Effect of Frequent Nocturnal Hemodialysis vs Conventional Hemodialysis on Left Ventricular Mass and Quality of Life: A Randomized Controlled Trial

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PRELIMINARY COMMUNICATION

Effect of Frequent Nocturnal Hemodialysis vs Conventional Hemodialysis on Left Ventricular Mass and Quality of Life

A Randomized Controlled Trial

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Context Morbidity and mortality rates in hemodialysis patients remain excessive. Alterations in the delivery of dialysis may lead to improved patient outcomes.

Objective To compare the effects of frequent nocturnal hemodialysis vs conventional hemodialysis on change in left ventricular mass and health-related quality of life over 6 months.

Design, Setting, and Participants A 2-group, parallel, randomized controlled trial conducted at 2 Canadian university centers between August 2004 and December 2006. A total of 52 patients undergoing hemodialysis were recruited.

Intervention Participants were randomly assigned in a 1:1 ratio to receive nocturnal hemodialysis 6 times weekly or conventional hemodialysis 3 times weekly.

Main Outcome Measures The primary outcome was change in left ventricular mass, as measured by cardiovascular magnetic resonance imaging. The secondary outcomes were patient-reported quality of life, blood pressure, mineral metabolism, and use of medications.

Results Frequent nocturnal hemodialysis significantly improved the primary outcome (mean left ventricular mass difference between groups, 15.3 g, 95% confidence interval [CI], 1.0 to 29.6 g; $P=.04$). Frequent nocturnal hemodialysis did not significantly improve quality of life (difference of change in EuroQol 5-D index from baseline, 0.05; 95% CI, –0.07 to 0.17; $P=.43$). However, frequent nocturnal hemodialysis was associated with clinically and statistically significant improvements in selected kidney-specific domains of quality of life ($P=.01$ for effects of kidney disease and $P=.02$ for burden of kidney disease). Frequent nocturnal hemodialysis was also associated with improvements in systolic blood pressure ($P=.01$ after adjustment) and mineral metabolism, including a reduction in or discontinuation of antihypertensive medications (16/26 patients in the nocturnal hemodialysis group vs 3/25 patients in the conventional hemodialysis group; $P<.001$) and oral phosphate binders (19/26 patients in the nocturnal hemodialysis group vs 3/25 patients in the conventional dialysis group; $P<.001$). No benefit in anemia management was seen with nocturnal hemodialysis.

Conclusion This preliminary study revealed that, compared with conventional hemodialysis (3 times weekly), frequent nocturnal hemodialysis improved left ventricular mass, reduced the need for blood pressure medications, improved some measures of mineral metabolism, and improved selected measures of quality of life.

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DESPITE ADVANCES IN DIALYSIS and medical therapies, patients with end-stage renal disease (ESRD) have annual mortality rates exceeding 15%.[1] Cardiovascular disease, manifesting frequently as heart failure or sudden death, is responsible for the majority of deaths.[1] This may be due to a high burden of exposure to traditional cardiovascular risk factors (before and after initiation of dialysis), as well as ongoing exposure to volume overload, hyperphosphatemia, chronic inflammation, and other uremia-related factors. Taken together, these factors may worsen disorders of left ventricular (LV) structure and function and promote progression of vascular disease.[2]

Recent case-control and cohort studies have suggested that nocturnal hemodialysis might improve clinical outcomes

For editorial comment see p 1331.

in ESRD patients. In these reports, patients switched to nocturnal hemodialysis 5-6 times weekly demonstrated improvements in LV mass,[3] systemic blood pressure,[3,4] mineral metabolism,[5] and health-related quality of life (HRQOL).[6-8] Given that conclusions based on observational data in dialysis patients are often refuted by randomized controlled trials,[9-13] we sought to determine the effects of frequent nocturnal hemodialysis compared with conventional hemodialysis on LV mass, HRQOL, blood pressure, and mineral metabolism in a randomized controlled trial.

METHODS

Study Participants

Eligible patients were actively recruited from 10 hemodialysis units at 2 universities (University of Calgary and University of Alberta) in Alberta, Canada. The first patient was enrolled in August 2004 and the study was completed in December 2006, 6 months after the enrollment of the last participant. Eligible patients were at least 18 years old, were receiving in-center, self-care, or home conventional hemodialysis 3 times weekly, and were interested and willing to train for and commence nocturnal hemodialysis. Patients were excluded if they lacked the physical or mental capacity to train for nocturnal hemodialysis. The categorization of race/ethnicity was by self-report; options included white, Aboriginal, African Canadian, Indo Asian, East Asian, and other. These same categories are used in the Canadian Organ Replacement Registry.

All patients provided written informed consent. The study protocol was approved by the local ethics committees of the University of Calgary and the University of Alberta.

