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Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative

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Abstract

Background. Longer and more frequent dialysis sessions have demonstrated excellent survival and clinical advantages, while online haemodiafiltration (OL-HDF) provides the most efficient form of dialysis treatment. The aim of this study was to evaluate the beneficial effects of a longer (nocturnal) and more frequent (every-other-day) dialysis schedule with OL-HDF at the same or the highest convective volume.

Methods. This prospective, in-centre crossover study was carried out in 26 patients, 18 males and 8 females, 49.2 ± 14 years old, on 4–5 h thrice-weekly post-dilution OL-HDF, switched to nocturnal every-other-day OL-HDF. Patient inclusion criteria consisted of stable patients with good vascular access and with good prospects for improved occupational, psychological and social rehabilitation. Patients were randomly assigned into two groups: Group A received the same convective volume as previously for 6 months followed by a higher convective volume for a further 6 months, while Group B received the same schedule in reverse order.

Results. Nocturnal every-other-day OL-HDF was well tolerated and 56% of patients who were working during the baseline period continued to work throughout the study with practically no absenteeism. The convective volume was 26.7 ± 2 L at baseline, 27.5 ± 2 with the unchanged volume and 42.9 ± 4 L with the higher volume. *eKt/V* increased from 1.75 ± 0.4 to 3.37 ± 0.9. Bicarbonate, blood urea nitrogen (BUN) and creatinine values decreased, while phosphate levels fell markedly with a 90% reduction in phosphate binders. Blood pressure and left ventricular hypertrophy (LVH) improved and the use of anti-hypertensive drugs decreased. In both groups, BUN, creatinine and β_2-microglobulin reduction ratios improved. Different removal patterns were observed for myoglobin, prolactin and α_1-acid glycoprotein.

Conclusions. Nocturnal every-other-day OL-HDF could be an excellent therapeutic alternative since good tolerance and occupational rehabilitation, marked improvement in dialysis dose, nutritional status, LVH, phosphate and hypertension control and a substantial reduction in drug requirements were observed. In this crossover study, different removal patterns of large solutes were identified.

Keywords: dialysis adequacy; every-other-day; nocturnal dialysis; online haemodiafiltration; solute removal

Introduction

Dialysis patients have a high mortality and morbidity rate, and their remaining life expectancy is lower than that of the general population. Mortality in patients undergoing a conventional dialysis regimen of three 4-h sessions/week is quadruple than that of the general population >65 years old [1, 2] and so new therapeutic regimens are required to improve patient survival, reduce dialysis time and frequency and develop techniques with a higher depurative capacity.

The results of the Tassin experience of long slow-flow haemodialysis (HD) sessions were first reported 25 years ago and showed excellent fluid and blood pressure control with the highest survival rates achieved at that time [3]. Since then, multiple publications have evaluated the superiority of long-duration HD over conventional therapy in blood pressure control, reduction of left ventricular hypertrophy (LVH) and reduced serum phosphate levels, often allowing phosphate binders to be discontinued [2, 4, 5].

A thrice-weekly frequency of HD sessions was established in the 1960s and has been widely accepted and maintained for logistic, pragmatic and economic reasons. However, there is growing interest in the use of more frequent dialysis schedules since long-term experiences of higher frequencies have shown good results [6–11]. In 1972, the Lecce centre started a scheme of every-other-day dialysis to avoid long weekend periods and reported a 60% survival at 10 years with a lower incidence of ischaemic heart disease, stable high depurative efficiency and improvements in anaemia, acid–base and nutritional status [8].

Online haemodiafiltration (OL-HDF) could offer an optimal form of extracorporeal treatment for dialysis patients. This technique, which combines diffusion with high convection, provides the highest clearances per unit of surface area for small, medium and large molecules. The same dialysis fluid, free of toxins and pyrogens, is used as a substitution solution. This technique is safe and well tolerated and provides good clinical results [12–15].

In this study, we sought to combine a more physiological and effective dialysis schedule—long (nocturnal) and more frequent (every-other-day) dialysis—with the dialysis modality offering the highest solute and uraemic toxin removal (OL-HDF). The aim of this study was to switch patients from standard, 4- to 5-h, thrice-weekly OL-HDF to 7- to 8-h, every-other-day OL-HDF in a crossover study with the same or higher convective volume and to evaluate the impact of this schedule on solute removal and analytical and clinical outcomes.

Materials and methods

This was a single-centre, crossover prospective study. Twenty-six patients, 18 men and 8 women, with a mean age of 49.2 ± 14 years (range 22–75), who were stable on HD over a period of 38.7 ± 70 months and on standard 4- to 5-h thrice-weekly OL-HDF for at least 3 months (6.8 ± 7 months) were switched to nocturnal every-other-day OL-HDF, 7–8 h per session and were randomly assigned to receive 6 months of the same convective volume (20–30 L; Group A) or a higher convective volume (35–50 L; Group B), followed by a further 6 months of the other convective volume (Figure 1). The underlying renal diseases were chronic glomerulonephritis in seven patients, diabetic nephropathy in five, polycystic kidney disease in five, nephroangiosclerosis in three, systemic diseases in two, urologic disease in two, chronic tubulo-interstitial nephritis in one and undiagnosed nephropathy in one. All patients signed informed consent forms approved by the hospital's Research Committee.

Patient inclusion criteria consisted of stable patients under HD with good vascular access and with good prospects for improved occupational, psychological and social rehabilitation. For this reason, the patients enrolled in this study were younger than the general dialysis population.

Baseline OL-HDF parameters were bicarbonate buffer, 1.4–1.8 m^2 high-flux helixone filter (FX60 or FX80; Fresenius), blood flow (Q_b) 440 ± 33 mL/min (range 400–500 mL/min), dialysate flow (Q_d) 800 mL/min, infusion flow (Q_i) included, which ranged from 90 to 110 mL/min, and a Fresenius 4008 or 5008 dialysis monitor. Re-infusion was always performed in a post-dilutional mode. All patients had native arteriovenous fistulae. The dialysers were not re-used. In all patients, 15-gauge needles were used. During the study, notable changes were a reduction of Q_d to 500 mL/min and a slightly lowered surface area filter (Table 1).

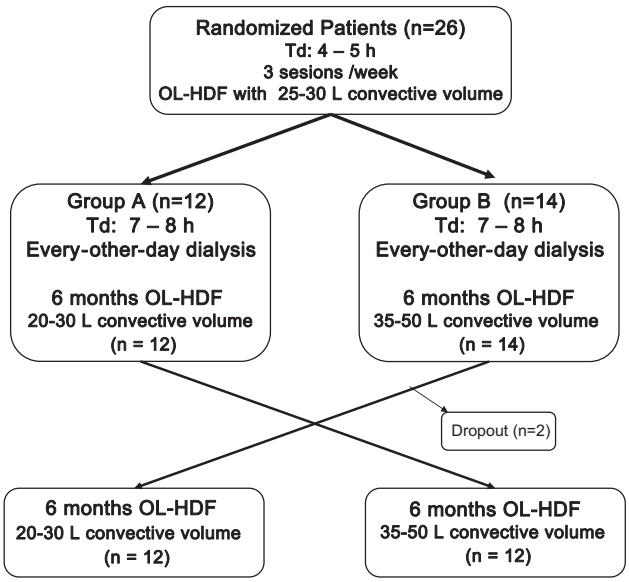

Fig. 1. Flowchart of patient randomization.

The following urea kinetic parameters were calculated: urea reduction ratio (URR), *Kt* [16], single-pool second-generation Daugirdas *Kt/V* (sp*Kt/V*) [17], equilibrated *Kt/V* (e*Kt/V*) [18], standard *Kt/V* (std*Kt/V*) [19], time-averaged concentration (TAC) and normalized protein catabolic rate (nPCR).

To compare removal capacity between the two treatment modes, removal of a wide spectrum of solutes was studied. Pre- and post-dialysis concentrations of urea (60 Da), creatinine (113 Da), β_2-microglobulin (11 800 Da), myoglobin (17 000 Da), prolactin (23 000 Da) and α_1-acid glycoprotein (44 000 Da) were measured. Pre-treatment blood samples were drawn immediately after access needle insertion. Post-treatment samples were drawn from the arterial blood line 60 s after the blood flow rate was decreased to 50 mL/min. The pre- to post-treatment reduction ratios in plasma for β_2-microglobulin, myoglobin, prolactin and α_1-acid glycoprotein were determined after post-dialysis concentrations were corrected using the method of Bergström and Wehle [20–21].

