

High-Frequency Hemodialysis: Rationale for Randomized Clinical Trials

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Hundreds of thousands of people with end-stage renal failure are alive today because they receive treatment with hemodialysis. Although kidney transplantation and peritoneal dialysis also are available to treat kidney failure, in-center hemodialysis remains the predominant form of renal replacement therapy in North America. Despite its dramatic success at saving lives, hemodialysis is far from perfect therapy: More than 20% of hemodialysis patients die each year (1). Even more troubling, the annual mortality rate has changed little in the past decade, despite some success in achieving evidence-based quality improvements (2–4). In addition, morbidity remains high, with frequent complications of heart disease, hypertension, anemia, bone disease, poor nutrition, inflammation, depression, and impaired cognitive and physical function. These result in impaired quality of life and contribute to diminished longevity. Observational studies (5,6) suggest that many of these adverse outcomes may be caused in part by inadequate dosage of dialysis. The Hemodialysis (HEMO) study was designed to test the hypothesis that a higher dosage of dialysis would enhance dialysis-related survival. This 2 × 2 factorial design, randomized clinical trial (RCT) compared outcomes of patients who were treated with eKt/V for urea of 1.45 with those with eKt/V for urea of 1.05, and high-flux *versus* low-flux dialysis (7). The results of this study were a surprise to many: There were no significant differences between the two dosage groups in mortality, hospitalizations, or other secondary end points. However, negative results from the HEMO trial do not rule out benefits of more intensive therapies that extend beyond the limits of conventional thrice-weekly hemodialysis. The “dosage of dialysis” in determining outcomes may involve more than urea removal. The removal of phosphate (8) and larger molecules may be important in determining outcomes. Longer treatment times are associated with prolonged survival (9,10), an association that may be independent of the dosage of dialysis as measured by Kt/V urea. However, Kt/V urea and session length are inexorably entangled, and only RCT can resolve the true effect of session length on outcomes (11). The combination of high-flux membranes and longer dialysis times for nocturnal dialysis result in higher clearance of both small

and larger molecular weight substances. In fact, it is possible that the effects of dosage or flux interventions on some secondary outcomes that were observed within some subgroups in the HEMO trial (12,13) reflect subtle benefits that could be magnified with the substantially higher dosage levels (14) that can be achieved with high-frequency hemodialysis.

Nephrologists and their patients have been experimenting with frequent hemodialysis for more than 40 yr (15). Since 1998, several studies of more frequent hemodialysis have been published. Recently, these studies were summarized and analyzed critically. A systematic review of nocturnal hemodialysis by Walsh *et al.* (16) summarized the important outcomes of this therapy reported through July 2003. These reports of nocturnal hemodialysis all were observational in nature (pre–post within-patient comparisons or case-controlled studies) and are somewhat difficult to interpret, with different or imprecisely described dialysis prescriptions and varying vascular access (some single needle, some two-needle hemodialysis). They reported improved BP control, anemia, and health-related quality of life, with mixed results for changes in left ventricular hypertrophy and mineral metabolism. A systematic review of daily hemodialysis studies through May 2005 was published by Suri *et al.* (17). Here again, differences in the duration of a single hemodialysis session make it difficult to draw definitive conclusions. They reviewed daily hemodialysis (home or in-center, 5 to 7 d/wk) studies of five or more patients who were followed for 3 mo or more. Most were observational studies (pre–post or parallel control groups). One small, crossover RCT of 12 patients was performed (18). Results for individual outcomes were variable. Better BP control was found consistently, but the effects of daily hemodialysis on quality of life, anemia, phosphorus control, and nutritional status were inconsistent. A reduction in cardiac left ventricular hypertrophy as assessed by echocardiography was seen, but the relative contribution of reduced extracellular water *versus* reduced muscle hypertrophy to these estimates is unclear. In both nocturnal and short daily studies, the degree to which observed improvements in BP were related to the method of measurement remains uncertain.

Given these uncertainties, we do not have sufficient data on the effects of daily and nocturnal hemodialysis to advocate for its widespread use and underwrite its cost. In 2001, Chertow (19) argued that a RCT of frequent hemodialysis was necessary to answer the fundamental questions of whether these treatments improve outcomes and, if so, by how much. He urged

