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Original Investigation

Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Dialysis Patients: A Cohort Study

Yoshitsugu Obi, MD, PhD,[1] Elani Streja, MPH, PhD,[1] Connie M. Rhee, MD, MSc,[1] Vanessa Ravel, MPH,[1] Alpesh N. Amin, MD, MBA,[2] Adamasco Cupisti, MD,[3] Jing Chen, MD, PhD,[4] Anna T. Mathew, MD, MPH,[5] Csaba P. Kovesdy, MD,[6,7] Rajnish Mehrotra, MD,[8] and Kamyar Kalantar-Zadeh, MD, MPH, PhD[1,9,10]

Background: Maintenance hemodialysis is typically prescribed thrice weekly irrespective of a patient's residual kidney function (RKF). We hypothesized that a less frequent schedule at hemodialysis therapy initiation is associated with greater preservation of RKF without compromising survival among patients with substantial RKF.

Study Design: A longitudinal cohort.

Setting & Participants: 23,645 patients who initiated maintenance hemodialysis therapy in a large dialysis organization in the United States (January 2007 to December 2010), had available RKF data during the first 91 days (or quarter) of dialysis, and survived the first year.

Predictor: Incremental (routine twice weekly for >6 continuous weeks during the first 91 days upon transition to dialysis) versus conventional (thrice weekly) hemodialysis regimens during the same time.

Outcomes: Changes in renal urea clearance and urine volume during 1 year after the first quarter and survival after the first year.

Results: Among 23,645 included patients, 51% had substantial renal urea clearance (≥3.0 mL/min/1.73 m^2) at baseline. Compared with 8,068 patients with conventional hemodialysis regimens matched based on baseline renal urea clearance, urine volume, age, sex, diabetes, and central venous catheter use, 351 patients with incremental regimens exhibited 16% (95% CI, 5%-28%) and 15% (95% CI, 2%-30%) more preserved renal urea clearance and urine volume at the second quarter, respectively, which persisted across the following quarters. Incremental regimens showed higher mortality risk in patients with inadequate baseline renal urea clearance (≤3.0 mL/min/1.73 m^2; HR, 1.61; 95% CI, 1.07-2.44), but not in those with higher baseline renal urea clearance (HR, 0.99; 95% CI, 0.76-1.28). Results were similar in a subgroup defined by baseline urine volume of 600 mL/d.

Limitations: Potential selection bias and wide CIs.

Conclusions: Among incident hemodialysis patients with substantial RKF, incremental hemodialysis may be a safe treatment regimen and is associated with greater preservation of RKF, whereas higher mortality is observed after the first year of dialysis in those with the lowest RKF. Clinical trials are needed to examine the safety and effectiveness of twice-weekly hemodialysis.

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Residual kidney function (RKF) in patients with end-stage renal disease plays a critical role in dialysis adequacy, quality of life, and survival by maintaining fluid and metabolic homeostasis, mitigating mineral abnormalities, optimizing uremic toxin clearance, and sustaining higher endogenous vitamin D and erythropoietin production.[1-4] Endogenous clearance conferred by RKF is associated with greater survival than dialysis clearance per se,[1,5] and at a certain RKF level, higher dialysis dose may not influence clinical outcomes in both peritoneal dialysis and hemodialysis patients.[6-8] Furthermore,

From the [1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, and [2]Department of Medicine, University of California Irvine, Orange, CA; [3]Division of Nephrology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [4]Division of Nephrology, Huashan Hospital, Fudan University, Yangpu, Shanghai, China; [5]Hofstra North Shore-LIJ School of Medicine, Division of Kidney Diseases and Hypertension, North Shore-LIJ Health System, Great Neck, NY; [6]Division of Nephrology, University of Tennessee Health Science Center; [7]Nephrology Section, Memphis VA Medical Center, Memphis, TN; [8]Kidney Research Institute and Harborview Medical Center, Division of Nephrology, University of Washington, Seattle, WA; [9]Fielding School of Public Health at UCLA, Los Angeles; and [10]Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA.

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Address correspondence to Kamyar Kalantar-Zadeh, MD, MPH, PhD, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, 101 The City Dr S, City Tower, Ste 400 – ZOT: 4088, Orange, CA 92868. E-mail: kkz@uci.edu

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randomized controlled trials have shown inconsistent results in terms of clinical benefit of higher dialysis dose or frequency,[9-14] and they may accelerate RKF decline.[15]

