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Short, frequent, 5 days per week in-center hemodialysis versus 3 days per week treatment: a randomized cross-over pilot trial through the Midwest Pediatric Nephrology Consortium

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Abstract

Background—No controlled trials in children with end-stage kidney disease have assessed the benefits of more-frequent hemodialysis (HD).

Methods—We conducted a multi-center, cross-over pilot trial to determine if short, more frequent 5 days per week of in-center HD was feasible and associated with improvements in blood pressure compared to 3 conventional HD treatments per week. Because adult studies have not controlled for the weekly duration of dialysis, we fixed the total treatment time at 12 weekly hours of dialysis during both three month study periods; only the frequency varied from 5 to 3 days per week between study periods.

Results—Eight children (median age 16.7 years) consented at three children's hospitals. The pre-specified primary composite outcome was a sustained 10 % decrease in systolic blood pressure and/or a decrease in antihypertensive medications, relative to each study period's baseline. Among the six subjects completing both study periods, 5/6 (83.3 %) experienced the primary outcome during 5 days per week HD, but not during 3 days per week and 1/6 (16.7 %)

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Compliance with ethical standards

Written consent was obtained from all participants or their parents/guardians and all participants also provided assent. The study was approved by the separate Institutional Review Boards at the three centers and was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01352455).

had the outcome during 3 days per week HD but not 5 days per week ($p=0.22$). During 5 days per week HD, the six subjects had significantly more treatments where their pre-HD systolic ($p=0.01$) or diastolic ($p=0.01$) blood pressure was 10 % lower than baseline.

Conclusions—We observed that more-frequent HD was feasible and associated with improved blood pressure control, but barriers to changing thrice weekly standard of care include financial reimbursement and the time demands of more frequent treatments.

Keywords

Children; end stage kidney disease; hypertension; more frequent hemodialysis

INTRODUCTION

Children with end-stage kidney disease (ESKD) receiving maintenance dialysis live 40–50 years shorter than healthy children [1]. Cardiovascular disease is the primary recorded cause of mortality, and cardiovascular morbidity includes a high prevalence of hypertension and left ventricular hypertrophy [2–5]. Although most children on maintenance dialysis eventually receive the benefits of a transplant, the cardiovascular damage may be irreversible [6].

Many older children with ESKD are treated with outpatient hemodialysis (HD) [7]. Research in patients with ESKD focuses on improving individual outcomes such as anemia or bone disease, instead of trying to treat more comprehensive, patient-focused outcomes. More-frequent and/or more intensified HD (longer total weekly dialysis times) may simultaneously improve several outcomes for children with ESKD [8–14]. However, no controlled trials have been performed in children to assess the benefits of more-frequent or more intensified HD.

In adults, the Frequent Hemodialysis Network (FHN) randomized trial demonstrated that an average of two extra in-center HD treatments was associated with improved survival and left ventricular hypertrophy [15]. However, the weekly duration of dialysis was not fixed, leading to the possibility that the total weekly HD time, and not the frequency, resulted in the benefit [16]. Because few trials in adults have controlled for dialysis duration when examining treatment frequency [17], we designed a cross-over pilot trial so the total weekly dialysis time was fixed at 12 hours. Our objective was to conduct a multi-center pilot trial among children with ESKD to determine if two extra days per week of in-center HD was feasible and was associated with improvements in systolic blood pressure and multiple additional outcomes.

METHODS

Population

Children and young adults, age 3–21 years, receiving outpatient HD for ESKD at Cincinnati Children's Hospital (CCHMC, March 2011–April 2012), The Children's Hospital of Philadelphia (CHOP, June 2012–September 2013), and The Hospital for Sick Children (SickKids, September 2012–May 2014) were screened. Inclusion criteria were a diagnosis of

hypertension, defined as the prescription of anti-hypertensive medication or a systolic blood pressure 95th percentile for age, gender, and height [18]. Exclusion criteria were receiving maintenance HD for <2 months, a living kidney transplant or switch to peritoneal dialysis in the next six months, already receiving >3 days or >12 hours per week of HD, receiving concomitant peritoneal dialysis, or the use of a temporary or femoral dialysis catheter. Children listed for a deceased donor transplant were not excluded. Written consent was obtained from all participants or their parents/guardians and all participants also provided assent. The study was approved by the separate Institutional Review Boards at the three centers and was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01352455). The datasets generated and analyzed during the current study are available from the corresponding author on request.

