Clinical Practice: Original Paper

nephron Clinical Practice

Nephron 2016;133:98–110
DOI: 10.1159/000446970

Received: April 1, 2016
Accepted: May 19, 2016
Published online: June 7, 2016

Eight-Year Experience with Nocturnal, Every-Other-Day, Online Haemodiafiltration

Francisco Maduell[a] Raquel Ojeda[a] Marta Arias-Guillen[a] Florencia Rossi[a] Néstor Fontseré[a] Manel Vera[a] Nayra Rico[b] Leonardo Nicolás Gonzalez[a] Gastón Piñeiro[a] Mario Jiménez-Hernández[a] Lida Rodas[a] José Luis Bedini[b]

Departments of [a]Nephrology and [b]Biochemistry, Hospital Clínic Barcelona, Barcelona, Spain

Key Words
Dialysis adequacy · Every-other-day · Morbidity · Nocturnal dialysis · Online haemodiafiltration

Abstract
Background: New haemodialysis therapeutic regimens are required to improve patient survival. Longer and more frequent dialysis sessions have produced excellent survival and clinical advantages, while online haemodiafiltration (OL-HDF) provides the most efficient form of dialysis treatment. ***Methods:*** In this single-centre observational study, 57 patients on 4–5-hour thrice-weekly OL-HDF were switched to nocturnal every-other-day OL-HDF. Inclusion criteria consisted of stable patients with good prospects for improved occupational, psychological and social rehabilitation. The aim of this study was to report our 8-year experience with this schedule and to evaluate analytical and clinical outcomes. ***Results:*** Nocturnal, every-other-day OL-HDF was well tolerated and 56% of patients were working. The convective volume increased from 26.7 ± 2 litres at baseline to 46.6 ± 6.5 litres at 24 months ($p < 0.01$). Increasing the dialysis dose significantly decreased bicarbonate, blood-urea-nitrogen and creatinine values. Predialysis phosphate levels fell markedly with complete suspension of phosphate binders from the second year of follow-up. Although haemoglobin was unchanged, there was a 50.4% reduction in darbepoetin dose at 24 months and a significant decrease in the erythropoietin resistance index. Blood pressure significantly decreased in a few months. Antihypertensive medication requirements were decreased by 60% after 3 months and by 73% after 1 year and this difference was maintained thereafter. ***Conclusions:*** Nocturnal, every-other-day OL-HDF could be an excellent therapeutic alternative since it is well tolerated and leads to clinical and social-occupational rehabilitation with satisfactory morbidity and mortality. These encouraging results strengthen us to continue and invite other clinicians to join this initiative.

Introduction

Patients undergoing a conventional dialysis regimen of three 4-hour sessions per week have high mortality and morbidity and their expected remaining lifetime is lower than that of the general population [1]. New therapeutic regimens are required to improve patient survival. Pos-

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Francisco Maduell, MD
Department of Nephrology
Hospital Clínic Barcelona, C/Villarroel, 170
ES–08036 Barcelona (Spain)
E-Mail fmaduell@clinic.ub.es

sible options are an increase in dialysis time and frequency [2] and the development of techniques with a higher depurative capacity.

Multiple publications have evaluated the superiority of longer haemodialysis over conventional therapy in blood pressure control, reduction of left ventricular hypertrophy and reduced serum phosphate levels [3–6].

A thrice-weekly frequency of haemodialysis sessions has been widely accepted and maintained for logistic, pragmatic and economic reasons. However, long-term experiences of higher frequencies have shown good results [7–9]. An every-other-day dialysis schedule is the first step to increase frequency and avoid long weekend periods and has been reported to lower the incidence of ischemic heart disease and to produce stable high depurative efficiency and improvements in anaemia, acid-base and nutritional status [10].

Online haemodiafiltration (OL-HDF) combines diffusion with high convection, providing the highest clearances for small, medium and large molecules. Postdilution high-volume OL-HDF is safe, produces good clinical results and has been shown to decrease overall and cardiovascular mortality [11–14].

To combine long (nocturnal) and more frequent (every-other-day) dialysis with the dialysis modality offering the highest solute and uremic toxin removal (OL-HDF), a 12-month pilot study was started in September 2007 and this study concluded that long-term, nocturnal, incentre, every-other-day, high-volume OL-HDF could be a good therapeutic dialysis schedule that could improve clinical and social-occupational rehabilitation [15]. The aim of this study was to report our 8-year experience with this long, nocturnal, every-other-day OL-HDF schedule and to evaluate analytical and clinical outcomes.

Patients and Methods

In this single-centre observational study, 57 patients (40 men and 17 women, with a mean age of 48.8 ± 12 (range 22–75)), who were stable on haemodialysis over a period of 26.7 ± 45 months and on standard 4–5 h thrice weekly OL-HDF for at least 3 months were switched to nocturnal every-other-day OL-HDF, 7–8 h per session. The underlying renal diseases were chronic glomerulonephritis in 14 patients, diabetic nephropathy in 11, polycystic kidney disease in 6, nephroangiosclerosis in 11, systemic diseases in 2, urologic disease in 3, chronic tubulo-interstitial nephritis in 5, and undiagnosed nephropathy in 5. All patients signed informed consent forms approved by the hospital's Research Committee. Inclusion criteria consisted of stable patients under haemodialysis with good vascular access and good prospects for improved occupational, psychological and social rehabilitation. For this reason, the patients enrolled in this study were younger than those in the general dialysis population. This was an in-centre hospital experience, dialysis sessions were carried out in a general room with capacity for 12 patients and nursing staff were present at all times. No special training was required by our nursing team. As the patients were more stable, the nurse/patient ratio was 1:5 instead of the usual 1:4. The patients received no special education or training. The patients lay on beds, there were no special sound barriers and the machines (including alarms) were the same as those used during the morning or afternoon shifts.

Baseline OL-HDF parameters were bicarbonate buffer, 1.4–1.8 m^2 high-flux helixone filter (FX60 or FX80, Fresenius, Bad Homburg, Germany), blood flow (Qb) 433 ± 30 ml/min (range 350–500 ml/min), dialysate flow (Qd) 679 ± 151 ml/min, infusion flow (Qi) ranging from 80 to 120 ml/min, and a Fresenius 4008 or 5008 dialysis monitor. Reinfusion was always performed in a postdilutional mode. All patients had native arteriovenous fistulae except for 3, who had a prosthetic fistula. The dialyzers were not reused. In all patients, 15-gauge needles were used and standard protocol fixing needles were maintained and the only modification was replacement of the usual sticking plaster by special transparent dressings (3M Tegaderm™ film). Anticoagulation was achieved with nadroparine or tinzaparine in 52 patients and with heparin sodium in the others. Residual renal function (diuresis >200 ml/24 h) was maintained only in 5 patients.

The first 26 patients were included in a previously published cross-over study [15], and during the first year they were assigned to receive the same convective volume (CV) as in baseline period (20–30 litres) for 6 months and a higher CV (35–50 litres) for the next 6 months. Because better removal patterns were achieved with higher CV in this study, subsequently, patients who had completed the 12 months and the new patients that joined received the maximum convective dose.

The following dialysis and urea kinetic parameters were recorded quarterly: Td, Qb, CV, dry body weight, Kt by ionic dialysance, urea reduction ratio (URR), single-pool second-generation Daugirdas Kt/V (spKt/V), equilibrated Kt/V (eKt/V), standard Kt/V (stdKt/V), time-averaged concentration and normalized protein catabolic rate (nPCR).

