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Hemodiafiltration in the pediatric population

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Abstract

Hemodiafiltration (HDF) is increasingly adopted as a safe and effective treatment compared to conventional hemodialysis (HD) in children. We describe the outcomes of prospective observational studies in children on HDF versus HD showing that HDF was associated with an attenuation of the cardiovascular risk profile, improved blood pressure control, reduced inflammation, improved bone health and growth, and most importantly, an improved health-related quality of life.

1 | INTRODUCTION

Hemodiafiltration (HDF), a combination of diffusive and convective dialysis, was first performed in children in the 1970s by Fischbach and colleagues in Strasburg, France. With the introduction of HD machines with automated convective dialysis options and optimized online fluid substitution, this group reported a dramatic improvement in catch-up growth as well as improved anemia control, reduced inflammation, a liberation from fluid and dietary restrictions, reduced medication burden, and an overall improvement in the child's quality of life.[1] However, in these early studies, a very high dialysis dose was delivered with over 18 h of HDF per week (3 h of pre-dilution HDF 6 days per week), making it difficult to tease out the benefits of the HDF modality versus those of frequent daily dialysis. Subsequent studies in children have confirmed that high convective volume HDF is safe, has been associated with improved outcomes in the adult trials,[2,3] and can also be achieved in children. Recently, the HDF, heart and height (3H) study, a multicenter, prospective observational study compared outcomes in children on HDF versus conventional hemodialysis (HD)[4] across 28 centers in 10 countries across Europe, providing an in-depth analysis of cardiovascular outcomes, growth, and health-related quality of life.[4]

In this review, we discuss the practical aspects of performing HDF in children and discuss recent studies that have compared outcomes on HDF versus conventional HD.

2 | TECHNICAL REQUIREMENTS FOR HDF—SPECIFICATIONS FOR CHILDREN

As with HDF in adults, the three essential requirements for performing HDF in children include "ultrapure" water for replacement of convective volume, high-flux dialyzer membranes, and dialysis machines that allow careful regulation of ultrafiltration (UF). Currently available HDF machines that are suitable for children are manufactured by Gambro and Fresenius Medical Care, although the Gambro AK200 Ultra-S and the Fresenius 5008 machines will soon be discontinued, leaving only the Fresenius 6008 dialysis machine which is suitable for children above 12 kg body weight when used with a pediatric circuit.

A pooled individual participant data analysis of four randomized controlled trials (RCTs) has suggested that any improved survival associated with HDF occurs when the convective volume is at least 23 L/session.[3] In the 3H study, it was shown that it is possible to achieve high convective volumes of 12–15 L/m^2 body surface area in children, equating to about 20–25 L/1.73 m^2/session in adults.[5] A high convective volume can be achieved by optimizing the blood flow and setting a high filtration fraction (up to 33% in post-dilution HDF) without increasing treatment time. The convective volume showed a strong linear relation with the blood flow rate, but importantly, the blood flow rates were comparable in HD and HDF cohorts and independent of vascular access type, implying that the improved outcomes seen in the HDF cohort cannot be attributed to an improved blood flow alone.[5]

HDF can be performed in pre- or post-dilution modes, depending on whether the replacement fluid is infused upstream or downstream of the dialyzer. Post-dilution HDF is performed in most pediatric centers, but a potential disadvantage is that hemoconcentration at high UF rates can concentrate proteins on the membrane surface, alter membrane permeability and performances, and facilitate clotting of the extracorporeal circuit. Pre-dilution HDF offers an interesting alternative to overcome the limitations of post-dilution HDF but may reduce the efficiency of both the diffusive and convective component by diluting the blood entering the dialyzer, but when performed with higher convective volumes (equal to the blood flow rate), an improved clearance of middle and larger molecular weight toxins may be achieved. Currently available dialyzers that perform mid-dilution or mixed dilution HDF have a surface area above 1.7 to 1.9 m^2 and are too large for use in most children.

3 | CLINICAL STUDIES IN CHILDREN

Following early reports of the benefits of HDF in children by Fischbach et al.,[1] some pediatric dialysis units in Europe, Asia, and the middle-east have been performing HDF, but there are few studies, mostly single center, cross-sectional, and with small patient numbers, examining outcomes. The 3H study is the first prospective, multicenter longitudinal study comparing outcomes on HDF versus conventional HD in children.[5] This study was performed within the International Pediatric Haemodialysis Network across 28 pediatric dialysis centers in 10 countries and included nearly 40% of all children on extracorporeal dialysis across Europe.[5] However, 3H is not an RCT, and given the small numbers of children on dialysis and a high transplantation rate, both incident and prevalent patients on dialysis were included. Nevertheless, children are uniquely suited to study the effects of dialysis treatment due to the absence of secondary pathologies typically present in adults, such as long-standing hypertension, diabetes, smoking, and preexisting cardiovascular disease. Key findings from 3H and other pediatric studies are described here and in Figure 1.

