

Original Article

Change from conventional haemodiafiltration to on-line haemodiafiltration

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Abstract

Background. On-line haemodiafiltration (HDF) is a technique which combines diffusion with elevated convection and uses pyrogen-free dialysate as a replacement fluid. The purpose of this study was to evaluate the difference between conventional HDF (1–3 l/h) and on-line HDF (6–12 l/h).

Methods. The study included 37 patients, 25 males and 12 females. The mean age was 56.5 ± 13 years and duration of dialysis was 62.7 ± 49 months. Three patients dropped out for transplantation, three patients died and three failed to complete the study period. Initially all patients were on conventional HDF with high-flux membranes over the preceding 34 ± 32 months. Treatment was performed with blood flow (QB) 402 ± 41 ml/min, dialysis time (Td) 187 min, dialysate flow (QD) 654 ± 126 ml/min and replacement fluid (Qi) 4.0 ± 2 l/session. Patients were changed to on-line HDF with the same filter and dialysis time, QD 679 ± 38 ml/min (NS), QB 434 ± 68 ml/min ($P < 0.05$) and post-dilutional replacement fluid 22.5 ± 4.3 l/session ($P < 0.001$). We compared conventional HDF with on-line HDF over a period of 1 year. Dialysis adequacy was monitored according to standard clinical and biochemical criteria. Kinetic analysis of urea and β_2 -micro-globulin (β_2m) was performed monthly.

Results. Tolerance was excellent and no pyrogenic reactions were observed. Pre-dialysis sodium increased 2 mEq/l during on-line HDF. Plasma potassium, pre- and post-dialysis bicarbonate, uric acid, phosphate, calcium, iPTH, albumin, total proteins, cholesterol and triglycerides remained stable. The mean plasma β_2m reduction ratio increased from $56.1 \pm 8.7\%$ in conventional HDF to $71.1 \pm 9.1\%$ in on-line HDF ($P < 0.001$). The pre-dialysis plasma β_2m decreased from 27.4 ± 8.1 to 24.2 ± 6.5 mg/l ($P < 0.01$). Mean Kt/V (Daugirdas 2nd generation) was 1.35 ± 0.21 in conventional HDF compared with 1.56 ± 0.29 in on-line HDF ($P < 0.01$), Kt/Vr (Kt/V taking into consideration post-dialysis

urea rebound) 1.12 ± 0.17 vs 1.26 ± 0.20 ($P < 0.01$), BUN time average concentration (TAC) 44.4 ± 9 vs 40.6 ± 10 mg/dl ($P < 0.05$) and protein catabolic rate (PCR) 1.13 ± 0.22 vs 1.13 ± 0.24 g/kg (NS). There was a significant increase in haemoglobin (10.66 ± 1.1 vs 11.4 ± 1.5) and haematocrit (32.2 ± 2.9 vs $34.0 \pm 4.4\%$), $P < 0.05$, during the on-line HDF period, which allowed a decrease in the erythropoietin doses (3861 ± 2446 vs 3232 ± 2492 UI/week), ($P < 0.05$). Better blood pressure control (MAP 103.8 ± 15 vs 97.8 ± 11 mmHg, $P < 0.01$) and a lower percentage of patients requiring antihypertensive drugs were also observed.

Conclusion. The change from conventional HDF to on-line HDF results in increased convective removal and fluid replacement (18 l/session). During on-line HDF treatment, dialysis dose was increased for both small and large molecules with a decrease in uraemic toxicity level (TAC). On-line HDF provided a better correction of anaemia with lower dosages of erythropoietin. Finally, blood pressure was easily controlled.