Every 3 months, pre-dialysis samples were analysed for haemoglobin, haematocrit, leukocytes, platelets, transferrin saturation (TS), ferritin, transferrin, bicarbonate, urea, creatinine, sodium, potassium, magnesium, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides, total protein, albumin, pre-albumin, C-reactive protein, β_2-microglobulin, glycated haemoglobin, calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone (iPTH). Postdialysis samples for urea, potassium, calcium, phosphorus were also analysed. Pretreatment blood samples were drawn immediately after access needle insertion. Posttreatment samples were drawn from the arterial blood line 60 s after the blood flow rate was decreased to 50 ml/min. The last month on conventional, 4–5-hour, thrice weekly OL-HDF, during which treatment conditions were unchanged, was taken as the baseline period. The epoetin resistance index, defined as the weekly epoetin-equivalent dose divided by g/l haemoglobin, was calculated. A ratio of 1:200 was used to convert darbepoetin-alpha to the epoetin-equivalent dose.

Predialysis blood pressure was measured immediately before treatment with an automatic blood pressure monitor. Doses of intravenous iron, erythropoiesis-stimulating agents (ESA), phosphate binders, paricalcitol, cinacalcet and antihypertensive medication were recorded.

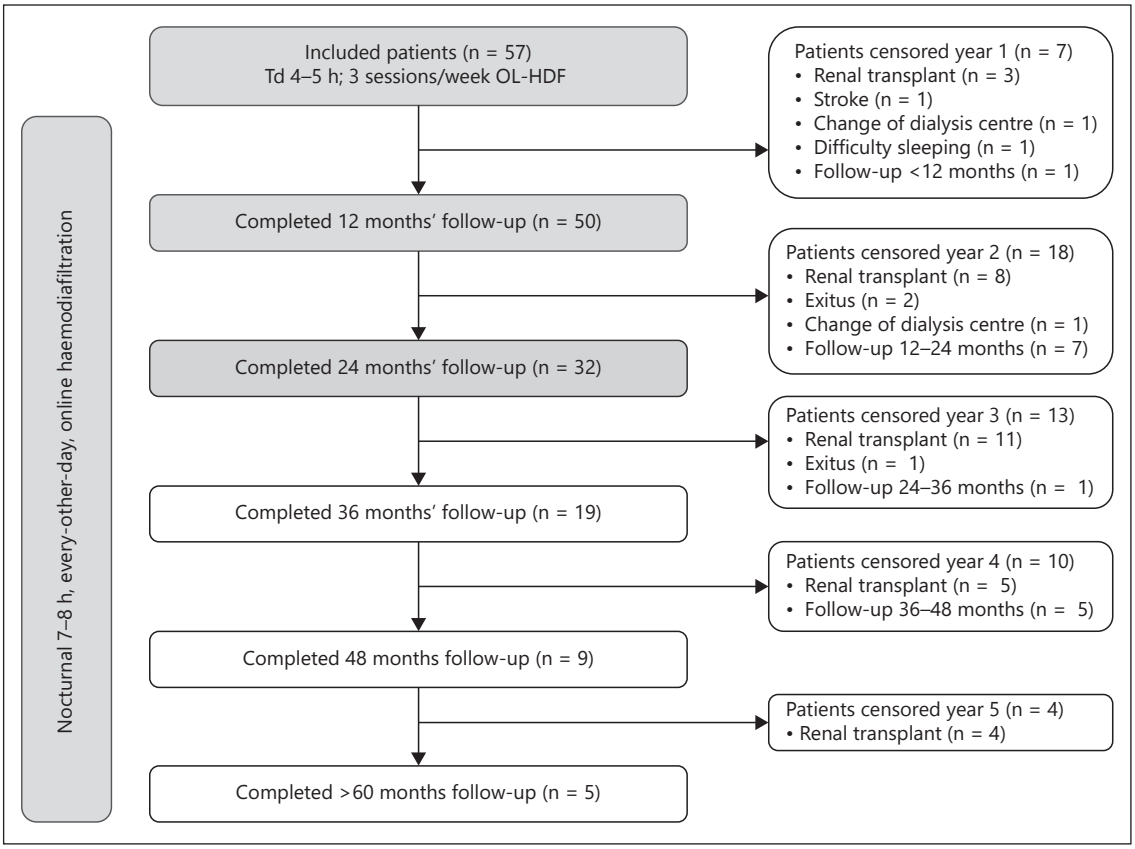


Fig. 1. Flowchart of included patients and follow-up.

To avoid intradialysis hypophosphatemia, the addition of phosphorus supplements during the study was required (Fosfosoda® (Casen fleet laboratories, Utebo, Spain): 45 ml of dodecahydrate phosphate 10.8 g + dehydrate monosodium phosphate 24.4 g) in acid dialysate. Between 10 and 30 ml of phospho-soda (each ml of phospho-soda contains 128.5 mg of phosphorus) were added to 11 litres of acid concentrate (1:35 dilution), which allowed 385 litres of dialysate and a phosphate dialysate concentration from 0.33 to 0.99 mg/dl.

The results are expressed as the arithmetic mean ± SD. Each patient served as his/her own control. The Student t test and analysis of variance test (repetitive data) were used in the analysis of differences in quantitative variables. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the RSigma Babel (Horus Hardware, Madrid) program.

Results

During the >8-year study period (September 2007 to March 2016), 57 patients were switched to nocturnal, every-other-day, OL-HDF and received >25,200 dialysis sessions. The mean follow-up was 29.4 ± 13 months (range 2–102 months). During follow-up, because the included population was young and most were on the transplant waiting list, 38 patients prematurely abandoned this dialysis schedule for the following reasons: 31 received a renal transplant, 2 moved from the centre, 1 had a stroke, 1 had difficulty sleeping, and 3 died (acute myocardial infarction in a diabetic patient, hepatocellular carcinoma in patient with chronic hepatitis C and postoperative cardiac valve replacement). Only 9 patients (16%) completed >4 years' follow-up, 19 patients (33%) completed 3 years, 32 patients (56%) completed 24 months and 50 patients (88%) completed 12 months' follow-up (fig. 1). For this reason, in this article, we decided to report the main data at 12 (n = 50) and 24 (n = 32) months' follow-up.

Thirty-five patients (63%) were working at baseline and continued working throughout the nocturnal treatment with practically no absenteeism. There were 5 secretary-administrators, 3 restaurant workers, 3 lawyers, 3 students, 2 legal and financial advisors, 3 workers at the National Organization for the Blind, 2 priests, 2 business

Table 1. Nocturnal, every-other-day, OL-HDF. Comparison of dialysis parameters and urea kinetics