This study was also designed to evaluate biochemical and clinical outcomes. The last month on conventional, 4- to 5-h, thrice-weekly OL-HDF, during which treatment conditions were unchanged, was taken as the baseline period before patients were switched to nocturnal every-other-day OL-HDF. Treatment was carried out >12 months. Each month at mid-week, pre-dialysis plasma analyses for haemoglobin, haematocrit, ferritin, transferrin saturation, urea, creatinine, sodium, potassium, uric acid, bicarbonate, calcium, phosphorus, intact parathyroid hormone, serum protein, albumin, pre-albumin, transferrin, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, β_2-microglobulin, myoglobin, C-reactive protein and glycated haemoglobin were carried out as well as a quarterly analysis of homocysteine, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor.

All patients completed a fatigue index questionnaire on the intensity, duration and frequency of post-dialysis fatigue [22] at baseline and every 6 months. Fatigue intensity was scored as follows: 1, none; 2, mild (noticeable but without effect); 3, moderate (felt sluggish); 4, severe (required rest) or 5, overwhelming (slept). Fatigue duration was scored as follows: 1, none; 2, mild (1–4 h); 3, moderate (6–12 h); 4, severe (12–24 h) or 5, overwhelming (>24 h).

Table 1. Change from thrice-weekly OL-HDF to nocturnal, every-other-day OL-HDF[a]

	Baseline	Month 6	Month 12
Q_b (mL/min)			
Group A	458 ± 28	421 ± 40[b]	426 ± 38[b]
Group B	421 ± 25	421 ± 25	425 ± 26
All	439 ± 33	421 ± 33	425 ± 32[c]
Q_d (mL/min)			
Group A	800	500	500
Group B	800	500	500
All	800	500	500
*T*d (min)			
Group A	277 ± 23	470 ± 23[b]	470 ± 23[b]
Group B	270 ± 13	475 ± 17[b]	475 ± 17[b]
All	273 ± 19	472 ± 22[b]	472 ± 22[b]
Surface area filter (m^2)			
Group A	1.60	1.44	1.44
Group B	1.51	1.43	1.43
All	1.55	1.43	1.43
Q_i (mL/min)			
Group A	90–110	50–60	90–110
Group B	90–110	90–110	50–60
All	90–110	50–110	50–110

[a]Group A (n = 12): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B (n = 12): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.
[b]$P < 0.01$.
[c]$P < 0.05$ with respect baseline value (analysis of variance repeated measures).

Pre-dialysis blood pressure was measured immediately before treatment with an automatic blood pressure monitor. LVH was evaluated by echocardiographic assessment. Measurements included left ventricular wall mass (LVM), LVM index (LVMI) and ejection fraction. All studies were performed and analysed by the same experienced cardiologist, who was blinded to the patients' data. Studies were performed on a midweek non-dialysis day and LVMI was calculated using the formula of Devereux and Reichek, modified in accordance with the recommendations of the American Society of Echocardiography [23].

The results were expressed as the arithmetic mean ± SD. Each patient served as his/her own control. Student's *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.

Results

The duration of dialysis sessions increased from 273 ± 19 min (range 240–300 min) at baseline to 471 ± 22 min (range 420–480 min) in nocturnal every-other-day OL-HDF ($P < 0.01$). Q_b was 439 ± 33 mL/min at baseline versus 427 ± 36 mL/min at 6 months and 421 ± 32 mL/min at 12 months ($P < 0.05$). The groups were randomized to receive different convective volumes (Figure 2). The baseline volume was 26.1 ± 2 L, which increased to 35.7 ± 9.6 L after 3 months (Group A 27.0 ± 2.4 L and Group B 44.3 ± 4.7 L).

All patients who were working (56%) during the baseline period continued to work throughout the study with practically no absenteeism. All patients completed the study except for two in Group B because one received a renal transplant and the other had a stroke and was sent to a rehabilitation centre because he lived alone. Nocturnal every-other-day OL-HDF was well accepted and tolerated. Fatigue intensity scores showed no significant changes: scores decreased from 2.92 ± 1.6 at baseline to 2.25 ± 1.1 in Group A (non significant) and 1.75 ± 1.0 to 1.75 ± 0.9 in Group B (non significant) at 12 months, while fatigue duration scores varied from 2.42 ± 1.1 at baseline to 2.08 ± 0.9 in Group A and 1.58 ± 0.5 to 1.58 ± 0.7 in Group B at 12 months (non significant).

Urea kinetics

At baseline, the patients received a high dialysis dose, which increased markedly throughout the study when the patients were switched to nocturnal every-other-day OL-HDF. *Kt* (L), URR (%), sp*Kt*/*V*, e*Kt*/*V*, std*Kt*/*V* and TAC (mg/dL) were significantly increased with respect to baseline (Table 2).

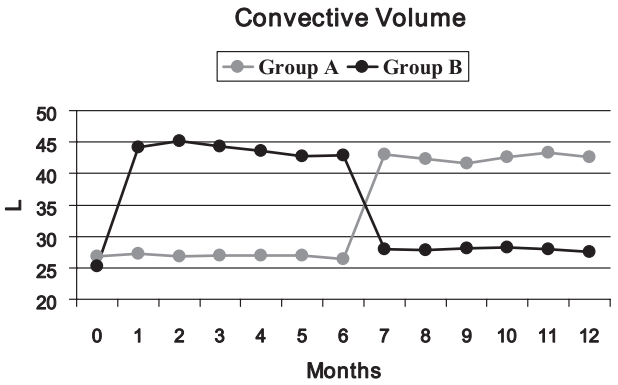

Fig. 2. Convective volume received by the two different groups. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.

Table 2. Change from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF[a]

	Baseline	Month 3	Month 6	Month 9	Month 12
Kt (L)					
Group A	73.7 ± 9	106.9 ± 10[b]	102.2 ± 10[b]	100.7 ± 13[b]	106.4 ± 11[b]
Group B	68.5 ± 7	110.4 ± 8[b]	105.5 ± 10[b]	103.3 ± 10[b]	102.4 ± 11[b]
All	71.1 ± 8	108.7 ± 9[b]	103.9 ± 10[b]	102.0 ± 12[b]	104.4 ± 11[b]
URR (%)					
Group A	80.8 ± 5	89.4 ± 4[b]	88.7 ± 3[b]	88.0 ± 5[b]	90.0 ± 3[b]
Group B	80.4 ± 7	90.6 ± 3[b]	90.5 ± 2[b]	90.2 ± 3[b]	90.0 ± 3[b]
All	80.6 ± 6	90.0 ± 3[b]	89.6 ± 3[b]	89.1 ± 4[b]	90.0 ± 3[b]
sp*Kt*/*V*					
Group A	2.04 ± 0.4	3.64 ± 0.9[b]	3.41 ± 0.9[b]	3.46 ± 1.1[b]	3.81 ± 1.0[b]
Group B	2.06 ± 0.5	4.03 ± 0.9[b]	3.98 ± 1.0[b]	3.86 ± 1.0[b]	3.91 ± 1.1[b]
All	2.05 ± 0.4	3.84 ± 0.9[b]	3.70 ± 1.0[b]	3.66 ± 1.0[b]	3.86 ± 1.1[b]
e*Kt*/*V*					
Group A	1.74 ± 0.3	3.18 ± 0.8[b]	2.98 ± 0.8[b]	3.03 ± 0.9[b]	3.33 ± 0.9[b]
Group B	1.75 ± 0.4	3.53 ± 0.8[b]	3.48 ± 0.9[b]	3.38 ± 0.8[b]	3.42 ± 1.0[b]
All	1.75 ± 0.4	3.35 ± 0.8[b]	3.23 ± 0.9[b]	3.21 ± 0.9[b]	3.37 ± 0.9[b]
std*Kt*/*V*					
Group A	2.56 ± 0.2	3.73 ± 0.2[b]	3.68 ± 0.2[b]	3.66 ± 0.3[b]	3.76 ± 0.2[b]
Group B	2.55 ± 0.2	3.81 ± 0.2[b]	3.80 ± 0.2[b]	3.78 ± 0.2[b]	3.78 ± 0.2[b]
All	2.55 ± 0.2	3.77 ± 0.2[b]	3.74 ± 0.2[b]	3.72 ± 0.2[b]	3.77 ± 0.2[b]
TAC_{BUN} (mg/dL)					
Group A	32.5 ± 8	26.2 ± 9[b]	27.5 ± 7[b]	26.6 ± 6[b]	23.0 ± 5[b]
Group B	33.8 ± 7	26.9 ± 8[b]	26.5 ± 9[b]	26.8 ± 10[b]	29.0 ± 9[c]
All	33.1 ± 8	26.5 ± 8[b]	27.0 ± 8[b]	26.7 ± 8[b]	26.0 ± 8[b]

[a]Comparison of urea kinetics during the two study periods. sp*Kt*/*V*, single pool *Kt*/*V*; e*Kt*/*V*, equilibrated *Kt*/*V*; std*Kt*/*V*, standard *Kt*/*V* (frequency independent). Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.
[b]$P < 0.01$.
[c]$P < 0.05$ with respect to baseline (analysis of variance repeated measures).