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that the primary outcome of such a trial should be mortality alone or mortality combined with a major morbid event. The studies that have been published since 2001 offer preliminary evidence for the effectiveness of these treatments but do not provide the grade of evidence necessary for unequivocal endorsement. Higher grades of evidence, provided by an RCT, have in the past reversed the consensus of opinion about a treatment efficacy. For example, before the HEMO trial, observational studies would have predicted that delivery of higher dosages of dialysis during conventional thrice-weekly hemodialysis resulted in better survival. The consensus of clinical nephrologists supported this conclusion until the HEMO RCT disproved it. In a similar reversal of popular consensus, we have seen a dramatic change in opinion about the safety and the efficacy of hormone replacement therapy (HRT). When large observational studies suggested that HRT had many benefits, including reduced risk for heart disease in postmenopausal women, this therapy was used widely for relief of postmenopausal symptoms and for cardioprotection. However a well-designed RCT showed higher incidence of heart disease and invasive breast cancer in women who received estrogen plus progestin (20), changing dramatically the use of HRT. An editorial entitled "Postmenopausal Hormone Replacement Therapy: How Could We Have Been So Wrong?" (21) underlines the importance of the RCT. Observational studies and registries are flawed by selection bias, dropout bias and non-representativeness of the studied population. The studies to date of frequent dialysis suffer from these shortcomings. The authors of recently published critical reviews of nocturnal and daily hemodialysis conclude that previous studies have been limited by inconsistent findings, small sample sizes, inadequate assessment of potential risks, and the biases that are inherent in observational studies. The current evidence does not support the widespread implementation of daily or nocturnal hemodialysis, also suggesting that an RCT is needed (16,17). In addition, there has been little information published on the feasibility, safety, and possible adverse effects of frequent hemodialysis. An RCT will test the feasibility and the safety of these treatments using a rigorous protocol. It also will enable us to perform an economic analysis of frequent hemodialysis compared with conventional therapy.

The National Institute of Diabetes and Digestive and Kidney Diseases, a division of the National Institutes of Health, and the Centers for Medicare and Medicaid Services have funded two parallel RCT, one on daily hemodialysis and the other on home nocturnal hemodialysis, both compared with conventional thrice-weekly therapy. The study designs are published elsewhere (22). For the daily study, hemodialysis will be delivered for 1.5 to 2.75 h 6 d/wk, with target eKt/V_n of ≥ 0.9 /session, compared with conventional thrice-weekly hemodialysis delivered for ≥ 2.5 h with target eKt/V of ≥ 1.1 /session. The home nocturnal hemodialysis trial will deliver dialysis for ≥ 6 h, 6 nights/wk with target $stdKt/V \geq 4.0$ /wk compared with conventional hemodialysis at home three times per week. The home thrice-weekly dose delivery targets will be the same as for thrice-weekly conventional dialysis patients in the daily trial. In both studies, creatinine clearance, weekly standardized

phosphate removal, and equivalent renal clearance of β -2 microglobulin will be measured. Participants will complete 1 yr of treatment randomized to frequent hemodialysis or conventional thrice-weekly treatments. Outcomes will include measures of safety, treatment burden, and efficacy. The studies are designed to examine outcomes in several domains, including health-related quality of life and physical function, cardiovascular structure and function, hypertension, mental health, cognitive function, nutrition and inflammation, mineral metabolism, anemia, hospitalizations, and death. The two co-primary outcomes of both studies are (1) composite of 1-yr mortality and change in SF-36 Physical Health Composite score and (2) composite of 1-yr mortality and change in left ventricular mass index by cine magnetic resonance imaging. In each study, the feasibility of recruitment, adherence, and retention will be assessed in an initial "Vanguard" design. The incremental cost of high-frequency dialysis will be estimated empirically.

Investigators and patients in the United States and Canada are participating in these trials. When these investigators considered study design, it became increasingly clear that a study that is powered to detect a mortality effect was not feasible at this time. We estimate that currently 55 centers in the United States and Canada are performing frequent hemodialysis five times per week or more. These centers are dialyzing a total of approximately 600 patients with high-frequency hemodialysis at home or in-center. Power analysis showed us that with 1 yr of follow-up, we would need to enroll >3500 patients in the daily study and >5000 in the nocturnal study to achieve 90% power to detect a relatively substantial 30% reduction in mortality. These numbers are severalfold higher than the total number of patients in North America who are receiving this treatment. With intensive recruitment efforts, we estimate that we will be able to enroll a total of 500 patients for the two RCT: 250 in the nocturnal study and 250 in the daily trial. It is for this reason that the co-primary outcomes of these RCT will be a composite of mortality and changes in left ventricular mass or physical symptoms that affect quality of life.

The study design will ensure the Kt/V urea dosage delivery is far higher than the dosage that was delivered in the HEMO trial. The target weekly or standard Kt/V for urea in the current frequent hemodialysis trials will be approximately 2.5 in the conventional thrice-weekly arm, 3.8 in the daily in-center hemodialysis arm, and 5.6 in the nocturnal arm. We estimate that phosphorus clearance will be approximately 40% higher in the short daily arm and 330% higher in the nocturnal arm compared with conventional thrice-weekly hemodialysis. An assessment of the representativeness of study enrollees to the general ESRD population will be made. In addition, these trials will give us information on technique survival—the willingness of patients to maintain high-frequency hemodialysis for 1 yr or longer.

These RCT will provide the best available evidence on the safety and the efficacy of high-frequency hemodialysis. Although their limited size will make it infeasible to measure mortality as an independent primary outcome, these trials will provide the strongest evidence available on the effect of frequent dialysis on the domains of care that are most important

to dialysis patients. Although these trials may not answer all questions definitively, they will give us far more dependable information than we now have with observational studies alone. Many authors of the published observational studies agree: They are the very investigators and clinical centers that are participating now in these trials. Our patients are expressing their trust in us and in the importance of an RCT by their enrollment. We trust that the results in multiple domains will give the nephrology community of patients, clinicians, and policy makers substantially better data for clinical and policy decisions.

Disclosures

None.

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