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Td, min									
12 m (n = 50)	277.2±26	476.4±14[a]	475.2±16[a]	475.2±16[a]	474.0±18[a]				
24 m (n = 32)	274.6±23	478.1±11[a]	476.2±15[a]	476.2±15[a]	476.2±15[a]	476.2±15[a]	476.2±15[a]	476.2±15[a]	476.2±15[a]
Qb, ml/min									
12 m (n = 50)	431±30	429±32	423±29[b]	425±29	425±29				
24 m (n = 32)	432±30	428±30[b]	425±28[b]	427±28[b]	427±28[b]	427±28[b]	427±28[b]	427±28[b]	425.0±31[b]
CV, litres									
12 m (n = 50)	26.4±3.9	40.5±10.8[a]	41.0±10.8[a]	41.4±10.5[a]	41.1±10.4[a]				
24 m (n = 32)	25.6±3.5	38.8±9.7[a]	39.7±10.0[a]	39.6±10.0[a]	39.4±10.0[a]	44.5±4.9[a]	44.9±4.5[a]	45.0±6.7[a]	46.6±6.5[a]
Initial weight, kg									
12 m (n = 50)	71.5±17.8	71.9±17.8	72.1±18.0	72.7±18.2[a]	73.2±18.1[a]				
24 m (n = 32)	72.3±17.2	72.4±17.0	72.7±16.9	73.2±17.1	73.9±17.2	73.8±16.7[b]	73.9±16.9	74.1±17.0[b]	74.2±16.8[b]
Final weight, kg									
12 m (n = 50)	69.0±17.3	68.8±17.3	69.3±17.6	69.7±17.7	70.1±17.5[b]				
24 m (n = 32)	69.7±16.9	69.3±16.5	69.8±16.5	70.2±16.8	70.5±16.6	71.0±16.5	71.0±16.7[c]	71.1±16.5[c]	71.3±16.4[c]
Weight gain, kg									
12 m (n = 50)	2.48±1.0	3.00±1.2[a]	2.77±0.9[a]	3.00±1.2[a]	3.14±1.2[a]				
24 m (n = 32)	2.55±0.9	3.10±1.3[a]	2.85±0.9[a]	3.00±1.1[a]	3.30±1.2[a]	2.80±1.1[a]	2.89±1.2[a]	3.00±1.1[a]	2.93±1.4[a]
Kt, litres									
12 m (n = 50)	70.5±9.3	108.9±10.7[a]	106.4±8.7[a]	105.3±11.7[a]	106.3±10.3[a]				
24 m (n = 32)	70.1±9.5	109.2±11.0[a]	108.0±8.6[a]	105.9±12.1[a]	108.3±10.0[a]	107.8±8.0[a]	109.4±9.8[a]	110.2±12[a]	110.2±12[a]
URR, %									
12 m (n = 50)	81.0±5.6	90.0±3.1[a]	89.6±3.5[a]	89.7±3.9[a]	89.7±3.9[a]				
24 m (n = 32)	80.1±5.7	90.0±2.5[a]	90.1±2.6[a]	90.1±2.5[a]	90.7±2.5[a]	90.2±2.6[a]	90.1±3.0[a]	90.6±2.5[a]	90.3±2.9[a]
spKt/V									
12 m (n = 50)	2.07±0.4	3.84±0.9[a]	3.77±1.1[a]	3.93±1.2[a]	4.07±1.3[a]				
24 m (n = 32)	2.01±0.4	3.86±0.8[a]	3.93±1.1[a]	3.91±1.0[a]	4.28±1.3[a]	3.93±1.0[a]	3.85±0.9[a]	4.05±0.9[a]	3.92±0.9[a]
eKt/V									
12 m (n = 50)	1.76±0.3	3.36±0.8[a]	3.30±0.9[a]	3.44±1.0[a]	3.50±1.2[a]				
24 m (n = 32)	1.71±0.3	3.37±0.7[a]	3.44±0.9[a]	3.42±0.9[a]	3.75±1.0[a]	3.44±0.9[a]	3.37±0.8[a]	3.54±0.8[a]	3.43±0.8[a]
stdKt/V									
12 m (n = 50)	2.56±0.1	3.77±0.1[a]	3.75±0.1[a]	3.77±0.2[a]	3.77±0.2[a]				
24 m (n = 32)	2.53±0.1	3.79±0.1[a]	3.78±0.1[a]	3.78±0.1[a]	3.82±0.1[a]	3.79±0.1[a]	3.78±0.1[a]	3.81±0.1[a]	3.79±0.1[a]
TAC, mg/dl									
12 m (n = 50)	32.5±7.2	25.1±7.2[a]	25.6±6.9[a]	25.3±7.2[a]	24.9±7.2[a]				
24 m (n = 32)	32.9±6.0	24.5±6.0[a]	25.6±7.0[a]	24.6±8.0[a]	24.6±7.0[a]	23.8±5.0[a]	22.3±7.0[b]	22.8±5.0[a]	23.5±6.0[a]

m = Months; TAC = time averaged concentration.
[a] $p < 0.01$, [b] $p < 0.05$ with respect to baseline (analysis of variance repeated measures), [c] $p < 0.05$ with respect to month 3.

owners, and 1 rigger, stretcher-bearer, security guard, monitor school, construction renovation worker, university professor, hairdresser, head of school, metallurgical worker, taxi driver, physician, and dance instructor.

In general, this technique was well tolerated by patients and only 115 (0.4%) incidents occurred during dialysis that required consultation with the on-call physician: fever or infectious process (n = 38), vascular access problems (n = 25), osteoarticular pain (n = 15), dizziness, cramps and/or hypotension (n = 10), hypertension (n = 3), palpitations or atrial fibrillation (n = 3), haematuria (n = 3), haemorrhoids (n = 2), angor (n = 2), dyspnoea (n = 2), clotting lines (n = 2), epigastric pain (n = 2), myalgia (n = 2), diarrhoea (n = 2), abdominal pain (n = 1), chest pain (n = 1), anal fissure (n = 1), and bladder spasms (n = 1).

Dialysis Parameters and Urea Kinetics

The duration of dialysis sessions increased from 274 ± 23 min (range 240–300 min) at baseline to 476 ± 15 min (range 420–480 min) in nocturnal every-other-day OL-HDF (table 1). Mean baseline Qb was 433 ± 30 ml/min,

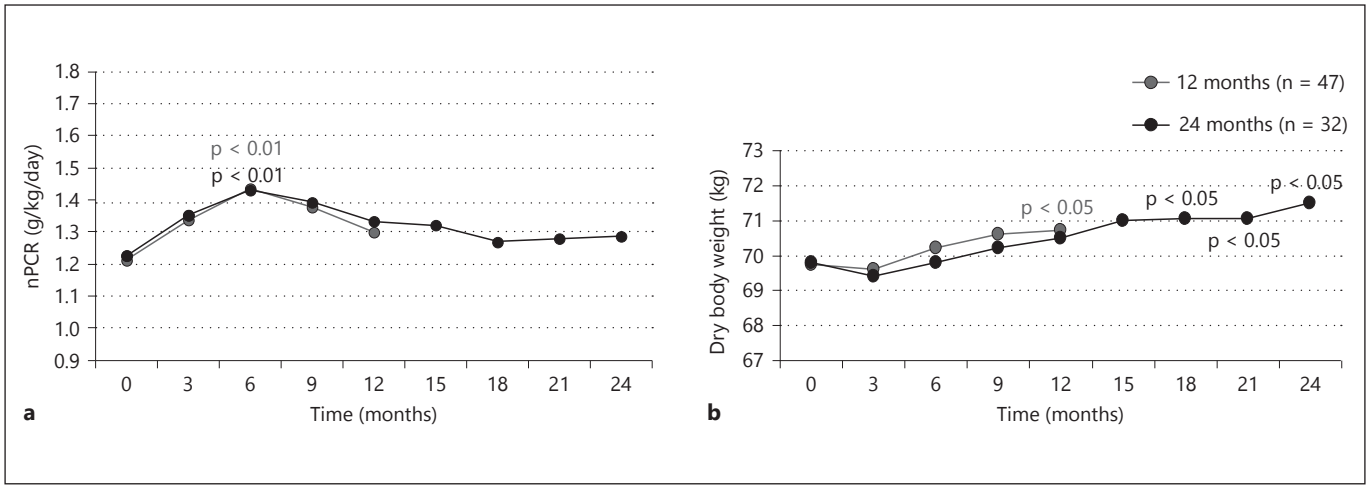


Fig. 2. Protein intake (**a**) and body weight (**b**) outcome when switching from thrice weekly OL-HDF to nocturnal every-other-day OL-HDF. Twelve months outcome (n = 50, grey line) and 24 months outcome (n = 32, black line). Significant p values are showed only where it was significant.

which decreased to 425 ± 31 ml/min at 24 months ($p < 0.05$).

