Survival comparison between intensive hemodialysis and transplantation in the context of the existing literature surrounding nocturnal and short-daily hemodialysis

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Abstract

Our contemporary paradigms of nocturnal and short-daily hemodialysis (NHD and SDHD) have their origins in the earliest era of dialysis care for end-stage renal disease. However, these therapies have received considerably more attention in recent years owing to an increasing body of literature, suggesting a myriad of benefits attributable to these intensive dialysis regimens compared with conventional thrice-weekly hemodialysis. Analyses suggest a survival benefit for NHD and SDHD versus traditional hemodialysis prescriptions, and it is in this context that survival comparisons between intensive dialysis and transplantation must be considered. This literature and its limitations are reviewed here.

Keywords: mortality; nocturnal hemodialysis; short-daily hemodialysis; survival; transplantation

Introduction

Transplantation is the accepted gold standard renal replacement therapy in end-stage renal disease (ESRD) owing to its superior survival and quality of life compared with conventional three-times-per-week hemodialysis [1, 2]. However, comparisons between more intensive dialysis regimens and transplantation have only recently emerged, and early reports suggest that the mortality benefit of nocturnal and short-daily hemodialysis (NHD and SDHD) is similar to recipients of deceased donor transplantation. The aim of this review is to contextualize this literature with respect to recently published survival studies in the domain of intensive hemodialysis.

What is intensive dialysis?

Intensive hemodialysis refers to any modality where treatment frequency, duration or both exceed that of conventional thrice-weekly hemodialysis with 3.5–4.5 h sessions. The predominant modalities include NHD, typically performed 4–6 nights per week with each session lasting 6–8 h, and SDHD, performed 5–7 days per week with each session lasting 1.5–3 h. Many patients perform their dialysis at home rather than in an in-center unit, thereby giving them much greater independence over the timing of dialysis. This flexibility complicates the categorization of intensive dialysis since prescriptions such as every-other-night long dialysis, or 3–4 h treatments on 4–5 evenings per weeks are common but do not fit into the traditional NHD/SDHD paradigm. Survival comparisons between NHD, SDHD or any number of hybrid approaches have not been performed, so there is little concrete evidence to favor one intensive therapy over the other.

Contemporary intensive dialysis survival literature

Our contemporary notion of intensive hemodialysis has its origins in the earliest era of hemodialysis where practitioners and their patients experimented with various combinations of treatment frequency and duration in an effort to achieve optimal outcomes. This was largely supplanted by conventional three-times-per-week hemodialysis and an era emphasizing the centrality of dialysis dosing guided by urea kinetics. However, since the mid-1990s, there has been a steady resurgence in interest in non-conventional hemodialysis paradigms that challenge this status quo. Spurred by the negative outcome of the HEMO study, where small differences in delivered Kt/V did not affect survival [3], and a growing body of observational and translational literature promising better clinical outcomes with more intensive dialysis modalities [4–6], the Frequent Hemodialysis Network (FHN) set out to compare NHD and SDHD with a conventional prescription.

The FHN trials were enormous undertakings, but even during the design stages, it was readily apparent that trials powered to detect differences in mortality as their primary outcome would be cost-prohibitive [7]. Instead, these studies were designed with a complex co-primary outcome of death or 12-month change in left ventricular mass and death or 12-month change in the physical health composite score of the RAND SF-36 health questionnaire. While the Short Daily trial demonstrated a benefit to SDHD, the
Nocturnal trial was substantially underpowered to draw such conclusions (although it could not refute them either) [8, 9]. The outcomes in both trails were almost exclusively driven by the non-mortality endpoints, so these results should not be interpreted as evidence for or against differences in survival between the intensive dialysis modality in question and conventional hemodialysis, nor should these trials be used to infer a comparison of one intensive modality to the other. Thus, actual survival comparisons between renal replacement modalities would need to rely on large matched cohort studies.

