Extended-hours hemodialysis is associated with lower mortality risk in patients with end-stage renal disease

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Extended-hours hemodialysis offers substantially longer treatment time compared to conventional hemodialysis schedules and is associated with improved fluid and electrolyte control and favorable cardiac remodeling. However, whether extended-hours hemodialysis improves survival remains unclear. Therefore, we determined the association between extended-hours compared to conventional hemodialysis and the risk of all-cause mortality in a nationally representative cohort of patients initiating maintenance dialysis in the United States from 2007 to 2011. Survival analyses using causal inference modeling with marginal structural models were performed to compare mortality risk among 1206 individuals undergoing thrice weekly extended-hours hemodialysis or 111,707 patients receiving conventional hemodialysis treatments. The average treatment time per session for extended-hours hemodialysis was 399 minutes compared to 211 minutes for conventional therapy. The crude mortality rate with extended-hours hemodialysis was 6.4 deaths per 100 patient-years compared with 14.7 deaths per 100 patient-years for conventional hemodialysis. In the primary analysis, patients treated with extended-hours hemodialysis had a 33% lower adjusted risk of death compared to those who were treated with a conventional regimen (95% confidence interval: 7% to 51%). Additional analyses accounting for analytical assumptions regarding exposure and outcome, facility-level confounders, and prior modality history were similar. Thus, in this large nationally representative cohort, treatment with extended-hours hemodialysis was associated with a lower risk for mortality compared to treatment with conventional in-center therapy. Adequately powered randomized clinical trials comparing extended-hours to conventional hemodialysis are required to confirm these findings.

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Although the past decade has witnessed a modest improvement in survival for patients undergoing maintenance dialysis in the United States, mortality continues to be unacceptably high, approaching 20% per year.[1] While early observational studies suggested that a higher delivered dose of dialysis may be associated with improved clinical outcomes, a benefit of increasing the dialysis dose above currently accepted standards has not been confirmed by randomized, controlled clinical trial results.[2–4] This has prompted a search for other modifiable dialysis parameters, including dialysis modality and treatment time, in order to improve long-term clinical outcomes. Consistent with this emphasis, the Institute of Medicine in the United States has identified comparative effectiveness of dialysis therapies as the only kidney disease-related topic among the top 100 national priorities for comparative effectiveness research.[5]

Numerous observational studies over the past 2 decades have demonstrated that shorter treatment times with conventional hemodialysis are associated with higher mortality.[6–10] Recently, an increasing number of patients are being treated with extended-hours hemodialysis consisting of substantially longer treatment times, which has been associated in observational studies with lower hospitalization rates and improvements in metabolic parameters, left ventricular mass, and hypertension.[11–14] However, there are limited data on the

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association of extended-hours hemodialysis with patient survival, as prior studies have been small or single-center investigations, or have not addressed the multiple time-varying and facility-level factors that can cause confounding.[15–19]

Randomized, controlled trials remain the gold standard for comparative effectiveness research. However, trials that have sought to randomly assign patients to 1 of 2 different dialysis modalities have encountered substantial challenges in enrolling the target number of patients.[20–22] These challenges suggest that most patients are not willing to leave the selection of dialysis modality to random assignment if the therapies have substantial and widely differing effects on lifestyle, schedule, and weekly commitment to dialysis-related treatment.[22] Additionally, no contemporary randomized, controlled trial has sought to test the effect of extended hemodialysis treatment time independent of increased treatment frequency. Observational studies using contemporary causal inference modeling such as marginal structural models utilize robust statistical tools that address time-varying exposures and confounding, and thus represent an important alternative method for investigating the comparative effectiveness of dialysis modalities.[23] In this study, we used marginal structural modeling to address the hypothesis that extended-hours hemodialysis is associated with lower risk for all-cause death compared to conventional hemodialysis.