Key words: adequate dialysis; convection; conventional haemodiafiltration; on-line haemodiafiltration

Introduction

Over the years, advances in technology have led to shorter haemodialysis treatments of increased efficacy and tolerance. Haemodiafiltration (HDF) techniques introduced in recent years would appear to offer an optimal form of treatment in patients with end-stage renal disease. There are several advantages of HDF over conventional haemodialysis. Firstly, HDF provides a greater clearing per unit surface area of both small and large molecules through the combination of diffusion and convection. Secondly, the convection techniques used increase haemodynamic stability, thereby reducing intradialysis symptoms [1–3] even in patients with increased cardiovascular risk [4]. Finally, the use of high permeability synthetic membranes in HDF provides, to date, the best biological compat-

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ability. There are various forms of HDF: biofiltration [5–6]; high-flux haemofiltration [7]; PFD (paired filtration dialysis) [8]; AFB (acetate-free biofiltration) [9]; and HDF with on-line production of substitution fluid.

On-line HDF is a technique that combines diffusion with elevated convection (infusion flux, Q_i , 3–12 l/h) in which the dialysis liquid, free of toxins and pyrogens, is used as the substitution fluid. The first works described in the literature to use the dialysis liquid as substitution solution were those of Shaldon *et al.* (1981) [11] using mixed haemofiltration, and later during the period 1982–1984 using high-flux HDF retrofiltration [7,12,13]. In each case, 2–4 patients were treated, using two filters in series with the objective of reducing dialysis treatment time to 2 h per session. In 1993, Canaud *et al.* [14,10] presented the first clinical results using on-line HDF.

On-line HDF when compared with other forms of HDF offers the advantages of a more simplified technology, allowing an elevated Q_i with high volumes of substitution liquid. The aim of this study was to change patients from a conventional HDF treatment (Q_i 1–3 l/h) to on-line HDF (Q_i 6–12 l/h), and evaluate their progress through biochemical analysis and clinical observation.

Subjects and methods

Thirty-seven patients, 25 males and 12 females, with a mean age of 56.5 years (range: 22–79 years), regularly treated with haemodialysis at the Hospitals of Alcoy (14 patients) and Castellón (23 patients) over a period of 62.7 ± 49 months were changed to on-line HDF. Residual renal function was negligible. The underlying renal diseases were chronic glomerulonephritis in 12 patients, polycystic kidney disease in five, chronic tubulo-interstitial nephritis in six, nephro-angiosclerosis in five, diabetes nephropathy in two patients, lupus nephritis in one and undiagnosed nephropathy in six patients. Three patients were excluded from receiving transplants, three died (myocardial infarction, stroke and mesenteric thrombosis), and, although another three continued with on-line treatment, they did not complete the 12 months outcome. As a result, the results of 28 patients are presented here.

The patients were on conventional HDF treatment (Q_i 1–3 l/h) with high permeability membranes for an average of 34 ± 32 months (ranging from 3 to 132 months). The last 6 months, during which conditions of treatment were not varied, were taken as the baseline period. The haemodialysis parameters were as follows: bicarbonate bath, blood flow (QB) 402 ± 41 ml/min (range 350–500), dialysate flow (QD) 654 ± 126 ml/min (range 500–750), dialysis time (Td) 187 ± 15 min, infusion flow (Q_i) 22 ± 12 ml/min equivalent to 4.1 ± 2.1 l/session (range 3–9), Monitral S dialysis monitor, dialysers 1.4 m² polysulphone in seven, 1.9 m² polysulphone in 10, 1.7 m² AN69 in two, 2.0 m² AN69 in six and cellulose triacetate in three patients; the replacement fluid had sodium 145, chloride 85 and bicarbonate 60 mEq/l. Interdialysis weight gain was 1.87 ± 0.95 kg.

During the period under study, the patients were changed to a Fresenius 4008B dialysis monitor, and on-line HDF was started using the same duration and dialyser. The QB was

434 ± 68 ml/min (range 350–600), $P < 0.05$, and QD (800 minus Q_i) 679 ± 38 ml/min (NS). The Q_i was 121 ± 35 ml/min equivalent to 22.5 ± 4.3 l/session (ranging from 18 to 36), $P < 0.001$. Re-infusion was always in post-dilution mode. Dialysers were not re-used. Treatment was carried out over 12 months.