Haematological parameters

There were no changes in haemoglobin, haematocrit, leucocyte count or transferrin saturation (Table 3). At baseline, ferritin levels significantly differed between the two groups: ferritin levels were lower in Group B (191 ± 133 ng/mL) than in Group A (457 ± 264 ng/mL, $P < 0.05$). Three months later, after iron adjustments, there were no significant differences and these results were sustained during the remainder of the study, with the same iron dose at the end of the protocol. Although the total dose of erythropoiesis-stimulating agents (ESA), using a conversion ratio for darbepoetin alfa to epoetin of 200:1 and the erythropoietin resistance index had a decreasing tendency over the 12-month period, there were no significant differences. This tendency was especially observed in Group B, which showed lower ferritin levels than Group A. Of the 24 patients, at baseline, only one patient (4%) did not receive ESA, while at 12 months, 7 patients (29%) were not receiving ESA.

Biochemical parameters

Bicarbonate levels were significantly higher in all patients with respect to baseline values. Blood urea nitrogen (BUN) and creatinine values at 3, 6, 9 and 12 months significantly decreased in nocturnal every-other-day OL-HDF. There were no changes in sodium, potassium, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride and uric acid levels during the study period (Table 4). However, in Group A, HDL values rose significantly from 42.1 ± 7 mg/dL at baseline to 47.7 ± 10 mg/dL at 3 months and this change was maintained at the 12-month outcome ($P < 0.01$) (Table 4). At baseline, two patients (one in each group) were taking statins and after the study began, three other patients (two in Group A and one in Group B) initiated this treatment.

β_2-Microglobulin levels

Baseline pre-dialysis β_2-microglobulin levels did not differ between the two groups during the study. In Group A, levels were 25.5 ± 7 mg/L at baseline and 23.4 ± 5, 23.7 ± 5, 24.2 ± 5 and 23.8 ± 4 mg/L at 3, 6, 9 and 12 months, respectively; in Group B, levels were 27.6 ± 14 at baseline and were 24.5 ± 10, 28.0 ± 13, 27.6 ±13 and 27.9 ± 13 at 3, 6, 9 and 12 months, respectively.

Table 3. Change from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF[a]

	Baseline	Month 3	Month 6	Month 9	Month 12
Haemoglobin (g/dL)					
Group A	11.53 ± 1.1	11.42 ± 1.3	12.01 ± 1.5	11.71 ± 1.4	11.83 ± 1.5
Group B	11.77 ± 1.4	11.67 ± 1.6	12.07 ± 1.2	11.97 ± 1.8	12.48 ± 1.1
All	11.65 ± 1.2	11.54 ± 1.5	12.04 ± 1.3	11.84 ± 1.6	12.15 ± 1.3
Haematocrit (%)					
Group A	35.58 ± 3.4	35.00 ± 3.8	37.42 ± 4.3	36.17 ± 3.9	35.92 ± 4.3
Group B	36.75 ± 4.4	35.75 ± 4.8	37.08 ± 3.8	36.92 ± 5.5	37.83 ± 3.1
All	36.17 ± 3.9	35.38 ± 4.2	37.25 ± 4.0	36.54 ± 4.7	36.88 ± 3.8
Leucocytes ($\times 10^3/\mu L$)					
Group A	7.10 ± 2.2	7.58 ± 1.4	7.48 ± 1.9	8.19 ± 2.2	7.32 ± 1.8
Group B	6.23 ± 1.8	7.33 ± 2.5	7.23 ± 2.0[b]	7.08 ± 2.1[b]	7.25 ± 2.7
All	6.67 ± 2.0	7.46 ± 2.0	7.36 ± 1.9	7.63 ± 2.2[b]	7.28 ± 2.2
TS (%)					
Group A	22.7 ± 7.0	21.5 ± 5.9	22.5 ± 5.3	21.4 ± 5.5	22.3 ± 9.3
Group B	24.2 ± 8.7	23.1 ± 8.1	25.6 ± 8.5	25.9 ± 8.4	25.3 ± 7.9
All	23.4 ± 7.7	22.3 ± 7.0	24.0 ± 7.1	23.7 ± 7.3	23.8 ± 7.9
Ferritin (ng/mL)					
Group A	457 ± 264	482 ± 299	542 ± 332	554 ± 315	505 ± 313
Group B	194 ± 131	319 ± 313	421 ± 281	573 ± 392	539 ± 252
	$P < 0.05$				
All	326 ± 244	401 ± 311	481 ± 307	563 ± 348	522 ± 279
Iron doses (mg/week)					
Group A	97 ± 38	84 ± 37	86 ± 41	70 ± 34	63 ± 42
Group B	98 ± 29	120 ± 65	122 ± 87	109 ± 70	78 ± 60
All	97 ± 33	102 ± 56	104 ± 69	90 ± 58	70 ± 51
ESA doses (IU/kg/week)					
Group A	7500 ± 4011	7000 ± 4134	7583 ± 5869	7417 ± 7012	7333 ± 7152
Group B	7167 ± 5219	6917 ± 5143	6667 ± 4716	6083 ± 4833	5167 ± 4783
All	7333 ± 4556	6958 ± 4563	7125 ± 5228	6750 ± 5929	6250 ± 6052
ERI					
Group A	8.58 ± 4.5	8.30 ± 5.0	9.02 ± 7.8	8.64 ± 8.0	8.73 ± 8.5
Group B	10.84 ± 10.0	10.50 ± 9.9	9.80 ± 9.4	9.23 ± 10.6	7.08 ± 7.9
All	9.71 ± 7.7	9.40 ± 7.7	9.41 ± 8.4	8.94 ± 9.2	7.90 ± 8.1

[a]Haematological parameters. TS, transferrin saturation; ESA, erythropoiesis-stimulating agents; ERI, erythropoietin resistivity index (ESA doses per haemoglobin). The iron dose was endovenous sodium ferric gluconate complex. Group A: convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B: convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.
[b]$P < 0.05$ with respect baseline value (analysis of variance repeated measures).

Table 4. Change from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF[a]

