Is There Not Sufficient Evidence to Show That Haemodiafiltration Is Superior to Conventional Haemodialysis in Treating End-Stage Kidney Disease Patients?

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Evidence-based medicine (EBM) is currently perceived as the new paradigm and a “gold standard” for guiding treatment practice changes in clinical medicine, including nephrology [1]. EBM relies on evidence generated by clinical trials and/or other studies, the highest level being supported by prospective randomized controlled trials (RCTs) that form the basis of meta-analyses [2]. Based on these findings, best practices guidelines are graded from high to low levels and guidelines are developed to support physicians in their decision-making in clinical practice [3]. This process is recognized by both the scientific community as well as health care providers as the most appropriate approach to improve value-based care in medicine. Nephrology, including renal replacement therapy (RRT) options, is hence within the scope of both EBM and value-based healthcare [4].

Application of EBM related to end-stage kidney disease (ESKD) patients and renal replacement therapies is fraught with a number of difficulties: Foremost, randomized controlled studies are scarce, weak, or even nonexistent, explaining why the present level of recommendations is relatively weak regarding best practice guidelines

for dialysis and ESKD. Second, most seminal interventional RCTs in dialysis have failed to reach their primary objective (e.g., the HEMO study [5], MPO study [6] Nocturnal FHN [7], IDEAL [8], 4D [9]). Third, ESKD and uremia are highly complex pathologies that combine several metabolic disorders interacting with one another with the consequence that specific interventions focusing on any one component are likely to fail to improve or impact patient outcome [10]. Fourth, dialysis patients are mostly elderly (~2/3 are over 65 years) often having multiple comorbid conditions (60% with past history of severe cardiovascular event) with renal rRRT being just one component of the overall outcome-based risk profile [11]. Finally, practice patterns in the RRT field are highly diverse, as shown by the Dialysis Outcomes and Practice Patterns Study (DOPPS) initiative, meaning that centre or care provider effects are significant confounding factors towards the eventual clinical outcome of the dialysis patient [12].

Furthermore, it is imperative to recognize that studies addressing specific questions in the treatment of ESKD patients will never be addressed by interventional randomized prospective study for ethical or legal reasons.

Would any ethics committee or executive review board agree to analyze patient outcomes in RCTs comparing peritoneal dialysis versus haemodialysis (HD)-treated patients, palliative care versus dialysis patients or dialysis versus kidney transplant patients? In such cases, the scientific community strongly advocates to consider moving to patient-centered care and to use cohort studies as valuable tools for providing answers to unanswered questions [13, 14]. In order to minimize bias and confounders, it is proposed to use more refined epidemiologic tools (e.g., Propensity Score Matching, Inverse Probability Treatment Weighting) to account for these factors [15].

Haemodiafiltration (HDF), widely recognized as the most efficient as well as innovative RRT for ESKD patients [16–18], is also rightly the subject of scientific scrutiny, to assess the evidence-based facts that support its purported clinical superiority and its added value in the RRT field [19]. The question raised by Kawanishi [20] regarding the soundness of evidence base for HDF is certainly valid. Considering HDF as potentially the most superior therapy option in ESKD patients, it is then worthwhile to examine where we are today in terms of the soundness of the clinical evidence in order to identify gap and generate complementary research questions [21].

Short-term prospective interventional studies have provided intermediary outcomes showing that HDF enhanced solute removal of middle and large molecular size solutes and were associated with clinical benefits. HDF provides enhanced clearance of β_2 -microglobulin compared to HD (30–40% higher with HDF than with high-flux HD) [22] and several large cohort studies have shown that the use of convective therapies has a beneficial impact on the development of β_2 -microglobulin amyloidosis, reducing the incidence of carpal tunnel syndrome and other related manifestations [23, 24].

Although somewhat controversial, HDF tends to remove 15–20% more phosphate than high-flux HD [25]. In the CONTRAST and French Convective versus Hemodialysis in Elderly (FRENCHIE) [26] studies, pre-dialysis serum phosphate levels were reduced by 5–10% and the percentage of patients reaching target pre-treatment serum phosphorus levels reached over 70%, whereas no difference was found in the ESHOL and Turkish studies [22, 43].

Other prospective studies have shown that HDF was associated with lower levels of CRP and other sensitive biomarkers of inflammation (e.g., IL-6 and/or proinflammatory cells) [27, 28]. It remains unclear if HDF has significant benefits in anaemia management. Erythropoie-

sis-stimulating agent dose has been reduced in several clinical studies in HDF-treated patients, the benefit being attributed to the combined effects of the higher removal of middle-sized uremic toxins and use of higher quality dialysate reducing inflammation [29, 30]. No effect on erythropoiesis-stimulating agent resistance was found in a secondary analysis of CONTRAST data [31], whereas a significant decrease was observed in a large observational study for incident patients treated with EPO who received a high convective volume [32].

A significant reduction in episodes of intradialytic hypotension in HDF compared to conventional HD has been observed in some studies [33] but was blunted when thermal balance control was applied in HD [34]. Benefits of HDF have been ascribed to negative thermal balance due to the infusion of relatively cool substitution fluid. Interestingly, a recent prospective study showed that compared to high-flux HD, high-dose HDF was associated with preservation of muscle mass, increased protein intake and reduced inflammation, suggesting that HDF could help prevent protein-energy wasting [35].

Meta-analyses and/or systematic reviews comparing HDF to standard HD have reported conflicting results [36, 37]. Unfortunately, most of these meta-analyses aggregated several different convection-based methods under the umbrella of “convective therapies” (e.g., HF, AFB, bag HDF...) and have been performed on historical cohort with outdated HDF practices, which in addition did not consider convective volume as a confounder [38, 39].

