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Rethinking Blood Pressure Management in Children Receiving Maintenance Hemodialysis

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Hypertension is a well-known complication of children on maintenance dialysis. Reports over the past 3 decades demonstrate a prevalence of hypertension at 50% to 75%. Similarly, the prevalence of left ventricular hypertrophy (LVH), the most common cardiac abnormality in children on maintenance dialysis, has not changed much from the initial reports in early 2000s, and most recent data demonstrate a frequency of approximately 50%.[1] Controlling hypertension and LVH is recognized as one of the most important strategies to prevent development of cardiovascular disease, most common cause of death in children and young adults with end-stage kidney disease. Although many previous studies have tried to address the causes of poor blood pressure (BP) and LVH control, most of them, including large international registries such as the North American Pediatric Renal Trials and Collaborative Studies or European Renal Association European Dialysis and Transplant Association, provided limited information due to lack of detailed data collection. Until recently, there have been no comprehensive studies examining the risk for hypertension and LVH in children with end-stage kidney disease.

In 2007, the International Pediatric Peritoneal Dialysis Network was established to prospectively collect data on children on maintenance peritoneal dialysis. This network produced seminal reports on many issues related to health of children on peritoneal dialysis.[2] In 2012, the International Pediatric Hemodialysis Network was formed. These 2 registries now operate under the name The International Pediatric Dialysis Network.

In this issue of the Journal, utilizing data from hemodialysis network, Borzych-Dużałka *et al.*[3] examined modifiable risk factors of hypertension and LVH in children on maintenance hemodialysis. In this largest observational study to date, the authors confirm the high prevalence of hypertension (76%), with three-fourths of these patients uncontrolled despite being on an average of 2.3 antihypertensive medications. Among the sample of the cohort with ambulatory BP monitoring available for analysis (24%), control of BP was even worse: 81% demonstrated uncontrolled hypertension, including 24% with masked hypertension. Most concerning, but not surprising, was the fact that elevated BP was the most significant risk factor for LVH, which was present in 51% of the cohort. Together, these findings prove that BP among children on hemodialysis is extremely poorly controlled (despite pharmacologic management), often leading to cardiovascular morbidity.

Consistent with previous investigations, poor fluid control was the main, and in fact the only modifiable risk factor for hypertension. Each 1% increase in interdialytic weight gain (IDWG) was associated with a 19% increase in systolic and 9% increase in diastolic BP-SD score, specifically quantifying the strong association of IDWG with hypertension. Furthermore, the 2 main predictors of IDWG were dialysate sodium and urine output. The lowering of dialysate sodium has been considered controversial. Although lower dialysate sodium may mitigate thirst and IDWG, it may also increase risk for intolerance of ultrafiltration and more intradialytic events.[4] However, in the current study, a sodium bath of ≤138 mEq/l was associated with improvement in IDWG without any increased risk of intradialytic hypotension. Diuretic use also mitigated IDWG in this study: among those who were prescribed diuretics, urine output was 2-fold

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higher compared to those who were not, a finding also supported by data in adults.[5] Diuretics have historically been used sparingly and erratically in patients on hemodialysis, and in the current study was only prescribed 17% of the entire cohort despite only 48% having oligoanuria. The results of this study indicate that modifications of dialysate sodium concentration and the use of diuretics may represent underutilized options to achieve better BP control in children on hemodialysis.

Achieving improved fluid control, although a cornerstone for BP management in children on hemodialysis, is often a difficult challenge that is recalcitrant to the standard dietary interventions of salt and fluid restriction. Lowering sodium dialysate concentration and diuretic therapy may also have limited to no effect for some patients. If these interventions fail, what are some additional measures to improve BP control? Although many patients remained hypertensive despite receiving multiple BP medications, a somewhat surprising and perhaps underemphasized finding was the effectiveness of beta-blockers compared to other antihypertensive medications. Among patients on monotherapy, only those receiving beta-blockers had a mean normotensive BP-SD score (1.12, 87th percentile). In contrast, the mean BP-SD score was 1.72 (96th percentile) in those on angiotensin-converting-enzyme inhibitors or angiotensin receptor blocker medication, and 1.97 (98th percentile) in those receiving calcium channel blockers. Beta-blockers may be more effective in patients on hemodialysis both in controlling BP and reducing cardiovascular morbidity by mitigating sympathetic overactivity.[6] However, these remain less often prescribed compared to calcium channel blockers and angiotensin-converting-enzyme inhibitors, possibly because beta-blockers are not considered first-line therapies according to the American Academy of Pediatrics guidelines for BP management in the general population. In contrast to current recommendations, the results of this study suggest that using beta-blockers may be a more effective approach to control BP and perhaps should be considered as a first-line therapy in children on hemodialysis. Evidence-based guidelines for treatment of hypertension in children receiving hemodialysis, a unique population whom the current general guidelines do not specifically address, are needed.

In clinical practice, however, BP control remains difficult despite exhausting all conservative options. Although more frequent hemodialysis is an option that has been shown to improve BP control,[7] this often requires a weekend dialysis session, which can be burdensome in terms of dialysis resources, and more importantly, patient quality of life. Recently, there has been growing data supporting the superiority of hemodiafiltration to conventional hemodialysis in improving BP control and cardiovascular outcomes. In the 3H study, which prospectively compared children receiving conventional hemodialysis and hemodiafiltration, the latter was associated with improved 24-hour ambulatory BP monitoring and decreased carotid intimal medial thickness. However, no improvement was seen in LVH during the study period.[8] In contrast, the current study demonstrated both an improvement in 24-hour ambulatory BP monitoring as well as LVH in patients receiving hemodiafiltration, compared to conventional hemodialysis, likely owing to increased power and a longer follow-time. Therefore, the current study demonstrates, for the first time, that hemodiafiltration has a measurable association with decreased risk of LVH in children. Although the mechanism for this is uncertain, it may be secondary to improved middle-molecule clearance and reduced inflammation. Another possibility is that hemodiafiltration may be better tolerated hemodynamically and allow for more effective achievement of dry weight. This is supported by improved subjective tolerance of hemodiafiltration in the 3H study and the decreased incidence of intradialytic hypotension in patients receiving hemodiafiltration reported in the current study. Taken together, these results indicate that hemodiafiltration may result in improved fluid balance and BP control; and therefore, it should be considered in those with uncontrolled hypertension.

The results of this large, multicenter study investigating hypertension and LVH in pediatric hemodialysis patients are timely, much needed, and extremely informative. The observational nature of the study, however, precludes any strictly causal inferences. Most notably, patient outcomes varied significantly according to region of residence, and thus residual confounding cannot be excluded. Randomized controlled trials comparing different BP control treatments and protocols, including hemodiafiltration, are needed. This notwithstanding, 2 main conclusions are unequivocal in children receiving hemodialysis. First, BP control in this patient population is woefully inadequate. Second, alternative strategies exist that may be more effective, including hemodiafiltration, lowering of dialysate sodium, and more aggressive use of beta-blockers and diuretics. It is therefore time to rethink BP

management in children receiving hemodialysis.

DISCLOSURE

All the authors declared no competing interests.

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