Study Protocol

This was a 2-group, parallel-design study. Those patients meeting the inclusion and exclusion criteria were randomized to either frequent nocturnal hemodialysis or the control group (conventional hemodialysis 3 times weekly) (FIGURE 1). Randomization was performed using a computer-generated sequence in blocks of 4 and was stratified by center and by baseline dialytic modality (in-center vs home or self-care). The use of sealed opaque envelopes helped ensure blinding. Given the logistics of training patients within a nocturnal hemodialysis program (ie, all patients randomized cannot be trained simultaneously), patient entry into the study (ie, baseline study visit) was staggered over time (using a random order) for both groups to allow nocturnal hemodialysis training in an orderly fashion. This approach avoided an imbalance in dropout rates between the 2 groups and created a similar number of intervention and control patients under observation at any given point. The baseline visit was done before a dialysis session for all patients, and for nocturnal hemodialysis patients, it occurred on the first day of training. Participants randomized to the control group were eligible for nocturnal hemodialysis training upon study completion.

Patients assigned to nocturnal hemodialysis were trained in-center 4 to 5 times per week, for 2 to 6 weeks, with direct nursing supervision and monitoring of biochemical parameters. Upon completion of training, nocturnal hemodialysis was performed at home by the patient, without remote monitoring, 5 to 6 nights per week for a minimum of 6 hours per night. Dialysis was performed using Bellco Formula (Mississauga, Ontario, Canada) machines using polysulfone synthetic membranes. Bloodflow rates up to 250 mL/min were prescribed and dialysate flow rates of 300 mL/min were used in all patients. The majority of patients used a single-needle single-pump dialysis setup. Water was purified using reverse osmosis and ultrapure dialysate was not used. Dialysate calcium was 5.0 to 7.0 mg/dL (1.25-1.75 mmol/L) and phosphate was added to the dialysate bath as needed to prevent hypophosphatemia. Patients assigned to conventional hemodialysis continued their prerandomization dialysis modality with thrice weekly hemodialysis and a dialysis prescription to target a single-pool Kt/V (normalized clearance by time product, a derived quantity related to treatment-related changes in urea concentrations) of greater than 1.2. Dialysate calcium was adjusted between 4.0 and 7.0 mg/dL (1.00-1.75 mmol/L) depending on the serum calcium level.

For both groups, comorbidity data were collected by chart review and direct patient interview conducted by one of the investigators. Blood pressure was managed by hemodialysis physicians according to a published algorithm[14] targeting a goal postdialysis blood pressure of less than 130/80 mm Hg. Anemia management was carried out according to a standardized nursing-led anemia protocol with a target hemoglobin of 11.0 to 12.5 g/dL using intravenously administered erythropoietic-stimulating proteins and iron supplements as necessary.[15] Mineral metabolism was managed to achieve local treatment goals of 8.0 to 10.2 mg/dL (2.00-2.55 mmol/L) for serum calcium, less than 5.6 mg/dL (1.80 mmol/L) for serum phosphate, and 150 to 300 pg/mL (150-300 ng/L) for intact parathyroid hormone.

Study Outcomes

The primary outcome was change in LV mass over the 6-month study period. Prespecified secondary outcomes included change in HRQOL; change in predialysis systolic blood pressure; change in erythropoietin-to-hematocrit ratio; and change in calcium-phosphate product.

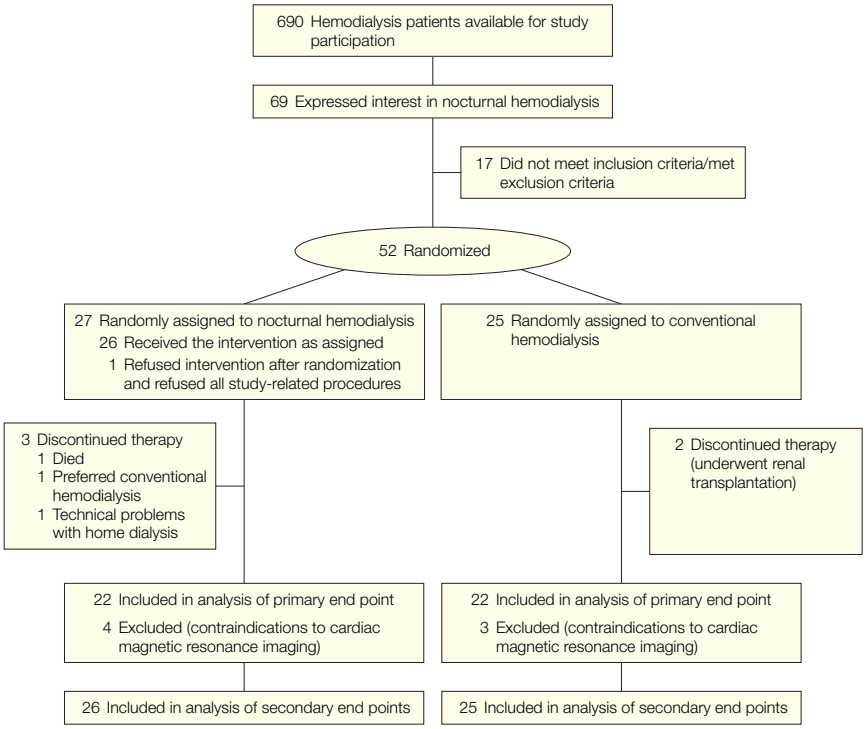
Left ventricular mass was measured within 2 weeks of the baseline visit and at 6 months using cardiovascular magnetic resonance (CMR). CMR was performed on 1.5-T MRI systems (Avanto or Sonata; Siemens Medical Solutions, Erlangen, Germany) with 8-channel cardiac coils. We applied standard, breath-held, retrospectively ECG-gated gradient-echo sequences (steady-state free precession) in contiguous short-axis views (25 phases, 8-mm slice thickness). The evaluation of the CMR images was performed in a professional core laboratory (CIRCLE International Ltd, Calgary, Alberta, Canada) by readers blinded to any clinical or group-specific information. Using validated software (Mass; Medis, Leiden, the Netherlands), volumes were measured on end-systolic and end-diastolic frames by manually tracing endocardial and epi-

cardial contours. Papillary muscles were included in the myocardial mass. The formula by DuBois and DuBois[16] was used to index LV mass to body surface area.

