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Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis

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Abstract

Background. Longer dialysis sessions may improve outcome in haemodialysis (HD) patients. We compared the clinical and laboratory outcomes of 8- and 4-h thrice-weekly HD.

Methods. Two-hundred and forty-seven HD patients who agreed to participate in a thrice-weekly 8-h in-centre nocturnal HD (NHD) treatment and 247 age-, sex-, diabetes status- and HD duration-matched control cases to 4-h conventional HD (CHD) were enrolled in this prospective controlled study. Echocardiography and psychometric measurements were performed at baseline and at the 12th month. The primary outcome was 1-year overall mortality.

Results. Overall mortality rates were 1.77 (NHD) and 6.23 (CHD) per 100 patient-years (P = 0.01) during a mean 11.3 ± 4.7 months of follow-up. NHD treatment was associated with a 72% risk reduction for overall mortality compared to the CHD treatment (hazard ratio = 0.28, 95% confidence interval 0.09–0.85, P = 0.02). Hospitalization rate was lower in the NHD arm. Post-HD body weight and serum albumin levels increased in the NHD group. Use of antihypertensive medications and erythropoietin declined in the NHD group. In the NHD group, left atrium and left ventricular end-diastolic diameters decreased and left ventricular mass index regressed. Both use of phosphate binders and serum phosphate level decreased in the NHD group. Cognitive functions improved in the NHD group, and quality of life scores deteriorated in the CHD group.

Conclusions. Eight-hour thrice-weekly in-centre NHD provides morbidity and possibly mortality benefits compared to conventional 4-h HD.

Keywords: in-centre haemodialysis; nocturnal; outcomes; survival

Introduction

The mortality rate of patients treated with haemodialysis (HD) remains unacceptably high despite several improvements in dialysis technology and general medical care [1]. The low level of quality of life (QOL) is also an important concern in this population.

The link between morbidity–mortality and the dose–frequency of dialysis has been a matter of debate since the beginning of the dialysis era. The National Cooperative Dialysis Study showed that increase in the dose of dialysis based on Kt/V improves the outcome [2]. However, the HEMO study failed to show an additional benefit on mortality with a further increase in Kt/V on the thrice-weekly regimen [3].

There has been a growing body of evidence showing that more frequent or longer HD sessions are associated with improvements in a wide spectrum of outcomes such as blood pressure (BP) control [4,5], left ventricular hypertrophy [6], anaemia management [7], phosphate control [8], nutritional status [9], QOL [6,10] and mortality [5]. Moreover, recently it has been demonstrated that survival of nocturnal home HD patients (6–8 h per session, 3–7 sessions per week) is comparable with that of recipients of cadaveric kidney recipients [11].

In this prospective, case-controlled study, we investigated whether an increase in the duration of dialysis sessions to 7–8 h thrice weekly during the night (NHD) provides better survival, less morbidity, higher QOL and lesser need of medications than conventional thrice-weekly 4-h HD (CHD).

Materials and methods

Study design

The 'Long Dialysis Study' is a prospective, non-randomized, case-controlled trial (ClinicalTrials ID, NCT00413803). Two-hundred and forty-seven prevalent HD patients underwent thrice-weekly in-centre 7–8-h nocturnal HD (nocturnal HD group, NHD) and then a 1:1 matched control group was constituted (conventional HD group, CHD). Participants were followed for 12 months. Echocardiography and psychometric measurements were performed at baseline and at the 12th month. The study was ended in February 2008. Primary and secondary outcomes were evaluated. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki; all patients provided written informed consent. The local ethics committee of the Ege University approved the study protocol. An independent institution (Data Management Service) in Ege University managed all collected trial data.

HD treatments

NHD was performed three times a week (between 10.00 PM and 06.00 AM) for 7–8 h a night; blood flow rate was planned to be between 200 and 250 mL/min. Patients assigned to CHD continued thrice-weekly (3.5–4.5 h) HD; blood flow rate was adjusted to 250–400 mL/min. Dialysate flow rate was kept at 500 mL/min in both groups. Dialysate composition was the same in 95 and 93% of patients in the two study arms (Na 138 mmol/L, K 2.0 mmol/L, Ca 1.5 mmol/L, HCO_3 36 mmol/L, glucose 5.5 mmol/L). Sodium modelling was not applied. The same model of dialyser was used during the study period in both groups (High flux, polysulfone, helixone; FX-60 and FX-80, Fresenius Medical Care, Bad Homburg, Germany). All cases were assessed three times weekly by physicians at the dialysis clinics according to national health authority regulations.

Patient selection

Between September 2006 and December 2006, all prevalent HD patients (n = 1257) treated in 10 HD centres operated by Fresenius Medical Care in south and southeast Turkey were informed about the in-centre NHD programme and were given the opportunity to participate (Figure 1). Based on the inclusion and exclusion criteria, 269 of the 287 patients who had agreed to participate in an NHD programme (NHD group) were planned to be enrolled. For compassionate reasons, NHD was also offered to 18 patients who did not fit the inclusion and exclusion criteria (two patients younger than 18, three patients on twice weekly HD, one patient scheduled for living-related renal transplantation, nine patients with urine output more than 250 mL/day, two patients with malignancy, one patient with liver cirrhosis). These patients were not included in the analysis.

Among the remaining 970 patients, 269 control cases were selected, matched for age-, sex- and diabetic status and HD duration (CHD).

Before the trial was started, 21 patients from the NHD group were withdrawn from the study: 19 did not want to have night dialysis, 1 was transferred to another dialysis centre and 1 was transplanted during baseline analyses. One patient from the CHD group was transferred to another dialysis centre. In order to keep an equal number of patients in each arm, the matched controls for those who were withdrawn were not included in the study. Thus, the trial was conducted in 494 prevalent HD patients (247 patients in each arm).

