Can Frequent Hemodialysis Be Too Frequent?

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Many nephrologists believe that more hemodialysis, whether in the form of longer treatments, more frequent treatments, or both, is better than less. Emerging evidence largely supports this view, with most, although not all studies, showing biochemical, cardiovascular, quality of life, or survival benefits with short daily or slow nocturnal hemodialysis.1–5 Much of the focus of studies thus far has been on outcomes expected to improve with intensive dialysis such as BP and phosphorous control. In this issue of JASN,6 Suri and colleagues provide detailed analyses of vascular access outcomes from the two Frequent Hemodialysis Network (FHN) trials, the largest randomized controlled trials of frequent maintenance hemodialysis.3,7 For both trials, vascular access events were prespecified safety outcomes because of concerns that potential benefits of more intensive dialysis might come at the cost of an increase in vascular access complications. The findings of these analyses suggest that the concerns were warranted.

The FHN trials randomly assigned 245 patients to in-center hemodialysis at a frequency of six times per week or three times per week in the “daily” trial, and 87 patients to nocturnal hemodialysis six times per week or to conventional hemodialysis three times per week, performed at home for most participants, in the “nocturnal” trial. As previously reported, a benefit of frequent dialysis on the two coprimary outcomes of death or change in left ventricular mass and death or change in self-reported physical health was found in the daily trial but not in the smaller nocturnal trial.3,7 For both trials, the primary vascular access outcome was the time to first access event (access repair, access loss, or access-related hospitalization). As reported by Suri and colleagues,6 in the daily trial, the hazard ratio (HR) for a first access event was 1.76 (95% confidence interval [95% CI], 1.17, 2.79; \( P = 0.02 \)) with dialysis six times per week compared with dialysis three times per week. Although not statistically significant, a trend toward increased risk of an access event with dialysis six times per week was also evident in the nocturnal trial (HR, 1.81; 95% CI, 0.94, 3.48; \( P = 0.08 \)). When arteriovenous (AV) accesses (fistulas and grafts) and tunneled dialysis catheters were analyzed separately, in both the daily and nocturnal trials the risk of an AV access event was greater with more frequent dialysis, with a HR of 1.90 (95% CI, 1.11–3.25; \( P = 0.02 \)) in the daily study and a HR of 3.23 (95% CI 1.07–10.35; \( P = 0.04 \)) in the nocturnal trial. In the daily trial, there was also a statistically nonsignificant trend toward a greater risk of a first catheter event (HR, 2.70; 95% CI, 0.71–10.2; \( P = 0.14 \)) with frequent dialysis.

Attempts to analyze grafts and fistulas separately were limited by small numbers, but the authors report a 2.2-fold increase in the rate of interventions for grafts with dialysis six times per week in the daily trial, without an increased rate for fistulas. In contrast, in the nocturnal trial, a trend toward a higher rate of fistula, but not graft, interventions was seen in the nocturnal group receiving dialysis six times per week. When the components of the composite vascular access outcome were evaluated individually, it was apparent that in both trials, the higher risks for AV access events with frequent dialysis were driven by access interventions (angioplasty, stenting, thrombectomy, and surgical revision) rather than losses (access abandonment or removal). It is notable that one patient in each treatment group of the daily trial (0.8%) died from AV access hemorrhage and one patient in the nocturnal trial (nocturnal arm) died from a catheter-associated air embolism; these risks of hemodialysis are probably underappreciated.8

How convinced should we be from the findings of Suri et al. that frequent dialysis increases the risk of vascular access complications? Other than access type, no information about the vascular accesses is provided, leaving open the possibility of imbalances between treatment arms in vascular access characteristics such as access age or number of previous repairs that might underlie differences in outcomes. As the authors point out, it is unlikely that the findings of increased risk are due simply to increased surveillance for access complications among the patients undergoing dialysis six times per week. In the frequent dialysis arm of the daily trial, thrombectomies comprised a large proportion of the access events; access thrombosis is an outcome that should not increase as a result of more intensive observation. Because vascular access outcomes were among many secondary outcomes for these trials, it is also possible that any individual statistically significant relationship is a chance
occlusion. However, the similar pattern of increased risk with frequent dialysis across two separate trials with different patient populations and with two very different approaches to providing more frequent hemodialysis, together with the biologically plausible a priori hypothesis linking frequent access use with complications, reduces concern that the findings of Suri and colleagues are anything but real.

