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Hemodiafiltration outcomes in special situations

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Abstract

This *Seminars in Dialysis* Hemodiafiltration Symposium includes many references regarding the outcomes of this modality in general. The results in special populations are included in some of the studies, but have not been compared in a systematic manner. The purpose of this review is to compile those outcome results in select populations.

1 | INTRODUCTION

Hemodiafiltration (HDF) is performed in parts of the United Kingdom, Europe, Asia, and Australia. While some studies have shown a benefit in special situations, there have been no publications describing adverse consequences. Herein, I address some special clinical situations. The rationale is that the benefits of HDF, especially with high convective volumes (CV), may differ. Most of the published studies have mentioned a few of these populations. There may not be data in many situations, so I attempt to categorize populations so to inform data collection in future pragmatic trials (Table 1). Large enough pragmatic trials could address many of the comorbidities in the specifically developed index for end-stage kidney disease (ESKD) (Table 2).[1] A more detailed index will allow for even more precise propensity score matching (PSM) of different blood purification therapies. First, I review the data regarding special circumstances.

2 | INCIDENT VERSUS PREVALENT PATIENTS AND VINTAGE

Kidney dysfunction and ultimate failure has many consequences which manifest variably, inconsistently, and over differing intervals. Patients may suffer comorbidities that resemble uremic manifestations. A patient with slowly progressive renal insufficiency compensates, adapts, and can maladapt with permanent harm that cannot be corrected even by kidney transplantation. The nature, duration, and care management of the progressive kidney disease before dialysis confound most results once dialysis is initiated. We attribute the improvement (or not) to a blood purification therapy when the causation may have little relationship with ESKD.[2] This affects both incident and prevalent patients, and in the latter, dialysis duration is calibrated as vintage. The concept of adjusting for vintage cannot account for the permanency of uremic complications. Consequently, studying outcomes is complicated. The study of incident patients versus prevalent patients attempts this, but this problem cannot be fully or accurately accounted for. Some studies do not separate incident versus prevalent subjects. Vintage varies from several months to 10 years. It is difficult to attribute regression of damage from retained toxins after such an indeterminant length of exposure. The four major randomized controlled trials (RCT) were performed on prevalent patients with adjustment for vintage only in the CONTRAST and Turkish studies.[3–6] In the FRENCHIE study, mean vintage was nearly 5 years, and the emphasis was on tolerance to therapy by high-flux hemodialysis (HD) versus HDF. That seems a far more reasonable parameter to study than neuropathy improvement with such a long period of a possibly irreversible malady. In large retrospective observational studies of REIN or DOPPS data, only the latter adjusted for vintage.[7,8] The FINESS RCT population was of similar vintage (>3 years), and the analyses specifically addressed it (see Section 6).[9]

Vintage was either adjusted for within proportional hazard models or equal at baseline and not adjusted. Vintage is considered a surrogate for residual kidney function (RKF), an important confounder. Unfortunately, RKF is not considered in most studies since urine is not easily collected and urine output likely to disappear after 6–12 months of regular treatment. Therefore, using a reliable biomarker such as ß2M would make sense to assess both blood purification efficacy and RKF. This is a complex issue. Does HDF compensate for the lost benefit of RKF to remove larger molecules? Therefore, is it the preferred modality once RKF is lost? As discussed below, HDF is associated with less frequent intradialytic hypotension and ischemic kidney insults.[10] In that case, would it be a less harmful modality than HD to RKF? Then HDF would be the preferred modality to protect RKF. Cumulative exposure to uremia is not a factor in the proportional

TABLE 1 Select populations in whom the benefits of high convective volume HDF may differ

Age (children to elderly)
Sex
Body size (small malnourished to morbidly obese), other nutritional makers than just albumin
Inflammatory state
Degree of residual kidney function versus anephric
Rapidity of progression to ESKD
Diabetes (Type 1 vs. Type 2)
Degrees of heart failure
Anemia (requires erythropoiesis stimulating agents vs. not)
Bleeding risks
Intradialytic hypotension
Baseline neuropathy
Low normal pre-dialysis BP without medication
Peripheral vascular disease (vascular stiffness)
Hyperphosphatemia
Quality of vascular access
Degree of intradialytic weight gain
Incident to degrees of vintage
Previous transplant (kidney, lung, liver, heart)
Dysnatremia
Nutritional status
Response to vaccines

Note: While there may not be data on many of these populations, the suggestion for future studies is to at least try to categorize subjects in pragmatic trials that have these characteristics.