CVs increased from 25.6 ± 3.5 litres at baseline to 39.4 ± 10 litres at 12 months ($p < 0.01$). Because the infusion flow was later maintained at high values, the CV increased to 46.6 ± 6.5 litres at 24 months ($p < 0.01$).

The dialysis dose significantly increased in all urea kinetic parameters evaluated: Kt increased from 70.1 ± 9.5 to 110.2 ± 12 litres at 24 months, accompanied by increases in URR, spKt/V, eKt/V and stdKt/V (table 1).

Residual renal function, measured as residual Kt/V, which at baseline was only maintained in 5 patients (0.374 ± 0.18), was progressively reduced to 0.301 ± 0.23, 0.188 ± 0.22, 0.203 ± 0.24 and 0.101 ± 0.14 at 6, 12, 18 and 24 months' follow-up, respectively.

Nutritional Parameters

Patients reported improved appetite and a tendency to increase protein intake (nPCR) in the first 6 months. This change remained stable (fig. 2a).

Long dialysis treatment allowed an adequate ultrafiltration rate and dry body weight was achieved more easily than with conventional treatment. Dry body weight showed an initial decrease after 3 months, from 69.8 ± 17 kg at baseline to 69.4 ±17 kg at 3 months, and subsequently gradually increased to 71.3 ± 16 kg at 24 months ($p < 0.05$ with respect to month 3; fig. 2b).

Interdialytic weight gain increased from 2.55 ± 0.9 at baseline to 3.30 ± 1.2 kg at 12 months and 2.93 ± 1.4 kg at 24 months ($p < 0.01$).

Haematological Parameters and ESA Dose

There were no changes in haemoglobin (fig. 3a), haematocrit, leukocyte, platelets, and TS (table 2), which were maintained within a normal range.

Ferritin was significantly lower at baseline, although the mean intravenous iron dose showed a gradual but non-significant decrease from 91 ± 37 to 58 ± 52 mg/week at 24 months.

The weekly ESA dose decreased significantly from 7,437 ± 4,103 at baseline to 3,750 ± 4,288 IU/week at 24 months (with $p < 0.01$; fig. 3b). Only 3.5% of patients did not require ESA treatment at baseline and this percentage increased to 29.8 and 31% at 12 and 24 months, respectively.

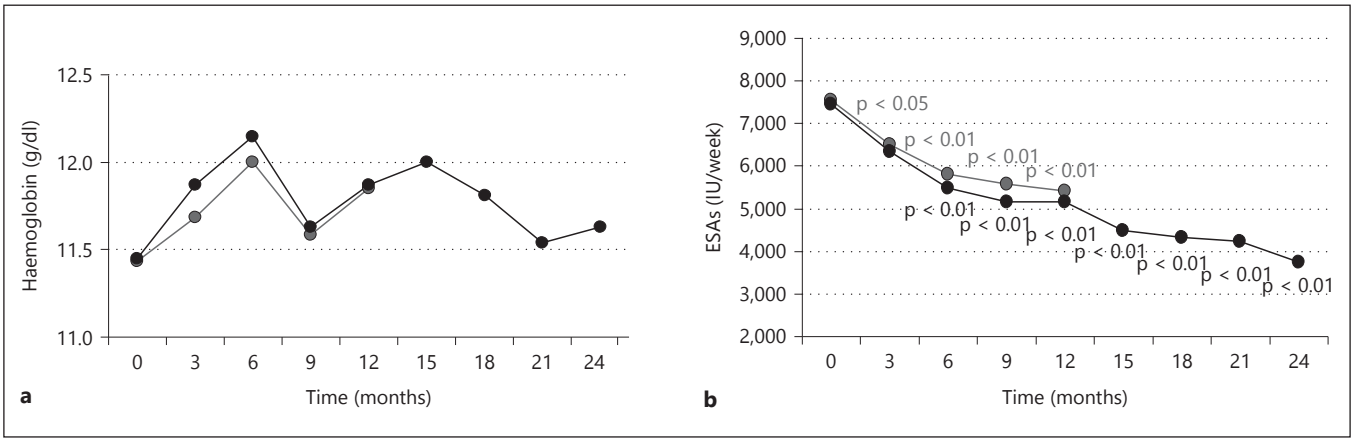
The erythropoietin resistance index significantly decreased over the 24-month period from 10.2 ± 7.4 to 4.8 ± 5.6 IU/week/kg/g of haemoglobin (fig. 3c).

Biochemical Parameters

Quarterly biochemical values are shown in table 3. Bicarbonate levels were significantly higher in all patients compared with baseline values (from 23.6 ± 2.7 to 26.7 ± 2.1 mmol/l at 24 months).

From the third month, blood-urea-nitrogen and creatinine values decreased significantly in nocturnal every-other-day OL-HDF.

There were no changes in sodium, potassium, magnesium, LDL-c, HDL-c, triglycerides, total proteins, albumin, pre-albumin, β_2-microglobulin and glycated haemoglobin levels during the study period (table 3).



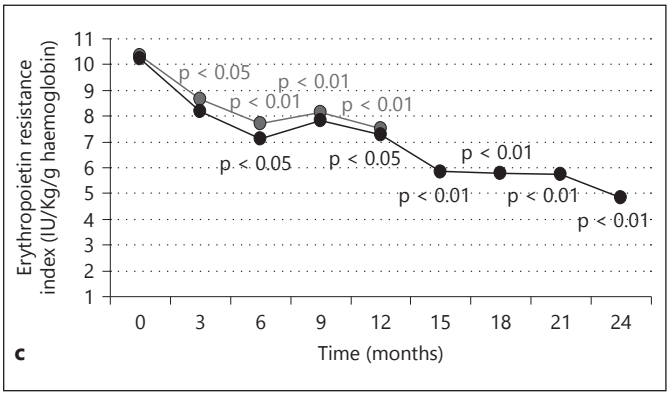


Fig. 3. Changes in anaemia, haemoglobin (**a**), ESAs (**b**) and erythropoietin resistance index (**c**) when switching from thrice weekly OL-HDF to nocturnal every-other-day OL-HDF. Twelve months outcome (n = 50, grey line) and 24 months outcome (n = 32, black line). Significant p values are showed only where it were significant.

Bone Profile

Pre-dialysis phosphorus levels fell from a mean of 5.0 ± 1.3 to 3.39 ± 0.9 mg/dl at 24 months (fig. 4a).

The decrease in serum phosphorus was such that, to avoid intradialysis hypophosphatemia, the addition of phosphorus supplements during the study was required in 66% of the patients at 12 months and in 78% at 24 months (fig. 4c).

The use of phosphate binders were reduced from 3.93 to 0.10 tablets/day at 12 months (only 2 patients) to nil after 24 months (fig. 4b).

No significant changes were observed in calcium, alkaline phosphatase and iPTH, and doses of paricalcitol and cinacalcet were unchanged (table 4).