	Baseline	Month 3	Month 6	Month 9	Month 12
Bicarbonate (mmol/L)					
Group A	22.0 ± 2.0	23.8 ± 2.4[b]	24.0 ± 2.4[b]	24.8 ± 2.2[b]	24.8 ± 3.5[b]
Group B	22.0 ± 2.4	23.2 ± 2.2	25.7 ± 3.0[c]	24.3 ± 2.9[b]	24.4 ± 1.7[b]
All	22.0 ± 2.2	23.5 ± 2.2[b]	24.8 ± 2.6[c]	24.5 ± 2.6[c]	24.6 ± 2.9[c]
BUN (mg/dL)					
Group A	60.0 ± 13	49.1 ± 17[c]	49.1 ± 14[c]	47.6 ± 10[c]	44.8 ± 11[c]
Group B	59.9 ± 17	51.0 ± 17[b]	50.6 ± 17[b]	49.4 ± 18[b]	53.2 ± 16[b]
All	60.0 ± 15	50.0 ± 16[c]	49.8 ± 15[c]	48.5 ± 14[c]	49.0 ± 14[c]
Creatinine (mg/dL)					
Group A	7.01 ± 1.5	5.84 ± 1.2[c]	6.09 ± 1.3[c]	6.29 ± 1.2[c]	6.09 ± 1.0[c]
Group B	7.41 ± 2.0	6.36 ± 1.3[c]	6.55 ± 1.3[b]	6.27 ± 1.3[c]	6.57 ± 1.2[c]
All	7.21 ± 1.8	6.10 ± 1.3[c]	6.32 ± 1.3[c]	6.28 ± 1.2[c]	6.33 ± 1.1[c]
Sodium (mmol/L)					
Group A	138.4 ± 2.0	139.4 ± 3.3	137.3 ± 2.1	138.7 ± 3.1	138.0 ± 2.9
Group B	139.7 ± 3.4	138.6 ± 2.8	139.7 ± 2.7	139.2 ± 3.6	139.3 ± 3.7
All	139.0 ± 2.8	139.0 ± 3.1	138.5 ± 2.7	138.9 ± 3.3	138.6 ± 3.3
Potassium (mmol/L)					
Group A	5.18 ± 0.8	4.43 ± 0.7[b]	4.80 ± 0.5	5.05 ± 0.8	4.90 ± 0.8
Group B	4.68 ± 1.1	4.25 ± 1.0	4.43 ± 1.2	4.32 ± 0.9	4.58 ± 0.8
All	4.93 ± 0.9	4.34 ± 0.9[c]	4.62 ± 1.0	4.68 ± 0.9	4.74 ± 0.8
Potassium post-dialysis					
Group A	3.32 ± 0.4	3.03 ± 0.4	3.25 ± 0.6	3.20 ± 0.4	3.11 ± 0.4
Group B	3.28 ± 0.4	3.11 ± 0.5	3.05 ± 0.5	3.10 ± 0.5	3.04 ± 0.5
All	3.30 ± 0.4	3.07 ± 0.4	3.15 ± 0.5	3.15 ± 0.4	3.08 ± 0.4
T-cholesterol (mg/dL)					
Group A	167 ± 29	179 ± 33	186 ± 31	179 ± 28	176 ± 28
Group B	182 ± 43	164 ± 40	168 ± 45	166 ± 37	163 ± 40
All	175 ± 36	172 ± 36	177 ± 38	173 ± 33	170 ± 34
LDL-c (mg/dL)					
Group A	91 ± 21	97 ± 26	98 ± 25	96 ± 27	93 ± 27
Group B	108 ± 32	86 ± 19[b]	94 ± 27	93 ± 28	86 ± 29[b]
All	100 ± 28	91 ± 23	96 ± 26	94 ± 27	90 ± 27
HDL-c (mg/dL)					
Group A	42.1 ± 7	47.7 ± 10[b]	47.3 ± 13[b]	48.1 ± 10[b]	48.5 ± 12[b]
Group B	44.3 ± 9	42.5 ± 5	40.6 ± 6	42.5 ± 9	39.3 ± 9
All	43.2 ± 8	45.1 ± 9	43.9 ± 10	45.3 ± 10	43.9 ± 11
Triglycerides (mg/dL)					
Group A	178 ± 189	227 ± 225	254 ± 262	215 ± 223	167 ± 117
Group B	169 ± 150	187 ± 127	173 ± 107	184 ± 121	175 ± 92
All	174 ± 167	207 ± 180	214 ± 200	199 ± 176	171 ± 104
Uric acid (mg/dL)					
Group A	6.57 ± 1.1	5.99 ± 0.8	6.52 ± 1.1	6.51 ± 1.0	6.29 ± 1.0
Group B	6.75 ± 1.5	6.96 ± 1.4	6.76 ± 1.0	6.88 ± 1.5	7.05 ± 1.3
All	6.66 ± 1.3	6.48 ± 1.1	6.64 ± 1.1	6.70 ± 1.3	6.67 ± 1.2

[a]Pre-dialysis levels of bicarbonate, BUN, creatinine, sodium, potassium, potassium post-dialysis, T-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and uric acid. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.
[b]$P < 0.05$ with respect baseline value (analysis of variance repeated measures).
[c]$P < 0.01$.

Bone and mineral parameters

Phosphorus levels significantly decreased and phosphate binders markedly decreased (Table 5). Pre-dialysis serum phosphorus significantly decreased in the overall group from 4.93 ± 1.5 to 3.74 ± 1 mg/dL at the end of the study, and similar behaviour was observed in post-dialysis serum phosphorus (Table 5). Phosphate binders were reduced from 3.38 ± 3.7 tablets/day at baseline to 0.33 ± 1.3 tablets/day after 3 months and 0.13 ± 0.6 tablets/day after 12 months ($P < 0.01$) in nocturnal every-other-day OL-HDF (Figure 3). The decrease in serum phosphorus was such that 55% of the patients required the addition of phosphorus supplements [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 40 mL of Fosfosoda® (Figure 3) were added in 11 L of acid concentrate (1:35 dilution), which allowed 385 L of dialysate. No significant changes were observed with calcium, alkaline phosphatase, intact parathyroid hormone, paricalcitol or cinacalcet dose (Table 5).

Nutritional and inflammatory parameters

Body weight (measured as dry weight after dialysis) showed an overall increase in the group taken as a whole from 70.1 ± 19 to 72.2 ± 19 kg ($P < 0.01$). A quarterly increment in Groups A and B is illustrated in Figure 4,

Table 5. Change from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF[a]

	Baseline	Month 3	Month 6	Month 9	Month 12
Calcium (mg/dL)					
Group A	8.74 ± 0.6	9.07 ± 0.6	9.10 ± 0.6	9.02 ± 0.5	8.85 ± 0.4
Group B	8.99 ± 0.9	9.69 ± 0.6[b]	9.33 ± 0.4	9.23 ± 0.5	9.03 ± 0.5
All	8.87 ± 0.7	9.38 ± 0.7[c]	9.22 ± 0.5	9.13 ± 0.5	8.94 ± 0.5
Phosphorus (mg/dL)					
Group A	4.71 ± 1.7	3.60 ± 1.8[b]	4.17 ± 1.4	3.83 ± 1.0	3.58 ± 1.1[b]
Group B	5.16 ± 1.5	3.95 ± 0.9[c]	3.94 ± 1.3[c]	3.83 ± 1.1[c]	3.89 ± 0.9[c]
All	4.93 ± 1.5	3.78 ± 1.4[c]	4.05 ± 1.3[c]	3.83 ± 1.1[c]	3.74 ± 1.0[c]
Phosphate binder dose					
Group A (tablets/day)	3.50 ± 4.1	0.00 ± 0.0[c]	0.00 ± 0.0[c]	0.17 ± 0.6[c]	0.00 ± 0.0[c]
Group B (tablets/day)	3.25 ± 3.7	0.67 ± 1.8[c]	0.67 ± 1.8[c]	0.75 ± 1.9[c]	0.25 ± 0.9[c]
All (tablets/day)	3.38 ± 3.7	0.33 ± 1.3[c]	0.33 ± 1.3[c]	0.46 ± 1.4[c]	0.13 ± 0.6[c]
Post-dialysis phosphorus					
Group A	2.14 ± 0.4	1.93 ± 0.4	2.62 ± 0.8[b]	2.04 ± 0.4	1.80 ± 0.4
Group B	2.37 ± 0.6	1.81 ± 0.5[c]	1.93 ± 0.6[c]	1.80 ± 0.4[c]	1.85 ± 0.4[c]
All	2.25 ± 0.5	1.87 ± 0.4[c]	2.27 ± 0.9	1.92 ± 0.4[c]	1.83 ± 0.4[c]
Fosfosoda® dose (mL)					
Group A	1.7 ± 6	12.9 ± 13[c]	16.4 ± 15[c]	13.2 ± 16[c]	12.3 ± 14[c]
Group B	0.0 ± 0	8.3 ± 8[c]	8.3 ± 8[c]	9.6 ± 8[c]	9.2 ± 9[c]
All	0.8 ± 4	10.6 ± 11[c]	12.3 ± 12[c]	11.5 ± 12[c]	10.8 ± 11[c]
Alkaline phosphatase					
Group A (mg/dL)	191 ± 72	178 ± 96	197 ± 78	211 ± 83	212 ± 66
Group B (mg/dL)	251 ± 239	265 ± 216	276 ± 205	315 ± 249	331 ± 266
All (mg/dL)	221 ± 176	222 ± 170	237 ± 157	263 ± 189	271 ± 199
iPTH (pg/mL)					
Group A	223 ± 140	198 ± 103	183 ± 93	228 ± 107	262 ± 132
Group B	269 ± 230	230 ± 185	239 ± 279	295 ± 263	326 ± 309
All	246 ± 187	214 ± 147	211 ± 205	261 ± 200	294 ± 235
Paricalcitol dose (μg/week)					
Group A	1.50 ± 2.7	2.50 ± 3.3	3.00 ± 3.8	2.50 ± 3.3	2.67 ± 3.5
Group B	1.50 ± 2.0	3.25 ± 4.7	4.00 ± 4.7	2.25 ± 2.9	3.25 ± 3.5
All	1.50 ± 2.3	2.88 ± 4.0	3.50 ± 4.2	2.38 ± 3.1	2.96 ± 3.4
Cinacalcet dose (mg/day)					
Group A	10.0 ± 23	10.0 ± 23	10.0 ± 23	7.5 ± 19	10.0 ± 20
Group B	2.5 ± 9	2.5 ± 9	5.0 ± 12	7.5 ± 19	10.0 ± 27
All	6.3 ± 18	6.3 ± 18	7.5 ± 18	7.5 ± 19	10.0 ± 23