TABLE 2 Hemmelgarn et al's new ESKD comorbidity weights derived from the original Charlson index each added to create comorbidity score

Comorbidity variable	New ESKD morbidity weight
Myocardial infarction	2
Congestive heart failure	2
Peripheral vascular disease	1
Cerebral vascular disease	2
Dementia	1
Chronic lung disease	1
Rheumatological	1
Peptic ulcer disease	1
Diabetes without complications	2
Diabetes with complications	1
Moderately severe liver disease	2
Metastatic disease	10
Leukemia	2
Lymphoma	5

Notes: Mild liver disease and hemiplegia were excluded because of too few numbers of patients. Renal disease was obviously excluded, and so was neoplasia. Adapted from Hemmelgarn et al.[1]

hazard model but is better addressed in the accelerated failure time model.[11] Future studies should consider this approach.

3 | AGE AND NUTRITIONAL STATUS

PSM and Cox regression models adjust for age. Most studies have not determined that age is an important factor in comparing depurative modalities. Observational studies can directly target age groups. Piccoli et al report on two populations in Le Mans, France, and Cagliari, Italy, with ages of 71 and 67 years, respectively.[12] Compare those ages to DOPPS (58–64 years), CONTRAST (64 years), ESHO (50 years), the Turkish Study (56 years), and REIN (71 years). Piccoli et al note that the Italians favor HDF over HD in the elderly, while the French favor HD. This is consistent with the French registry data in REIN with the oldest population reported in HDF outcomes. Piccoli et al describe the complex relationship among age, inflammation, and nutrition. These factors affect outcomes differently. When inflamed or undernourished, the mortality in HDF may be higher than in HD, especially in the elderly. In part, this is attributed to protein issues in high CV therapies. In the pooled data of the RCTs' age >65 versus <65 years, HDF was associated with a 20%–30% risk reduction for all-cause and cardiovascular mortality compared to HD,[13] findings similar to those of REIN. This subsequently led to the FRENCHIE RCT to compare high-flux HD to HDF regarding intradialytic tolerance in prevalent ESKD subjects >65 years old.[6] The HDF group had fewer episodes of asymptomatic hypotension and muscle cramps than the HD cohort. Arrhythmias were more frequent in the HDF group. [Albumin] remained stable and was similar in both groups. Hospitalizations and all-cause and cardiovascular mortality were not different. CV dichotomization at 20 L also did not show any survival difference. In a New Zealand observational study, HDF conferred an all-cause mortality benefit, but a decreased cardiovascular mortality benefit compared to HD in subjects >65 years old.[14] Many small trials described outcomes in these age groups, but the trials were so underpowered that meaningful conclusions regarding the effect of age on outcomes cannot be drawn.

Observational studies might provide some insight into HDF effects on nutritional status. Neither Vilar et al nor DOPPS found a difference in [albumin] in patients treated with HDF versus HD, but in the English study, the body mass index was higher in those treated with HFD.[8,15] [Albumin] as a surrogate is often used and was specified as such in CONTRAST, ESHOL, the Turkish trial, FRENCHIE, and the optimal CV dose report.[3–6,16] No other nutritional specifics were described. RCTs usually specify a life expectancy as an entry criterion, so malnourished subjects were likely to be excluded. Furthermore, nutritional status is linked to inflammation, and these interactions confound looking only at one aspect. Inflammation is discussed in another section of this symposium. Peters et al pooled data from these four RCTs, dichotomized [albumin] to <4 versus >4 g/dl, and found no statistical difference in either all-cause or cardiovascular mortality.[13] However, the Piccoli study described above did raise concern over a possible increased mortality risk of HDF in the elderly.[12]

4 | SIZE

Scaling (normalization to size) has been a long-standing topic of biologic investigation.[17] In almost every report cited herein, CV dose delivery was not dependent on body size, but rather either arbitrarily delivered or based on the quality of the vascular access to deliver a high enough blood flow rate (Qb) so that the filtration fraction could achieve an ultrafiltration rate.[18] Scaling dialytic convective dose makes sense for a population-based approach. The four RCTs were developed in a European population with relatively homogeneous anthropometrics profile, ethnicity, lifestyle, treatment schedule, etc. The average dry body weight of European dialysis patients is 85 kg, in Japan 55 kg, and in the United States 85 kg. The extrapolation of findings in one population to another must be only done cautiously. In a follow-up of the four RCTs, Davenport et al concluded that body size should be accounted for in any evaluation of CV dosing.[19]

5 | DIABETES

The presence of diabetes varies nationally and regionally. In a retrospective observational study of patients receiving HD or low-moderate CV HDF, diabetic disease demonstrated a 34% increased hazard ratio compared to standard HD-treated patients.[15] In a pooled RCT data there was a 23% hazard ratio reduction for all-cause mortality in HDF-treated subjects, but a less significant benefit noted for cardiovascular mortality.[13] Despite a 40% prevalence of diabetes, FRENCHIE did not focus on specific outcomes in diabetics.[6] One-quarter of the CONTRAST subjects were diabetic, and outcomes did not differ from nondiabetics.[3] In ESHOL where higher CVs were delivered, diabetics represented a fourth; HDF-treated subjects experienced a significant mortality benefit over HD-treated subjects.[4] In the Turkish trial, about 35% were diabetic; the HDF-treated subjects experienced a 26% lower relative risk of the composite outcomes (mortality and first nonfatal cardiovascular event) than those subjects treated by HD.[5]