Four such studies have been published since the unveiling of the FHN trials at the American Society of Nephrology meeting in 2010. Nesrallah et al. [10] from North America and Europe reported improved survival among 338 patients from the International Quotidian Dialysis Registry (IQDR) receiving an average of 7.4 h of dialysis on 4.8 days per week compared with a matched cohort of 1388 patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS) receiving conventional hemodialysis, with a hazard ratio of 0.55 [95% confidence interval (CI) 0.34, 0.87]. Virtually, all of these patients were receiving home NHD. Weinhandl et al. [11] reported improvement in survival among 1873 daily hemodialysis patients using the NxStage System One platform compared with a matched cohort of 9365 conventional hemodialysis patients from the United States Renal Data System (USRDS) with a hazard ratio of 0.87 (95% CI 0.78, 0.97). Lacson et al. demonstrated improved survival for 746 patients on three-times-per-week in-center NHD receiving an average of 7.85 h of dialysis per treatment matched to conventional hemodialysis patients in a 1:3 ratio. The data were obtained from Fresenius Medical Care North America facilities, and demonstrated a 2-year mortality of 19 versus 27% for NHD and conventional dialysis, respectively; hazard ratio 0.75 (95% CI 0.61, 0.91) [12]. Two of these studies used propensity score matching while a third used a sophisticated matching algorithm; all used intention-to-treat analysis where deaths were ascribed to the original modality in order to avoid the potential bias of informative censoring. The latter issue is important since bias is introduced if patients switch modalities imminently prior to death and then are not included in the mortality analysis for their original/predominant renal replacement modality. In a fourth study from Turkey, 1257 conventional dialysis patients were offered enrollment in an in-center thrice-weekly NHD program of whom 269 accepted. Of the remaining 970 eligible patients, the best possible 1:1 match was found to serve as controls. Ok et al. [13] report a survival advantage for in-center NHD with a hazard ratio of 0.28 (95% CI 0.09, 0.85). The results of these four studies are in keeping with previous modality comparisons based on smaller cohorts and/or indirect standardization [14–18].

However, for all the statistical sophistication of these analyses, there are a number of concerns regarding internal validity that warrant consideration. With the exception of the Turkish study, all others are retrospective registry-based cohorts with the inherent biases associated with data that were never collected for the purpose of the hypothesis being tested (a source of information bias). Not only is the granularity of data within registries often crude, but there may also be differences in exposure and outcome definitions between registries. This is particularly relevant when using more than one data source for the intervention and control arms within the same study. The second concern is that the duration of follow-up of contemporary intensive dialysis cohorts is relatively short. However, optimistic modality comparisons may appear, it is unknown if the benefits are sustained over time or whether longer-term complications (e.g. complications of vascular access) potentially outweigh the early reported benefits. A final, and arguably most critical, point to consider relates to the self-selection of patients to perform intensive dialysis. Observational studies have demonstrated that intensive hemodialysis patients are younger, predominantly Caucasian males, with few comorbidities and specifically less diabetes, of a longer ESRD vintage and of higher socioeconomic strata compared with the general dialysis population. While such variables are relatively easily controlled for analytically, others are not. Motivation, psychological fortitude, social supports, functional status, health literacy and severity of comorbidity (rather than simply its presence or absence) are a few examples of factors that may influence outcomes but that are difficult or impossible to ascertain. While randomization is assumed to distribute such variables equally among comparator groups, this almost certainly does not happen in observational cohorts such as those in question here. The result is residual confounding by unmeasured or unmeasurable variables. This is particularly relevant the closer the point estimate of the hazard ratio (or its 95% CI) is to one. Given that the majority of NHD and SDHD patients currently dialyze at home, it is instructive to recall that Woods et al. [19] demonstrated a decade and half ago that patients self-selecting to home dialysis had superior survival compared with in-center patients, despite a similar dialysis dose. This suggests that treatment setting (in-center versus home) plays a key role in determining outcome. Stated differently, factors associated with the ability to dialyze at home (rather than locale per se) are probably residual confounders which explain the observed effect. The extent to which such bias is relevant in contemporary intensive hemodialysis studies is obviously not known, but prudent interpretation of this literature would not ignore the possibility.

A compelling comparison

Bearing in mind the aforementioned limitations, why might comparing intensive hemodialysis with transplantation be any more compelling? The reason is because intensive hemodialysis patients (who are most often self-dialyzing at home) and transplant recipients are both highly selected among ESRD patients. In fact, transplant recipients are arguably the most screened subgroup since they frequently undergo extensive cardiac testing, must be free of comorbid diseases precluding surgery, undergo surveillance monitoring while waitlisted and subsequently live long enough to be transplanted. While NHD and SDHD patients are more selected than conventional
hemodialysis patients, they are certainly not as stringently screened as transplant recipients and are frequently referred for intensive dialysis as a rescue therapy after failing to thrive with peritoneal dialysis or conventional hemodialysis. If anything, bias in comparing these treatments is likely to favor transplantation.

