

The re-emergence of short daily haemodialysis

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Abstract

Thrice weekly in-center hemodialysis is the standard of care for dialysis patients with end-stage renal disease (ESRD). However, there is ongoing debate as to whether more frequent hemodialysis, with its readier management of both toxin and fluid removal, benefits patients. New evidence from recent studies, both in center dialysis and in home haemodialysis patients, adds further confirmation of improved cardiovascular outcome and quality of life in patients undergoing short daily hemodialysis. A paradigm shift in ESRD care delivery may be facilitated due to new technology enabling daily therapy at home.

Keywords: FHN trial; FREEDOM study; home hemodialysis; short daily hemodialysis

Introduction

Recent results from the National Institutes of Health (NIH) Frequent Hemodialysis Network (FHN) daily trial and the Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements (FREEDOM) study have provided confirmation of the clinical and quality of life (QoL) benefits of short daily hemodialysis (SDHD) when compared to conventional thrice weekly in-center hemodialysis (CHD).

The FHN study was conducted in-center; however, SDHD in the USA is more commonly performed as a home therapy and is not offered as a standard treatment modality in most dialysis clinics. Although it has been nearly 50 years since the early pioneers such as Belding Scribner and Stanley Shaldon began dialyzing patients in their homes, peaking at ~40% of all US dialysis patients in 1973, the popularity of home hemodialysis (HD) has been limited in the USA for a number of reasons, including lack of suitable equipment and increased cost [1]. The last few years, however, have seen a revival in home HD, resulting in renewed interest in the various forms of more frequent therapy, including SDHD. The revival of home dialysis was led in the mid 1990s by Robert Uldall, Andreas Pierratos and others in Canada, gradually spreading throughout the USA.

This re-emergence has been made possible by recent advances in technology, including portable and more user-friendly

machines designed specifically for use in the home environment. In 2005, the FDA cleared the first HD machine for home use in the USA, the NxStage System One™. FDA clearance was based on an open-label, prospective, two-treatment two-period crossover study on 32 patients to compare SDHD performed in-center (prescribed six times/week) versus SDHD performed at home. The study was conducted at six centers in the USA under an Investigational Device Exemption. This study showed SDHD was delivered as efficiently in the home environment as in-center, with 98.5% of treatments performed successfully in-center versus 97.3% at home. Notably, the composite rate of intra-dialytic and inter-dialytic adverse events was significantly higher during the in-center phase when compared with the home phase (5.3 versus 2.1 adverse events/100 treatments; $P = 0.007$), suggesting HD therapy is at least as safe at home as in-center. When comparing clinical parameters from the period immediately preceding the study when patients were treated with conventional thrice weekly center HD, home SDHD was associated with reductions in blood pressure, antihypertensive medications and interdialytic weight gain [2].

Since the clearance of the NxStage System One™ in the USA, the number of patients now performing home dialysis is estimated to be ~5000, with the majority of these patients performing SDHD. Although this represents a considerable increase over the past 5 years, it is still only ~1% of the total end-stage renal disease (ESRD) population. SDHD offers the promise of improved clinical outcomes in patients with kidney failure, and given the positive results recently released from both the FHN and FREEDOM studies outlined below, SDHD has the potential to become a more viable and popular choice amongst many ESRD patients.

Benefits of SDHD

Results recently published from the FHN daily trial, funded by the NIH, showed that in-center SDHD (prescribed six times/week), provided significant benefits in both composite co-primary outcomes of death or 12-month change in left ventricular mass (LVM) and death or 12-Month change in the RAND-36 physical health composite (PHC) score. Specifically, the FHN daily trial showed patients randomized to SDHD reduced their LVM by 16.3 ± 35.3 g ($P < 0.001$) and improved their PHC score by 3.3 ± 8.9 points ($P = 0.004$), after 12 months. SDHD was also associated with improved

control of hypertension and hyperphosphatemia. However, patients on SDHD were more likely to undergo interventions related to vascular access, a result which will require further elucidation with the ongoing analysis of the trial [3]. The FHN trial will be a tremendous source of data to further dissect the advantages seen with daily therapy in the coming years.

The FREEDOM study is an ongoing prospective cohort study investigating the clinical and economic benefits of SDHD. The objectives of the FREEDOM study are to compare a cohort of patients starting SDHD using the NxStage System One™ to a matched cohort of patients receiving CHD for all-cause hospitalizations and non-treatment-related medical expenditures. This study is funded by NxStage Medical, Inc. Using a 10-to-1 ratio, totaling 5000 patients, the matched thrice weekly in-center HD cohort will be obtained from the US Renal Data System (USRDS) database. In addition, changes in QoL measures, urea kinetics, management of anemia, bone and mineral metabolism, nutrition, vascular access interventions and use of medications will be examined. The FREEDOM study will involve up to 70 clinical sites and 500 participants, with a minimum 1-year follow-up. Study participants complete QoL surveys at the time of study enrollment, at 4 and 12 months and every 6 months thereafter [4].

Interim data recently released from the FREEDOM study has shown that SDHD, performed in the home environment, is associated with significant improvements in several important clinical and QoL measures when compared to conventional thrice weekly in-center HD.

