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On-line haemodiafiltration: long term outcomes

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ABSTRACT

Background: Conventional haemodialysis is associated with a high mortality rate and is less efficient than on-line haemodiafiltration (olHDF), which enlarges the spectrum of cleared middle-size uraemic toxins, such as β2-microglobulin, as it combines convective and diffusive transportation.

In the present study we intend to evaluate and compare long-term outcomes of this technique with previous low-flux haemodialysis results for the same patients.

Patients and Methods: From June 1996 to March 2007, fifty-six end-stage renal disease patients were treated with olHDF at our unit. The study population comprised fourteen patients dialysed with on-line haemodiafiltration for seven years after a median period of six years [1-10] on low-flux haemodialysis. They were 62.4±11.3 years old and predominantly female (6M:8F). We compared the last six months on conventional haemodialysis to the second subsequent halfyears of on-line haemodiafiltration over the course of seven years.

Results: After a seven year period of olHDF, this technique was superior to low-flux haemodialysis in terms of urea clearance (Kt/Vsp 2.05±0.48 *vs.* 1.67±0.25; p<0.05), reduction of prehaemodialysis β2-microglobulin (24.7±4.7 *vs.* 33.6±9.5 mg/l; p<0.05) and anaemia control (haemoglobin 12.8±1.3 *vs.* 11.6±1.1 g/dl; p<0.05).

Six of these patients suffered from clinical carpal tunnel syndrome (CTS) before the shift to olHDF, but only one underwent neurolysis of the median nerve at that time. Nevertheless three of the remaining five had that surgery on olHDF. In fact only five surgeries were actually performed because one patient had bilateral median nerve neurolysis. We registered two new cases of CTS after the implementation of olHDF.

Triglycerides (182±66 *vs.* 125±47 mg/dl; p<0.05) and total cholesterol (179±53 *vs.* 154±32 mg/dl; p<0.05) decreased and HDL cholesterol increased (41±9 *vs.* 52±21 mg/dl; p<0.05) with olHDF. Normalised Protein Nitrogen Appearance (nPNA) and C-reactive protein (CRP) remained stable during olHDF but albumin progressively decreased (3.93±0.32 *vs.* 3.32±0.29 g/dl; p<0.05).

With olHDF there was an increase of iPTH (80 [16-687] *vs.* 190 [15-1845] pg/ml; p<0.05) and serum phosphorus remained stable.

olHDF was not superior to low flux haemodialysis in terms of intradialytic cardiovascular stability as shown by an increase of hypotensive episodes and a progressive reduction of BP over the years on olHDF. Pyrogenic reactions were absent and hospital admissions remained stable throughout the study.

Conclusions: Long-term on-line haemodiafiltration appears to be more effective in dialysis dose, metabolic control and patient safety than low-flux haemodialysis. We could not find any superiority of the technique in terms of intradialytic haemodynamics after the first two years of this technique.

Key-Words:
β2-microglobulin; dialysis adequacy; dialysis-related amyloidosis; intradialytic hypotension; on-line haemodiafiltration.

INTRODUCTION

Considering that a weekly urea Kt/V of 3.6 approximately corresponds to a glomerular filtrate of 13 mL/min/1.73 m^2 and that chronic dialysis patients mortality rate is around 50% in five years, conventional haemodialysis is far from optimal renal substitution therapy. High efficiency and high-flux haemodialysis (hfHD) using higher area and permeability membranes increase the clearance of small and medium molecular weight uraemic toxins. Although some observational reports[1,2] suggest higher patient survival on hfHD, the prospective and randomised HEMO study[3] did not confirm it. Nevertheless, the European Dialysis Outcome and Practice Patterns Study (DOPPS)[4] revealed that high replacement volume haemodiafiltration (>15 litres/session) patients had 35% lower mortality risk than patients receiving low-flux haemodialysis (lfHD). The Membrane Permeability Outcome (MPO)[5] study did not detect a significant survival benefit with either high-flux or low-flux membranes in the population overall, but the use of high-flux membranes conferred a significant survival benefit in patients with serum albumin 4 g/dl. Despite of the lack of survival benefit in hfHD patients, secondary analysis showed a mortality reduction for patients with diabetes mellitus or serum albumin lower than 4 g/dl.

The benefits of on-line haemodiafiltration (olHDF) may be explained by the increase of small and medium molecular weight uraemic toxin clearance[6], as it combines diffusion and convection. In order to optimise convective transport, ultrafiltration greatly exceeds the desired net loss for each session, so a pre- or postfilter substitution of replacement liquid is performed.

HDF was described for the first time by Leber[7] in 1978. Countless contributions to this technique progress have been achieved since then, including high permeable and more biocompatible membranes, ultrafiltration control systems and on-line production of the replacement fluid. In addition, convection has been associated with better intradialytic haemodynamic stability[8].

We began olHDF at our haemodialysis unit in 1996. In a previous study[9] we found some favourable outcomes after one year of this technique: improvement in intradialytic haemodynamic stability, dialysis dose, anaemia and lipid correction, and also a lower hospital admission rate. However, predialysis β2-microglobulin did not reduce significantly.

In this study, we intend to assess and compare the same outcomes during a seven year period of olHDF to results obtained for the same patients on their last six months of low-flux haemodialysis (lfHD).