After completion of baseline analysis, the NHD programme was consecutively started in the 10 centres between December 2006 and March 2007. The patients in the CHD cohort started the study at the same time as the nocturnal patient to whom they were matched.

Eligibility criteria were as follows: age more than 18 years, being on thrice-weekly 12 h/week HD and willingness to participate in the study. Exclusion criteria were as follows: scheduled for living donor renal transplantation, serious life-limiting comorbid situations (namely active malignancy, active infection, end-stage cardiac, pulmonary or hepatic disease), urine output more than 250 mL/day, temporary catheter access and mental incompetence.

Study outcomes

The primary outcome was total mortality. Secondary outcomes were cardiovascular mortality, hospitalization rate and changes in the following parameters: BP, left ventricular geometry and function, post-dialysis body weight, haemoglobin, phosphorus, albumin, total cholesterol, triglyceride, high-density and low-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP), β-2 microglobulin, health-related QOL, depression burden and cognitive function. In addition, the required medications were assessed.

Follow-up visits were performed monthly during the study period. Biochemical parameters were studied monthly, except parathyroid hormone, ferritin, transferrin saturation, lipid parameters and hs-CRP, which were measured every 3 months. All blood samples were analysed at a central laboratory (DIALAB) registered to several external quality control programmes. For post-dialysis body weight, interdialytic weight gain and BP, mean of values was recorded in all dialysis sessions performed in each month. BP measurements were made manually using an Erka sphygmomanometer after a 5-min rest just before the dialysis session. All repeated measures of each patient during the study period were averaged for time-averaged data.

Echocardiography. Echocardiographic examinations (two-dimensional and M-mode, 2.5 MHz transducer, Envisor C, Philips) were performed by the same cardiologist who was unaware of the treatment arms. The examinations were in accordance with the American Society of Echocardiography recommendations [12] and on a midweek intradialytic day at baseline and at the end of the follow-up. Left ventricular mass was calculated by the method of Devereux and Reichek [13]. All measurements were indexed for body surface area (m^2). Echocardiography was carried out in 285 patients at baseline but only the 176 patients who had both baseline and final echocardiographic examinations were included in the analysis. The baseline echocardiography results were similar between patients who had a 12th month follow-up echocardiogram and those who did not have. The reasons why echocardiography was not done in all cases were unwillingness or unavailability at the time of examination; drop out from the study or death. There was no difference in baseline characteristics between patients from the NHD and the CHD groups, in whom two echocardiography were performed.

Evaluation of QOL, cognitive functions and depression status. All were done during the first hour of a dialysis session and blindly evaluated by the same psychologist in a standard manner at baseline and at 12 months. The SF-36 Health Survey, including multi-item scales measuring each of eight generic health concepts (physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality tapping energy levels and fatigue, social functioning, role limitations due to emotional problems and mental health), was self-administrated in all patients [14]. The Mini Mental State Examination, Trail Making Test B and Rey Auditory Verbal Learning Test were used to assess cognitive

functions [15–17]. For assessment of depression and anxiety status, the Hospital Anxiety and Depression Scale was used [18]. Although all study patients were asked to complete the questionnaires, roughly half of the study cases from the groups could not fill out the forms sufficiently at baseline because of unwillingness, low educational level or medical comorbidities such as visual disturbances. Second analyses were requested only from patients who had completed the first evaluation. The baseline psychometric measurement results were similar between patients who had a 12th month follow-up evaluation and those who did not. There was no difference in baseline characteristics between patients from the NHD and the CHD groups, in whom two analyses were completed.

Statistical analysis

Data were expressed as mean ± SD. Baseline and time-averaged values of the two groups were compared using paired or unpaired Student's *t*-tests, as appropriate; chi-square test was used for categorical data. Survival analysis was performed using Kaplan–Meier and Cox proportional hazards analysis. The primary analysis of survival was performed according to the per protocol population (all patients who started the study). The patients were censored at the time of transfer to other dialysis facilities or to other renal replacement modalities. The data of the patients who were transferred to another treatment modality or to other dialysis centres were recorded until premature termination was included in all analyses. The sensitivity of univariate analysis results was checked by adding confounding parameters (e.g. duration of HD) to the models or comparing the analyses performed with the study groups including or excluding patients who did not complete the whole study period. Statistical significance was defined as $P < 0.05$. All analyses were performed using SPSS software version 13.0 (SPSS Inc, Chicago, IL).

Sample size justification. In Charra's data, 5-year patient survival was 87% in patients on 3 × 8-h/week HD (annual mortality <3%) [19]. Annual mortality rate of HD patients in these regions of Turkey is around 15%. Sample size was estimated using the following hypotheses: 12-month follow-up, 12-month survival of the control group would be 85%, bilateral alpha risk equal to 5%, expectation that 12-month survival would be 95% with 8-h dialysis, an 85% power to detect the decrease in annual mortality by 8-h dialysis compared to 4-h dialysis and a 10% dropout rate. The required sample is a total of 410 patients.

Then we considered the acceptance and compliance rates for the NHD programme based on a pilot trial of an NHD programme we had done in a dialysis clinic where more than 200 HD patients were being treated. Based on this experience, we expected that 20% of prevalent HD patients