Impact of SDHD on depressive symptoms

Interim results from the FREEDOM study investigating the effect of SDHD on depressive symptoms were recently published [5]. Depressive symptoms were examined in 248 participants at enrollment and at 4 and 12 months by administering the validated Beck Depression Inventory (BDI)-II survey. The study protocol requires that the site investigator be notified immediately of a BDI score >10, with mild and moderate to severe depressive symptoms defined as BDI scores of 11–15 and >15, respectively. In summary, SDHD was associated with a significant improvement in mean BDI score over 12 months [11.2, 95% confidence interval (CI) 9.6–12.9, versus 7.8 (95% CI 6.5–9.1); $P < 0.001$], in the per-protocol (PP) cohort. Similar results were found in the intent-to-treat (ITT) cohort. For participants with moderate to severe depressive symptoms, the BDI scores almost halved over 12 months [24.4 (95% CI 19.4–29.4) versus 12.6 (95% CI 8.0–17.2); $P < 0.001$]. It should be noted that a BDI score >15 previously has been shown to be highly predictive of a diagnosis of clinical depression [6]. The percentage of participants with depressive symptoms (BDI score >10) significantly decreased during 12 months (41 versus 27%; $P < 0.03$). Similarly in the FHN study, patients participating in the daily arm did show a trend toward improvement after 12 months when compared to baseline (12.6 ± 8.7 versus 10.4 ± 8.5 , $P = 0.1$). Although this trend was not statistically significant, one

might speculate that undergoing daily dialysis therapy at home may contribute to this improvement.

Considering the practical feasibility of daily dialysis both from a logistical and a patient comfort perspective, one might hypothesize that the home setting may further enhance the benefits of SDHD experienced in-center.

Impact of SDHD on post-dialysis recovery time

The long-term effect of SDHD on post-dialysis recovery time was also assessed in the FREEDOM study by administering the following previously validated question: ‘How long does it take you to recover from a dialysis session and resume your normal, usual activities?’ [7] Interim results were recently published [5] and confirmed that SDHD is associated with a significant decrease in post-dialysis recovery time [476 min (95% CI 359–594) versus 63 min (95% CI 32–95); $P < 0.001$]. These results were very similar to previously published results in a smaller cohort [7]. The percentage of participants experiencing prolonged post-dialysis recovery time (>60 min) also significantly decreased over the 12-month period (81 versus 35%; $P < 0.001$).

Impact of SDHD on blood chemistry

The FHN daily trial showed significant improvements in control of hyperphosphatemia for patients on SDHD [3]. A significant reduction in mean serum phosphate was also reported in an interim report from the FREEDOM study [5], along with significant reductions in the calcium \times phosphate product, serum creatinine, serum potassium and a trend toward a reduction in blood urea nitrogen. Both the FHN daily trial and an interim analysis from the FREEDOM study showed no change in serum albumin levels.

Impact of SDHD on sleep and restless legs syndrome

Well-known uremic symptoms, including restless legs symptoms (RLS) and poor sleep quality are common in the HD population [8]. Poor sleep quality and RLS have both been linked to increased risk of death for these patients [9, 10]. A recent interim report from the FREEDOM study demonstrated initiation of SDHD at home is associated with significant improvement in RLS and sleep disturbances [11]. Results from 235 patients found 40% suffered from RLS at baseline, which was associated with poorer sleep quality and respiratory disturbances. Among patients with RLS, the mean IRLS (International Restless Legs Severity Scale) score improved significantly at Month 12, after adjustment for use of RLS-related medications (18 versus 11, $P < 0.0001$). Among patients with moderate-to-severe RLS (IRLS score ≥ 15), there was an even greater improvement in the IRLS score (23 versus 13, $P < 0.001$). Over the 12-month period, there was decline in the percentage of patients reporting RLS (35 versus 26%, $P = 0.05$) and those reporting moderate-to-severe restless legs symptoms (59 versus 43%, $P = 0.06$). There was a similar

and sustained improvement in several scales of the Medical Outcomes Study sleep survey over 12 months, after adjustment for presence of RLS and use of anxiolytics and hypnotics.

Summary

Recent results from both the FHN daily trial and FREEDOM study have shown that SDHD, performed either in-center or at home, is associated with several important clinical and QoL benefits when compared to conventional thrice weekly HD. The improvements in left ventricular mass, control of hypertension and improvement in hyperphosphatemia demonstrated in the FHN trial, in conjunction with the positive interim findings from the FREEDOM study, including improvements in depressive symptoms, post-dialysis fatigue, various laboratory parameters, restless leg syndrome and sleep disorders, confirm the anecdotal benefits of SDHD seen and reported by many practicing nephrologists and their patients. Until now, a complex variety of reasons has hindered the more widespread use of SDHD in the USA and globally. However, the results of these studies may provide a new impetus for ESRD patients and nephrologists to reconsider the paradigm of thrice weekly center HD as the 'default therapy'. Such a paradigm shift will likely increase the possibility for improved clinical outcomes and overall patient care for those affected by ESRD.

Conflict of interest statement. None declared.

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