Source water was treated with water softeners, charcoal filtration and reverse osmosis. The monitors volumetrically mixed treated water with bicarbonate concentrate, yielding the following final composition: Na 140, Cl 106.5, K 1.5, Ca 1.5, Mg 0.5, HCO₃ 35 and acetate 4 mmol/l, glucose 1 g/l. The generated dialysis fluid was filtered through the polysulphone hollow-fibre ultrafilter (Diasafe®). We renewed this filter every 3 months. The replacement fluid was filtered further by a second security polysulphone hollow-fibre ultrafilter (On-line HDF filter system®) which was renewed every 50 HDF sessions.

Each month at mid-week, pre-dialysis serological analyses for haematocrit, haemoglobin, ferritin, transferrin saturation (TS), urea, creatinine, uric acid, sodium, potassium, pre- and post-dialysis bicarbonate, magnesium, calcium, phosphorus, intact parathormone (iPTH), serum protein, albumin, cholesterol, triglycerides, and β_2 -microglobulin (β_2m) were carried out, as well as a bimonthly analysis of aluminium. Monthly calculations were made of the urea kinetics: second generation Daugirdas Kt/V [15], urea reduction ratio (URR), estimated urea rebound [16], Kt/V and URR taking into consideration post-dialysis urea rebound (Kt/Vr and URRr) using the formulae of Maduell *et al.* [16,17], normalized protein catabolic rate (nPCR) and TAC (BUN). Treatment of water and dialysis liquid was also monitored using monthly microbiological cultures and analysis of aluminium. On the day of analytical control, pre-dialysis blood pressure was measured immediately before treatment with an automatic BPM 4008 blood pressure monitor (Fresenius).

The results are shown as the arithmetic mean \pm the standard deviation. The Student *t*-test (paired data) and ANOVA (repetitive data) were used in the analysis of differences in quantitative variables. A value of $P < 0.05$ was considered statistically significant.

Results

On-line HDF was well accepted by both the patients and health care workers at the unit. From a clinical viewpoint, there was a good tolerance to on-line HDF, there were no observed reactions to pyrogens and the patients felt better in subjective terms. The number of hypotensive episodes was not changed between the two treatment schedules. Normal body weight was maintained precisely despite the high volumes of substitution solution, 22.5 l/session, and ultrafiltration, interdialysis weight gain was 1.97 ± 0.98 kg.

The limiting factors for Q_i were: QB (maximum: QB/3); transmembrane pressure (TMP) which rose in proportion to Q_i ; the gain in interdialysis weight (UF); haematocrit (greater haematocrit = greater viscosity = greater TMP); and Td, normally on-line HDF was started with Q_i at one-third or less of the QB value and was then reduced during the course of the session due to increased TMP.

There were few biochemical changes, as can be seen in Table 1. Values were normal for acidosis, ionogram, calcium, phosphorus, iPTH, cholesterol, triglycerides,