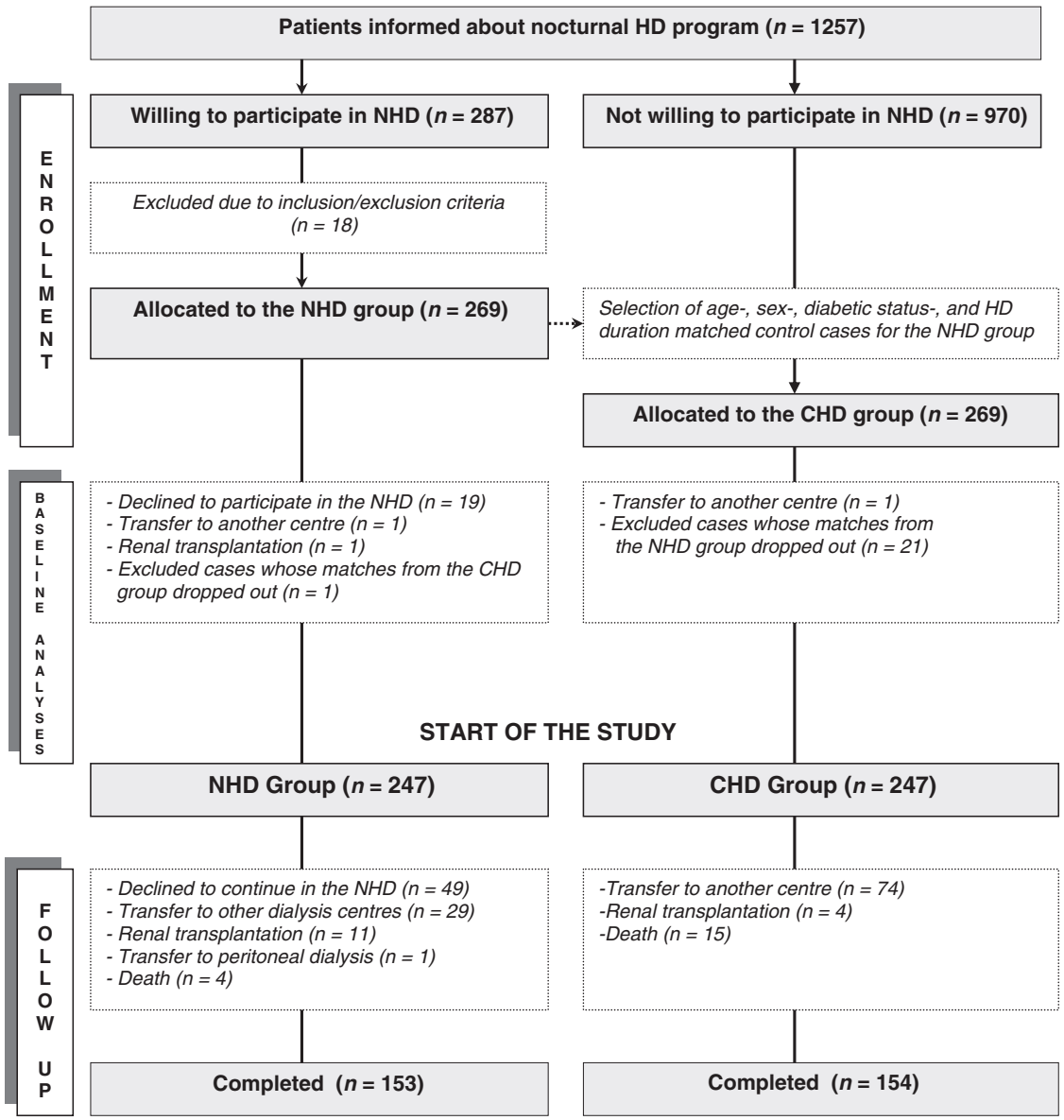

Fig. 1. Flow chart of study participation.

may be willing to undertake such a treatment modality but that as many as 20% of these might withdraw later due to finding it uncomfortable to spend the night and/or to sleep at the centre. Therefore, we calculated a need to enrol 256 patients to the NHD arm and we had to approach 1280 prevalent HD patients in order to enrol 256 patients who would be willing to enter such a programme.

Results

Patients in the two groups were well matched regarding baseline characteristics and concomitant treatment (Table 1).

During the course of the study, 49 patients (19%) in the NHD group quit the nocturnal dialysis programme because they found centre dialysis at night uncomfortable, 29 patients were transferred to other dialysis centres, 11 were transplanted and 1 patient was switched to peritoneal dialysis. In the CHD group, 74 patients were transferred to other dialysis centres and 4 were transplanted. There was no difference in demographical, clinical and laboratory parameters between the patients who remained in the study (after exclusion of cases who were transferred to another treatment modality or to other dialysis centres) from the

Table 1. Baseline characteristics[a]