HRQOL questionnaires were self-administered prior to randomization (before patients were aware of the treatment allocation), at baseline, and at 6 months (study exit). The primary HRQOL outcome was change in the EuroQol EQ-5D index score, which measures overall quality of life (scale range 0.0 [dead] through 1.0 [full health]).[17,18] A minimum increment of 0.03 in the EQ-5D index score is considered clinically important.[17] Other HRQOL measures included the EQ-5D visual analog scale score (0-100, with 100 representing perfect health), and the Kidney Disease Quality of Life–Short Form (KDQOL-SF) questionnaire. The KDQOL-SF includes questions targeted at particular health-related concerns for individuals undergoing dialysis. Scores on each KDQOL-SF dimension range from 0 through 100, with higher scores reflecting better HRQOL. Since nocturnal hemodialysis would be unlikely to impact all of the 11 kidney-specific quality of life domains, we selected 4 dimensions a priori that we thought would be most likely affected (kidney disease–related symptoms/problems, effects of kidney disease, and burden of kidney disease, and sleep).

Study physicians measured patients' blood pressure using a mercury sphygmomanometer. Three sitting blood pressure measurements were taken 5 minutes apart with the average of the last 2 measurements used for this study. Additional details of the study protocol and outcome measurements are described elsewhere.[14]

Figure 1. Patient Flow Through the Study



For patients who died or underwent transplantation during follow-up, final data were imputed as described in the "Statistical Analysis" section.

Statistical Analysis

The precision of cardiovascular magnetic resonance allowed a substantially smaller sample size than would be needed if echocardiography was used to measure LV mass.[19] For the primary end point, we assumed that the standard deviation for the difference in change in LV mass between groups would be 8 g.[19] We also assumed that 20% of participants would discontinue the study due to transplantation or death over 6 months, and that 10% of enrolled participants would have a contraindication to magnetic resonance imaging. These patients would still be enrolled to capture secondary outcomes. We therefore calculated that 52 patients would be required to achieve 95% statistical power to detect a significant 10-g difference (2-tailed $\alpha = .05$) in change in LV mass between the groups.

For all outcomes, the primary analyses used the intention-to-treat approach for all patients who had at least 1 baseline measurement. Analyses were based on the difference between groups for the change in the outcome after 6 months of therapy. We used a last-value-carried-forward approach for missing values, including data for patients who underwent transplantation or who died. This approach was supplemented by secondary analyses including only observed cases (ie, patients with measurements at baseline and 6 months), preserving the intention-to-treat principle. For quality of life analyses, given that HRQOL questionnaires are subjective and may be affected by knowledge of randomization allocation, we also considered additional analyses comparing change in quality of life values from prerandomization (when patients were not aware of their treatment allocation) to 6 months. Comparison of normally distributed variables was performed using *t* tests for independent samples. We also performed sensitivity analyses using analysis of covariance (ANCOVA), with the 6-month value as the dependent variable and the baseline value treated as a covariate, to account for differences in baseline measures of the primary and secondary outcomes, and for baseline blood pressure in the primary outcome analyses. Nonparametric comparisons were performed using the Wilcoxon rank sum test. Categorical measures were compared using the χ^2 test or Fisher exact test, as appropriate. Data are presented as means (SDs), unless otherwise indicated. All analyses were performed using SPSS software version 13.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Patient Characteristics

Sixty-nine patients expressed an interest in nocturnal hemodialysis : 17 did not meet inclusion criteria or fulfilled exclusion criteria. Fifty-two patients were enrolled in the study, but 1 patient randomized to nocturnal hemodialysis was excluded due to refusal to participate in any study-related procedures including baseline data collection and hemodialysis training (Figure 1). Therefore, the intention-to-treat population included 26 patients randomized to nocturnal hemodialysis and 25 patients randomized to conventional hemodialysis. In the nocturnal hemodialysis group, 1 death occurred, 1 patient returned to conventional hemodialysis citing patient preference, and 1 patient started in-center, short daily dialysis due to technical problems associated with home dialysis. Two patients assigned to conventional hemodialysis received a kidney transplant during the follow-up period. These 5 patients were included in the intent-to-treat population.