Table 1. Change from conventional HDF to on-line HDF. Biochemical outcome

	Baseline	3 months	6 months	9 months	12 months
Creat. (mg/dl)	9.57 ± 1.5	9.12 ± 1.8	9.17 ± 1.8	9.42 ± 2.1	9.45 ± 2.1
Urea (mg/dl)	152 ± 26	135 ± 34**	140 ± 33*	142 ± 33	138 ± 38*
Sodium (mEq/l)	139.7 ± 2.7	141.6 ± 4.3*	141.2 ± 3.7	141.2 ± 4.0	141.1 ± 4.5*
Potassium (mEq/l)	5.4 ± 0.8	5.5 ± 0.9	5.4 ± 0.8	5.5 ± 0.6	5.4 ± 0.6
Bicarb. pre (mEq/l)	22.9 ± 2.9	22.8 ± 2.5	23.3 ± 2.5	23.3 ± 2.5	23.1 ± 2.8
Bicar. post (mEq/l)	27.6 ± 2.0	27.4 ± 2.3	28.4 ± 1.5	28.2 ± 2.1	28.3 ± 1.8
Uric acid (mg/dl)	5.9 ± 0.9	6.1 ± 1.0	6.0 ± 1.3	5.8 ± 0.9	6.3 ± 1.1
Magnesium (mg/dl)	2.7 ± 0.3	2.8 ± 0.4	2.6 ± 0.4	2.5 ± 0.3	2.7 ± 0.3
Calcium (mg/dl)	9.8 ± 0.9	10.4 ± 1.0**	10.1 ± 0.7	10.1 ± 0.8	10.5 ± 1.0**
Phosphorus (mg/dl)	5.4 ± 0.9	4.9 ± 1.5	4.9 ± 1.5	5.0 ± 1.3	5.0 ± 1.2
iPTH (pg/dl)	223 ± 188	153 ± 149	214 ± 238	244 ± 271	200 ± 216
Cholesterol (mg/dl)	179 ± 46	193 ± 54	186 ± 38	188 ± 38	187 ± 48
Triglycerides (mg/dl)	130 ± 66	136 ± 65	137 ± 84	127 ± 60	148 ± 73
Prot. totales (g/dl)	6.9 ± 0.5	6.7 ± 0.5	6.8 ± 0.4	6.8 ± 0.4	6.7 ± 0.4
Albumin (g/dl)	4.18 ± 0.5	4.08 ± 0.4	4.15 ± 0.4	4.20 ± 0.4	4.22 ± 0.3
Aluminium (µg/l)		25.2 ± 14	32.1 ± 16	28.7 ± 17	30.0 ± 17

* $P < 0.05$ with respect to baseline value; ** $P < 0.01$ with respect to baseline value.

protein and albumin. The only statistically significant increase was in the levels of sodium. It was not possible to compare changes in aluminium (base level 17.2 ± 7.3 mg/l) due to a change in the laboratory carrying out the analysis which gave increased values in both conventional and on-line HDF.

The β_2 m reduction ratio increased from $56.1 \pm 8.7\%$ in conventional HDF to $71.1 \pm 9.1\%$ in on-line HDF ($P < 0.001$). Figure 1 shows that there was a significant decrease in pre-dialysis β_2 m during the first 2 months of treatment, which returned to initial levels after 3–5 months, followed by a slight decrease.

There was a significant increase in haemoglobin and haematocrit values which stabilized after the fourth month at 11.3–11.5 g/dl haemoglobin and 34–35% haematocrit (see Figure 2). Erythropoietin doses could be reduced progressively from the third month. There were no significant changes in ferritin, or transferrin saturation (Table 2).

Urea kinetics (see Table 3 and Figure 3). The dialysis doses expressed as Kt/V , Kt/V_r , PRU or PRUr increased significantly with a consequent increase in the urea rebound. The levels of urea toxicity expressed as the TAC of BUN decreased significantly from the first month. Protein intake expressed as the normalized

PCR for dry body weight was similar during both types of treatment. The tendency towards increased dry body weight became statistically significant (1 kg above baseline) after 11–12 months of treatment.

During the baseline period, nine patients (32%) had high blood pressure (pre-dialysis MAP > 110 mmHg) and 18 were receiving medication for high blood pressure. Average values were: SBP 148.4 ± 24 ; DBP 81.5 ± 13 ; and MAP 103.8 ± 16 . In the last months of on-line HDF treatment, only two patients had high blood pressure and 11 were receiving medication, SBP was 138.5 ± 18 ($P < 0.01$), DBP 77.4 ± 9.6 ($P < 0.05$) and MAP 97.8 ± 11 ($P < 0.01$).

Microbiological analysis of dialysis water always gave negative results. Analysis of aluminium levels in the water gave results consistently below $5 \mu\text{g/l}$, and in most cases was undetectable.

Discussion

On-line HDF is a safe technique well tolerated by the patient that allows a considerable increase in convection thanks to its simple technology and the lower costs involved due to the use of dialysis liquid as substitution solution.

The total infusion volume is only limited by the QB ($1/3$ of QB) and the PTM, which is influenced by ultrafiltration, haematocrit and duration of the session. In our patients with elevated QB (average 434 ml/min), we have been able to achieve high Q_i values, reaching an infusion volume of 22.5 l/session, representing an increase of > 18 l/session when compared with conventional HDF.