Blood Pressure Control

Excellent blood pressure control was observed with long nocturnal scheme. Mean systolic, diastolic and mean blood pressure significantly decreased in a few months (fig. 5a). Pre-dialysis systolic blood pressure decreased from 141 ± 27 mm Hg at baseline to 130 ± 21 mm Hg at 3 months, 123 ± 20 at 12 months and the values subsequently remained stable.

Requirements for antihypertensive medication were drastically decreased from 1.0 ± 1.1 tablets/day to 0.43 ± 0.2 tablets/day after 3 months and 0.27 ± 0.2 tablets/day after 1 year and this difference was subsequently maintained (fig. 5b).

Hospitalizations and Vascular Access Interventions

During follow-up, there were 62 hospital admissions with a total of 249 days of hospital stay, representing 0.44 hospitalizations/patient/year and 1.78 days hospitalization/patient/year. Twenty-four patients (42%) were admitted at least once and the main causes of admission were infectious (30.6%), vascular access dysfunction (24.2%), surgery (14.5%), cardiovascular (12.9%), gastrointestinal (6.5%), orthopaedic (6.5%) and other causes (4.8%).

Several vascular access-related interventions occurred during follow-up. There were 10 thrombectomies (80% in prosthetic accesses), representing 0.072 thrombosis/patient/year (vascular access clinical guidelines recommend thrombosis AV fistula <0.125 and thrombosis prosthetic accesses <0.5 thrombosis/patient/year) and 27 cases of vascular access dysfunction, requiring angioplas-

Table 2. Nocturnal, every-other-day, OL-HDF. Change in haematological parameters

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Haemoglobin, g/dl									
12 m (n = 50)	11.43±1.4	11.68±1.5	12.00±1.2	11.58±1.5	11.85±1.3				
24 m (n = 32)	11.44±1.3	11.86±1.5	12.14±1.2	11.62±1.7	11.86±1.2	11.99±1.3	11.80±1.4	11.53±1.3	11.62±1.2
Haematocrit, %									
12 m (n = 50)	35.52±4.2	35.70±4.7	36.64±3.7	35.58±4.5	36.12±4.4				
24 m (n = 32)	35.68±3.9	36.06±4.6	37.15±3.6	35.75±5.2	36.06±4.0	36.9±3.8	35.12±4.5	35.31±4.5	35.78±4.1
Leukocytes, $\times 10^3$/ml									
12 m (n = 50)	6.82±2.2	7.28±1.9	7.26±1.8	7.38±2.2	7.09±2.2				
24 m (n = 32)	6.83±2.1	7.43±1.9	7.38±1.8	7.68±2.3	7.31±2.2	7.58±2.4	7.18±2.2	7.14±1.8	7.14±1.9
Platelets, $\times 10^9$/l									
12 m (n = 50)	213±71	206±62	206±68	201±57	205±59				
24 m (n = 32)	227±70	214±55	214±58	212±52	210±53	215±62	212±55	212±56	217±53
TS, %									
12 m (n = 50)	23.7±9.7	23.0±7.2	23.3±7.6	22.6±8.5	22.4±8.1				
24 m (n = 32)	23.0±8.8	22.6±7.7	23.9±7.5	23.4±9.0	22.1±6.7	23.9±7.6	22.0±7.4	21.9±7.5	23.6±8.9
Ferritin, ng/ml									
12 m (n = 50)	386±300	486±318	552±308[a]	557±296[a]	542±294[a]				
24 m (n = 32)	324±247	497±326[b]	530±284[b]	585±312[a]	565±280[a]	593±354[a]	554±331[a]	511±327[b]	477±279[b]
Transferrin, mg/dl									
12 m (n = 50)	1.79±0.3	1.76±0.3	1.78±0.3	1.83±0.3	1.84±0.30				
24 m (n = 32)	1.85±0.3	1.80±0.3	1.80±0.2	1.85±0.3	1.83±0.31	1.81±0.2	1.86±0.36	1.84±0.37	1.85±0.38
Iron doses, mg/week									
12 m (n = 50)	87±37	98±68	90±69	77±60	71±72				
24 m (n = 32)	91±37	110±77	99±78	89±66	89±83	79±77	62±39	66±41	58±52
ESA doses, IU/week									
12 m (n = 50)	7,540±4,009	6,500±4,111[b]	5,800±4,594[a]	5,560±5,019[a]	5,400±5,222[a]				
24 m (n = 32)	7,437±4,103	6,343±4,037	5,468±4,165[a]	5,156±4,899[a]	5,156±5,175[a]	4,468±4,832[a]	4,312±4,468[a]	4,218±4,233[a]	3,750±4,288[a]
ERI, IU/week/kg/g haemoglobin									
12 m (n = 50)	10.35±7.1	8.62±6.3[b]	7.70±6.9[a]	8.14±8.6[a]	7.48±7.6[a]				
24 m (n = 32)	10.22±7.4	8.17±6.6	7.10±6.6[b]	7.82±9.4	7.24±7.9[b]	5.85±6.6[a]	5.78±6.1	5.71±5.9[a]	4.80±5.6[a]

m = Months; ERI = erythropoietin resistivity index (ESA doses/haemoglobin). The iron dose was endovenous sodium ferric gluconate complex.
[a] $p < 0.01$, [b] $p < 0.05$ with respect baseline value (analysis of variance repeated measures).

ty (0.193 angioplasties/patient/year) in 14 patients (25% with a prosthetic fistula). Temporary placement of tunnelled catheters was required on 7 occasions.

Discussion

This dialysis treatment, which combines long haemodialysis sessions, every-other-day dialysis and OL-HDF, was first used in 2007. The prime motivation for providing this schedule in our centre was the belief that longer dialysis might improve outcomes and that the option of overnight haemodialysis might be socially attractive to some patients. We found that it was well tolerated and accepted by patients and allowed adequate social and occupational rehabilitation; the dialysis dose increased by nearly 60% and the convective dose by >75%. After 8 years of follow-up, with >25,000 sessions, the most important clinical benefits were improvement in hyperphosphatemia, metabolic acidosis, anaemia, hypertension control and nutritional status and a marked reduction in the use of phosphate binders, ESA and antihypertensive medication. As a consequence of all these benefits, the results in terms of mortality and hospitalization have been extremely satisfactory.

Our results show that the nocturnal schedule is well tolerated, as evidenced by the fact that the most common reason for discontinuing the technique was to receive a kidney transplant (54%). Only 1 patient withdrew from the program voluntarily because of difficulty faced in sleeping and one patient returned to conventional HD because of a change in his medical condition. The low

Table 3. Nocturnal, every-other-day, OL-HDF. Changes in biochemical parameters with nocturnal OL-HDF