Table 1. Baseline Characteristics[a]

Characteristic	No. (%)	
	Nocturnal Hemodialysis (n = 26)	Conventional Hemodialysis (n = 25)
Age, mean (SD), y	55.1 (12.4)	53.1 (13.4)
Male sex	18 (69)	14 (56)
White race	23 (88)	21 (84)
Body mass index, mean (SD)[b]	26.2 (5.5)	23.9 (5.1)
Time receiving dialysis, mean (SD), y	5.5 (5.3)	4.8 (3.8)
Median (interquartile range), y	3 (1-9)	4 (2-6)
Prior renal transplantation	7 (27)	9 (36)
Baseline dialysis modality		
In-center hemodialysis	18 (69)	13 (52)
Home hemodialysis	6 (23)	7 (28)
Self-care hemodialysis	2 (8)	5 (20)
Vascular access		
Arteriovenous fistula	15 (58)	14 (56)
Tunneled dialysis catheter	7 (27)	6 (24)
Arteriovenous graft	4 (15)	5 (20)
Cause of ESRD		
Diabetic nephropathy	7 (27)	8 (32)
Glomerulonephritis	5 (19)	8 (32)
Urologic	3 (12)	3 (12)
Polycystic kidney disease	3 (12)	1 (4)
Hypertension/vascular	2 (8)	2 (8)
Other	6 (24)	3 (12)
Comorbid illnesses		
Diabetes mellitus	10 (38)	11 (44)
Ischemic heart disease	10 (38)	10 (40)
Congestive heart failure	6 (23)	5 (20)
Peripheral vascular disease	4 (15)	4 (16)
Cerebrovascular disease	5 (19)	3 (12)
Medication use		
Acetylsalicylic acid	11 (42)	10 (40)
ACE inhibitor or angiotensin II receptor antagonist	14 (54)	18 (72)
Calcium channel blocker	12 (46)	11 (44)
β-Blocker	10 (38)	9 (36)
Other antihypertensive	2 (8)	5 (20)
Any antihypertensive	21 (81)	20 (80)
Calcium-containing phosphate binder	18 (69)	19 (76)
Sevelamer	6 (23)	6 (24)
Serum albumin, mean (SD), g/dL	3.7 (0.5)	3.6 (0.4)
Iron saturation, mean (SD), %	28.5 (10.0)	33.1 (10.1)
Serum ferritin, mean (SD), ng/mL	427 (264)	493 (318)
Time from randomization to baseline visit, mean (SD), wk	14.3 (9.4)	10.0 (6.0)

Abbreviations: ACE, angiotensin-converting enzyme; ESRD, end-stage renal disease.
SI conversion factors: To convert albumin to g/L, multiply values by 10; to convert ferritin to pmol/L, multiply values by 2.247.
[a] $P > .05$ for all comparisons between nocturnal and conventional hemodialysis groups.
[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

Baseline characteristics between the groups were similar (TABLE 1). Specifically, no baseline differences were noted between the groups in LV mass, blood pressure, antihypertensive medication use, or prevalent cardiovascular disease. Twenty patients (39%) were performing self-care or home hemodialysis at study initiation. Mean prerandomization EQ-5D index scores were 0.705 (95% confidence interval [CI], 0.611-0.800) for the conventional hemodialysis group and 0.683 (95% CI, 0.579-0.786) for the nocturnal hemodialysis group ($P = .74$).

Primary Outcome

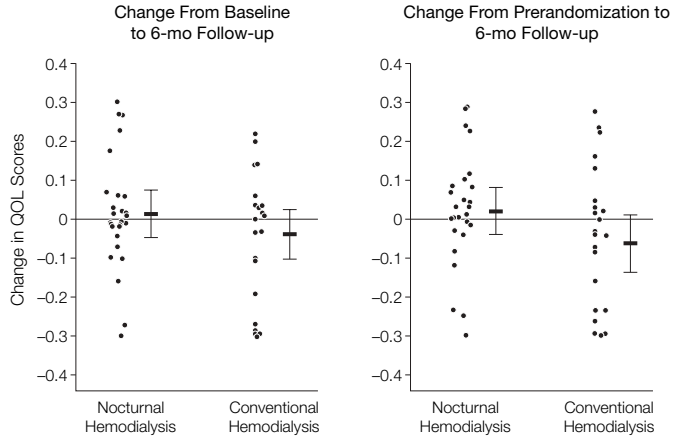
In the intention-to-treat analysis, considering the 44 patients who underwent baseline magnetic resonance imaging and assuming no change in LV mass for 9 patients who either refused follow-up cardiac imaging (n = 6; 4 patients from the nocturnal hemodialysis group), underwent transplantation (n = 2), or died (n = 1), LV mass decreased by a mean (SD) of 13.8 (23.0) g in the nocturnal hemodialysis group and increased by 1.5 (24.0) g in the conventional hemodialysis group (difference, 15.3 g; 95% CI, 1.0-29.6 g; $P = .04$) (TABLE 2). In the modified intent-to-treat analysis, using an observed cases approach (ie, only those patients with baseline and 6-month cardiovascular magnetic resonance results [n = 35]), LV mass decreased by 17.8 (24.8) g in the nocturnal hemodialysis group and increased by 1.8 (26.7) g in the conventional hemodialysis patients (difference, 19.7 g; 95% CI, 1.9-37.4 g; $P = .03$). This difference

Table 2. Outcomes for LV Mass, Blood Pressure, Anemia, and Mineral Metabolism[a]