[a]Pre-dialysis levels of calcium, phosphorus, alkaline phosphatase and iPTH. Phosphate binders, phosphosoda, paricalcitol and cinacalcet doses. iPTH, intact parathyroid hormone. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.
[b]$P < 0.05$ with respect baseline value (analysis of variance repeated measures).
[c]$P < 0.01$.

showing an increase of 2.4 kg in Group A and 1.9 kg in Group B at the end of the study. This weight increase was accompanied by an increasing tendency in interdialytic weight gain and protein intake. There were no significant changes in the following nutritional and inflammatory parameters: nPCR, total protein, albumin, pre-albumin and transferrin, C-reactive protein, homocysteine, glycated haemoglobin, IL-1, IL-6 and tumour necrosis factor (Tables 6 and 7).

Cardiovascular parameters

During the study period, pre-dialysis systolic blood pressure decreased in both groups taken as a whole from baseline with a significant change at 12 months (132 ± 25 to 121.8 ± 26; $P < 0.05$). No significant changes were observed in diastolic or mean blood pressure (Table 8). There were significant differences in anti-hypertensive drugs between the two groups at baseline: practically, no anti-hypertensive drugs were prescribed in Group A (0.25 ± 0.5) compared with Group B (1.42 ± 1.4, $P < 0.05$). The number of anti-hypertensive drugs was significantly reduced from baseline to the 12-month evaluation (from 1.42 ± 1.4 to 0.25 ± 0.9 in Group B and from 0.83 ± 1.2 to 0.17 ± 0.6 in the whole group) (Table 8).

The echocardiographic parameters in Table 8 show that there was a significant rise in ejection fraction from 54.5 ± 9 to 62.2 ± 10% in Group A ($P < 0.05$) and 57.9 ± 8 to 62.7 ± 8% in the whole group ($P < 0.01$). LVM significantly decreased in Group B at the 6- and 12-month evaluations from 260 ± 62 g (baseline) to 219 ± 69 and 222 ± 44 g, respectively ($P < 0.05$). LVMI was also decreased in Group B at the 6- and 12-month evaluations as well as in the whole group at the end of the study from 139 ± 36 to 123 ± 22 g/m^2 ($P < 0.05$).

Solute removal

The mean session values for urea and creatinine reduction ratios were significantly increased in both groups on

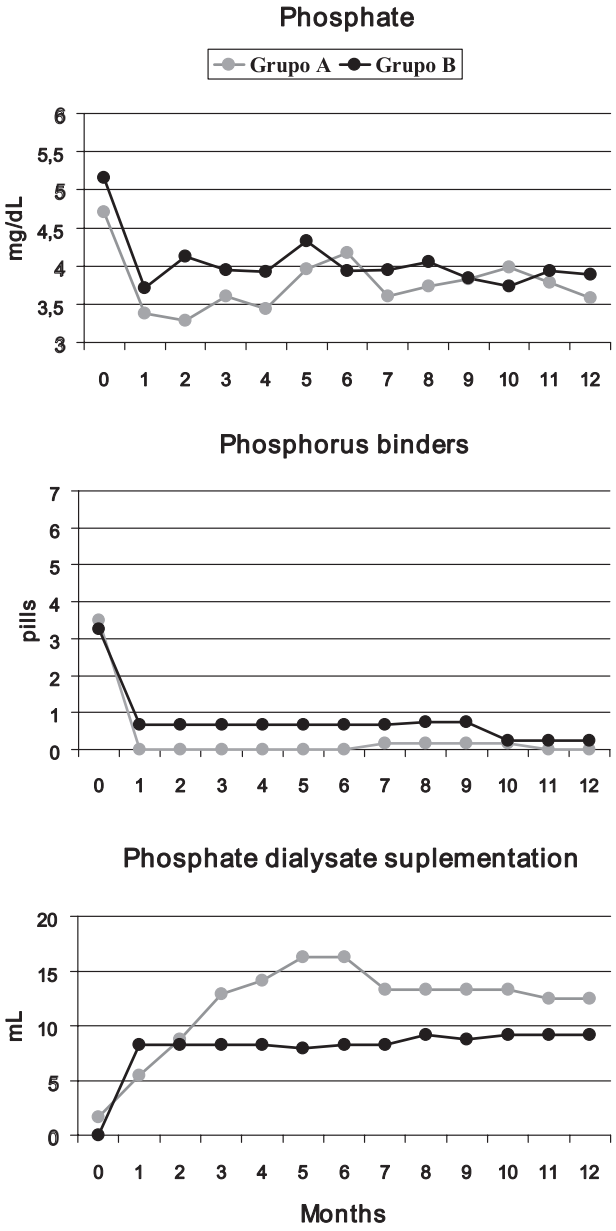

Fig. 3. Evolution of serum phosphate, phosphorus binders and phosphate dialysis supplement when switching from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF. Patients were randomized to 6 months with the same convective volume as previously (20–30 L) followed by 6 months with a higher (35–50 L) convective volume (Group A) or to the same two schedules but in reverse order (Group B).

every-other-day nocturnal OL-HDF compared with baseline values (Figure 5).

A different pattern was observed in the β_2-microglobulin reduction ratio, which significantly increased after 6 months of the higher convective volume (35–50 L) in both groups on nocturnal every-other-day OL-HDF. In Group A, the baseline value increased from 80.3 ± 4.2 to 85.6 ± 3.2% at 3 months and 84.2 ± 4.3% at 6 months ($P < 0.01$). In Group B, this increment was observed at 9 and 12 months (Figure 6).

Another pattern was observed in myoglobin and prolactin reduction ratios (Figure 7), which significantly decreased

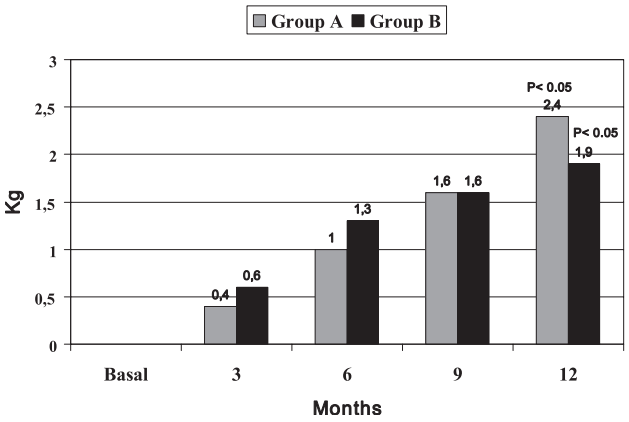

Fig. 4. Gain in body weight when switching from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.

with nocturnal every-other-day OL-HDF during the 6-month period with the same (20–30 L) convective volume. However, no significant changes were found in the myoglobin and prolactin reduction ratios when the higher convective volume (35–50 L) was used.

Finally, α_1-acid glycoprotein reduction ratios, the highest molecular weight measured, showed a small but significant increase with nocturnal every-other-day OL-HDF. In Group A, the baseline value of 4.2 ± 8% increased to 13.3 ± 6% ($P < 0.01$), 13.4 ± 8% ($P < 0.01$), 14.2 ± 7% ($P < 0.01$) and 15.0 ± 6% ($P < 0.01$) at 3, 6, 9 and 12 months, respectively; in Group B, these values were 7.5 ± 7% to 12.1 ± 7%, 10.0 ± 6%, 18.4 ± 8% ($P < 0.01$) and 14.6 ± 7%, respectively.

Discussion

An every-other-day HD model was used by the Lecce group since 1972 to avoid long weekend periods but no other experiences have been reported. Thrice-weekly prolonged HD has been used by the Tassin group for >28 years, and interest in this modality has grown in the last 5 years with several publications from Canada [4], USA [24], UK [25], Germany [5] and Turkey [26]. Nowadays, OL-HDF provides the most efficient form of dialysis and the use of this modality has markedly increased in Europe and Asia in recent years with abundant publications.