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Bicarbonate, mmol/l									
12 m (n = 50)	24.1±3.0	25.3±2.9[a]	26.2±2.9[a]	25.8±2.7[a]	26.0±2.9[a]				
24 m (n = 32)	23.6±2.7	25.7±2.7[a]	26.2±3.2[a]	25.8±2.9[a]	26.0±2.8[a]	26.4±2.4[a]	26.7±2.4[a]	27.0±2.5[a]	26.7±2.1[a]
BUN, mg/dl									
12 m (n = 50)	58.6±13	47.7±14[a]	45.9±13[a]	45.8±12[a]	45.9±12[a]				
24 m (n = 32)	58.6±13	45.9±13[a]	46.5±13[a]	45.0±13[a]	46.5±13[a]	45.0±11[a]	41.8±14[a]	42.4±10[a]	44.2±12[a]
Creatinine, mg/dl									
12 m (n = 50)	7.4±1.7	6.1±1.1[a]	6.3±1.3[a]	6.3±1.1[a]	6.4±1.1[a]				
24 m (n = 32)	7.0±1.5	6.0±1.0[a]	6.1±1.2[a]	6.0±0.9[a]	6.2±0.9[a]	6.4±1.1[a]	6.3±1.1[a]	6.2±1.0[a]	6.3±1.1[a]
Sodium, mmol/l									
12 m (n = 50)	140±2.8	140±3.4	139±2.9	140±3.2	140±3.1				
24 m (n = 32)	139±2.5	139±2.8	139±2.8	139±2.8	139±3.2	140±2.9	140±2.1	140±2.1	140±2.6
Potassium, mmol/l									
12 m (n = 50)	4.8±0.9	4.3±0.8	4.5±0.8	4.4±0.8	4.5±0.7				
24 m (n = 32)	4.6±0.9	4.2±0.9	4.4±0.9	4.3±0.8	4.4±0.8	4.3±0.6	4.2±0.6	4.3±0.7	4.4±0.7
Potassium post-dialysis									
12 m (n = 50)	3.12±0.4	3.02±0.4	3.10±0.5	3.04±0.4	3.03±0.4				
24 m (n = 32)	3.19±0.4	3.06±0.4	3.13±0.5	3.03±0.3	3.02±0.4	3.01±0.3	3.04±0.4	3.01±0.4	3.05±0.5
Magnesium, mg/dl									
12 m (n = 50)	2.32±0.26	2.30±0.22	2.33±0.30	2.25±0.19	2.26±0.19				
24 m (n = 32)	2.31±0.26	2.32±0.22	2.36±0.36	2.28±0.20	2.28±0.21	2.28±0.26	2.25±0.22	2.21±0.19	2.20±0.18
LDL-c, mg/dl									
12 m (n = 50)	93±30	88±23	90±27	92±28	87±26				
24 m (n = 32)	97±27	89±22	89±27	91±25	85±25	92±25	92±26	93±27	93±27
HDL-c, mg/dl									
12 m (n = 50)	42.7±11	45.4±11	43.8±11	45.3±10	43.3±11				
24 m (n = 32)	42.9±11	43.6±9	41.3±8	44.6±9	40.9±8	40.8±8	41.3±10	41.3±10	41.4±11
Triglycerides, mg/dl									
12 m (n = 50)	159±126	214±176[b]	208±172[a]	207±162[b]	208±134[b]				
24 m (n = 32)	154±117	197±124	183±114	186±101	189±94	185±101	176±87	191±117	197±107
Total protein, mg/dl									
12 m (n = 50)	6.61±0.5	6.61±0.5	6.69±0.4	6.60±0.5	6.64±0.5				
24 m (n = 32)	6.53±0.5	6.60±0.4	6.70±0.4	6.59±0.4	6.61±0.5	6.63±0.5	6.63±0.5	6.55±0.5	6.58±0.4
Albumin, mg/dl									
12 m (n = 50)	3.94±0.4	3.89±0.4	3.90±0.3	3.87±0.3	3.93±0.3				
24 m (n = 32)	3.89±0.3	3.90±0.2	3.89±0.2	3.85±0.2	3.94±0.2	3.93±0.2	3.91±0.2	3.86±0.2	3.87±0.3
Prealbumin, mg/dl									
12 m (n = 50)	0.30±0.07	0.28±0.08	0.30±0.09	0.30±0.07	0.31±0.08				
24 m (n = 32)	0.30±0.06	0.28±0.06	0.30±0.07	0.31±0.07	0.30±0.06	0.31±0.08	0.30±0.07	0.29±0.08	0.29±0.07
C-reactive protein, mg/dl									
12 m (n = 50)	1.08±2.1	0.94±1.1	0.62±0.8	1.24±2.4	0.71±0.9				
24 m (n = 32)	1.09±2.4	1.03±1.2	0.50±0.5	1.40±2.9	0.68±0.8	1.31±2.4	0.76±1.05	0.91±1.09	1.09±2.00
β_2-Microglobulin, mg/dl									
12 m (n = 50)	27.7±10	24.8±7	26.1±9	25.6±8	25.9±9				
24 m (n = 32)	27.8±11	25.5±7	26.9±9	26.4±9	26.6±9	27.1±9	25.8±7	26.7±9	26.3±8
Glycated haemoglobin, %									
12 m (n = 50)	5.37±1.7	5.40±1.7	5.54±2.2	5.46±1.6	5.39±1.3				
24 m (n = 32)	5.21±1.7	5.16±1.6	5.14±1.4	5.33±1.6	5.17±1.1	5.28±1.1	5.30±1.1	5.31±1.2	5.34±1.2

Pre-dialysis levels of bicarbonate, BUN, creatinine, sodium, potassium, potassium post-dialysis, magnesium, LDL-c, HDL-c, triglycerides, total protein, albumin, pre-albumin, β_2-microglobulin, glycated haemoglobin. m = Months.

[a] $p < 0.01$, [b] $p < 0.05$ with respect baseline value (analysis of variance repeated measures).