We have seen few biochemical changes from the baseline. The change in treatment did not modify acidosis, phosphataemia, calcaemia or metabolism of proteins and lipids. There was an increase in pre-dialysis sodium which had no effect on interdialysis weight or on the control of blood pressure. There was

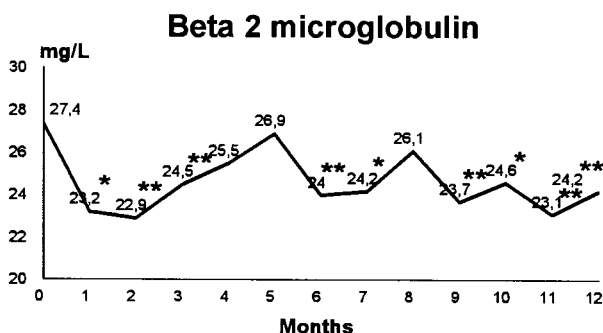


Fig. 1. Change from conventional HDF to on-line HDF: pre-dialysis β_2 m outcome over 12 months in 28 patients (* $P < 0.05$, ** $P < 0.01$).

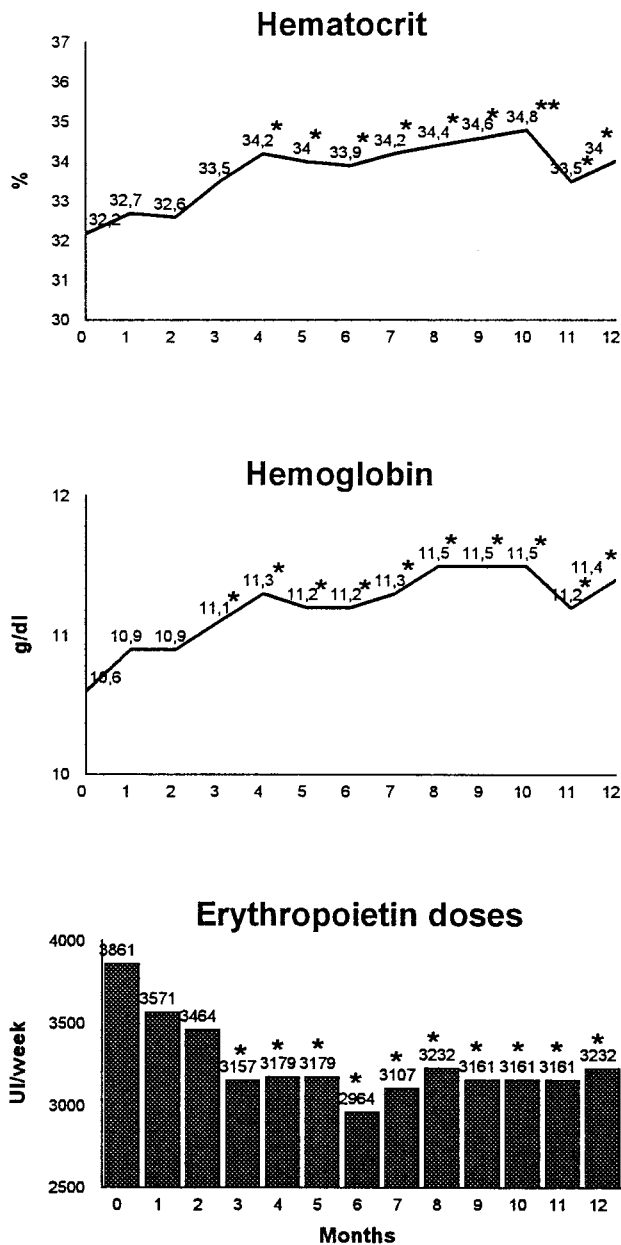


Fig. 2. Change from conventional HDF to on-line HDF: haematocrit, haemoglobin and erythropoietin doses outcome over 12 months in 28 patients (* $P < 0.05$).

a clear improvement in blood pressure, and a reduction in the number of hypertensive patients and its treatment.