Characteristic	Nocturnal Hemodialysis[b] (n = 26)	Conventional Hemodialysis[b] (n = 25)	Between-Group Comparison (95% CI)[c]
LV mass, mean (SD), g			
Baseline	177.4 (51.1)	181.5 (92.3)	−4.1 (−49.5 to 41.3)
Exit	163.6 (45.2)	183.0 (84.2)	−19. 4 (−60.5 to 21.7)
Change	−13.8 (23.0)	1.5 (24.0)	−15.3 (−29.6 to −1.0)[d]
LV mass, mean (SD), g/m^2			
Baseline	92.4 (26.6)	101.8 (50.6)	−9.4 (−34.0 to 15.2)
Exit	85.3 (23.2)	102.8 (46.1)	−17. 5 (−39.8 to 4.6)
Change	−7.1 (12.4)	1.0 (14.1)	−8.1 (−16.2 to −0.1)[d]
Blood pressure, mean (SD), mm Hg			
Systolic			
Baseline	129 (23)	135 (19)	−6 (−17 to 6)
Exit	122 (23)	139 (20)	−17 (−28 to −4)
Change	−7 (29)	4 (17)	−11 (−24 to 2)
Diastolic			
Baseline	75 (14)	77 (16)	−2 (−10 to 7)
Exit	68 (16)	75 (12)	−7 (−15 to 1)
Change	−7 (16)	−2 (12)	−5 (−13 to 2)
Anemia, mean (SD)			
Hemoglobin, mean (SD), g/dL			
Baseline	11.9 (1.2)	11.7 (1.3)	0.2 (−0.4 to 0.9)
Exit	11.6 (1.2)	11.8 (1.1)	−0.2 (−0.8 to 0.5)
Change	−0.3 (1.3)	0.1 (1.4)	−0.4 (−1.2 to 0.3)
Darbepoietin-hematocrit ratio, mean (SD)			
Baseline	556 (116 to 1116)	320 (173 to 889)	*P* = .60
Exit	524 (54 to 1174)	333 (151 to 894)	*P* = .69
Change	0 (−115 to 302)	0 (−121 to 197)	*P* = .79
Mineral metabolism			
Serum calcium, mean (SD), mg/dL			
Baseline	9.5 (0.6)	9.1 (1.2)	0.4 (−0.1 to 0.9)
Exit	9.4 (0.7)	8.9 (0.8)	0.5 (0.00 to 0.8)
Change	−0.1 (0.8)	−0.2 (0.5)	0.1 (−0.3 to 0.4)
Serum phosphate, mean (SD), mg/dL			
Baseline	5.5 (1.5)	4.9 (1.3)	0.6 (−0.2 to 1.4)
Exit	4.4 (1.7)	5.3 (1.9)	−0.9 (−1.9 to 0.1)
Change	−1.1 (1.8)	0.4 (1.8)	−1.5 (−2.5 to −0.5)[e]
Calcium-phosphate product, median (IQR), mg^2/dL^2			
Baseline	51.8 (13.6)	44.9 (13.8)	6.9 (−0.8 to 14.7)
Exit	40.6 (16.3)	47.3 (18.9)	−6.7 (−16.7 to 3.3)
Change	−11.2 (16.2)	2.4 (16.8)	−13.6 (−22.3 to −4.3)[e]
Elemental calcium use, mg/d			
Baseline	900 (0 to 1800)	900 (300 to 1800)	*P* = .78
Exit	0 (0 to 0)	900 (600 to 1650)	*P* <.001
Change	−750 (−1800 to 0)	0 (0 to 0)	*P* <.001
Parathyroid hormone, median (IQR), pg/mL			
Baseline	249 (140 to 388)	140 (68 to 380)	*P* = .12
Exit	202 (75 to 282)	184 (83 to 401)	*P* = .85
Change	−84 (−155 to 125)	15 (−6 to 122)	*P* = .05

Abbreviations: CI, confidence interval; IQR, interquartile range; LV, left ventricular.
SI conversion factors: To convert calcium to mmol/L, multiply by 0.25; to convert phosphate to mmol/L, multiply by 0.323; to convert calcium phosphate product to mmol^2/L^2, multiply by 0.0808.
[a] Baseline values for serum calcium, serum phosphate, calcium-phosphate product, hemoglobin, and erythropoietin dose were calculated as the mean of 2 measurements preceding the baseline visit; exit values for these variables were calculated as the mean of 2 measurements obtained at months 5 and 6. Unless otherwise stated, all analyses use intention-to-treat with the last value carried forward for missing values.
[b] n = 22 patients for the LV mass outcome for both frequent nocturnal hemodialysis and conventional hemodialysis groups.
[c] Between-group comparisons were performed using the 2-sample *t* test for normally distributed variables and the Wilcoxon rank sum test for darbepoietin-hematocrit ratio, elemental calcium use, and parathyroid hormone.
[d] *P* <.05 and >.01.
[e] *P* ≤.01 and >.001.