RESULTS

Study cohort

The study sample comprised 136,207 individuals with end-stage renal disease who initiated maintenance dialysis from 2007 to 2011 treated in dialysis facilities operated by a large US dialysis provider. Compared to individuals treated exclusively with conventional hemodialysis ($n = 111{,}707$), patients categorized as treated with extended-hours hemodialysis for 1 or more 91-day periods ($n = 1206$) were younger and more likely to be male, be black, have diabetes or comorbid cardiovascular disease, have primary insurance other than Medicare or Medicaid, and live in the western region of the United States (Table 1). Other patients, who were never treated with extended-hours hemodialysis and were treated with at least 1 modality other than conventional hemodialysis, differed from both extended-hours and exclusively conventional hemodialysis patients (Table 1). However, in the first 91-day period of dialysis, laboratory and treatment parameters were similar among patients ever treated with extended-hours hemodialysis, patients exclusively treated with conventional hemodialysis, and other patients (Table 1).

Patients who initiated extended-hours hemodialysis following 1 or more 91-day periods of conventional hemodialysis had higher serum alkaline phosphatase, ferritin, parathyroid hormone, and spKt/V, and lower serum phosphorous, cumulative iron dose (prescribed over each 91-day period), and median erythropoietin dose during treatment with extended-hours hemodialysis compared to values during treatment with conventional hemodialysis prior to transfer (Supplementary Table S1).

The average delivered treatment time per session with extended-hours hemodialysis was 399 ± 64 minutes, compared to 211 ± 27 minutes with conventional hemodialysis (intra-patient coefficient of variation 10.8% and 6.8%, respectively) (Figure 1). Treatment frequency was similar among patients treated with extended-hours hemodialysis (2.8 treatments per week, interquartile range [IQR 2.4, 2.9]) and conventional hemodialysis (2.9 treatments per week, [IQR 2.7, 2.9]). Among extended-hours hemodialysis patients, extended-hours hemodialysis was the initial dialysis modality for 353 patients (29.3%); 823 patients (68.2%) started dialysis with conventional hemodialysis, 37 (3%) started with peritoneal dialysis, and 6 (0.5%) initiated with home hemodialysis or in-center hemodialysis less than 3 times per week. Overall, median time from initiation of dialysis to start of treatment with extended-hours hemodialysis was 6.7 months (IQR 1.0, 19.2). The median duration between initiation of hemodialysis and transfer to another modality, censoring, or death was 7.6 months (IQR 2.3, 17.6) for conventional hemodialysis and 7.2 months (IQR 3.4, 15.1) for extended-hours hemodialysis. Of patients treated with extended-hours hemodialysis, 535 (44%) transferred to another dialysis modality for 1 or more 91-day periods. Of these patients, none died and 78 were censored (66 due to end of follow-up) within 91 days of transfer from extended-hours hemodialysis. Of patients treated with conventional hemodialysis, 10% later transferred to another modality.

Extended-hours hemodialysis and all-cause mortality

In total, 82 patients died during a 91-day period in which they were receiving extended-hours hemodialysis, compared to 29,778 deaths during periods of conventional hemodialysis. Crude mortality rates were 6.4 and 14.7 deaths per 100 patient-years for extended-hours and conventional hemodialysis, respectively (Table 2). Adjusted for treatment history and time-varying laboratory and treatment parameters using marginal structural models, as well as for case-mix factors, patients treated with extended-hours hemodialysis had a 33% lower adjusted risk for death compared to those treated with conventional hemodialysis (95% confidence interval [CI] 7% to 51% lower) (Table 2).

Attributing deaths to the dialysis modality 90 days prior to death did not meaningfully change the risk estimate (Table 2). An extreme approach—attributing all deaths following initiation of extended-hours hemodialysis to extended-hours hemodialysis, regardless of the actual modality at the time of death—increased the number of deaths attributed to extended-hours hemodialysis to 126, but the risk ratio between extended-hours and conventional hemodialysis did not change substantially (HR 0.62 [0.47 to 0.81]. (Table 2).

Starting follow-up from the 91st day after start of dialysis, further adjustment for vascular access type, or restricting the cohort to patients for whom extended-hours dialysis treatment was most likely to be available did not meaningfully