	Nocturnal HD (n = 247)	Conventional HD (n = 247)
Age (years)	45.2 ± 13.9	45.8 ± 12.9
Female (%)	31.9	31.9
Diabetes (%)	21.0	21.0
Duration of HD (months)	60.6 ± 44.9	59.5 ± 44.4
Residual urine output (mL/day)	56.5 ± 125.6	63.7 ± 129.7
Cardiovascular disease in history (%)	14.3	13.9
Arteriovenous fistula (%)	90.6	91.9
Causes of end-stage renal failure (%)		
Diabetic nephropathy	19.8	19.8
Glomerulonephritis	18.2	16.2
Hypertension	28.3	30.8
Other	33.6	33.2
Former smoker (%)	16.6	14.5
Current smoker (%)	19.2	23.9
Post-dialysis body weight (kg)	65.4 ± 14.2	64.9 ± 14.6
Body mass index (kg/m^2)	23.1 ± 4.6	23.6 ± 4.8
Interdialytic weight gain (kg/day)	1.23 ± 0.51	1.26 ± 0.56
Systolic blood pressure (mm Hg)	125.0 ± 18.1	124.9 ± 19.2
Diastolic blood pressure (mm Hg)	77.4 ± 10.2	77.4 ± 9.3
Pre-dialysis urea (mg/dL)	131.0 ± 31.3	133.0 ± 32.5
Pre-dialysis creatinine (mg/dL)	8.96 ± 2.20	8.96 ± 2.25
Potassium (mEq/L)	5.04 ± 0.69	5.01 ± 0.69
Calcium (mg/dL)	8.78 ± 0.84	8.67 ± 0.74
Phosphate (mg/dL)	4.63 ± 1.32	4.82 ± 1.26
Calcium–phosphate product (mg^2/dL^2)	40.5 ± 12.4	41.7 ± 11.5
Parathormone (pg/mL)	296 ± 291	314 ± 324
Urea reduction rate (%)	74.7 ± 7.2	74.2 ± 6.5
Equilibrated Kt/V	1.25 ± 0.29	1.21 ± 0.24
Albumin (g/dL)	3.94 ± 0.28	3.94 ± 0.32
Total cholesterol (mg/dL)	169 ± 42	169 ± 42
Triglyceride (mg/dL)	179 ± 110	181 ± 106
HDL cholesterol (mg/dL)	45.9 ± 10.4	44.3 ± 10.6
LDL cholesterol (mg/dL)	90.2 ± 33.9	89.5 ± 32.2
Haemoglobin (g/dL)	11.28 ± 1.60	11.25 ± 1.84
Ferritin (ng/mL)	918 ± 786	936 ± 811
Transferrin saturation (%)	30.6 ± 15.9	32.7 ± 17.7
Bicarbonate (mEq/L)	22.4 ± 2.3	22.3 ± 2.4
hs-CRP (mg/dL)	1.79 ± 2.71	1.64 ± 2.44
Erythropoietin use (%)	55.5	51.8
Subcutaneous erythropoietin dose (U/week)	3026 ± 3484	2620 ± 3013
Intravenous iron use (%)	49.7	44.9
Intravenous iron dose (mg/week)	37 ± 67	34 ± 65
Phosphate binders use (%)	83.0	84.1
Phosphate binder dose (elementary Ca, mg/day)	697 ± 565	746 ± 554
Vitamin D use (%)	29.2	24.1
Intravenous vitamin D dose (mcg/week)	0.90 ± 1.71	0.72 ± 1.50

[a]$P > 0.05$ for all comparisons between the NHD group and the CHD group (mean ± SD); to convert values for blood urea to blood urea nitrogen as millimoles per litre, multiply by 0.1668; to convert values for creatinine to micromoles per litre, multiply by 88.4; to convert values for total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol to millimoles per litre, multiply by 0.02586; to convert values for triglyceride to millimoles per litre, multiply by 0.01129; to convert haemoglobin levels to millimoles per litre, multiply by 0.5206; to convert values for calcium to millimoles per litre, multiply by 0.250; to convert values for phosphate to millimoles per litre, multiply by 0.3229.

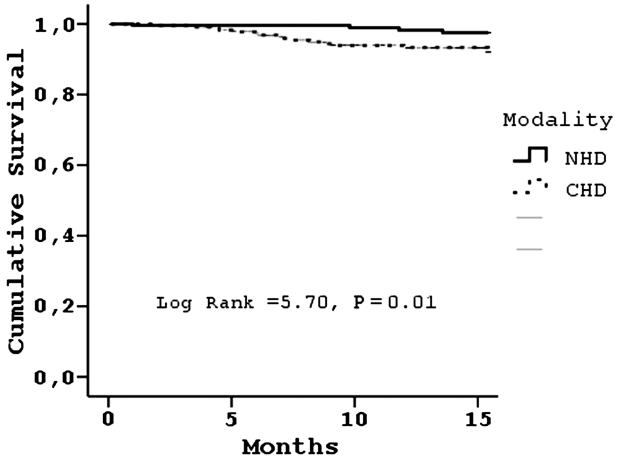

Fig. 2. Kaplan–Meier survival curves of 1-year overall mortality.

NHD group (n = 157) and from the CHD group (n = 169) (data not shown).

During the study, the duration of the HD sessions was 455 ± 20 min in the NHD and 236 ± 7 min in the CHD group (P < 0.001). Mean blood flow rate was 240 ± 35 mL/min in the NHD and 292 ± 32 mL/min in the CHD patients (P < 0.001). As expected, urea reduction rate and equilibrated Kt/V were significantly higher in the NHD patients (83.1 ± 5.8% vs 73.6 ± 6.9%, P < 0.001; 1.87 ± 0.36 vs 1.38 ± 0.24, P < 0.001).

Primary outcome

Mean follow-up was similar in the two groups: 10.9 ± 5.0 months in the NHD group (range 0.1–15.4 months) and 11.5 ± 4.5 months in the CHD group (range 0.2–15.4 months) (P = 0.15). Overall mortality rate was lower in the NHD than in the CHD arm: 1.77 (n = 4) vs 6.23 (n = 15) per 100 patient-years, respectively (P = 0.01). One-year survival rate was significantly better in the NHD group compared to the CHD group (98.4% versus 93.9%, P = 0.01) (Figure 2). The hazard ratio (HR) was 0.28 [95% confidence interval (95% CI) 0.09–0.85] for mortality in unadjusted Cox regression at per protocol analysis (P = 0.02). To be treated with NHD was associated with 68% risk reduction for mortality in multivariate analysis adjusted with age, gender, time on HD and presence of diabetes (95% CI 0.10–0.98, P = 0.04). Additional analysis using the study group excluding patients who did not complete the whole study period yielded results very similar to the primary analysis (HR = 0.28, 95% CI 0.08–0.81, P = 0.01).

The baseline characteristics of patients who dropped out of the study were not different than those of the patients who remained in the study except for time on HD (52 ± 42 months and 62 ± 45 months, respectively, P = 0.01). In Cox regression analysis adjusted with duration of HD, HR for mortality was 0.30 (95% CI 0.10–0.92) in the NHD group (P = 0.03).

Secondary outcomes

Cardiovascular mortality. One NHD and six CHD patients died of cardiovascular causes (P = 0.057). One NHD (pneumonia) and four CHD patients (two pneumonia, one vascular catheter infection, one septicaemia due to diabetic foot infection) died from infections (P = 0.17).