Figure 2. Change in Quality-of-Life Scores (EuroQol-5D Index) by Intent-to-Treat Analysis



The horizontal bars indicate mean change and error bars indicate 95% confidence intervals (CIs). Quality-of-life (QoL) scores at baseline were –0.003 (–0.10 to 0.096) for nocturnal hemodialysis patients and –0.05 (–0.12 to 0.02) for conventional hemodialysis patients. Values at prerandomization were 0.683 (95% CI, 0.579-0.786) for nocturnal hemodialysis patients and 0.705 (95% CI, 0.611-0.800) for conventional hemodialysis patients.

persisted in sensitivity analyses with adjustment for baseline LV mass and systolic and diastolic blood pressure (difference, 19.7 g; 95% CI, 4.4-34.8 g; $P=.01$). The baseline characteristics of the 35 patients who underwent both baseline and follow-up cardiac imaging did not differ from the 16 patients who did not have imaging performed at both time points.

Secondary Outcomes

In the primary analysis, nocturnal hemodialysis did not improve the change in EQ-5D index scores from baseline to 6 months compared with conventional hemodialysis (between-group difference, 0.05; 95% CI, –0.07 to 0.17; $P=.43$) (FIGURE 2). When values were obtained at the time of randomization, rather than at baseline, the between-group difference was larger (0.12 for the change; 95% CI, –0.005 to 0.25; $P=.06$) (Figure 2). Similar findings were noted for the EQ-5D visual analog score; a statistically significant difference between nocturnal hemodialysis and conventional hemodialysis was not noted comparing the change from baseline to 6-month values ($P=.90$), but a clinically and statistically significant 10-point change was noted when comparing scores obtained at the time of randomization with 6-month values ($P=.03$). In analyses that focused on the kidney disease domains of interest (specified a priori), nocturnal hemodialysis statistically improved the domains "effects of kidney disease" and "burden of kidney disease" compared with conventional hemodialysis (FIGURE 3). Analyses using observed cases only and per-protocol analyses gave similar results. Moreover, these results did not appreciably change when adjusted for baseline HRQOL values and baseline dialysis modality.

Antihypertensive medication use was reduced or discontinued in 16 of 26 patients randomized to nocturnal hemodialysis and only 3 of 25 patients randomized to conventional hemodialysis ($P<.001$). Despite the reduction in use of antihypertensive medications in the nocturnal hemodialysis group, 6-month systolic blood pressure decreased in patients randomized to nocturnal hemodialysis by 7 mm Hg and increased in patients randomized to conventional hemodialysis by 4 mm Hg (mean difference, 11 mm Hg; 95% CI, –2 to 24 mm Hg) (Table 2). After adjustment for baseline systolic blood pressure, this mean difference between the groups increased to 14 mm Hg (95% CI, 3 to 26 mm Hg; $P=.01$).

Compared with conventional hemodialysis, nocturnal hemodialysis was more effective at lowering serum phosphate, calcium-phosphate product, and parathyroid hormone levels (Table 2). At baseline, 37 patients were using oral calcium-based phosphate binders and 12 patients were taking sevelamer either alone (n=5) or in combination (n=7) with calcium-based binders. A reduction or discontinuation of oral phosphate binders occurred in 19 of 26 patients in the nocturnal hemodialysis group and only 3 of 25 patients in the conventional hemodialysis arm ($P<.001$). As a result, oral daily elemental calcium intake was reduced in the nocturnal hemodialysis patients but not in the patients treated with conventional hemodialysis.

No differences in anemia control or anemia management were observed between the groups (Table 2).

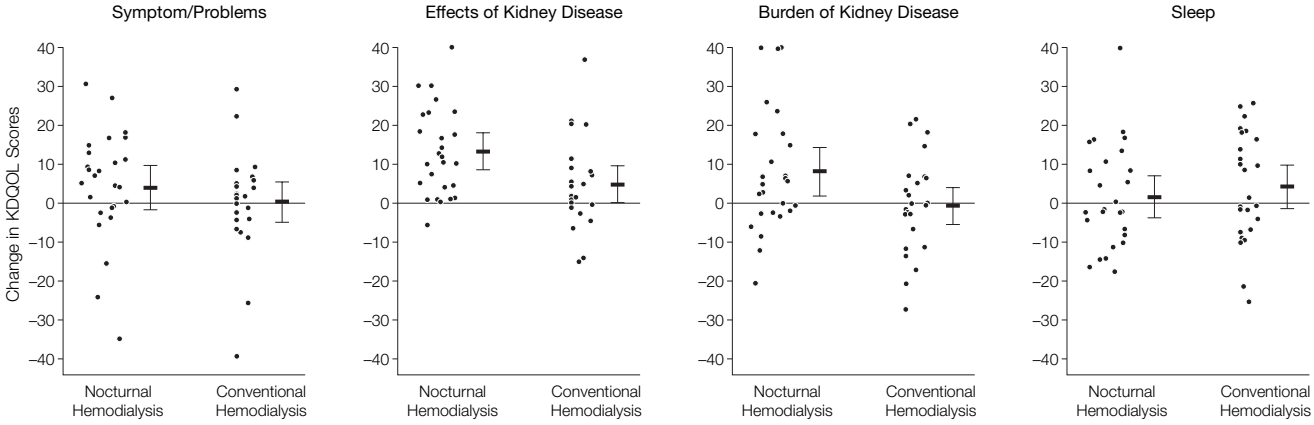
Adverse Events

The mean number of hospitalizations per patient from baseline to study exit was similar for patients randomized to nocturnal hemodialysis (0.62; 95% CI, 0.24-1.00) and conventional hemodialysis (0.84; 95% CI, 0.18-1.50). Likewise, the median length of stay for patients randomized to nocturnal hemodialysis (0; interquartile range, 0-3) and conventional hemodialysis (0; interquartile range, 0-4) was similar. Complications related to vascular access including bacteremic episodes, angiograms, and surgical interventions occurred in 10 of 26 patients randomized to nocturnal hemodialysis and 8 of 25 patients randomized to conventional hemodialysis ($P=.85$) (TABLE 3).