To our knowledge, our study is the first experience reported in the literature to combine long HD sessions, every-other-day dialysis and the dialysis modality that offers the highest solute and uraemic toxin removal (OL-HDF). This was a cross-sectional study, which compared the effect of a switch from 4 to 5 h thrice-weekly OL-HDF to 7–8 h nocturnal every-other-day OL-HDF with the same (20–30 L) or higher (35–50 L) convective volume. This protocol achieved adequate social and occupational rehabilitation and clinical and biochemical parameters, with remarkable improvement in nutritional status, regression of LVH, phosphate and hypertension control and a marked reduction in

Table 6. Change from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF[a]

	Baseline	Month 3	Month 6	Month 9	Month 12
nPCR (g/kg/day)					
Group A	1.12 ± 0.3	1.26 ± 0.4	1.38 ± 0.4[b]	1.34 ± 0.4[b]	1.12 ± 0.3
Group B	1.36 ± 0.5	1.54 ± 0.7	1.50 ± 0.7	1.53 ± 0.8	1.60 ± 0.8
All	1.24 ± 0.4	1.40 ± 0.5	1.44 ± 0.6	1.44 ± 0.7	1.36 ± 0.7
Body weight (kg)					
Group A	76.3 ± 21	76.7 ± 21	77.3 ± 21	77.9 ± 21	78.7 ± 22[b]
Group B	63.9 ± 15	64.5 ± 14	65.2 ± 14	65.5 ± 14	65.8 ± 14[b]
All	70.1 ± 19	70.6 ± 19	71.3 ± 19[b]	71.7 ± 19[c]	72.2 ± 19[c]
Weight gain (kg)					
Group A	2.76 ± 1.1	3.39 ± 0.8	2.99 ± 0.7	3.18 ± 1.3	3.30 ± 1.2
Group B	2.48 ± 1.0	3.09 ± 1.5	2.91 ± 1.3	3.16 ± 1.6	3.35 ± 1.6
All	2.62 ± 1.1	3.24 ± 1.2	2.95 ± 1.0	3.17 ± 1.5	3.33 ± 1.4
Total protein (mg/dL)					
Group A	6.64 ± 0.6	6.66 ± 0.5	6.86 ± 0.4	6.70 ± 0.7	6.51 ± 0.6
Group B	6.59 ± 0.7	6.48 ± 0.4	6.80 ± 0.4	6.63 ± 0.4	6.68 ± 0.5
All	6.62 ± 0.6	6.57 ± 0.4	6.83 ± 0.4	6.66 ± 0.5	6.59 ± 0.5
Albumin (mg/dL)					
Group A	3.98 ± 0.3	3.98 ± 0.4	3.96 ± 0.2	3.88 ± 0.2	3.85 ± 0.2
Group B	3.98 ± 0.5	3.88 ± 0.3	3.88 ± 0.3	3.89 ± 0.2	3.95 ± 0.3
All	3.98 ± 0.4	3.93 ± 0.3	3.92 ± 0.3	3.88 ± 0.2	3.90 ± 0.3
Prealbumin (mg/dL)					
Group A	0.31 ± 0.06	0.30 ± 0.07	0.33 ± 0.06	0.33 ± 0.04	0.34 ± 0.09
Group B	0.33 ± 0.06	0.30 ± 0.08	0.32 ± 0.07	0.33 ± 0.08	0.31 ± 0.07
All	0.32 ± 0.06	0.30 ± 0.07	0.33 ± 0.06	0.33 ± 0.06	0.32 ± 0.08
Transferrin (mg/dL)					
Group A	1.68 ± 0.26	1.61 ± 0.21	1.62 ± 0.33	1.77 ± 0.49	1.77 ± 0.45
Group B	1.90 ± 0.30	1.90 ± 0.40	1.85 ± 0.31	1.87 ± 0.31	1.78 ± 0.34
All	1.79 ± 0.29	1.76 ± 0.34	1.74 ± 0.34	1.82 ± 0.41	1.77 ± 0.39

[a]Nutritional findings. CRP, C-reactive protein. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.
[b]$P < 0.05$ with respect baseline value (analysis of variance repeated measures).
[c]$P < 0.01$.

phosphate binders and anti-hypertensive medication. Importantly, during the baseline period, the patients received a high dialysis dose; and anaemia, inflammation and blood pressure were well controlled.

A retrospective analysis of the United States renal data system database of patients entering dialysis from 1992 to 2003 found that the major factor affecting employment was patients' co-morbidities and recommended treating anaemia before patients entered dialysis and educating them on work-friendly home dialysis [27]. There was a significant relationship between the length of dialysis sessions, level of fatigue and amelioration of uraemia-associated clinical parameters [28]. In nocturnal HD, patients are free to carry out their routine activities during the day, which enhances their quality of life. According to Pipkin *et al.* [29], lack of patient or family motivation and fear of the dialysis process are surmountable barriers to the acceptance of home HD and the in-centre nocturnal HD option is a good alternative that should be encouraged because of its clinical, social and occupational rehabilitation benefits.

Other studies with prolonged duration were performed with a Q_b of between 200 and 400 mL/min, a Q_d of 500–800 mL/min and elevated dialysis dose. The Tassin experience [3] reported an spKt/V of 1.67 in 445 patients with a mean Q_b of 220 mL/min and Q_d of 500 mL/min. In 2009, Bugeja *et al.* [4] and Powell *et al.* [25] reported a URR of 89 and 77% in 39 and 146 patients, respectively, with a Q_b of 300–400 mL/min and Q_d of 500–700 mL/min. Finally, Ok *et al.* [26], Lacson *et al.* [24] and David *et al.* [5] reported an eKt/V of 1.87, 2.21 and 2.70 in 153, 655 and 13 patients, respectively. Our study represents a higher dialysis dose per session than that reported by other groups with thrice-weekly dialysis. stdKt/V has been proposed to measure the dialysis dose in dialysis regimens with frequency independency. The Lecce experience reported a weekly Kt/V of 4.6, which is approximately an stdKt/V of 2.36, while in our study, we achieved an stdKt/V of 3.77.

The haematocrit in Lecce dialysis was significantly higher (31.1%) than that in a population from the same region on standard HD (25.7%) [8]. Excellent anaemia control has been observed in all studies of long-duration dialysis. A decrease in erythropoietin dose has been reported by Bujeja *et al.* [4], David *et al.* [5] and Ok *et al.* [26], with reductions of 2089, 1512 and 1329 UI/week, respectively. In the present study, we observed this tendency with a reduction of 1083 UI/week and, at the end of the study, ESA treatment was discontinued in 29% of the patients.

During the follow-up, bicarbonate levels significantly increased compared with baseline data. These results are supported by those of Ok *et al.* [26] with nocturnal dialysis and by the Lecce experience of every-other-day dialysis [8]. As expected, BUN and serum creatinine levels were also significantly reduced. The remaining biochemical parameters

Table 7. Change from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF[a]