Design

We conducted a prospective, open-label, randomized, cross-over pilot trial over two successive 12 week (3 month) study periods (Figure 1). Subjects were randomized to the treatment sequence: either 3 days per week conventional HD for four hours per treatment (12 hours total per week, control) followed by 5 days per week short, more frequent HD for two hours and 25 minutes per treatment (12 hours total per week, intervention), or vice versa.

Measures

Beginning with the first baseline week, blood pressure, the primary outcome, was measured before a dialysis treatment using each unit's automated oscillometric device in an upper extremity, with the patient seated for 5 minutes before measurement, as standardized in the study protocol. These pre-dialysis blood pressure measurements were performed in triplicate and averaged for the analysis. To prevent bias from having to compare data among subjects with different numbers of blood pressure measurements, clinical data, with the exception of adverse events, were only collected three days per week (Monday/Wednesday/Friday, or Tuesday/Thursday/Saturday) across both study periods; no measurements were obtained during the two extra treatments during the 5 day per week period. Pre- and post-dialysis weights and changes to anti-hypertensive therapy, made at the discretion of the treating provider, were also recorded. Administration of antihypertensive therapy was not standardized and subjects took their medications as individually prescribed. A pre-HD electrolyte panel and post-HD complete blood count was obtained every two weeks. Every four weeks, we recorded the dialysis prescription, concomitant medications, dry weight, post-dialysis albumin, pre- and post-HD blood urea nitrogen, intact parathyroid hormone, and iron studies. Dry weight was assessed clinically at the discretion of each center and also with the use of an in-line continuous hematocrit monitor (CHOP and SickKids). Any changes in dry weight were recorded by each site on a monthly basis. To account for the different frequencies of dialysis, adequacy was reported as a standard Kt/V, calculated by first converting each subject's single-pool Kt/V [19] to an equilibrated Kt/V [20] and then to a weekly standard Kt/V [20, 21]. Blood inflammatory markers (C-reactive protein, beta-2 microglobulin, and homocysteine) were drawn during the baseline week and at week 12 for each study period.

Each subject received three echocardiograms during the trial to assess for changes in left ventricular hypertrophy; at baseline, midway during the study after the first study period, and again at the end of the second study period. Echocardiograms were performed during the middle of the week, after a dialysis session, and were read centrally at CCHMC, blinded to subjects' treatment assignment. We also obtained quality of life assessments at baseline and after 12 weeks for each study period. Quality of life assessed in both parents and subjects was measured with The PedsQL 4.0 Generic Scale and 3.0 ESRD Scale, and was scored from 0–100, with higher scores representing better QOL [22, 23]. Only parents of two subjects filled out the quality of life instruments, so only the subject-reported data was included.

End points

The primary outcome was an improvement in pre-HD systolic blood pressure control, sustained for three consecutive treatments. Based on prior observational studies [12], the pre-specified primary composite endpoint was a decrease in the pre-HD systolic blood pressure by 10 % or a decrease in the number or dosage of required anti-hypertensive medications, relative to each study period's baseline (the last baseline treatment prior to starting each study period). Pre-specified secondary outcomes included assessment of adverse events and changes in diastolic blood pressure, erythropoietin and iron use, serum phosphate and use of phosphate binders, serum parathyroid hormone and use of vitamin D analogs, inflammatory markers, quality of life, echocardiogram-measured left ventricular mass, dry weight changes, and inter-dialytic weight gains.

Post-hoc, we examined the number of treatments where a subject had ≥ 4 % fluid overload at the start of dialysis, a value associated with worse outcomes in HD patients [24–26]. This inter-dialytic percent fluid overload was calculated as the pre-dialysis weight minus the post-dialysis weight divided by each subject's dry weight, times 100. We also compared achievement of dry weight between the study periods, examined as a post-dialysis weight within 0.5 kg of each subject's dry weight.