COMMENT

To our knowledge, this is the first completed randomized controlled trial of frequent nocturnal hemodialysis compared with another dialysis modality for patients with ESRD. Our findings indicate that frequent nocturnal hemodialysis improves LV mass, systemic blood pressure, abnormalities of mineral metabolism, and possibly HRQOL compared with conventional thrice-weekly

Figure 3. Change in Selected KDQOL Kidney Disease Domain Scores by Intent-to-Treat Analysis



KDQOL indicates Kidney Disease Quality of Life questionnaire. The horizontal bars indicate the mean change and the error bars indicate 95% confidence intervals (CIs). Mean baseline scores for symptoms/problems were 69.7 (95% CI, 62.4 to 77.0) for the nocturnal group and 66.1 (95% CI, 58.2 to 74.1) for the conventional group; for effects of kidney disease: 51.6 (95% CI, 42.1 to 61.0) for the nocturnal group and 45.0 (36.5 to 53.5) for the conventional group; for burden of kidney disease: 37.3 (95% CI, 23.9 to 50.6) for the nocturnal group and 26.0 (95% CI, 16.6 to 35.4) for the conventional group; and for sleep: 57.3 (95% CI, 50.4 to 64.1) for the nocturnal group and 45.6 (95% CI, 37.1 to 54.1) for the conventional group. The mean change (nocturnal−conventional) was 3.7 (95% CI, −3.8 to 11.2) (P=.33) for symptoms/problems; 8.6 (95% CI, 2.0 to 15.2) (P=.01) for effects of kidney disease; 9.4 (95% CI, 1.3 to 17.5) (P=.02) for burden of kidney disease; and −2.6 (95% CI, −10.2 to 5.0) (P=.49) for sleep.

hemodialysis. Anemia control was not affected by nocturnal hemodialysis. Results of this trial support several observations made in prior nonrandomized studies, which have shown that receipt of nocturnal hemodialysis is associated with improvements in systemic blood pressure and LV mass.[3,4] Our results also help clarify the uncertainty around the effects of nocturnal hemodialysis on anemia management, measures of mineral metabolism, and HRQOL.[20]

In the general population, LV mass is an independent predictor of cardiovascular disease events and mortality.[21] Regression of LV mass favorably modifies risk of major cardiovascular events independent of improvements in blood pressure control,[22] suggesting that regression of LV mass may be a valid surrogate end point for the occurrence of cardiovascular events, at least in individuals not undergoing dialysis. In ESRD patients, LV hypertrophy is common, affecting up to 75% of patients with incident ESRD,[23] and has been shown to be an independent predictor of cardiovascular disease events and survival.[24,25] Although progression of LV hypertrophy appears to be the norm in dialysis patients,[26] regression of LV mass can occur and is associated with improved outcomes.[27] Although several investigators have reported improvements in LV mass with nocturnal hemodialysis[3] or short-daily hemodialysis,[28] these studies did not use randomized group comparisons, thus potentially introducing bias secondary to selection, residual confounding, or regression to the mean. To our knowledge, our results are the first to demonstrate LV mass regression in patients treated with sustained dialysis within the setting of a randomized trial.

Table 3. Complications Related to Vascular Access, by Treatment Group

Complication	Nocturnal Hemodialysis (n = 26)	Conventional Hemodialysis (n = 25)
Bacteremia		
No. of patients experiencing ≥1 event	4	4
Total No. of events	5	4
Insertion or replacement of tunneled dialysis catheter		
No. of patients experiencing ≥1 event	7	5
Total No. of events	7	7
Vascular access angiogram		
No. of patients experiencing ≥1 event	8	5
Total No. of events	14[a]	8
Vascular access surgical intervention (including percutaneous angioplasty of arterial or venous stenosis)		
No. of patients experiencing ≥1 event	3	5
Total No. of events	4	10[b]

[a] Includes 1 patient who underwent 5 vascular access angiograms.
[b] Includes 1 patient who had 4 vascular access surgical interventions.

Although the confidence intervals around the estimate of the treatment effect were relatively wide, nocturnal hemodialysis induced regression of LV mass, and this remained clinically and statistically significant after adjustment for baseline LV mass and systolic and diastolic blood pressure. The mechanisms responsible for this improvement in LV mass are uncertain but likely multifactorial. One could speculate that better control of extracellular

fluid volume (a difficult variable to adequately quantify) led to the beneficial changes in LV mass and blood pressure. Unfortunately, we did not measure extracellular fluid volume and therefore we were unable to determine if the beneficial effects of nocturnal hemodialysis on LV mass and blood pressure were a result of differences in relative volume control between groups. Alternatively, decreased nocturnal hypoxemia,[29] reduced levels of catecholamines,[30] or improved endothelial function[30] may have contributed. It is unlikely that the observed changes in mineral metabolism led to a reduction in vascular calcification and consequent improvement in vascular compliance and afterload over a relatively short 6-month period.

