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Narrative Review

Intensive Hemodialysis and Potential Risks With Increasing Treatment

Michael A. Kraus, MD,[1] Sheru Kansal, MD,[2] Michael Copland, MD,[3] Paul Komenda, MD,[4,5,6] Eric D. Weinhandl, PhD, MS,[7] George L. Bakris, MD,[8] Christopher T. Chan, MD,[9] Richard J. Fluck, MA (Cantab), MBBS,[10] and John M. Burkart, MD[11]

Although intensive hemodialysis (HD) can address important clinical problems, increasing treatment also introduces risks. In this review, we assess risks pertaining to 6 domains: vascular access complications, infection, mortality, loss of residual kidney function, solute balance, and patient and care partner burden. In the Frequent Hemodialysis Network (FHN) trials, short daily and nocturnal schedules increased the incidence of access complications, although the incidence of access loss was not statistically higher. Observational studies indicate that infection-related hospitalization is an ongoing challenge with short daily HD. Excess risk may be catalyzed by poor infection control practices in the home setting in which intensive HD is typically delivered, but with fixed probability of bacterial contamination per cannulation, greater treatment frequency necessarily increases the risk for infectious complications. Buttonhole cannulation may increase the risk for metastatic infections. However, intensive HD in the home setting is associated with lower risk for infection than peritoneal dialysis. Data regarding mortality are equivocal. With extended follow-up of individuals in the FHN trials, short daily HD was associated with lower risk relative to the usual schedule, whereas nocturnal HD was associated with higher risk. In many, but not all, observational studies, short daily HD has been associated with lower risk than both in-center HD and peritoneal dialysis; however, observational studies are subject to unmeasured confounding. Intensive HD can accelerate the loss of residual kidney function in new dialysis patients with substantial urine output and can deplete solutes (eg, phosphorus) to the extent that supplementation is necessary. Finally, intensive HD may increase burden on patients and caregivers, possibly leading to technique failure. Some of these problems might be addressed with careful monitoring, so that relevant interventions (eg, antibiotics, retraining, and respite care) can be delivered. Ultimately, intensive HD is not a panacea for end-stage renal disease. Potential benefits and risks of treatment should be jointly considered.

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Intensive hemodialysis (HD) is defined, relative to conventional HD, as any schedule that increases the number of treatment sessions per week (thus eliminating multiple-day intervals between consecutive sessions) and/or the number of hours per session. As discussed in other reviews in this supplement, intensive HD can address important clinical problems: left ventricular hypertrophy, hypertension, hyperphosphatemia, low quality of life, and poor tolerability of HD.[1-5] However, like any medical intervention, intensive HD may increase the risks for specific complications. In this review, we examine the influence of intensive HD on the incidence of vascular access complications, infection, and mortality; the role of intensive HD in the loss of residual kidney function and development of hypophosphatemia; and the burden imposed by intensive HD on both patients and caregivers. Several of these issues are discussed in the

From the [1]Indiana University Medical School, Indianapolis, IN; [2]Department of Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; [3]Division of Nephrology, University of British Columbia, Vancouver; [4]Section of Nephrology, Department of Medicine, and [5]Department of Community Health Sciences, University of Manitoba; [6]Seven Oaks General Hospital Renal Program, Winnipeg, Canada; [7]Department of Pharmaceutical Care and Health Systems, College of Pharmacy, University of Minnesota, Minneapolis, MN; [8]American Society of Hypertension Comprehensive Hypertension Center, Section of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Chicago Medicine, Chicago, IL; [9]Division of Nephrology, Department of Medicine, University Health Network, Toronto, Canada; [10]Department of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; and [11]Wake Forest University Medical Center, Winston-Salem, NC.

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Address correspondence to Eric D. Weinhandl, PhD, MS, Department of Pharmaceutical Care and Health Systems, College of Pharmacy, University of Minnesota, Weaver-Densford Hall, 7th Fl, 308 Harvard St SE, Minneapolis, MN 55455. E-mail: wein0205@umn.edu

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recent update to the NKF-KDOQI (National Kidney Foundation–Kidney Disease Quality Initiative) clinical practice guideline for HD adequacy.[6]

VASCULAR ACCESS COMPLICATIONS

HD requires access to vasculature. Methods of access comprise a central venous catheter (CVC), arteriovenous fistula, or arteriovenous graft. Fistulas are preferable because they associate with fewer complications and better patient survival than CVCs and grafts.[7] Because intensive HD increases the number of access cannulations per week and overall stress on the access, patients undergoing intensive HD may have a higher incidence of access complications. In a meta-analysis of 15 studies, including 3 randomized clinical trials, intensive versus conventional HD was associated with 6.7 additional vascular access events per 100 patient-years (PY; $P = 0.009$); for patients with a fistula, graft, or CVC, rate differences for intensive versus conventional HD were 2.7 ($P = 0.2$), 37.6 ($P = 0.1$), and 16.9 ($P = 0.1$), respectively.[8]