Sample Size and Randomization

The anticipated sample size was based on the number that could feasibly be enrolled during the study period. We planned to enroll 10 patients, randomizing each to start with control or intervention HD periods at a ratio of 1:1. Randomization codes that were used to assign patients to their treatment sequence were generated by the study biostatistician using SAS PROC PLAN.

Analysis

The primary outcome was analyzed with the exact McNemar test, comparing events, dichotomized as yes versus no and paired by subject, for those completing both study periods of the trial. Analyses including count data (i.e. the number of treatments where a subject had a 10 % reduction in blood pressure or came to dialysis with ≥ 4 % fluid overload) were conducted using Poisson regression with terms for subject, study period, and treatment.

For the pre-specified secondary outcomes, we present descriptive data with medians and interquartile ranges (IQR). Comparisons between study periods for the secondary outcomes were made using a mixed effects analysis of variance model with terms for control versus intervention period and with a term for subject included as a random effect. The baseline measurement before each study period was used as a covariate in the model. The study data were collected using REDCap (Research Electronic Data Capture) hosted at CCHMC [27]. Analyses were conducted using STATA Version 12 (College Station, Texas) and SAS Version 9.3 (Cary, North Carolina) and a two-side p-value of <0.05 was considered statistically significant.

RESULTS

Subjects

A total of 72 children and adolescents who received maintenance HD at the three study centers during the enrollment period were screened; 20 were eligible and eight consented to participate: four at CCHMC, two at CHOP, and two at SickKids (Figure 2). Two subjects withdrew from the study early, both during 3 days per week treatment; one subject had completed 5 days per week HD but did not want to continue four hour treatments during the 3 days per week period and the second subject received a kidney transplant. Of the six subjects who completed the study, three started the trial with 3 days per week HD and three started with 5 days per week HD.

Table 1 shows the demographic characteristics of the six subjects completing the trial. The subjects were adolescents with a median age of 16.7 years, 83.3 % were female, and 50 % African-American. Subjects were previously treated with a median of 9.8 hours [IQR 9.0–11.3 hours] per week of HD and most (66.7 %) had a central venous catheter. The characteristics of the two subjects not completing the trial were similar to the included six subjects (not shown).

Blood pressure outcomes

The primary composite outcome was defined as either a 10 % reduction in systolic blood pressure or a reduction in antihypertensive medication number or dosage, sustained for three consecutive days. Of the six subjects completing the trial, 5/6 (83.3 %) had the primary composite outcome during 5 days per week HD but not during 3 days per week HD and the remaining subject (16.7 %) had the event on 3 days per week HD but not 5 days ($p=0.22$).

Examining each component of the primary outcome individually, in the six subjects that completed the trial, 2/6 (33.3 %) had a 10 % reduction in systolic blood pressure relative to baseline, sustained for three consecutive treatments, during 5 days per week but not during 3 days per week. The remaining 4/6 (66.7 %) subjects did not experience this event during either treatment period ($p=0.5$). Regarding medication changes (Table 2), 4/6 (66.7 %) subjects had a decrease in antihypertensive medication number or dosage, sustained for three consecutive treatments, during 5 but not 3 days per week HD. One subject had this event on 3 days per week HD but not 5 days per week and the remaining one subject did not have this

event during either study period ($p=0.38$). Further details regarding each subject's blood pressure outcomes by treatment sequence are shown in Supplemental Table 1.

To illustrate changes in blood pressure across the study periods, we graphed the number of treatments where each subject had a pre-HD systolic (Figure 3a) or diastolic (Figure 3b) blood pressure that was 10 % lower than baseline. As shown in Figure 3, subjects had significantly more sessions with a pre-HD systolic ($p=0.01$) or diastolic ($p=0.01$) blood pressure 10 % lower than baseline during 5 days per week treatment.

Post-hoc analyses also examined the number of treatments where a subject was 4 % fluid overloaded pre HD. Five days per week HD was associated with significantly fewer days ($p=0.03$) of this degree of fluid overload (Figure 4). There was no difference in achievement of dry weight (post-HD weight within 0.5 kg of dry weight) between the treatment groups ($p=0.19$).