	Baseline	Month 3	Month 6	Month 9	Month 12
CRP (mg/L)					
Group A	1.80 ± 2.0	1.66 ± 1.6	1.11 ± 0.9	1.43 ± 1.7	1.18 ± 1.2
Group B	0.14 ± 0.1	0.30 ± 0.4	0.27 ± 0.3	0.49 ± 0.9	0.28 ± 0.3
All	0.97 ± 1.6	0.98 ± 1.3	0.69 ± 0.8	0.96 ± 1.4	0.73 ± 1.0
β_2-Microglobulin (mg/L)					
Group A	25.5 ± 7	23.4 ± 5	23.7 ± 5	24.2 ± 5	23.8 ± 4
Group B	27.6 ± 14	24.5 ± 10	28.0 ± 13	27.6 ± 13	27.9 ± 13
All	26.5 ± 11	24.0 ± 8	25.8 ± 10	25.9 ± 10	25.9 ± 10
Homocysteine (μmol/L)					
Group A	21.0 ± 8.7	20.0 ± 7.0	20.5 ± 6.6	20.0 ± 6.6	19.8 ± 6.6
Group B	22.4 ± 7.7	20.4 ± 6.8	22.9 ± 6.9	22.1 ± 7.4	20.8 ± 6.9
All	21.7 ± 8.1	20.2 ± 6.8	21.7 ± 6.7	21.1 ± 7.0	20.3 ± 6.6
Glycated haemoglobin (%)					
Group A	4.79 ± 1.0	5.00 ± 1.4	5.76 ± 3.6	5.11 ± 1.2	5.18 ± 1.4
Group B	4.63 ± 1.4	4.59 ± 1.4	4.75 ± 1.6	5.04 ± 2.1	4.84 ± 1.0
All	4.71 ± 1.2	4.80 ± 1.4	5.25 ± 2.8	5.08 ± 1.7	5.00 ± 1.2
IL-1 (pg/mL)					
Group A	5.42 ± 9	3.00 ± 2	2.92 ± 3	2.00 ± 0	2.00 ± 0
Group B	2.00 ± 0	2.00 ± 0	2.00 ± 0	2.00 ± 0	2.00 ± 0
All	3.71 ± 4	2.50 ± 1	2.46 ± 2	2.00 ± 0	2.00 ± 0
IL-6 (pg/mL)					
Group A	28.3 ± 56	37.1 ± 63	39.6 ± 57	23.5 ± 36	19.3 ± 25
Group B	6.3 ± 8	15.2 ± 17	12.8 ± 16	13.4 ± 21	10.2 ± 13
All	17.3 ± 32	26.2 ± 40	26.2 ± 37	18.5 ± 28	14.8 ± 19
TNF (ng/mL)					
Group A	25.4 ± 10	23.3 ± 10	29.3 ± 13	30.0 ± 9	29.4 ± 10
Group B	22.5 ± 7	25.7 ± 11	27.1 ± 10	28.3 ± 15	24.8 ± 12
All	23.9 ± 9	24.5 ± 10	28.2 ± 12	29.2 ± 12	27.1 ± 11

[a]Inflammatory findings. CRP, C-reactive protein; TNF, tumor necrosis factor. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.

evaluated showed no significant changes, except for an increase in HDL levels in Group A, although a confounding factor may be that some patients in Group A started statins during the study period.

Hyperphosphataemia is an independent predictor of mortality and has been associated with vascular calcification [30]. Most studies have found that phosphate removal is better with long-duration nocturnal HD than with conventional treatment because the increased time allows more efficient equilibration between the intracellular and extracellular compartments. In a case-controlled study, Powell *et al.* [25] observed no differences in pre-dialysis serum phosphate between conventional 4–5 h HD and 6–7 h overnight HD but did report a small decrease in phosphate binders from 92.5 to 86.8%. In a comparative trial after conversion from conventional 4-h dialysis to in-centre 7–8 h thrice-weekly nocturnal HD, Bugeja *et al.* [4] reported that phosphorus decreased from 5.9 to 3.7 mg/dL and the use of phosphate binders was reduced from 6.2 to 4.9 tablets/day at the end of the study. In a 655 patient cohort of in-centre long-term dialysis, Lacson *et al.* [24] found a significant reduction in serum phosphate of 0.2 mg/dL with no mention of phosphate binders. When comparing conventional with nocturnal HD, Ok *et al.* [26] found that serum phosphate levels significantly decreased (from 4.63 to 3.87 mg/dL) and that the need for phosphate binders was reduced (from 83 to 22.4%). In our study, better phosphate control was also observed (from 4.93 to 3.74 mg/dL) with a decrease in the need for phosphate binders from 77 to 4%. Moreover, in our study, the addition of phosphorus supplements in the dialysate was required in 55% of the patients. This improved phosphate control could be explained by the sum of several factors. Firstly, the dialysis dose was higher than in other studies; secondly, some studies have demonstrated that OL-HDF increases phosphate depuration with a reduction in pre-dialysis levels [31, 32] and finally, the increased frequency (every-other-day) is another advantage as studies of daily nocturnal dialysis have observed excellent phosphate control without phosphate binders and with phosphate supplementation in the dialysate [33, 34].

Some authors have suggested that long-duration nocturnal HD could improve nutritional status through an anti-inflammatory effect and increased appetite, energy and body weight [35, 36]. In a prospective evaluation of in-centre nocturnal HD, David *et al.* [5] found a significant improvement in nutritional status assessed by body weight (1.2 kg after 12 months), body mass index, nPCR and bioelectrical impedance. Another study of long-term dialysis [26] found that body weight increased 1.8 kg in patients who completed 1 year of follow-up. In the present study, improvements in certain causes of anorexia such as better appetite, reduced fluid overload and uraemic milieu could explain these nutritional advantages with the switch to 7–8 h nocturnal every-other-day OL-HDF. Importantly, the improvement of nutrition was without

Table 8. Change from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF[a]

	Baseline	Month 3	Month 6	Month 9	Month 12
SBP (mmHg)					
Group A	130.9 ± 29	129.3 ± 18	122.6 ± 21	116.1 ± 22[b]	118.8 ± 27
Group B	133.0 ± 21	131.3 ± 19	126.3 ± 22	126.4 ± 27	124.8 ± 24
All	132.0 ± 25	130.3 ± 18	124.4 ± 21	121.3 ± 24[b]	121.8 ± 26[b]
DBP (mmHg)					
Group A	69.8 ± 15	69.9 ± 13	62.3 ± 12	62.8 ± 10	64.2 ± 14
Group B	71.7 ± 15	73.4 ± 10	71.2 ± 17	69.3 ± 17	71.4 ± 17
All	70.7 ± 15	71.7 ± 12	66.8 ± 15	66.0 ± 14	67.8 ± 16
MBP (mmHg)					
Group A	90.1 ± 18	89.7 ± 12	82.4 ± 13	80.6 ± 11	82.4 ± 17
Group B	92.1 ± 15	92.7 ± 12	89.5 ± 17	88.3 ± 19	89.2 ± 19
All	91.1 ± 16	91.2 ± 12	86.0 ± 15	84.4 ± 16	85.8 ± 18
Anti-hypertensive (drug/day)					
Group A	0.25 ± 0.5	0.17 ± 0.4	0.08 ± 0.3	0.08 ± 0.3	0.08 ± 0.3
Group B	1.42 ± 1.4	0.58 ± 1.2[c]	0.50 ± 1.2[c]	0.25 ± 0.9[c]	0.25 ± 0.9[c]
	$P < 0.05$				
All	0.83 ± 1.2	0.38 ± 0.9[c]	0.29 ± 0.9[c]	0.17 ± 0.6[c]	0.17 ± 0.6[c]
EF (%)					
Group A	54.5 ± 9		58.7 ± 7		62.2 ± 10[b]
Group B	61.4 ± 5		63.3 ± 4		63.5 ± 5
All	57.9 ± 8		61.1 ± 7[b]		62.7 ± 8[c]
LVM (g)					
Group A	233 ± 71		238 ± 79		225 ± 60
Group B	260 ± 62		219 ± 69[b]		222 ± 44[b]
All	246 ± 66		230 ± 63		221 ± 63
LVMI (g/m^2)					
Group A	126 ± 36		127 ± 39		119 ± 23
Group B	152 ± 33		128 ± 21[b]		126 ± 31[b]
All	139 ± 36		127 ± 34		123 ± 22[b]

[a]Blood pressure and echocardiography parameters. CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, median blood pressure; EF, ejection fraction. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 month of 20–30 L.
[b]$P < 0.05$ with respect baseline value (analysis of variance repeated measures).
[c]$P < 0.01$.

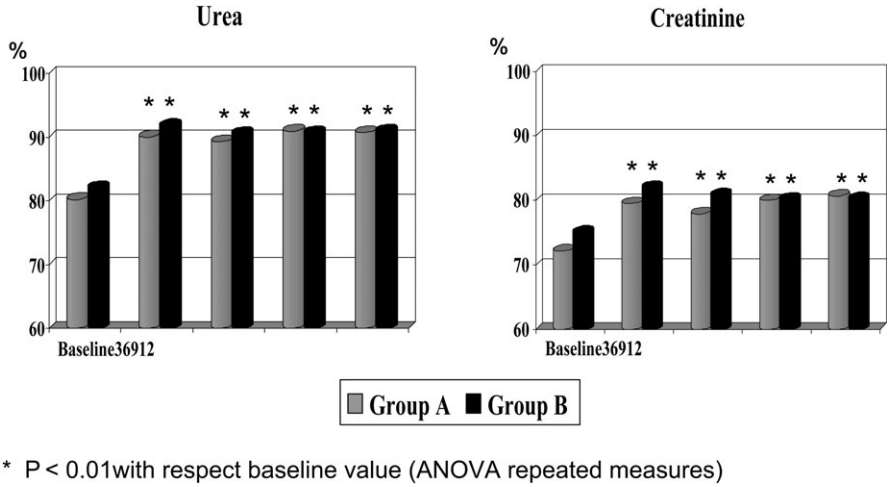

Fig. 5. Comparison of percentages of the reduction ratio in urea (60 Da) and creatinine (113 Da). Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.

significant changes in inflammation markers probably because the patients were not previously inflammed and received treatment with biocompatible dialysers, ultrapure dialysis fluid and convective techniques.