Several retrospective large cohort studies suggested that HDF had beneficial effects on patient survival. The DOPPS first suggested that patients treated with relatively higher volume HDF (15–25 L/session) had a 35% lower mortality than those treated with low-flux HD [40] even if this landmark finding could not be confirmed in a recent analysis of DOPPS [41].

Early results of cohort studies triggered 4 European RCTs to examine the survival rates associated with HDF. The primary analysis of 2 studies (CONTRAST [42] and Turkish [43]) failed to show beneficial effects on all-cause or cardiovascular mortality, although post hoc analyses of both studies showed beneficial effects in patients with high convection volumes (>22 L/session). The fact that two third of patients enrolled in CONTRAST did not achieve the targeted convection volume could be considered a weakness of that study [44]. However, recently, the same group reported that after the implementation of a stepwise approach and nurse training, over 80% of patients could achieve the threshold convection volume suggesting that failure to achieve the target was not inher-

ent to HDF but related to its clinical implementation [45]. The third study (ESHOL), which achieved a convection volume of 22.9 L or more, demonstrated in the primary analysis of that patients treated with HDF had a 30% lower risk of both all-cause and cardiovascular mortality than patients treated with high-flux HD [46]. The fourth study (FRENCHIE) was performed in patients over 65 years and focused on dialytic tolerance and patient reported outcomes [47]. The primary analysis showed that the proportion of patients experiencing at least one treatment-associated adverse event did not differ between HDF and high-flux HD; the secondary analyses at the session level showed a significantly lower occurrence of intradialytic symptomatic hypotension and muscle cramps in the HDF-treated group.

All these studies indicate the critical question related to the magnitude of the convection volume, namely, the *convective dose*, as to how much of it should be delivered to achieve a positive outcome [48]. This question has been best addressed in a meta-analysis of individual patient data pooled from the 4 European RCTs (CONTRAST, Turkish study, ESHOL and FRENCHIE) [49, 50]. In brief, 769 of 2,793 patients had died, with 292 of the deaths being cardiovascular after a median follow-up of 2.5 years. HDF patients were then divided into tertiles based on delivered convection volume and mortality compared to those with HD using hazard ratios calculated using Cox proportional hazard regression models [49, 50]. HDF was associated with a reduction in relative risk of mortality (all-cause and cardiovascular) for patients in the highest tertile of convection volume, whatever anthropometric standardizing factor was used [50]. In aggregate, HDF was shown to reduce the relative risk of all-cause mortality by 14% and cardiovascular mortality by 23% compared to HD [49]. The greatest benefit was for patients receiving the highest delivered convection volume (>23 L/session or 25.7 L/1.73 m² body surface area). Furthermore, in this pooled individual patient data meta-analysis, it was also shown that for some pre-selected subgroups of patients (e.g., elderly, cardiac, vintage on dialysis) HDF may have additional benefits with highest convective volumes [50].

With the extensive, worldwide clinical experience with the HDF modality, it is important to emphasize that there are no concerns about the safety and efficacy of sterilizing ultrafiltration for producing online substitution fluid and/or reliability of HDF monitors [51, 52]. To support this notion, one must keep in mind that today more than 180,000 patients are treated daily by HDF worldwide [53], with no reports questioning the safety the therapy or of

online-prepared substitution fluid. On the contrary, all clinical findings suggest that outcome benefit is dose-related with a threshold volume of ultrafiltration that is equivalent to 23 L/session (25.7 L/1.73 m²) in post-dilution mode [49]. From a clinical perspective, the critical challenge is now to implement high-volume HDF best practices in dialysis units and to provide adequate training to caregivers with precise targets and quality assurance control tools.

What then are the remaining questions to bridge the gap and prove the superiority of HDF in the RRT field? First, to confirm that high-volume HDF is indeed superior to conventional high-flux HD, an RCT adequately powered and designed addressing both patient outcome and patient perception is required. This question is currently being addressed by the CONVINCe study, a European Community-funded study, that plans to enroll 1800 prevalent ESKD patients and to compare in 2 arms (of 900 patients each), high-flux HD and high-volume HDF (>23 L/session) over a 3-year follow-up period [54]. The primary objective is mortality (all-cause and cardiovascular causes) and the secondary objective is to obtain patient perception (Patient Reported Outcome and Patient Reported Experience) using an innovative tool [PROMIS]. Second, regarding the clear trend towards increasing convective volumes to improve outcomes, it is now time to revisit electrolyte prescription, that is, not just the Na as emphasized in the editorial of Kawanishi [20] but all electrolytes (e.g., K, HCO₃, Ca, Mg) in order to prevent long-term imbalance and their associated side effects. Third, it is imperative today to carry out solid health economic analyses alongside clinical trials to assess the outcome vs. cost aspect to guide non-clinical budget holders on value-based renal care (e.g., hospitalization rate, vascular access dysfunction, anemia management with respect to the outcome/cost ratio) or to best integrate HDF in ESKD patient trajectory and/or to explore cause-specific morbidity and mortality [55, 56].

In conclusion, it is rather encouraging to witness increased scientific activity striving to prove clinical superiority and added value of HDF over conventional HD focusing on patient outcome-related RCT studies. However, this quest for more definitive evidence should not hinder or restrict clinician practitioners from prescribing HDF to patients who could already benefit from the modality today. Not offering potentially superior treatment options today could be perceived tomorrow as a lost opportunity of better outcomes for ESKD patients – once it is definitively proven in the future that HDF is indeed superior to conventional HD treatment options.

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