Secondary outcomes

There were no significant changes in erythrocyte stimulating agent dosing, post-dialysis hemoglobin, or iron dosing (Supplemental Table 2). There were no significant changes in serum phosphorus, calcium, intact parathyroid hormone, the number of phosphate binders prescribed, or activated vitamin D dosing across either period of the trial. Finally, there were no significant changes in inflammatory markers during the study. Additional laboratory values, including electrolytes and albumin, and the dialysis prescription, did not significantly change during the course of the study (Supplemental Table 3).

The changes in echocardiogram-measured left ventricular mass are shown in Supplemental Figure 1. For the subjects who started with 5 days per week HD and then received 3 days per week HD, left ventricular mass did not appear to change during the study. For the subjects who started with 3 days per week HD and then received 5 days per week HD, there was a decrease or no change in their left ventricular mass by the midpoint of the trial (after the 3 days per week period). After 5 days per week HD, one subject had an unexplained increase in left ventricular mass while the other two had no change by the end of the trial. The results of the quality of life assessments are shown in Table 3. Patient reported assessments on both the generic ($p=0.18$) and ESKD ($p=0.20$) instruments were stable across the study.

At baseline, the weekly standard Kt/V was 2.1 (IQR 2.0 to 2.5) before the 3 days per week study period and was 3.2 (IQR 3.1 to 3.4) before the 5 days per week period. However, after 12 weeks, the weekly standard Kt/V was similar in the 3 days per week (2.5, IQR 2.4 to 2.7) and the 5 days per week (2.5, IQR 2.3 to 2.6) ($p=0.70$) periods.

All subjects reported at least one adverse event during 3 days and 5 days per week treatment. No notable difference in the number of subjects reporting adverse events was observed (Table 4). There were a total of 169 adverse events reported by the 8 subjects during 3 days per week treatment, with 155 (92 %) reported as mild, 11 (7 %) as moderate, and 2 (1 %) as severe (both blood transfusions). There were a total of 175 adverse events reported by the 7 subjects during 5 days per week treatment, with 166 (95 %) reported as mild, 5 (3 %) as moderate, and 4 (2 %) as severe (one access dysfunction, one blood transfusion, one

scheduled admission for fistula creation, and one hyperkalemia/fluid overload). Regarding access dysfunction, during 3 days per week, one subject had bleeding at their access site and the next day developed thrombosis of their graft. Another subject had three episodes of central venous catheter malfunction, with one episode requiring tissue-plasminogen activator (TPA) instillation. During 5 days per week treatment, one subject had a catheter leak requiring rewiring and a second subject had two episodes of access dysfunction necessitating TPA administration. There were no reported episodes of fever or infection during the study.

DISCUSSION

We conducted a randomized, cross-over pilot trial in six adolescents with ESKD to determine if 5 days per week in-center HD was feasible and associated with improved blood pressure control. Even with a small sample size of only six subjects, we observed that subjects had statistically significant improvements in blood pressure control and fluid overload while receiving 5 days per week HD. The protocol was feasible as no subject withdrew during 5 days per week treatment. Importantly, and in contrast to most prior studies in adults [17], we controlled for the duration of weekly dialysis across both study periods while examining the benefits of more-frequent treatments over a relatively short follow-up period of 12 weeks.

We were able to consent eight subjects out of 72 (11.1 %) patients receiving HD at the three sites. However, only six subjects could be fully analyzed after completing both 12 week study periods. This small sample size was likely due to a combination of our inclusion criteria and the time burden required for coming to the clinic 5 days per week for HD. The adult FHN trial also demonstrated significant challenges to enrollment with 378 subjects consenting to participate (245 randomized) in the 1 year study out of 6276 patients screened (6.0 %) [28]. For future trials to feasibly enroll, it will be crucial to test HD schedules that incorporate patient/family preferences while still offering the health benefits of more-frequent or more intensive (longer total dialysis time per week) treatments.

As noted, in contrast to the adult FHN trial, the weekly duration of dialysis was fixed at 12 hours across both 12 week study periods, allowing us to focus on the benefits of extra treatments without the confounding of total weekly treatment time [16]. Accordingly, our calculated weekly standard Kt/V, which allows dialysis adequacy to be compared across different schedules of dialysis frequency and duration [20], was similar and above >2.4 in both treatment periods after 12 weeks of treatment. While the optimal dialysis dose in children remains unknown, a weekly standard Kt/V 2.2 has been correlated with a goal single-pool Kt/V 1.4 [21].