**NHD and SDHD versus transplantation**

The body of literature comparing these therapies is limited to two studies. Kjellstrand et al. [20] reported the survival of 274 home SDHD patients from France, Italy, Britain and the USA compared with recipients of deceased donor transplantation from the USRDS. The survival curves are virtually superimposable (Figure 1). The mean age of the SDHD cohort was 49 years, while the transplant cohort had a mean age of 50. However, besides these demographic data, no detailed characteristics about these groups are reported, nor is a statistical comparison with adjustment for covariates and confounders provided. Although the face validity of this comparison is attractive, it is challenging to draw a meaningful conclusion based solely on this report.

Although the comparison between transplantation and NHD is more rigorous, this study also has important limitations. Our group compared the survival of 177 NHD patients matched with recipients of standard criteria deceased donor and living donor transplant recipients in a 1:3:3 ratio from an era spanning 1994 to 2006 [21]. Patients were matched on the basis of cause of ESRD, race and dialysis vintage, with adjustment for age, sex, body mass index, history of cancer/ischemic heart disease/peripheral vascular disease, era, and duration of conventional dialysis prior to NHD or transplantation. Table 1 and Figure 2 show that the unadjusted survival of NHD is very similar to deceased donor transplantation. As expected, recipients of living donor transplantation had the best overall survival; this was confirmed after multivariable adjustment with a hazard ratio of 0.51 (95% CI 0.28, 0.91). The adjusted hazard ratio of deceased donor transplantation compared with NHD was 0.87 (95% CI 0.50, 1.51), suggesting that survival between these modalities is similar. What makes this comparison even more compelling is that the NHD patients had higher baseline rates of cancer and vascular comorbidity than the transplant recipients (presumably biasing against NHD) so the fact that we did not detect a difference in outcomes between deceased donor transplantation and NHD underscores the potential benefit of intensive dialysis in a sicker cohort. However, one must also consider a number of limitations that may dampen such an optimistic interpretation. The sample size was still small, raising the possibility that an absence of a demonstrable difference may simply reflect an underpowered study rather than a true absence of effect. Secondly, this study compares a Canadian NHD cohort with transplant data from the USRDS. Canadian transplant recipients may fare better than their American counterparts, so a local transplant comparator would have been desirable [22]; however, Canadian data sources were not validated for the outcome of death at the time of analysis. This study is also subject to potential bias from informative censoring as well as residual confounding and information bias as with the cohort studies outlined in the previous sections.

![Fig. 1. Survival estimates of patients receiving home SDHD compared with deceased donor transplantation [20].](https://academic.oup.com/ndt/article-abstract/28/1/44/1829159/fig-1)

![Fig. 2. Kaplan–Meier curves for survival of NHD patients compared with standard criteria deceased donor and living donor renal transplantation [21].](https://academic.oup.com/ndt/article-abstract/28/1/44/1829159/fig-2)
Conclusions

Survival comparisons between intensive dialysis strategies and transplantation prompt us to consider where NHD and SDHD fit into the treatment spectrum of ESRD. This is especially relevant since transplantation is the gold standard treatment but represents a limited resource with ever-increasing demand. While transplantation should still be considered the best option for renal replacement therapy for most patients, it is welcome evidence that intensive dialysis modalities appear to result in a survival advantage over conventional dialysis and could potentially be viewed as a reasonable alternative to transplantation for some patients. Larger, rigorously conducted cohort studies are needed to better characterize the survival of various forms of intensive hemodialysis compared with different transplantation options. The quality of life trade-offs of these therapies are also unknown nor do we know whether NHD or SDHD is preferable over transplantation in specific subpopulations with ESRD. One can imagine patients with a high degree of immunological sensitization, or those considering the use of extended criteria donors as particular beneficiaries of intensive dialysis relative to their transplantation options. These issues are areas of ongoing investigation.

Conflict of interest statement. This is a review article of published literature and the views expressed are wholly by the author. No primary data are presented that have been published previously in whole or in part.

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