1. *Cardiovascular outcomes*. Subclinical cardiovascular disease is prevalent in children on dialysis. A primary outcome measure of the 3H study was the change in cardiovascular outcomes on HDF versus HD.[4] The scarcity of hard endpoints for cardiovascular outcomes in children necessitated studies of surrogate markers including the carotid intima-media thickness (cIMT) measured by high-resolution ultrasound of the common carotid arteries and expressed as standard deviation score (SDS). Within 1 year of conventional HD, the cIMT increased by 0.41 SDS, whereas there was no change in HDF patients.[4] After adjusting for potential confounders (age, sex, country, blood flow, and water quality) using the propensity score approach, children on HD had a +0.47 greater increase in annualized cIMT-SDS change (95% CI 0.07–0.87; $p = 0.02$) compared to those on HDF, correlating with improved fluid removal as well as clearance of middle molecular weight uremic toxins by HDF.[4] Similarly, the left ventricular mass index was higher in HD compared to HDF patients in the 3H study and closely correlated with the improved fluid control on HDF.[4] A further study from an Egyptian

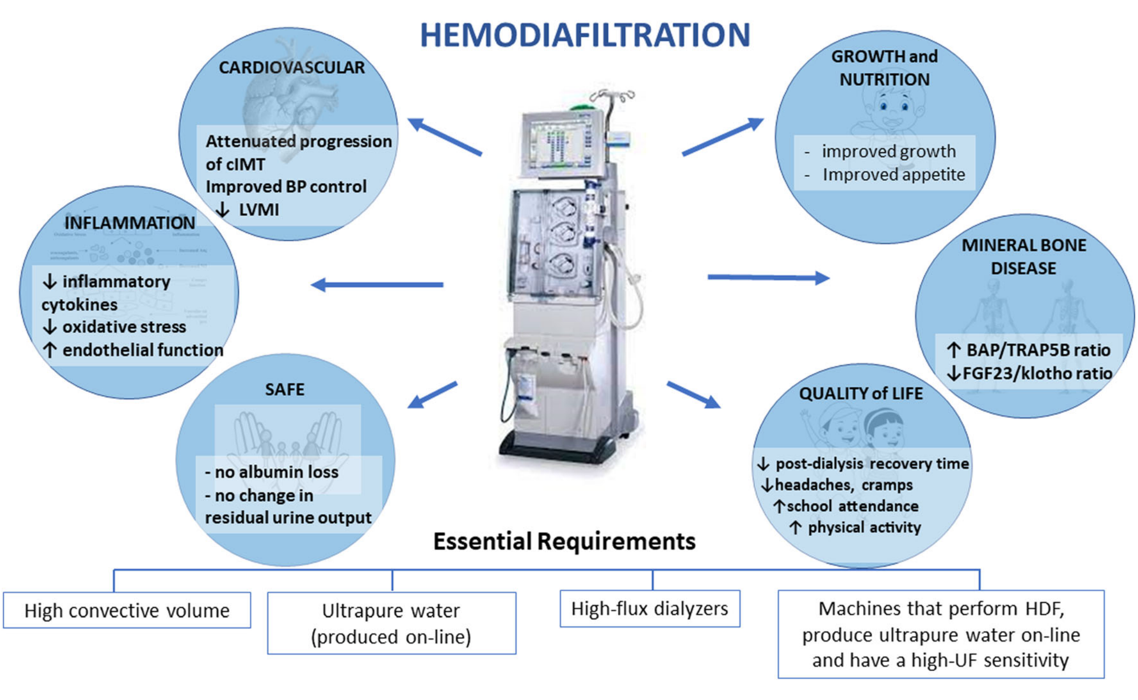

FIGURE 1 Essential requirements for performing HDF and the benefits of HDF in children. BAP, bone-specific alkaline phosphatase; BP, blood pressure; cIMT, carotid intima-media thickness; FGF23, fibroblast growth factor 23; LVMI, left ventricular mass index; TRAP5B, tartrate resistant acid phosphatase 5B

group has shown that when children were moved from HD to HDF, within a 6-month period, an improvement in systolic function and a decrease in diastolic dysfunction were noted, although the left ventricular mass was unchanged.[6]