Given our short trial duration with a short follow-up period and open label design, it is possible that the observed improvements in blood pressure were related to patients receiving 12 hours of weekly dialysis for six months, independent of the extra treatments. Notably, pre-study, 6/8 (75 %) of our subjects were receiving <12 hours of weekly dialysis. Only the 2 subjects treated in Canada were receiving 12 hours of weekly dialysis pre-study, which was their center's standard of care. Regarding fluid status, in the 5 days per week treatment period, there was a significant reduction in the number of treatments where subjects were

4 % fluid overloaded pre-dialysis (Figure 4). Importantly, this degree of inter-dialytic fluid overload has been associated with a higher risk for left ventricular hypertrophy in children [29]. In adults, dialysis treatment times >4 hours, slower ultrafiltration rates, and lower inter-dialytic fluid gains have been independently associated with lower mortality rates in observational studies [25, 29–31]. Determining the optimal dialysis duration and frequency remains an ongoing area of study. The Time to Reduce Mortality in End-Stage Renal Disease (TiME) Trial in adults is actively enrolling over 6000 adults to determine if dialysis sessions 4.25 hours, provided 3 days per week, decreases mortality in adults [32]. Based on our observations and the existing adult literature, we suggest that future trials in children include a minimum of 12 hours of weekly HD as a comparator.

After conducting this pilot trial, we learned about the practical barriers to providing more-frequent or more intensive HD regimens. Specifically, we observed significant challenges in obtaining transportation for the extra two weekly treatments, especially because most children are brought to dialysis without their parents. In most of our subjects, we hired private taxi companies, some of whom were already contracting with patients' insurance to provide ESKD transportation. To change the standard of cares, future studies will need to show that alternative dialysis treatment schedules are cost-saving, or at the very least cost neutral, to be able to cover the costs of staffing, supplies, and transportation. The time demands on providers, families, and patients must also be addressed. More time spent receiving HD may decrease school attendance and performance for our patients, and given the school time that children are already missing and the cognitive challenges that children with ESKD experience [33, 34], this is an area that deserves further study.

To our knowledge, this is the first randomized trial in children designed to test the benefits of more frequent HD. Additional strengths of our study include the multi-center enrollment and the collection of data that was mostly standard of care, hopefully informing the design of future, more pragmatic clinical trials. The study was of course limited by its small size, relatively short follow-up period, enrollment of only adolescents, lack of 24 hour ambulatory blood pressure monitoring, antihypertensive medication administration that was non-standardized, recording of changes in dry weight only once a month, and a cross over design that had the potential for unequal carryover effects across study periods.

Although dialysis is lifesaving, children and adults with ESKD suffer from unacceptably high rates of morbidity and mortality. While these rates have decreased over time, it is alarming that despite increasing evidence supporting the benefits of more dialysis, we have actually decreased the amount of time that patients are dialyzed compared to decades ago [25]. We believe our results provide a foundation for further, systematic investigations, to improve the health of children with ESKD receiving long-term HD. This is important because although transplant remains the optimal treatment for ESKD, most children will require dialysis at some point in their lifetime [4, 35]. Significant barriers exist, but we call upon patients, parents, providers, administrators, researchers, teachers, and payers to come together towards improving outcomes further for this vulnerable, resource intensive, patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Study design

Subjects were enrolled in a 29-week, randomized, cross-over trial. After consent, subjects began a 2-week run-in period where all subjects received 3 days per week, four hours per treatment of hemodialysis (HD). During the first baseline week, subjects continued to receive 3 days per week, four hours per treatment of HD and three casual blood pressure measurements were obtained prior to each HD session with the last treatment's measurement averaged to become the baseline for each study period. Subjects were then randomized to the first treatment sequence (5 days versus 3 days per week HD, each for 12 hours total per week), during which three casual blood pressure measurements were obtained and averaged prior to each HD session, three days per week, regardless of which treatment frequency they were receiving. Following a 1-week wash-out where all subjects again received 3 days per week, four hours per treatment of HD, subjects completed the last 12 weeks of the trial with the treatment sequence they had not received in the first study period.