Suri et al[9] reported vascular access outcomes in the Frequent Hemodialysis Network (FHN) trials. In the FHN Daily Trial, individuals were randomly assigned to receive HD for either 6 short sessions (mean duration, 2.6 hours) per week (n = 125) or 3 conventional sessions per week (n = 120) for 12 months, whereas in the FHN Nocturnal Trial, individuals were randomly assigned to receive home HD for either 6 nocturnal sessions (mean duration, 6.3 hours) per week (n = 45) or 3 conventional sessions per week (n = 42). The primary vascular access outcome was time to first access repair, access loss, or access-related hospitalization. Repair was defined as any access procedure that resulted in continued use of the access (including angioplasty, stenting, surgical revision of a fistula, thrombectomy, and fibrin sheath stripping or broken component repair of a CVC). Loss was defined as abandonment or removal of the access, but excluded elective removal of a CVC upon successful use of a new fistula or graft.

In the Daily Trial, primary outcome rates were 40 and 23 events/100 PY with intensive and conventional HD, respectively; the hazard ratio (HR) was 1.76 (95% confidence interval [CI], 1.11-2.79).[9] With intensive HD, there were 33 repairs and 15 losses, but no access-related hospital admissions, whereas with conventional HD, there were 17 repairs, 11 losses, and 1 admission. In the subset of individuals with either a fistula or graft, the HR of the primary outcome was 1.90 (95% CI, 1.11-3.25) for intensive versus conventional HD; in those with a CVC, the HR was 2.70 (95% CI, 0.71-10.2). The rate of all (ie, first and subsequent) repairs in individuals with either a fistula or graft was 69 events/100 PY with intensive HD and 43 events/100 PY with conventional HD; the HR was 1.68 (95% CI, 1.13-2.51). Excess risk was driven by more thrombectomies and surgical revisions with intensive HD. Rates of loss in individuals with either a fistula or a graft were 21 events/100 PY with intensive HD and 17 events/100 PY with conventional HD; the HR was 1.21 (95% CI, 0.61-2.39). Although the risk for access loss was not significantly higher with intensive HD, the aforementioned CI admits the possibility of clinically meaningful excess risk. Furthermore, in the absence of earlier interventions, the relative risk for access loss with intensive versus conventional HD might have been even greater. This is concerning because the FHN Daily Trial was conducted in health care facilities, where access complications may have been promptly identified and referred. Patients dialyzing in the home setting may require similarly aggressive monitoring.

In the Nocturnal Trial, primary outcome rates were 58 and 32 events/100 PY with intensive HD and conventional HD, respectively; the HR was 1.81 (95% CI, 0.94-3.48), thus in line with the Daily Trial despite lacking statistical significance.[9] With intensive HD, there were 10 repairs, 12 losses, and 1 access-related hospital admission, whereas with conventional HD, there were 5 repairs and 10 losses, but no admissions. In the subset of individuals with either a fistula or graft, the HR of the primary outcome was 3.23 (95% CI, 1.07-10.35) for intensive versus conventional HD; in those with a CVC, the HR was 1.45 (95% CI, 0.59-3.58). Rates of all repairs in individuals with either a fistula or graft were 66 events/100 PY with intensive HD, but only 29 events/100 PY with conventional HD; that rate ratio was 2.29 (95% CI, 0.94-5.59). Excess risk was driven by more angioplasties with intensive HD. Risks for access loss were nearly equal with intensive and conventional HD.

Jun et al[10] reported access-related adverse event–free survival in a cohort of 286 Australian patients who initiated HD therapy for at least 24 hours per week. More than 95% of patients underwent HD at home; HD was typically performed at night, for at least 3.5 sessions per week. Access-related adverse events were defined as any access-related intervention. In intention-to-treat (ITT) analysis, 1-, 3-, and 5-year access-related event-free survival estimates were 80%, 68%, and 61%, respectively. The most common access-related adverse event was infection. Importantly, the HR of an access-related adverse event was 1.56 (95% CI, 1.03-2.36) for each 1-session increment in dialysis frequency. This association is compatible with results of the FHN trials.

Observational studies are mixed and prospective cohort studies with parallel treatment groups are few. In the London Daily/Nocturnal Hemodialysis Study,