Incremental hemodialysis regimens (eg, dialysis therapy initiation at a lower frequency) were first suggested based on urea kinetic models in the late 1990s.[16,17] Less frequent hemodialysis has been commonly prescribed in countries such as China and India,[18-20] and its combination with low-protein diet has been suggested for select patients on transition to dialysis therapy.[21,22] The NKF-KDOQI (National Kidney Foundation−Kidney Disease Outcomes Quality Initiative) guidelines also suggested a twice-weekly schedule for patients with "substantial residual renal urea clearance" (ie, ≥3.0 mL/min/1.73 m^2) in 2006.[1] Nevertheless, most patients initiating maintenance hemodialysis therapy in the United States are prescribed thrice-weekly treatments irrespective of RKF. Given that estimated glomerular filtration rate is >10 mL/min/1.73 m^2 upon initiation of maintenance dialysis therapy in up to 45% of patients in the United States,[23,24] the incremental hemodialysis regimen may preserve RKF and offer both clinical and economic advantages.[25-28]

More frequent hemodialysis may lead to faster loss of RKF through several mechanisms, such as the release of nephrotoxic inflammatory mediators during hemodialysis and ischemic kidney damage caused by intradialytic hypotension and postdialytic hypovolemia.[29,30] The marked reduction in blood urea levels by more frequent hemodialysis therapy can also decrease osmotic diuresis,[31] and intense dialysis may deactivate the remaining nephrons (intact nephron hypothesis in reverse).[32] Moreover, previous studies have suggested that hemodialysis patients on twice-weekly schedules may have similar or lower risk for death compared with those on thrice-weekly schedules.[27,33,34] However, differences in RKF were not appropriately taken into account in these studies, an important consideration because higher RKF is consistently associated with better survival.[4-6] Therefore, we investigated the association of the incremental regimen with longitudinal trends in RKF and survival in a cohort of incident hemodialysis patients from a large dialysis organization in the United States. We hypothesized that an incremental hemodialysis regimen is associated with greater preservation of RKF over time without compromising survival among patients with substantial RKF.

METHODS

Patients

We retrospectively extracted, refined, and examined electronic data from all incident in-center hemodialysis patients 18 years or older treated in facilities operated by a large dialysis organization in the United States from January 1, 2007, through December 31, 2010.[35] Patient follow-up time was divided into patient-quarters (91-day periods from date of initial dialysis). For each patient-quarter, patients were assigned a modality if they received treatments at least 45 days within the patient quarter. Patient who received a consistent treatment schedule (eg, Monday/Thursday or Monday/Friday) of twice-weekly hemodialysis for more than 6 continuous weeks within the first patient-quarter were categorized as the incremental-regimen group. The rest of the patients were categorized as the conventional-regimen group.

To examine trends of RKF during 1 year after the baseline quarter (eg, the first 91 days of dialysis, or months 1-3),[4] we selected 23,645 incident in-center hemodialysis patients who had both residual renal urea clearance and urine volume data at baseline and retained a mean treatment frequency of 1.5 to less than 3.5 times per week during the first 4 patient-quarters (Fig S1, available as online supplementary material). The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA and University of California Irvine Medical Center. Given the large sample size, anonymity of the patients studied, and nonintrusive nature of the research, requirement for consent was exempted.

Demographic, Clinical, and Laboratory Measures

Information for self-reported race/ethnicity, primary insurance, access type, and the presence of comorbid conditions at baseline was obtained from the electronic database of the dialysis provider.

Among 61,492 urine collections during months 1 to 15, a total of 98% of samples were collected over 24 hours, whereas others were collected over 12 hours or 44 hours or longer and corrected to 24-hour–equivalent values. Blood samples were drawn using uniform techniques in all dialysis clinics and transported to the central laboratory in Deland, FL, typically within 24 hours. All laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly, whereas serum ferritin and intact parathyroid hormone were measured at least quarterly and hemoglobin was measured weekly to biweekly in most patients. Dialysis dose, renal urea clearance, weekly percentage interdialytic weight gain (IDWG), and normalized protein catabolic rate (nPCR) were calculated using urea kinetic modeling equations (see Item S1 for details).[1,36-41]

To minimize measurement variability, all repeated measures for each patient during any given patient-quarter (91 days) were averaged and the quarterly mean values in each quarter were used in all analyses.

Statistical Methods

To examine associations of incremental hemodialysis with changes in RKF indexes and survival, we matched patients by using coarsened exact matching with weighting based on baseline renal urea clearance (cutoff points: 1.5, 3.0, 6.0, and 9.0 mL/min/1.73 m^2), urine volume (cutoff points: 300, 600, 1,200, and 1,800 mL/d), age (cutoff points: 50, 65, and 80 years), sex, race, central venous catheter as vascular access, and diabetes.[42] Six of 351 patients with the incremental regimen were not matched originally with coarsened exact matching, but each was subsequently matched to the closest possible unmatched case with appropriate weighting.

Because of its right-skewed distribution, renal urea clearance and urine volume were natural log (ln)-transformed after adding 1 and 100, respectively. Changes in RKF indexes, dialysis frequency, dialysis treatment time, and selected laboratory variables between incremental versus conventional regimens were estimated by fitting linear mixed-effects models using the maximum-likelihood estimator, in which interaction terms between patient-quarters and hemodialysis regimen represent differences in the slopes for each