BP control and changes in echocardiographic parameters. At baseline, BP control was acceptable in both treatment arms (Table 1). Despite no change in BP levels in either group (systolic BP/diastolic BP 124 ± 15/77 ± 7 and 125 ± 17/77 ± 7 mm Hg in the NHD and CHD groups, respectively), the need for antihypertensive medications declined from 22 to 8% in NHD patients (P = 0.02), while it did not change in the CHD arm.

Baseline characteristics of the patients from the NHD and the CHD groups regarding echocardiographic measurements were similar. At the end of the follow-up, left atrium and left ventricle end-diastolic diameters decreased and ejection fraction improved in the NHD group, while no change was detected in the CHD group (Table 2). Left ventricular mass index significantly regressed in the NHD group compared to the CHD group.

Nutritional and inflammatory status. There was no significant difference in time-averaged post-dialysis body

Table 2. Changes in echocardiographic parameters

	Nocturnal HD (n = 91)	Conventional HD (n = 85)	Group differences (P-value)
Left atrium diameter (cm/m^2)			
Baseline	2.35 ± 0.40	2.33 ± 0.34	0.67
Final	2.17 ± 0.34[a]	2.28 ± 0.33	0.03
Left ventricle end-diastolic diameter (cm/m^2)			
Baseline	2.57 ± 0.44	2.60 ± 0.47	0.62
Final	2.40 ± 0.45[a]	2.61 ± 0.40	0.004
Ejection fraction (%)			
Baseline	63 ± 10	63 ± 10	0.96
Final	66 ± 11[b]	63 ± 12	0.34
Left ventricular mass index (g/m^2)			
Baseline	140 ± 44	142 ± 52	0.89
Final	116 ± 34[a]	139 ± 45	<0.001

In the NHD group, baseline versus final analyses (mean ± SD).
[a]P < 0.001.
[b]P < 0.05.

Table 3. Time-averaged data of nutritional status, mineral metabolism and anaemia control

	Nocturnal HD (n = 227)[a]	Conventional HD (n = 242)[a]	P-value
Nutritional status			
Post-dialysis body weight (kg)	66.6 ± 14.4	65.2 ± 14.3	0.32
Albumin (g/dL)	4.02 ± 0.24	3.94 ± 0.29	0.001
Total cholesterol (mg/dL)	174 ± 41	165 ± 42	0.03
Triglyceride (mg/dL)	209 ± 136	184 ± 117	0.04
HDL cholesterol (mg/dL)	46 ± 11	43 ± 10	0.07
LDL cholesterol (mg/dL)	87 ± 29	85 ± 30	0.70
hs-CRP (mg/dL)	1.40 ± 1.37	1.67 ± 1.71	0.06
Bicarbonate (mEq/L)	23.8 ± 1.7	23.1 ± 1.8	<0.001
Mineral metabolism			
Phosphate (mg/dL)	3.87 ± 1.20	4.96 ± 1.14	<0.001
Calcium–phosphate product (mg^2/dL^2)	34.9 ± 11.3	43.9 ± 11.0	<0.001
Calcium (mg/dL)	9.00 ± 0.66	8.83 ± 0.79	0.001
Parathormone (pg/mL)	375 ± 344	381 ± 288	0.86
Phosphate binder use (%, at 12th month)	22.4	82.9	<0.001
Phosphate binder dose (elementary Ca, mg/d)	276 ± 385	689 ± 537	<0.001
Vitamin D use (%, at 12th month)	33.7	32.2	0.74
Intravenous vitamin D dose (mcg/week)	0.84 ± 1.06	0.84 ± 1.24	0.97
Anaemia control			
Haemoglobin (g/dL)	11.8 ± 1.4	11.4 ± 1.6	0.02
Ferritin (ng/mL)	783 ± 617	893 ± 714	0.08
Transferrin saturation (%)	27.2 ± 14.4	31.7 ± 16.4	0.004
Erythropoietin use (%, at 12th month)	24.7	53.7	<0.001
Intravenous iron use (%, at 12th month)	63.1	57.4	0.35
Subcutaneous erythropoietin dose (U/week)	1697 ± 2102	2819 ± 2397	<0.001
Intravenous iron dose (mg/week)	26 ± 33	20 ± 21	0.51

[a]All results are time-averaged data from 227 NHD and 242 CHD patients who were in the study at the end of the first month (mean ± SD) except percentage of patients using phosphate binder, intravenous vitamin D, erythropoietin and intravenous iron at the 12th month (n = 155 in the NHD arm and n = 156 in the CHD arm). To convert values for total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol to millimoles per litre, multiply by 0.02586; to convert values for triglyceride to millimoles per litre, multiply by 0.01129; to convert haemoglobin levels to millimoles per litre, multiply by 0.5206; to convert values for calcium to millimoles per litre, multiply by 0.250; to convert values for phosphate to millimoles per litre, multiply by 0.3229.

weight between the groups of patients who were in the study at the end of the first month (Table 3). However, in the patients who completed 1 year of follow-up, body weight increased (from 65.0 ± 14.5 to 66.8 ± 14.9 kg, P < 0.001) in the NHD group (n = 153) and remained stable (from 64.1 ± 13.8 to 64.5 ± 13.8, P = 0.14) in the CHD arm (n = 155). Time-averaged interdialytic weight gain was higher in the NHD group than the CHD group (1.41 ± 0.48 and 1.24 ± 0.42 kg/day, respectively, P < 0.001). In addition, time-averaged levels of serum albumin, triglyceride and cholesterol were significantly higher in the NHD group in comparison with the CHD group, reflecting better nutritional status.