The main objective in changing from conventional to on-line HDF was to achieve a greater filtration of medium and large sized molecules through an increase in convection. There was a corresponding 12% reduction in plasma β_2m over a 12 month period. Plasma β_2m reduction ratio increased from 56 to 71% in on-line HDF. The reduced levels of β_2m could be explained by the low distribution volume ($\sim 20\%$) of this molecule [18,19], or a slow equilibrium with the plasma volume. Gotch *et al.* [20] postulated various possible mechanisms to explain the increase of plasma β_2m at the end of dialysis sessions and the difficulty in reducing pre-dialysis levels: (i) an immunological response to the dialysis with an increment in β_2m production by immunoreactive cells; (ii) an increase in post-dialysis cellular catabolism; and (iii) mobilization of β_2m in areas of high concentration (similar to allopurinol in gout).

We should not forget, however, that β_2m is a large molecule (11 800 Da), and the role of medium sized molecules is not well understood. Unfortunately, there are no medium sized molecules that can be used as a marker to trace their elimination. Vitamin B12 (mol. wt 1355 Da) is not useful for *in vivo* studies because of its high binding affinity for plasma proteins [21]. Ahrenholz *et al.* [22] in an *in vitro* study of three patients compared HD without re-infusion with on-line HDF (Qi 85 ml/min) and found that clearance of vitamin B12 increased from 107 to 169 ml/min (a 59% increase) and of inulin (mol. wt 5200 Da) from 56 to 128 ml/min (a 229% increase).

Dialysis during the baseline period met with recommendations from multicentre studies carried out in Northern America [23], $Kt/V = 1.3$, guidelines published by the National Kidney Foundation (DOQI) [24], $Kt/V = 1.2$, and a HEMO study [25,26], $Kt/V = 1.25$ or $Kt/Vr = 1.05$. Our patients with a basal Kt/V of 1.35 or Kt/Vr of 1.12 showed a 15% increase with on-line HDF (Kt/V 1.55–1.56 and/or Kt/Vr 1.28–1.29). This improvement is due primarily to the increase in infusion volume but is also explained in part by the increase in QB (50 ml/min). This high dialysis dose is accompanied by a beneficial decrease in the levels of urea toxicity (TAC). The results of the HEMO high dose (Kt/V 1.6 and/or Kt/Vr 1.45) studies

Table 2. Change from conventional HDF to on-line HDF. Haematological outcome

	Baseline	3 months	6 months	9 months	12 months
Haemoglobin (g/dl)	10.66 ± 1.1	11.13 ± 1.4*	11.20 ± 1.6*	11.49 ± 1.4**	11.36 ± 1.5*
Haematocrit (%)	32.2 ± 2.9	33.5 ± 4.1	33.9 ± 4.8*	34.6 ± 3.8**	34.0 ± 4.4*
Ferritin (ng/ml)	312 ± 112	353 ± 209	365 ± 224	327 ± 156	341 ± 201
Transferrin saturation (%)	40.1 ± 17	42.6 ± 14	40.9 ± 13	42.9 ± 15	45.2 ± 16
Erythropoietin doses (U/week)	3861 ± 2446	3157 ± 2632	2964 ± 2441*	3161 ± 2453*	3232 ± 2492*

* $P < 0.05$ with respect to baseline value; ** $P < 0.01$ with respect to baseline value.