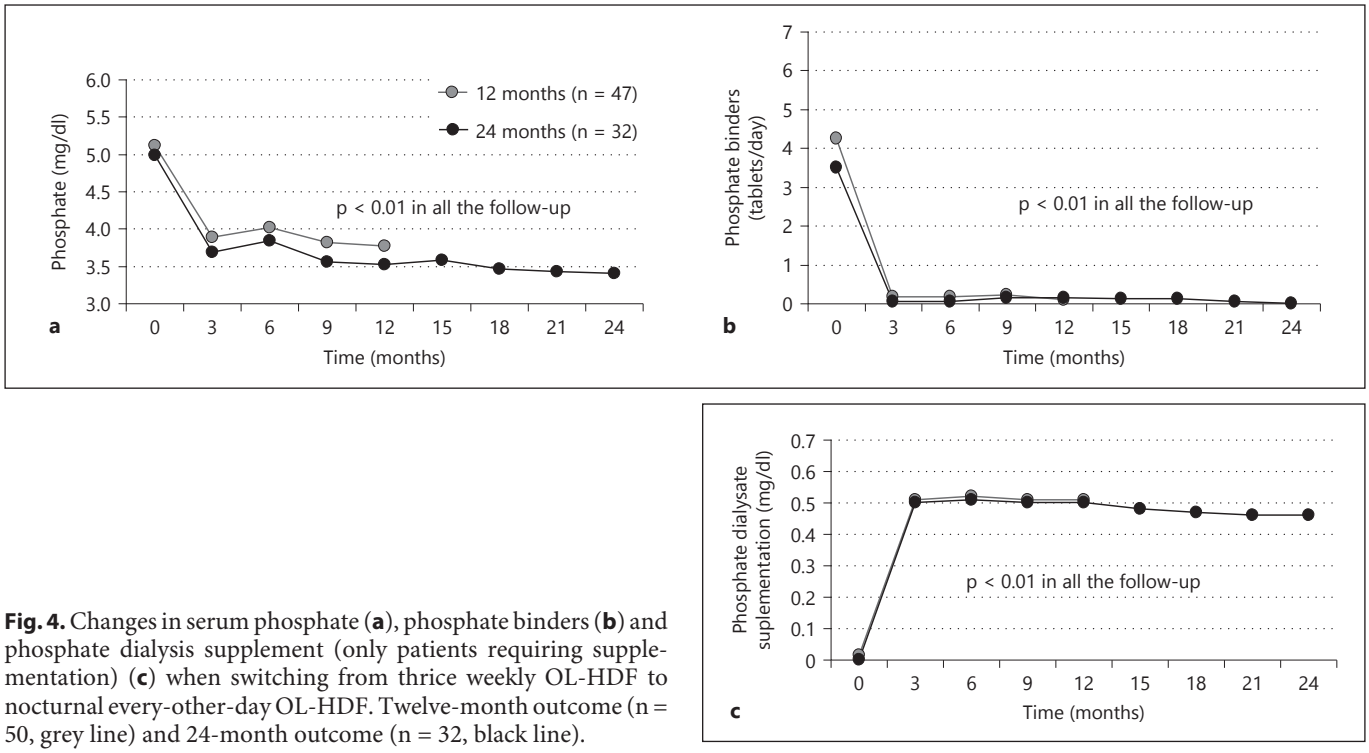


Fig. 4. Changes in serum phosphate (**a**), phosphate binders (**b**) and phosphate dialysis supplement (only patients requiring supplementation) (**c**) when switching from thrice weekly OL-HDF to nocturnal every-other-day OL-HDF. Twelve-month outcome (n = 50, grey line) and 24-month outcome (n = 32, black line).

percentage of withdrawals from the program can be largely attributed to the patients' free choice, compatible with their lifestyles and daily activity, and the schedule resolved chronic medical problems such as hyperphosphatemia, volume overload and hypertension. We did not perform a quality of life test, but from the comments collected from the patients, their experience was extremely good. Some of this was due to many of them reporting they had increased daytime energy levels, more time during the day for social and leisure activities and that they found it easier to get jobs done in the daytime. Several patients also reported that it was the closest they would ever get to 'having a transplant'.

Despite continuous improvement in haemodialysis devices, membrane biocompatibility and dialysate purification, mortality among these patients remains unacceptably high [1]. Since 1980, in-centre thrice weekly prolonged haemodialysis has been used by the Tassin group with the best survival results published to date [4]. Since then, the contribution of dialysis duration has been under debate. However, similar experiences were published only after 2009 from Canada [5, 16], the United Kingdom [17, 18], the United States [19], Germany [6], Turkey [20, 21], and Slovenia [22]. An every-other-day haemodialysis scheme has been used by the Lecce group since 1972 to avoid long weekend periods [10], but no other experiences have been reported, even though the long weekend interval is known to increase the risk of mortality [23, 24]. Finally, high-volume OL-HDF marks a new step towards native kidney blood purification, offers more effective uremic substance removal over a wider range of molecular sizes and has been associated with lower overall and cardiovascular mortality [11–14]. The combination of long dialysis, avoiding a long weekend interval, and the application of the highly convective technique shown in this study have produced highly encouraging results in terms of morbidity and mortality. There has also been a report of the same nocturnal, every-other-day, OL-HDF experience in 7 children [25].

Our schedule represents a better dialysis and convective dose per session than previously reported. Unlike other studies of long nocturnal dialysis, we committed to maintaining high Qb because it allowed the achievement of an elevated dialytic dose as well as a high convective dose (infusion flow in post-dilution OL-HDF is between 25 and 33% of Qb). We believe that this requirement was positive and did not lead to problems in controlling electrolytes, intradialysis symptoms or vascular access.

In this study, improvements in certain causes of anorexia, such as lack of appetite, reduced fluid overload and uremic milieu could explain the nutritional advantages with the switch to 7–8 h nocturnal, every-other-

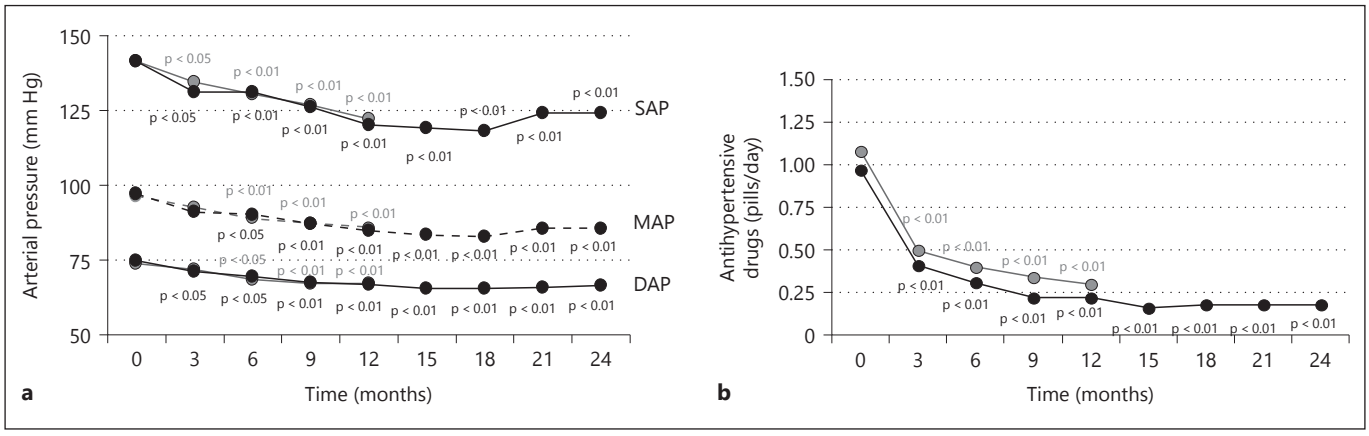


Fig. 5. Changes in arterial blood pressure (**a**) and antihypertensive therapy (**b**) when switching from thrice weekly OL-HDF to nocturnal every-other-day OL-HDF. Twelve-month outcome (n = 50, grey line) and 24-month outcome (n = 32, black line). Significant p values are showed only where it was significant.

Table 4. Nocturnal, every-other-day, OL-HDF. Change in bone and mineral parameters

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Calcium, mg/dl									
12 m (n = 50)	8.77±0.7	9.13±0.7[a]	9.00±0.5[b]	9.05±0.6[b]	9.00±0.5[b]				
24 m (n = 32)	8.74±0.6	9.17±0.7[b]	9.00±0.4	9.004±0.4[a]	8.93±0.5[a]	8.94±0.7	8.95±0.5	8.89±0.6	8.85±0.8
Phosphorus, mg/dl									
12 m (n = 50)	5.11±1.6	3.88±1.2[a]	4.01±1.2[a]	3.82±1.1[a]	3.77±1.1[a]				
24 m (n = 32)	5.00±1.3	3.70±1.0[a]	3.84±1.0[a]	3.55±0.9[a]	3.52±0.8[a]	3.57±1.0[a]	3.46±1.0[a]	3.42±0.8[a]	3.39±0.9[a]
Phosphate binder dose, tablets/day									
12 m (n = 50)	4.24±3.5	0.16±0.9[a]	0.16±0.9[a]	0.22±1.0[a]	0.10±0.5[a]				
24 m (n = 32)	3.50±3.0	0.06±0.3[a]	0.06±0.3[a]	0.15±0.6[a]	0.15±0.6[a]	0.12±0.5[a]	0.12±0.5[a]	0.06±0.3[a]	0.00±0.0[a]
Post-dialysis phosphorus, mg/dl									
12 m (n = 50)	2.13±0.5	1.76±0.4[a]	1.92±0.7[b]	1.80±0.4[a]	1.76±0.4[a]				
24 m (n = 32)	2.23±0.5	1.71±0.3[a]	1.85±0.5[b]	1.74±0.4[a]	1.72±0.3[a]	1.94±1.4[b]	1.67±0.4[a]	1.66±0.3[a]	1.72±0.4[a]
Phosphate dialysate suplementation, mg/dl									
12 m (n = 50)	0.013±0.1	0.280±0.3[a]	0.336±0.3[a]	0.320±0.3[a]	0.310±0.3[a]				
24 m (n = 32)	0.000±0.0	0.273±0.2[a]	0.346±0.3[a]	0.343±0.2[a]	0.326±0.2[a]	0.346±0.2[a]	0.326±0.2[a]	0.353±0.2[a]	0.353±0.2[a]
Alkaline phosphatase, mg/dl									
12 m (n = 50)	248±247	262±248	260±254	264±232	269±220				
24 m (n = 32)	267±264	272±241	295±293	292±259	295±236	304±260	300±229	246±177	242±177
iPTH, pg/ml									
12 m (n = 50)	293±200	300±346	323±416	341±413	381±437				
24 m (n = 32)	279±188	276±400	278±438	304±463	381±832	318±186	283±166	315±254	304±223
Paricalcitol dose, μg/week									
12 m (n = 50)	2.08±3.0	2.30±3.8	2.31±3.8	1.45±2.4	1.76±2.8				
24 m (n = 32)	2.62±3.3	2.59±3.8	2.59±3.8	1.78±2.5	2.07±3.0	1.48±2.2	1.95±2.9	1.93±2.7	1.93±2.7
Cinacalcet dose, mg/day									
12 m (n = 50)	12.6±26	9.9±25	9.9±25	10.2±25	11.4±26				
24 m (n = 32)	11.2±24	8.4±21	9.3±22	9.3±22	10.3±24	13.1±26	15.0±28	12.1±24	11.2±25