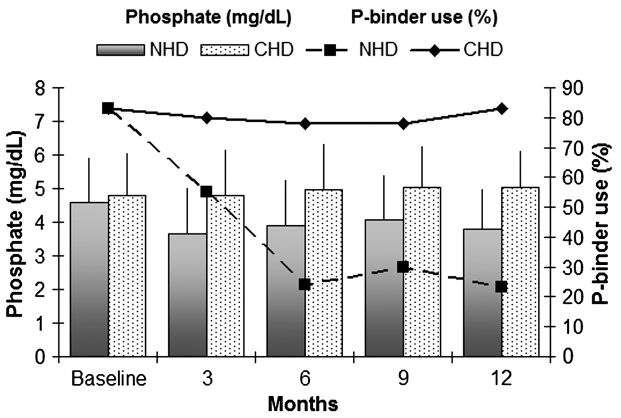

Fig. 3. Mean serum phosphate level and use of Ca-based phosphate binders during the study period. During the follow-up, there were significant differences in the mean serum phosphate level and phosphate binder usage between the two groups (*P < 0.001 between the groups at 3, 6, 9 and 12 months).

During the follow-up, NHD patients showed higher serum bicarbonate levels compared to CHD patients. Mean hs-CRP, a surrogate marker of inflammation, tended to be lower in NHD patients than in CHD patients (P = 0.06). When patients with a baseline CRP level above 10 mg/dL who may have acute inflammatory condition are excluded (three patients from NHD and two patients from CHD groups), time-averaged mean CRP levels were lower in the NHD arm than that in the CHD arm (1.37 ± 1.30 versus 1.67 ± 1.71 mg/dL, P = 0.03).

Mineral metabolism. Serum phosphate levels significantly declined along with a decreased need for phosphate binders from 83.0 to 22.4% in NHD patients, whereas no change was noticed in the CHD group (Figure 3). Moreover, the mean amount of phosphate binders required was significantly lower in the NHD arm (Table 3). Mean serum phosphate and calcium–phosphate product during follow-up were lower and calcium levels were higher in the NHD arm than in the CHD arm; parathormone levels and vitamin D dosage were similar in both groups.

Anaemia control. Although haemoglobin levels increased in both groups during the follow-up (from 11.28 ± 1.60

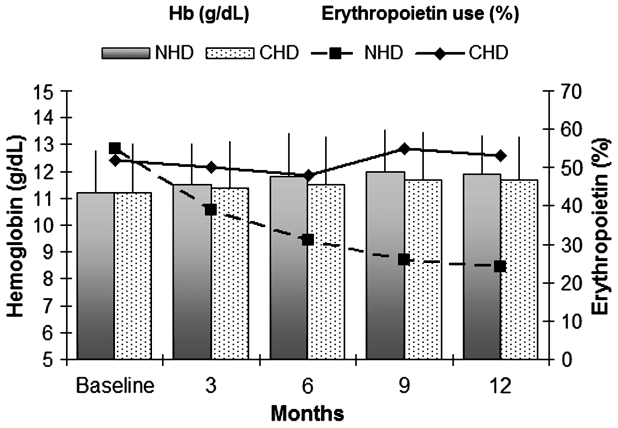

Fig. 4. Mean haemoglobin levels and erythropoietin use during the study period. Mean haemoglobin levels were not different between the groups except at the 9th month (higher haemoglobin level in the NHD group, P = 0.03) together with a decrease in erythropoietin use in the NHD group compared to the CHD group (P < 0.001 at 6, 9 and 12th months).

to 11.96 ± 1.48 g/dL in NHD patients, P < 0.001; from 11.25 ± 1.84 to 11.73 ± 1.64 g/dL in CHD patients, P = 0.007) (Figure 4), time-averaged mean haemoglobin level was significantly higher in the NHD as compared to the CHD group (Table 3). Moreover, the percentage of patients on erythropoietin treatment decreased from 55.5 to 24.7% in the NHD group (P < 0.001), while the dose of erythropoietin also decreased from 3026 ± 3484 to 1697 ± 2102 U/week (P < 0.001). In the CHD arm, both the frequency of use and the dose of erythropoietin remained stable. Mean transferrin saturation was lower in the NHD arm during the study period.

β-2 microglobulin levels. Baseline β-2 microglobulin levels were not different between the groups (39.8 ± 19.7 mg/L in NHD, 36.9 ± 15.0 mg/L in CHD, P = 0.29). However, β-2 microglobulin level increased by 13% in the CHD group (delta β-2 microglobulin 4.86 ± 10 mg/L), while it remained unchanged (delta 0.41 ± 14 mg/L) in the patients on NHD (P = 0.003).

Psychometric measurements. At baseline, there was no difference between the groups in parameters of cognitive functions, QOL, depression and anxiety. Memory functions assessed by Rey Auditory Verbal Learning Test improved in the NHD group (n = 63), reflected by increases in immediate and delayed recall scores (from 4.8 ± 2.9 to 5.5 ± 2.3, P = 0.004 and from 6.7 ± 2.5 to 7.5 ± 2.7, P = 0.02, respectively); they remained stable in the CHD group (n = 45). The parameters of the other two cognitive function tests showed no significant change in either group. Though all dimensions of health-related QOL were unchanged in the NHD arm (n = 86), three of them significantly deteriorated in the CHD arm (n = 61) (bodily pain from 64.9 ± 29.6 to 57.1 ± 28.8, P = 0.03; mental health from 69.2 ± 23.9 to 65.1 ± 23.1, P = 0.04; vitality from 68.7 ± 24.3 to 64.4 ± 25.2, P = 0.01). Neither depression nor anxiety scores were significantly changed with either treatment.

Adverse events. The frequency of intradialytic hypotensive episodes defined as BP drop requiring saline infusion markedly decreased in the NHD patients (from 60.4 at the baseline to 21.2 per 1000 HD sessions at the 12th month, P < 0.001), while it increased slightly in the CHD arm (from 67.0 to 84.3 per 1000 HD sessions, P = 0.15).

During follow-up, the hospitalization rate was lower in the NHD group in comparison with the CHD group (5.43 vs 18.78 days per 100 patient-months, P = 0.002).