2. *Blood pressure control*. Hypertension (measured by 24-h ambulatory blood pressure recording and expressed as the mean arterial pressure [MAP]-SDS) was significantly more common and increased more rapidly in children on conventional HD compared to HDF.[4] Over a 1-year follow-up, the MAP increased by 0.98 SDS in HD patients while there was an attenuated and nonsignificant increase of 0.15 SDS in HDF patients.[7] A significant risk factor that correlated with change in the MAP-SDS was the interdialytic weight gain (IDWG%), a surrogate for sodium mass removal rate, suggesting that effective volume control is key to managing hypertension in children on dialysis. A further study suggests that switching children from nocturnal in-center HD to nocturnal in-center HDF may significantly improve their BP, phosphate, and PTH control.[8]
3. *Inflammation and oxidative stress*. Conventional HD is known to cause a pro-inflammatory milieu due to an increased production and reduced clearance of inflammatory cytokines by diffusive therapy alone. Several inflammatory cytokines are large middle-sized molecules that are cleared by convection on HDF. The 3H trial showed that inflammatory cytokines such as IL-6, TNF-α, and high sensitivity CRP were higher in HD compared to HDF patients at baseline and continued to increase significantly in HD, but no change was seen in the HDF cohort over the follow-up period of up to 1 year.[4,9,10] Similar findings were shown in the SWITCH study: When patients on HD were "switched" to HDF keeping all other dialysis related parameters unchanged, a significant reduction in several markers of inflammation, oxidative stress, and endothelial dysfunction was seen after just 3 months on HDF.[9]
4. *Bone health and growth*. Most children on dialysis develop profound dysregulation of their mineral bone metabolism and poor growth. The 3H study investigated bone-specific alkaline phosphatase (BAP) a marker of bone formation and tartrate-resistant acid phosphatase 5b (TRAP5b), a bone resorption marker. The BAP-to-TRAP5b activity remained almost constant in children on HD, while children on HDF had an increase in the BAP/TRAP ratio that was comparable to levels seen in healthy children, implying an osteoanabolic process.[10] Fibroblast growth factor 23, also a middle molecular weight substance, is effectively cleared by HDF with levels decreasing by 25% in HDF over the 1-year follow-up but increasing by over 100% in children on HD.[10] A significant and consistent lowering of FGF23 by HDF may partially explain the lower left ventricular mass in the 3H cohort[4] and reduced cardiovascular mortality in adults on HDF compared to those on conventional HD.[2]

In earlier studies, Fischbach et al. showed that intensified HDF promotes impressive catch-up growth.[1] All patients also received growth hormone treatment (GH-Rx), but the effect was more pronounced than expected with GH-Rx alone and was closely associated with the onset of six times weekly online HDF daily.[1] In line with this, the annualized change in height-SDS in the 3H study remained static in HD but showed a small but statistically significant increase in HDF that was independent of GH-Rx.[4] Interestingly, an inverse correlation between height-SDS increase and β2M was demonstrated, suggesting that clearance of middle-molecular-weight compounds including inflammatory cytokines and endogenous somatomedin and gonadotropin inhibitors may partly alleviate resistance to GH in patients on HDF.

5. *Health-related quality of life*. In self-reported quality of life questionnaires, children on HDF had fewer episodes of headaches, dizziness, and cramps as well as a reduction in the post-dialysis recovery time compared to those on HD.[4] HDF patients had lower UF rates compared to HD; a low UF rate facilitates vascular refilling during the dialysis session, reducing the propensity for hypotensive episodes, which, in turn, allows better patient tolerance and fewer symptoms. The Standardized Outcomes in Nephrology (SONG-Kids) workgroup has identified fatigue as one of the most highly prioritized outcomes for dialysis patients and clinicians, and HDF was shown to promote "life participation" by improving school attendance and physical activity.[4]
6. *Safety*. There was no reduction in serum albumin levels and no difference in the rate of change of residual kidney function in children on HD or HDF.

4 | CONCLUSIONS AND FUTURE DIRECTIONS

Studies in children suggest that HDF may attenuate the progression of vascular changes, improve BP control with a consequent regression of left ventricular hypertrophy, reduce inflammation and oxidative stress, promote growth, improve anemia control, and improve the tolerability of dialysis as well as the overall quality of life. Importantly, there are no randomized trials in children, so these data must be interpreted with caution. Also, the true extent of benefits achieved with convective purification cannot be discerned from the benefits of high-flux HD with ultrapure dialysis water. However, until a formal RCT is conducted, the current body of literature demonstrates that HDF is a safe, feasible, and well-tolerated treatment, and based on biological plausibility, data from adult RCTs, and a large pediatric cohort study, HDF may be considered for all children on in-center dialysis therapy.

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