Figure 2.
Patient eligibility, enrollment, and randomization

(a) Pre-hemodialysis average systolic blood pressures compared to baseline

(b) Pre-hemodialysis average diastolic blood pressures compared to baseline

Figure 3. Changes in systolic and diastolic blood pressure

Each row represents each of the six subjects completing the trial and each column is a treatment day where blood pressure was recorded for the study (three days per week across both study periods). Subject 5 and 8 were excluded because they did not complete the trial. The green boxes represent an average pre-HD systolic (Figure 3a) or diastolic (Figure 3b) blood pressure that was 10 % lower than the baseline (defined as the last treatment before the start of each study period). The red boxes represent an average pre-HD blood pressure that was within 10 % of the baseline. The white boxes represent a day data was missing. Compared to 3 days per week hemodialysis, 5 days per week treatment was associated with significantly more days where the pre-HD systolic ($p=0.01$ by Poisson regression) or diastolic ($p=0.01$ by Poisson regression) decreased by 10 % relative to baseline.

Pre-hemodialysis fluid overload

Figure 4. Pre-hemodialysis fluid overload
The percent fluid overload pre-hemodialysis was calculated as the pre-hemodialysis weight minus the post-hemodialysis weight divided by each subject’s dry weight, times 100. Each row represents each of the six subjects completing the trial and each column is a treatment day where pre- and post-weights were recorded for the study (three days per week across both study periods). Subject 5 and 8 were excluded because they did not complete the trial. The green boxes represent fluid overload <4 %, the red boxes fluid overload ≥ 4 %, and the white boxes a day when data was missing. Compared to 3 days per week hemodialysis, 5 days per week treatment was associated with fewer days of fluid overload ≥ 4 % (p=0.03 by Poisson regression).

Table 1

Subject demographics

	N=6 subjects completing both study periods
Age (years)	16.7 [15.9–8.0]
Gender (female)	5 (83.3 %)
Race	
African-American	3 (50.0 %)
Asian	2 (33.3 %)
Caucasian	1 (16.7 %)
Duration of end stage kidney disease (years)	2.8 [1.7–7.1]
Received prior kidney transplant	2 (33.3 %)
Active on deceased donor transplant list	2 (33.3 %)
Primary diagnosis	
Glomerular	5 (83.3 %)
Dysplasia	1 (16.7 %)
Pre-trial dialysis days per week	3
Pre-trial dialysis hours per week	9.8 [9.0–10.5]
Vascular access	
Central venous catheter	4 (66.7 %)
Fistula	1 (16.7 %)
Graft	1 (16.7 %)
Study Site	
Cincinnati	4 (66.7 %)
Philadelphia	1 (16.7 %)
Toronto	1 (16.7 %)

Data presented as median [interquartile range] or n (%)

Table 2

Changes in antihypertensive therapy during the study

Subject	Treatment sequence: 3 days per week then 5 days per week			
	3 days per week hemodialysis		5 days per week hemodialysis	
	Baseline	Week 12	Baseline	Week 12
1	lisinopril 40 mg daily atenolol 12.5 mg BID nifedipine XL 90 mg BID	lisinopril 40 mg daily atenolol 12.5 mg BID	lisinopril 40 mg daily atenolol 12.5 mg BID	lisinopril 40 mg daily atenolol 12.5 mg BID
3	losartan 25 mg TIW	losartan 25 mg TIW	losartan 25 mg TIW	none
6	losartan 100 mg daily amlodipine 10 mg daily	losartan 100 mg daily amlodipine 10 mg daily	losartan 100 mg daily amlodipine 10 mg daily	none
8†	amlodipine 5 mg twice daily	none(week 8)†	†withdrew/transplant	
Subject	Treatment sequence: 5 days per week then 3 days per week			
	5 days per week hemodialysis		3 days per week hemodialysis	
	Baseline	Week 12	Baseline	Week 12
2	none	none	none	none
4	lisinopril 20 mg daily amlodipine 10 mg daily	none	none	none
7	amlodipine 5 mg daily	none	none	amlodipine 5 mg daily
5‡	atenolol 25 mg daily losartan 100 mg daily	lisinopril 10 mg daily	lisinopril 10 mg daily	lisinopril 10 mg daily (week 2)‡

Shaded squares are treatment period 1 and non-shaded squares are treatment period 2. Subject 8[†] withdrew from the study due to kidney transplant during treatment period 1 and subject 5[‡] withdrew two weeks after starting the 3 days per week study period (treatment period 2). XL, extended release; BID, twice daily; TIW, three times a week.