6 | NEUROPATHY

Peripheral neuropathy in ESKD patients is extremely variable and often confounded by comorbidities. In two small observational studies, some symptoms were less frequent with high-volume HDF.[20,21] Of the RCTs, only ESHOL reported on neuropathies, and the benefit was not statistically better with HDF. Two Australian RCTs were performed to specifically evaluate the potential neuropathic benefit of HDF. Arnold et al longitudinally followed nine and eight patients treated by high-flux HD or HDF, respectively.[9] Nerve excitability in HDF-treated patients was significantly closer to normal values than in HD-treated patients. The follow-up open-label, blinded end point assessment controlled FINESSE trial that compared HDF-treated incident and prevalent patients to high-flux HD-treated patients, followed for 48 months. HDF treatment did not affect neuropathy progression compared to HD treatments.[22] The duration of the antecedent CKD was not reported. Vintage (dichotomized to <12 or >12 months) did not affect the outcome results. From this study, one must conclude that in typical ESKD patients receiving less than high CV, HDF did not improve some neuropathies.

7 | CARDIOVASCULAR OUTCOMES

The interpretation of cardiovascular finding is complex. Events are variably defined, and the relationship to interdialytic weight gain rarely described. Intradialytic events might include both symptomatic and non-symptomatic episodes.

Early in the hemofiltration experience with critically ill subjects, myocardial depressant substances were theorized to be removed better by convection versus diffusion.[23,24] This began the thought that convective therapies might positively influence cardiovascular events in ESKD patients. Mion et al applied HDF to high cardiovascular risk patients with positive results.[25] A direct event in this population would be intradialytic hypotension. A transmembrane [Na] gradient of 9–5 mEq/L compensates for the Donnan effect in HDF.[26] Applying this reasoning, de Vries et al showed that the blood volume decrease during conventional HD was higher than during hemofiltration.[27] Observational studies described less frequent episodes of intradialytic hypotension in HDF treatments compared to HD treatments.[14,28] In FRENCHIE, there were significantly fewer episodes of intradialytic hypotension and muscle cramps in HDF-treated patients.[6] ESHOL found a lower frequency of intradialytic hypotension with HDF but did not find a decrease in intradialytic arrhythmias.[4] Meta-analyses support the findings that HDF reduces symptomatic hypotension events.[29,30] Daugirdas suggests that this phenomenon is mediated by the extracorporeal circuit temperature rather than the removal of a blood pressure lowering uremic toxins.[31] Donauer et al performed crossover studies in patients with a high frequency of intradialytic hypotensive events.[32] Hypotensive events were less frequent when HDF was compared to regular HD, but when dialysate was cooled in HD, the event frequency was similar to that during HDF.

In the four pooled RCTs, the cardiovascular mortality risk in HDF-treated patients was reduced by 23% compared to HD-treated patients.[13] This mortality risk dropped further by 31% when the highest CVs were achieved. In a PSM study of 1012 incident patients in Spanish Fresenius units utilizing HDF with CV > 21 L/session, all-cause and cardiovascular mortality were significantly less in the HDF-treated subjects.[33] The apparent advantage of higher CVs was explored further using PSM of two HDF populations with different CV (<4.6 and >64.8 L/wk).[16] Cardiovascular disease within the Charlson index was not specifically reported. However, these thought leaders reviewed and theorized on the possible mechanisms by which high-volume HDF may reduce cardiovascular mortality.[35] Suggested key mechanisms were less frequent episodes of intradialytic hypotension and arrhythmias and more frequent achievement of estimated dry weight. In a meta-analysis, convective modalities did not reduce cardiovascular events but did reduce the frequency of symptomatic

hypotension.[29] Using different criteria, another meta-analysis suggests that convective modalities may reduce cardiovascular mortality and intradialytic hypotension but have uncertain effects on nonfatal cardiovascular events.[30] These meta-analyses evaluated RCTs as well as retrospective observational studies. Probably, the most important thing we can learn from these investigations is that high-volume convective therapies may be beneficial in reducing cardiovascular event risks when specific prescriptive details are followed. This may explain why the ESHOL trial demonstrates a 33% lower cardiovascular mortality. The study center staff were specifically trained, encouraged and tracked to achieve high CVs.[4]

8 | CONCLUSION

There clearly are circumstances where HDF may be a better blood purification approach than conventional high-flux HD. RCTs are expensive and difficult to conduct and require a very long time to complete. Thus, the future evaluations may well be in large pragmatic trials. Table 1 lists many of the subsets that may be of interest in the data collection of such very large pragmatic trials.

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