Despite higher heparin dosage per HD session in the NHD arm (9141 ± 3457 vs 4806 ± 1766 U, P < 0.001), no significant differences in minor or major episodes of haemorrhage were observed between the groups.

Discussion

To our knowledge, this is the first prospective study to compare the effects of 8- and 4-h dialysis sessions on a wide spectrum of parameters in prevalent HD patients. Although most of the findings presented here were well known in the early years of chronic HD, a systematic comparison with gradually accepted shorter dialysis times has not yet been performed.

During the early years of HD, treatment sessions were as long as 20 h once or twice a week in the centre depending on residual function and symptoms [20]. With the introduction of thrice-weekly home HD in 1964 [21] and Shaldon's report on overnight home HD [22], thrice-weekly overnight HD for 6–8 h became widely used with good results (excellent BP control, rare intradialytic BP drops, satisfactory nutrition, sufficient red blood cell production, no neuropathy, nearly full rehabilitation). In 1972, ~40% of US dialysis patients were on home dialysis [23]. After the duration of dialysis sessions was shortened in the 1980s, patients and nephrologists were faced with several problems, including frequent intradialytic symptoms, post-dialysis fatigue, decreased QOL and shortened life expectancy.

Recent Dialysis Outcomes and Practice Patterns data indicated that longer treatment time is associated with lower mortality [24]. Indeed, the best survival data in the literature were reported from Tassin, France, where 8-h thrice-weekly HD had been used for more than 20 years [19].

Our results show that longer HD sessions are associated with better overall survival and also with improvement in several important outcomes. These data support previously published uncontrolled, observational or retrospective studies that have shown favourable effects of prolonged nocturnal thrice-weekly HD [5,25,26]. It should be noted that the very low number of deaths precludes assessment of the exact magnitude of this beneficial effect. However, the decreased mortality rate was also supported by the improvement in several surrogate markers for mortality such as serum albumin, serum phosphate, β-2 microglobulin and left ventricular mass index.

The quite low mortality rate seen also in the control group is possibly due to the relatively healthy study population reflected by younger age (mean 45 years in the study population versus 56 years in the whole population treated in these dialysis centres), the lower frequency of diabetes (21% versus 33%) and of a history of cardiovascular disease (14% versus 24%). Indeed, the mortality rate of the study control group is compatible with the mortality rate

in the population with a similar risk profile in the Fresenius Medical Care Turkey Database (7.11 per 100 patient-years). The reason for the relatively healthy study population is the unwillingness of many older and diabetic patients to enter a nightly dialysis programme. The same situation has been observed in a recent study from the USA [27].

Although BP was similar and relatively well controlled in both groups, the need for antihypertensive medication was significantly reduced in the NHD patients. The regression of left atrial and left ventricular diameters suggests a decline in extracellular fluid volume. In fact, reduction of extracellular fluid volume was documented in a subgroup of our study population by bioimpedance analysis in the NHD group (Demirci C, *et al.* NDT Plus 2008; 1 Suppl 2: ii179). Another major finding in the current study is the significant regression of left ventricular mass in the NHD patients. Additionally, we detected a small but significant increase in ejection fraction. Regression of left ventricular mass has been reported in six times a week NHD at home [6,28] but not in thrice-weekly prolonged centre dialysis. We also noted fewer hypotensive episodes with NHD, similar to the experience reported with home NHD [29]. Interdialytic weight gain was greater in the NHD group, reflecting more intake of food without reduction of the salt content, due to increased appetite. These beneficial effects might have been even more pronounced if better salt restriction had been achieved.

In accordance with previous reports [8,19], extended HD treatment decreased serum phosphate level, an independent predictor of mortality, along with a reduced need for phosphate binders. Hyperphosphataemia has been associated with vascular calcification and arterial stiffness [30]. Recently, reduced progression of coronary artery calcification has been shown in patients switched from CHD to nocturnal home HD [31]. In the subgroups of our study population, we could document a lower progression rate of coronary artery calcification (Duman S, *et al.* JASN 2008; 19: 70A) and also improvement of arterial stiffness (Demirci MS, *et al.* JASN 2008; 19: 71A) with prolonged HD sessions compared to CHD.

We found increases of dry weight, serum albumin and lipid levels in NHD patients. This suggests improved nutritional status. Indeed, the increases in dry lean mass (3.2%) and body fat mass (6.7%) were detected by bioimpedance analysis in a subgroup of our NHD patients (Demirci C, *et al.* NDT Plus 2008; 1 Suppl 2: ii179). Extended HD treatment also improved haemoglobin levels with less need for erythropoietin, as also reported by others [32]. The decrease in transferrin saturation may be explained by more effective erythropoiesis in prolonged NHD patients because of less bone marrow suppression. Compared to the data in the literature, the already lower erythropoietin requirement in the whole study population may be due to the relatively healthier patient group, reasonable volume control reflected by lower need of antihypertensive medication and more liberal iron treatment.

In the present study, extended HD was also associated with some other important benefits. β-2 microglobulin level, an independent predictor of overall mortality [33], increased in the CHD arm, but not with NHD. It has been shown previously that NHD treatment six times a week increases the clearance of β-2 microglobulin, leading to a decrease in β-2 microglobulin levels in the long term [34]. In patients with baseline CRP levels below 10 mg/dL, we found lower levels of CRP in the NHD group. In a small-sized cross-sectional study, lower interleukin-6 levels have been found in the NHD patients compared to the CHD patients [35]. Less inflammation may have contributed to the improvement in anaemia, nutritional status and survival. Better control of acidosis in the NHD group, demonstrated in our study, may also have a role in improved nutrition.