Assuming the conclusion is correct that more frequent hemodialysis increases the risk of access complications, how reassured should we be by the finding of the FHN trials that frequent dialysis was associated with more access interventions but not a greater rate of access loss? Given what we know about the mechanisms underlying AV graft and fistula failure, published observations, and our own clinical experience, it is likely that the observed increases in access repairs with frequent dialysis would have been accompanied by greater risks of access loss if follow-up in the FHN trials had been longer than 12 months.

How might frequent hemodialysis lead to more vascular access complications? For AV accesses, it could simply be the mechanical trauma from cannulation and/or the need to compress the access after dialysis to stop bleeding. Other potential mechanisms include stimulation of thrombosis, fibrosis, oxidative stress, inflammation, vascular smooth muscle proliferation, and endothelial dysfunction from needle-induced trauma, turbulent flow, or even greater exposure to dialysis water. Because the groups receiving dialysis six times per week in both trials had not only more frequent dialysis but also a greater number of weekly dialysis hours (an average of 2.3 and 18.2 more hours per week in the frequent arms of the daily and nocturnal trials, respectively), we cannot exclude the possibility that the longer cumulative dialysis duration contributed to the observed higher complication rates. However, at least for short daily dialysis, the much greater increase in frequency relative to time makes it likely that higher dialysis frequency is the more important, although not necessarily the only, underlying factor.

Where do we go from here? The FHN trials suggest there are risks with frequent dialysis to both fistulas and grafts and that the risks might differ for short daily and longer nocturnal treatments.

However, because of the small size of the study populations, the trials do not tell us whether one type of AV access is preferable; future studies are needed to better understand the best match between hemodialysis protocol and AV access type. Given the paucity of information about the effects with frequent dialysis of pharmacologic, biologic, and endovascular interventions on AV access survival, infection prophylaxis for tunneled catheters, and the buttonhole cannulation technique for fistulas, inclusion of patients undergoing frequent dialysis in future studies evaluating vascular access interventions and practices should also be encouraged. The authors appropriately caution that the seemingly low absolute number of catheter events in both trials does not support preferential use of catheters for patients receiving frequent hemodialysis. The event rates with catheters were in fact clinically quite significant, at 69 and 77 per 100 patient-years in the frequent arms of the daily and nocturnal trials, respectively, with >40% of catheter losses across the two trials due to infection, the access complication with the most devastating consequences.

In the FHN daily trial, the average number of delivered treatments per week was 5.17 in the frequent arm and 2.88 in the conventional arm. In the nocturnal trial, patients in the frequent arm had 5.06 treatments per week compared with 2.91 in the conventional arm. Although one might conclude from this that five treatments per week is more harmful to vascular access than three treatments per week, without additional analyses of the FHN trial data to determine whether there was a direct relationship between the number of treatments per week and access events, it is not possible to identify a dialysis frequency above which AV access risk increases.

It might be that four treatments per week of 4–6 hours duration is the hemodialysis sweet spot—enough dialysis but not too much and more frequent but not too frequent, providing more dialysis than most patients get currently without causing unacceptably high vascular access complication rates. A dialysis regimen with treatments four times per week or every other day would also avoid the potential dangers of the long interdialytic interval of current thrice-weekly regimens. This needs to be studied. In the meantime, the important findings reported by Suri and colleagues should be part of discussions between nephrologists and patients so that informed decisions can be made with individualized consideration of potential benefits and risks of available hemodialysis modalities.

Not surprisingly, the FHN trials tell us that frequent dialysis is neither all good nor all bad. Benefits with respect to some outcomes and harm with respect to others make sense and are typical of most medical treatments. The use of thrice-weekly hemodialysis treatments of relatively short duration has become standard practice in the United States, but we all are aware of the staggering mortality rates facing our patients even when the Kt/V tells us that their treatments are adequate. Continued evaluation of frequent hemodialysis and other alternatives to our current norm should help clarify the tradeoffs faced by patients, care providers, and society as we attempt to improve the quality of life and survival of patients with ESRD.

DISCLOSURES

None.

REFERENCES