Pre-dialysis levels of calcium, phosphorus, alkaline phosphatase and iPTH. Phosphate binders, phospho-soda, paricalcitol and cinacalcet doses. m = Months.

[a] $p < 0.01$, [b] $p < 0.05$ with respect baseline value (analysis of variance repeated measures).

day OL-HDF. Importantly, the nutritional improvement was without significant changes in inflammation markers probably because the patients did not previously have inflammation and received treatment with biocompatible dialyzers, ultrapure dialysis fluid and convective techniques. David et al. [6] found a significant improvement in nutritional status assessed by body weight (1.2 kg after 12 months), body mass index, nPCR and bioelectrical impedance. Both Turkish studies of long-term dialysis [20, 21] found that body weight increased by 1.6–1.8 kg in patients who completed 1 year of follow-up.

All studies of long-duration dialysis have reported excellent anaemia control. Some studies have reported a significantly higher haematocrit [4, 6, 16, 17, 20] while another observed a decrease in ESA dose [5, 6, 20]. In this study, haematocrit showed a trend to increase with a 50% reduction in ESA treatment and the erythropoietin resistance index. The discontinuation of ESA treatment in 28% of our patients was also reported by Poon et al. [26] in 26% of 23 patients under nocturnal home haemodialysis and by Ok et al. [20] in 30% of 247 patients in 8-hour in-centre haemodialysis. Longer duration of dialysis and OL-HDF provided increased clearance of middle and high molecular uremic toxins, which were found to be inhibitory on erythropoiesis [27].

Hyperphosphatemia is an independent predictor of mortality and has been associated with vascular calcification [28]. Most studies have found that phosphate removal is better with long-duration nocturnal haemodialysis than with conventional treatment and that there is a lower use of phosphate binders [5, 6, 16, 20–22]. In our study, better phosphate control was also observed with a reduced need for phosphate binders from 84% to total withdrawal. Moreover, to avoid intradialysis hypophosphatemia, the addition of phosphorus supplements in the dialysate was required in 80% of the patients as in daily nocturnal dialysis [29, 30]. Monitoring post-dialysis phosphate to maintain levels above 1.0 mg/dl is an adequate method to avoid intradialysis hypophosphatemia. This goal can be achieved by maintaining a concentration of phosphate in dialysate around 0.5 mg/dl.

Hypertension is strongly associated with mortality and is highly prevalent in dialysis patients. Reduction of antihypertensive therapy has been published in several reports of in-centre long nocturnal treatments [5, 6, 20, 21, 31]. It has been suggested that long haemodialysis controls hypertension by reducing sympathetic tone [32] and by more efficiently removing pressor substances [33] and that low ultrafiltration rates reduce the risk of intradialytic hypotensive episodes and fluid overload [34]. In our study, although our patients were relatively well controlled at baseline, dry body weight could be reduced in the first months and blood pressure control improved, with only 10% patients requiring antihypertensive medications at the end of the study.

The results of this study confirm the lower risk of hospitalization in long nocturnal treatment published in 2010 by Lacson et al. [19] in 655 patients under in-centre nocturnal haemodialysis, with 1.26 hospitalization events per patient-year and 9.6 hospital days per patient-year in comparison with conventional HD. The lower risk of hospitalization with OL-HDF was also observed in the ESHOL study with 0.475 hospitalization events per patient-year [13].

The greatest difficulties in implementing a nocturnal programme probably involve organizational factors and its higher cost. The reimbursement per OL-HDF session was unchanged, although the duration of this nocturnal shift was 10 instead of 7 h. On the other hand, the nurse/patient ratio was reduced to 1:5 instead of 1:4. There were no extra physician costs because it was covered by the duty doctor and clinical and analytical monitoring was carried out by the team in their regular schedule. Consumables (dialyzer, dialysate, lines, needles, etc.) and analytical controls were similar. However, any cost analysis should include the reduced medication, the lowest rate of hospitalizations and the increased survival. In addition, this type of long nocturnal schedule must be accepted by the patient and would be especially beneficial for those patients who are occupationally active. Regarding operational difficulties, there was an occasional need for the ward house staff to assess urgent issues during the nocturnal treatment. Although the requirement for physician presence during nocturnal treatments was rare, it did occur, and dialysis programmes considering in-centre nocturnal haemodialysis will need to allow for this possibility. Some patient adjustments would also be necessary such as accepting the absence of physicians during the treatment and adjusting to sleeping at the hospital. In our study, while 60% of the patients were able to sleep for at least 6 h, 40% of these individuals required the initiation of hypnotic agents after nocturnal conversion.

This study has some limitations. First, this was an observational cohort study. Second, the sample size was small. Third, there was no control group (each patient served as his or her own control). Under ideal circumstances, the impact of this nocturnal schedule on clinically relevant outcomes would be examined in a well-de-

signed randomized controlled trial with a conventional haemodialysis control group. However, as evidenced by the failure of the FHN Nocturnal trial to recruit its target sample size, such a trial is unlikely to materialize [35].

To our knowledge, ours is the only group performing long nocturnal, every-other day, OL-HDF in adults. The strengths of this study are our long experience of this unusual haemodialysis treatment, with probably the highest convective dose reported to date, and our practical management of phosphate dialysate supplementation.

In conclusion, conversion from 4–5 h thrice weekly OL-HDF to 7–8 h every-other-day OL-HDF with high CV could be a good therapeutic dialysis schedule that could improve clinical and social-occupational rehabilitation. The morbidity and mortality results have been satisfactory as a consequence of marked improvement in hyperphosphatemia, metabolic acidosis, anaemia, hypertension control and nutritional status, and a marked reduction in the use of phosphate binders, ESAs and antihypertensive medication. These promising results have encouraged us to continue this long haemodialysis schedule and to invite other clinicians to join this initiative with a view to corroborating the advantages already described and discovering new ones.

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