully dialyzed using 4.0- to 4.5-F dual-lumen catheters. The circuit offers a significant improvement in UF accuracy of ~ 1 g and reinfusion or dialysis-flow errors ranging from −8 to 7.5 %. [4].

Ronco and colleagues reported on their initial experiences with the CARPEDIEM for treating a critically ill neonate weighing 2.9 kg with multiple organ failure and severe fluid overload. The baby was treated with CRRT through a 5-cm dual-lumen 4-F catheter surgically placed into the femoral vein. Blood flow of 9–13 ml/min was achieved, with daily clearance between 2.2 and 2.8 L. The baby then developed severe hyperbilirubinaemia secondary to liver dysfunction and massive subgaleal haemorrhage reabsorption. Consequently, CVVH treatment was alternated with blood exchange (three sessions with 475 ml blood volume exchanged at an isovolumetric exchange rate of 5 ml/min), single-pass albumin dialysis (two sessions of 17 h each with 4 % albumin dialysate) and plasma exchange (four sessions each with 270 ml plasma volume exchange). After 30 days, the patient was breathing normally without supplemental oxygen, making adequate amounts of urine and had normal liver function; at 39 days, she was discharged from the PICU [4].

Nidus

The Nidus is an HD circuit with a capability of treating babies weighing between 800 g and 8 kg. The extracorporeal circuit volume < 10ml, and thus even in the smallest of babies, no blood prime is required. In my opinion, the most innovative feature of the NIDUS is the uncoupling of blood flow through the dialyser from the baby's blood flow. A prescribed volume of blood is removed from the patient and then passes twice through a high flux polysulfone 0.045 m^2 hollow-fibre haemofilter to allow dialysis and UF and is then returned to the baby; the cycle is repeated. This strategy also makes it possible to dialyse infants through a single-lumen catheter without excessive recirculation. The UF capability of the circuit is 0–60 ml/h, and UF accuracy matches that of the CARPEDIEM.

In this volume of *Pediatric Nephrology*, Coulthard et al. report on their experience of safely treating eight babies weighing between 1.8 and 7.0 kg without any detectable hemolysis. Urea, creatinine and phosphate clearances were significantly higher than that of PD, at 1.5–2.0 ml/min versus 0.2–0.8 ml/min. UF was precise, and fluid balance was more tightly maintained than with intermittent HD in the outpatient setting [5].

Conclusion

Expert paediatric nephrologists took the lead, collaborating with colleagues to design, develop and test dialysis systems specific to infants. There is now access to two new circuits that can dialyse safely infants weighing < 8 kg. I look forward to seeing more data reporting on the capability of these circuits and am curious to see how this will influence the clinician's approach to managing babies requiring RRT.

Conflict of interest None

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