While our study could be criticized for measuring surrogate end points that have not been validated in ESRD, it is important to note that we also measured HRQOL, an important outcome in a chronic disease such as ESRD. We found no difference in the primary quality of life measure comparing change from baseline to 6 months, but noted statistically and clinically significant improvements in 2 of 4 kidney-specific measures of quality of life comparing change from baseline to 6 months. For our primary quality of life end point, we found that scores appeared to deteriorate consistently over time in patients randomized to conventional hemodialysis and be maintained or increase slightly in patients randomized to nocturnal hemodialysis . These changes, which were observed at baseline and before exposure to the intervention, may have resulted from the subjective nature of "overall" quality of life measures such as the EQ-5D index score, and might represent an artificial anticipatory effect, rather than a true effect from nocturnal hemodialysis per se. It is interesting to note that these results (a slight increase in the quality of life in nocturnal hemodialysis patients and a reduction in quality of life in control patients) was also noted in a previous nonrandomized report[31] and warrants further study, given that our study was not powered for quality of life outcomes. These limitations acknowledged, the magnitude of the change noted in utility scores comparing 6 months and randomization is similar to the mean change observed in dialysis patients who receive a kidney transplant, suggesting this difference in quality of life could be very clinically significant.[32]

Although the current study provides new information on the benefits of nocturnal hemodialysis , the results should be interpreted within the context of its limitations. First, the sample size was small and the duration of follow-up was limited. Using cardiovascular magnetic resonance to measure LV mass, the study was powered for the primary end point. However, the small sample size likely meant that the study was underpowered to detect clinically significant differences in several of the quality of life outcome measures and adverse event rates, including hospitalizations and vascular access complications. Similarly, the study was underpowered to detect differences in major cardiovascular events or survival. We believe the ultimate proof of the clinical value of nocturnal hemodialysis should be provided with large-scale multicenter randomized trials with hard clinical end points. Although the National Institutes of Health is currently sponsoring a larger trial of nocturnal hemodialysis vs home hemodialysis 3 times weekly,[33] it is equally unlikely that a trial of 250 participants will provide definitive data on major clinical outcomes. As described recently by this research group, more than 5000 patients would be needed to detect a 30% difference in 1-year mortality between nocturnal hemodialysis and conventional hemodialysis patients.[34] Given the complexity and intrusiveness of dialysis modality interventions, as illustrated by the difficulty of other dialysis modality trials to sufficiently recruit patients,[35,36] and a concern that randomizing patients to "inferior" therapy is unethical,[37] physicians may be required to make decisions on nocturnal hemodialysis using surrogate end point data as provided in this clinical trial. Recognizing that most clinical trials are not sufficiently powered to adequately address safety concerns, we also believe that any future observational studies, including nocturnal hemodialysis registry trials,[38] should identify data collection for hospitalizations and vascular access complications as high priority.

Second, as with the majority of randomized controlled trials, caution should be exercised when generalizing study results to the underlying population. A large proportion of our study patients were recruited from home hemodialysis or self-care hemodialysis programs, perhaps enriching our sample with patients who were less likely to have problems mastering nocturnal hemodialysis. Also, the mean dialysis vintage for our patients exceeded 5 years. It is uncertain whether frequent nocturnal hemodialysis would be associated with regression of LV mass in newly diagnosed hemodialysis patients in whom volume control, due to preserved residual renal function, is less problematic than in patients receiving long-term hemodialysis.

Finally, dose of dialysis using urea kinetics or other measures was not formally collected in the frequent nocturnal hemodialysis group. A widely acceptable method to accurately define dose of solute clearance in frequent nocturnal hemodialysis has not been defined. In this study, a minimum of 30 hours and a maximum of 48 hours of dialysis per week was delivered to patients within the nocturnal hemodialysis group. In contrast, weekly dialysis for conventional hemodialysis patients ranged from 10.5 to 13.5 hours per week. We believe the observed differences in outcomes within this trial were secondary to the wide separation in delivered dialysis time between groups. The additional dialysis time with frequent nocturnal hemodialysis theoretically provides better volume control and improved solute clearance compared with conventional hemodialysis. In a similar light, the time spent undergoing dialysis is likely the critical element in the intervention within this trial. The nocturnal aspect of the intervention sim-

ply allows a patient to perform normal day-to-day activities without the limitations typically associated with frequent daily dialysis.

CONCLUSIONS

In conclusion, compared with conventional hemodialysis, nocturnal hemodialysis regressed LV mass, reduced blood pressure, improved measures of mineral metabolism, and improved selected measures of HRQOL. It is unlikely that future studies will be powered to detect differences in clinical outcomes such as mortality. Cost analyses are planned alongside this clinical trial. If it is found that nocturnal hemodialysis has a favorable cost-benefit profile compared with other dialysis therapies, then consideration should be given to expansion of nocturnal hemodialysis centers, specifically for patients who wish to trade a more demanding therapy for less cardiovascular risk and a potential of improved quality of life.

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