Cardiovascular disease is the most common cause of mortality in chronic HD patients, being the attributed cause of death in ~50%. The outline of this study has contributed greatly to reduce these cardiovascular risk factors specially

the reduction pre-dialysis phosphorus levels, blood pressure control and partial regression of LVH, which confirms the importance of increasing the duration of the sessions and higher frequency.

Hypertension is strongly associated with mortality and is highly prevalent in dialysis patients. It is not known for how long HD controls hypertension but has been suggested by reductions in serum norepinephrine levels and the improvement of heart rate response to pulsatile blood pressure (baroreceptor response and arterial compliance) [35]; an additional factor is the slower ultrafiltration rate in a longer time period. Charra *et al.* [36] suggest that factors hampering blood pressure control are the reduction in session time, an insufficient dialysis dose and increases in salt intake. In our study, although our patients were relatively well controlled at baseline, better blood pressure control was achieved, with only 8% of patients requiring anti-hypertensive medications at the end of the study.

LVH is an independent cardiovascular risk factor and is strongly associated with mortality in dialysis patients [37]. LVH is present in 70–80% of the dialysis population [38]. Hypertension, poor extracellular fluid volume control, anaemia and uraemia (accumulation of uraemic toxins and circulatory vasoconstrictors) have been implicated in the pathophysiology of LVH. In the present study, we observed a regression of LVH with the LVMI being reduced by 12% after 1 year. Other authors have reported regression of cardiac hypertrophy measured with echocardiography. Ok *et al.* [26] reported an LVMI reduction of 17% in patients receiving thrice-weekly nocturnal dialysis and Chan *et al.* [39] reported an LVMI reduction of 22% in 28 patients receiving slow nocturnal daily dialysis.

The authors were surprised of the fact that plasma level of β_2-microglobulin was not decreased during the follow-up in spite of a significant increase of infused volume and also by increasing time and frequency scheme. Previously published data [40] have shown that there are a direct correlation between infusion volume and β_2-microglobulin reduction ratio but this probably does not mean that it could reduce the pre-dialysis levels. This difficulty could be also explained by the low distribution volume of β_2-microglobulin [41]. Previous published studies have shown that pre-dialysis levels of β_2-microglobulin have been reduced when switching from low-flux to high-flux HD, low-flux HD to OL-HDF [42–44], high-flux HD to OL-HDF [14, 45], high-flux HD to daily, 8 h, nocturnal high-flux HD [46] and thrice a week, 4.0–5.0 h OL-HDF to daily, 2.0–2.5 h OL-HDF [47]. However, Ok *et al.* [26] reported that could not reduce pre-dialysis levels of β_2-microglobulin only changing dialysis duration.

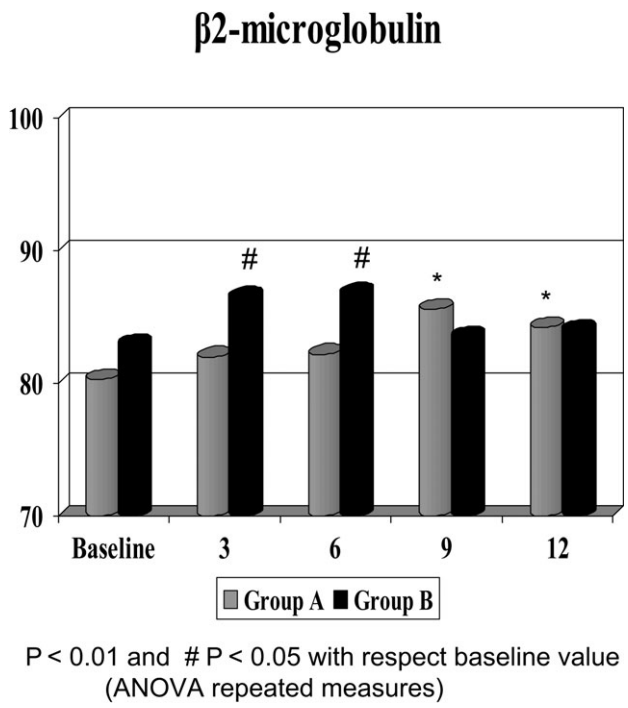

Fig. 6. Comparison of β_2-microglobulin (11 800 Da) reduction ratio for each study situation. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.

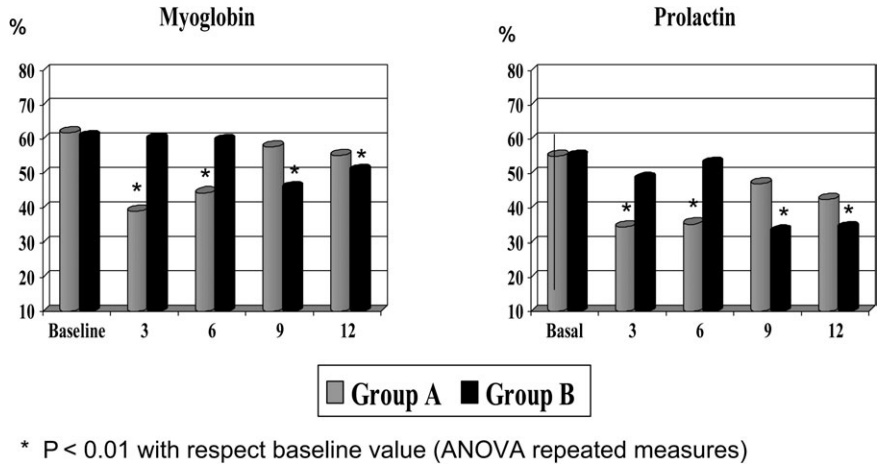

Fig. 7. Comparison of percentages of the reduction ratio in myoglobin (17 184 Da) and prolactin (23 000 Da) for each study situation. Group A ($n = 12$): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B ($n = 12$): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L.

Solute and fluid removal are the major goals of dialysis. Reduction of elevated pre-dialysis uraemic toxin levels may prevent or postpone the onset of dialysis-related complications. Resistance to diffusion within tissues and organs creates solute disequilibrium gradients. The resistance to diffusion can be quantitated as the intercompartment mass transfer coefficient (*K*c) and is molecular size-sensitive. Our crossover and randomized study allowed us to observe distinct patterns of molecule removal. The change to nocturnal every-other-day OL-HDF, 7–8 h per session. In this study, increased removal in urea (13%) and creatinine (9%) were shown.

The result of β_2-microglobulin removal, as a marker of middle molecule solutes, largely depends on convection processes. In this study, there were no differences between values at baseline and at 6 months with the same convective volume, indicating that removal of β_2-microglobulin mainly depends on the total convective volume, independent of the dialysis time. A different pattern was demonstrated for larger molecules than β_2-microglobulin. Plasma removal of myoglobin and prolactin reduction ratios was significantly decreased in Groups A and B in 6-month periods with the same convective volume. This finding could be explained by the different speed of infusion flow, which was 90–110 mL/min at baseline and in 6-month periods of 35–50 L convective volume but was 50–60 mL/min in 6-month periods with the same convective volume. Finally, α_1-acid glycoprotein reduction ratios, despite increasing from 4 to 14% in this study, showed the difficulty of removing molecules with a molecular weight >40 kDa. We conclude that conversion from 4–5 h thrice-weekly OL-HDF to 7–8 h every-other-day with online HDF in a crossover study with the same or higher convective volume shows excellent clinical tolerance and patient acceptance, adequate social and occupational rehabilitation, better dialysis adequacy, remarkable improvement in nutritional status, regression of LVH, good phosphate and hypertension control and a marked reduction of phosphate binders and anti-hypertensive medication. Different patterns of solute removal were observed, which were related to dialysis time, convective volume and/or to the infusion flow rate. Therefore, long-term, nocturnal, in-centre, every-other-day and online HDF with high convective volume could be a good therapeutic dialysis model that could improve clinical and social–occupational rehabilitation.

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Conflict of interest statement. None declared.

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