Table 3. Change from conventional HDF to on-line HDF. Urea kinetics outcome

	Baseline	3 months	6 months	9 months	12 months
Urea rebound (%)	22.8 ± 3.4	26.9 ± 4.5**	27.1 ± 4.9**	26.9 ± 4.7**	26.3 ± 4.9**
Kt/V (Daug. 2nd gen)	1.35 ± 0.2	1.54 ± 0.2**	1.55 ± 0.2**	1.55 ± 0.2**	1.52 ± 0.2**
Kt/Vr	1.12 ± 0.17	1.27 ± 0.2**	1.28 ± 0.2**	1.28 ± 0.2**	1.26 ± 0.2**
URR (%)	68.8 ± 5.1	73.5 ± 4.8**	73.7 ± 5.2**	73.5 ± 5.0**	72.9 ± 5.1**
URRr (%)	61.8 ± 5.1	66.6 ± 5.0**	66.8 ± 5.4**	66.6 ± 5.2**	66.0 ± 5.3**
TAC (BUN), (mg/dl)	44.4 ± 9.0	37.6 ± 10**	39.0 ± 10**	41.2 ± 10*	40.6 ± 10*
nPCR (g/kg)	1.13 ± 0.22	1.08 ± 0.22	1.12 ± 0.24	1.17 ± 0.23	1.13 ± 0.24
Dry weight (kg)	63.4 ± 8.6	63.7 ± 8.9	63.8 ± 8.5	64.1 ± 8.7*	64.4 ± 8.8**

* $P < 0.05$ with respect to baseline value; ** $P < 0.01$ with respect to baseline value.

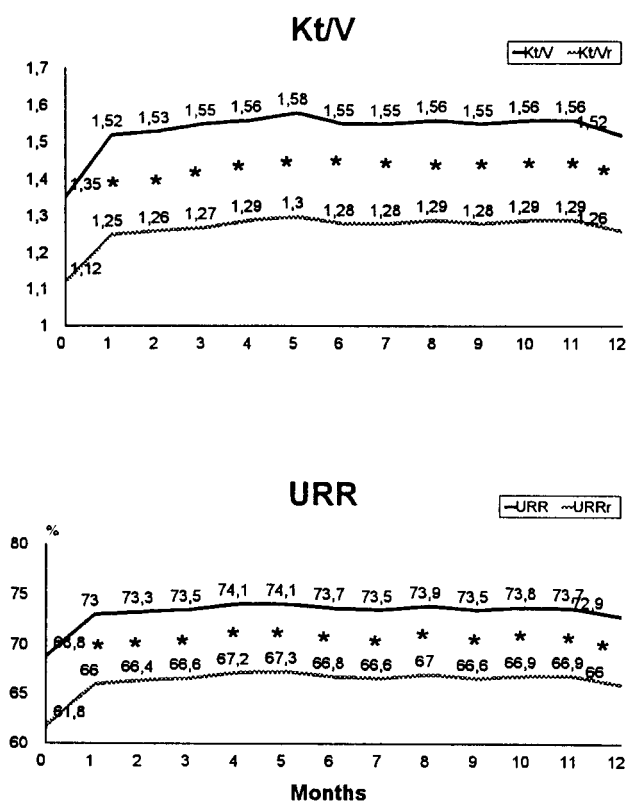


Fig. 3. Change from conventional HDF to on-line HDF: dialysis dose (Kt/V and URR) and equilibrated dialysis dose (eKt/V and eURR according to the formulae of Maduell) outcome over 12 months in 28 patients (* $P < 0.01$).

due to end in the year 2000 [26] will be needed to corroborate the beneficial effects resulting from increased dialysis.

The good evolution of the anaemia has also been observed by other authors [27]. One possible explanation could be that the increased dialysis dose favours a greater erythropoietin response [28–30]. Other authors [31] have attributed the erythropoietin response to the greater elimination of middle and large sized molecules. In our study, both criteria are met.

Nutritionally, there is a greater loss of proteins with on-line HDF treatment [32], reflected in our study by the reduction of albumin in the first months and of total protein in the final months, neither reaching

statistically significant levels. The patients had a good appetite as a result of improved anaemia and maintained PCR; the dry weight increased slowly and steadily, reaching statistical significance in the last 2 months.

We conclude that the change from conventional to on-line HDF permits a marked increase in convection (18 l/session) with good clinical tolerance. The principal advantages were in the increased dialysis dose both for middle and large molecules, a reduction of urea toxicity levels (TAC), a reduction in the dose of erythropoietin needed to correct anaemia, and better control of blood pressure.

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