Better general cognitive functions have been reported with six times a week nocturnal home HD [36], but there are no data in the literature about the effects of in-centre prolonged HD on cognitive function, QOL, depression and anxiety. We found a significant improvement of memory as assessed by RAVLT in the NHD group, although a relatively small group has completed psychometric measurements. While we observed no change in QOL scales in the NHD arm, significant deteriorations in some scales were observed in the CHD group. Improvement of QOL measures, varying from minimal to marked enhancement, has also been reported after conversion to nocturnal home HD [10,37]. We detected no change in the scores of depression and anxiety in either group.

This study demonstrates many advantages of thrice-weekly in-centre prolonged HD. The major limitation is that this is not a randomized trial. Although NHD and CHD arms were quite well matched, we cannot exclude some undetected differences between the groups (i.e. factors related to being willingness or unwillingness for NHD). Certainly, it would be more ideal to conduct a randomized study. However, in a pilot trial of NHD that we had performed prior to the current study in one centre, we felt that it is hardly practicable to randomize a patient, who was willing to accept prolonged NHD because of its previously documented benefits, to the control arm. The second limitation is the fact that the high dropout rates occurring in both groups resulted from either transfer to conventional daytime dialysis or to other dialysis centres may potentially lead to a selection bias. However, all baseline characteristics were similar in patients from both arms who remained in the study. Additionally, sensitivity analysis including censored patients who dropped out showed similar results to those of primary analysis. The reason why so many patients were transferred to other centres was the fact that the number of dialysis centres was insufficient in these relatively less developed areas of the country and when a new dialysis clinic was opened near to their home they preferred to migrate to it. The number of the patients who were transferred to other dialysis centres was lower in the NHD group compared to the CHD group (29 versus 74, respectively, $P < 0.001$) because patients in the NHD group did not want to lose the opportunity of longer dialysis which was not available in the new centres. Another limitation is that these results come from a relatively healthy population (younger, fewer diabetics and fewer patients with a history of cardiovascular disease) and may not be applicable to all HD populations. However, survival advantage with longer dialysis sessions has been shown even in patients with cardiovascular disease aged up to

80 years and those with diabetes up to 70 years in a retrospective, controlled study [26].

In conclusion, thrice-weekly in-centre prolonged NHD is associated with better outcomes in comparison to CHD. It provides improvements in mineral disturbances, anaemia, nutrition status, cardiac hypertrophy and dilatation and cognitive functions along with lesser need for medications and reduced hospitalizations. Survival advantage with in-centre prolonged NHD suggested in this study needs to be confirmed by larger prospective studies.

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Conflict of interest statement. E.O. and H.Z.T. are members of the scientific advisory board of Fresenius Medical Care, Turkey. S.M.A. is an employee in Fresenius Medical Care, Turkey. S.D., G.A., H.T., M.O., M.K., M.T., M.Y. and O.O.S. declare that they have no conflicts of interest.

(See related article by Piccoli et al. The never-ending search for the perfect dialysis. Should we move from the best treatment to the best system? *Nephrol Dial Transplant* 2011; 26: 1128–1131)

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Removal of uraemic retention solutes in standard bicarbonate haemodialysis and long-hour slow-flow bicarbonate haemodialysis

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Abstract

Background. Several studies already stressed the importance of haemodialysis (HD) time in the removal of uraemic toxins. In those studies, however, also the amount of dialysate and/or processed blood was altered. The present study aimed to investigate the isolated effect of the factor time *t* (by processing the same total blood and dialysate volume in two different time schedules) on the removal and kinetic behaviour of some small, middle and protein-bound molecules.

Methods. The present study had a crossover design: 11 stable anuric HD patients underwent two bicarbonate HD sessions (~4 and ~8 h) in a random sequence, at least 1 week apart. The GENIUS® single-pass batch dialysis system and the high-flux FX80 dialysers (Fresenius Medical Care, Bad Homburg, Germany) were used. The volume of blood and dialysate processed, volume of ultrafiltration, and dialysate composition were prescribed to be the same. For each patient, blood was sampled from the arterial line at 0, 60, 120, 180 and 240 min (all sessions), and at 360 and 480 min (8-h sessions). Dialysate was sampled at the end of HD from the dialysate tank. The following solutes were investigated: (i) small molecules: urea, creatinine, phosphorus and uric acid; (ii) middle molecule: β_2M; and (iii) protein-bound molecules: homocysteine, hippuric acid, indole-3-acetic acid and indoxyl sulphate. Total solute removals (solute concentration in the spent dialysate of each analyte × 90 L − the volume of dialysate) (TSR), clearances (TSR of a solute/area under the plasma water concentration time curve of the solute) (*K*), total cleared volumes (*K* × dialysis time) (TCV), and dialyser extraction ratios (*K*/blood flow rate) (ER) were determined. The percent differences of TSR, *K*, TCV and ER between 4- and 8-h dialyses were calculated. Single-pool *Kt*/*V*urea, and post-dialysis percent rebounds of urea, creatinine and β_2M were computed.

Results. TSR, TCV and ER were statistically significantly larger during prolonged HD for all small and middle molecules (at least, $P < 0.01$). Specifically, the percent increases of TSR (8 h vs 4 h) were: for urea 22.6% ($P < 0.003$), for creatinine 24.8% ($P < 0.002$), for phosphorus 26.6% ($P < 0.001$), and for β_2M 39.2% ($P < 0.005$). No statistically significant difference was observed for protein-bound solutes in any of the parameters being studied. Single-pool *Kt*/*V*urea was 1.41 ± 0.19 for the 4-h dialysis sessions and 1.80 ± 0.29 for the 8-h ones. The difference was statistically significant ($P < 0.0001$). Post-dialysis percent rebounds of urea, creatinine and β_2M were statistically significantly greater in the 4-h dialysis sessions (at least, $P < 0.0002$).

Conclusions. The present controlled study using a crossover design indicates that small and middle molecules are removed more adequately from the deeper compartments when performing a prolonged HD, even if blood and dialysate volumes are kept constant. Hence, factor time *t* is very important for these retention solutes. The kinetic be-