Table 3

Patient-reported quality of life assessments

N=6 subjects	3 days per week hemodialysis			5 days per week hemodialysis			p-value*
	Baseline n=6	Week 12 n=6	% baseline	Baseline n=6	Week 12 n=6	% baseline	
Generic Score	67.9 [48.9, 81.5]	71.2 [55.4, 79.3]	2.7 % [-2.2%, 8.7 %]	64.1 [61.8, 80.4]	65.2 [55.4, 80.4]	0 % [-3.3%, 1.1 %]	0.18
End-stage renal disease Score	68.8 [63.2, 77.3]	74.6 [64.7, 88.9]	1.0 % [-1.8 %, 15.0%]	62.9 [54.4, 72.1]	61.4 [52.4, 69.9]	-3.4 % [-5.6 %, -3.1%]	0.20

Each quality of life instrument is scored from 0–100 with higher scores indicating better quality of life.

* Mixed effects analysis of variance model with terms for treatment period and subject included as a random effect.

Table 4

Adverse events

Adverse Event	Per subject		Per dialysis treatment	
	3 days per week N=8 subjects	5 days per week N=7 subjects	3 days per week N=270 treatments*	5 days per week N=441 treatments*
Hypotension	4 (50.0 %)	4 (57.1 %)	17 (6.3 %)	23 (5.2 %)
Headache	6 (75.0 %)	4 (57.1 %)	20 (7.4 %)	14 (3.2 %)
Cramping	3 (37.5 %)	5 (71.4 %)	21 (7.8 %)	10 (2.3 %)
Nausea	3 (37.5 %)	3 (42.9 %)	14 (5.2 %)	7 (1.6 %)
Vomiting	2 (25.0 %)	1 (14.3 %)	11 (4.1 %)	2 (0.4 %)
Need Oxygen	2 (25.0 %)	2 (28.6 %)	8 (3.0 %)	5 (1.1 %)
Pain from access	0 (0 %)	1 (14.3 %)	0 (0 %)	1 (0.2 %)
Access dysfunction	3 (37.5 %)	2 (28.6 %)	5 (1.9 %)	3 (0.7 %)
Syncope	0 (0 %)	1 (14.3 %)	0 (0 %)	1 (0.2 %)
Blood transfusion	1 (12.5 %)	1 (14.3 %)	2 (0.7 %)	1 (0.2 %)
Clotting of dialysis circuit	2 (25.0 %)	0 (0 %)	2 (0.7 %)	0 (0 %)
Other	8 (100 %)	7 (100 %)	69 (25.6 %)†	108 (24.5 %)‡

* total dialysis treatments during the baseline and treatment weeks for each treatment period

† During 3 days per week treatment, Other adverse events (number of events) were recorded as: hypotension (14), rinseback (14), feeling hot (8), tachycardia (4), dizziness (2), lightheaded (2), back pain (2), abdominal pain (2), malaise (2) and one event each for hypertension, shortness of breath, machine malfunction, tooth pain after surgery, chest pain, hold losartan, passed out, scheduled echocardiogram, general machine alarm, dialysis stopped, limping, throat squeezing, sore throat, arterio-venous graft thrombosis, feeling wiped out, low white count, target goal decreased, postoperative pain, and not feeling well.

‡ During 5 days per week treatment, Other adverse events (number of events) were recorded as: rinseback (28), feeling hot (18), hypotension (16), back pain (6), abdominal pain (5), dizziness (5), tachycardia (4), hypertension (2), malaise (2), not feeling well with dry weight challenge (2), lightheaded (2), and one event each for swollen lymph nodes, axillary boil, breast pain, gastrointestinal virus, post-dialysis complete blood count drawn, placed in minimum ultrafiltration, shortness of breath, system clotted, cold symptoms, flank pain, weak, blood leak, scheduled arterio-venous fistula creation, high fluid gain, numbness, hyperkalemia, sore throat, tired.