PATIENTS AND METHODS

Fifty-six end-stage renal disease patients were treated with olHDF at our unit from June 1996 to March 2007. At the start of olHDF therapy they were 62.8±13.9 years old and predominantly male (33M:23F). In the present study, we have selected 14 patients that were on olHDF for at least seven years. Some clinical and laboratory data from the last six months of low-flow haemodialysis (lfHD) were compared with the second semester of olHDF each year during the follow-up. A six month wash-out period was implemented after each evaluation period according to the modified Bernard Canaud model[10].

We evaluated the following parameters: intradialytic haemodynamic stability, delivered dialysis dose (Kt/Vsp), predialysis serum β2-microglobulin, anaemia control, phospho-calcium metabolism, nutritional and inflammatory variables, serum aluminium, lipid profile, pyrogenic reactions and finally hospital admissions (Table I).

In all the phases, the same dialysis machine was used, a Fresenius 4008H. When used for olHDF, sterile pyrogen-free substitution was prepared on-line from ultrapure dialysis fluid by an additional step of ultrafiltration using a sterile ultrafilter.

The hygiene of the fluid pathway was assured by chemical disinfection after each treatment. The monitor and the filters were treated with peracetic acid disinfectant overnight and over weekends.

The ultrafilters were changed monthly and microbiological surveillance was performed according to the manufacturer's instructions.

Table I

Clinical, biochemical and haematology parameters

	lfHD	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Pre-HD mean BP	111	116*	119*	115	115	111	107*	103*
Hypotension (% of sessions)	11	12	11	14*	13*	16*	18*	18 *
Qb (ml/min)**	384±23	389±27	385±29	384±19	378±28	368±36	360±34*	362±42 *
Reposition volume (litres/session)	–	16.4	16.6	18.6	20.0	20.0	20.0	20.0
Kt/V *sp*	1.67±0,25	1.81±0.25*	1.89±0.24*	1.96±0.28*	2.01±0.44*	2.03±0.43*	2.11±0.35*	2.05±0.48 *
PNAn (g/kg/dia)	1.07±0.22	1.02±0.20*	1.02±0.20*	0.99±0.24*	1.02±0.22*	1.03±0.23	1.03±0.27	1.05±0.24
Pre HD β2-M (mg/l)	33.6±9.5	30.1±12.3	21.2±2.3*	22.2±2.1*	23.4±2.6*	24.2±4.7*	22.3±3.5*	24.7±4.7 *
CRP (mg/dl)	0.8 [0.6-2.7]	0.6 [0.4-4.4]	0.8 [0.5-4.9]	0.5 * [0.3-1.2]	0.7 [0.6-1.5]	0.7 [0.2-1.1]	0.5* [0.1-1.3]	0.5* [0.1-1.4]
Aluminium (µg/l)	17.8±11.4	15.0±11.5	14.1±8.1	12.8±9.1	10.5±5.4*	10.7±5.4*	10.5±6.4*	9.0±5.0 *
Aluminium hydroxide (n. patients)	4	3	4	4	4	1*	1*	0*
iPTH (pg/ml)	80 [16-687]	116 [12-715]	162* [26-673]	182* [16-602]	252* [27-1070]	298* [26-1454]	225* [55-662]	190 [15-1845]
Calcium (mg/dl)	10±0,6	9.8±0.7	9.8±0.6	9.9±0.8	9.9±0.6	10.0±0.8	9.8±0.8	9.6±0.7*
Ca Dialysate (mEq/l)	3.2±0.4	3.1±0.4*	2.8±0.3*	2.9±0.4*	2.8±0.3*	2.8±0.3*	2.9±0.3*	2.8±0.3*
Calcium carbonate (g/day)	2 [0-6]	2 [0-6]	0* [0-6]	2 [0-6]	2 [0-6]	1 [0 – 8]	0* [0-12]	0* [0-9]
Phosphate (mg/dl)	5.3±1.8	5.0±1.6	5.3±1.7	5.4±1.4	5.5±1.4	5.3±1.4	4.8±1.4	4.6±1.3*
Albumin (g/dl)	3.93±0.32	3.79±0.35*	3.79±0.30*	3.76±0.25*	3.74±0.26*	3.50±0.27*	3.37±0.28*	3.32±0.29*
Haemoglobin (g/dl)	11.6±1.1	11.8±1.2	11.8±1.6	12.4±1.3	12.8±1.3*	12.8±1.5*	12.9±1.5*	12.8±1.3*
EPO (U/week); n	4100; 10	4900; 10	7000; 12	6000; 12	4000; 9	2000; 11	6100; 12	5500; 11
Transferrin saturation (%)	18.3±8.0	19.9±9.4	23.0±14.4*	23.6±11.8	25.1±9.4*	25.4±10.1*	25.6±10.3*	24.5±11.9*
Ferritin (ng/ml)	315±271	218±127*	263±120	286±191	313±107	215±104	269±128	233±143*
Total cholesterol (mg/dl)	179±53	178±39	183±40	176±60*	176±53*	155±40*	159±42*	154±32*
HDL cholesterol (mg/dl)	41±9	42±9*	39±13	41±11	47±11*	47±15*	42±11*	52±21*
Triglycerides (mg/dl)	182±66	141±51*	144±58	147±76*	109±45*	112±44*	111±41*	125±47*
Hospital admission rate (n/ patient-year)	0.14/	0.43	0.07	0.14	0.29	0.50	0.29	0.43
hospital admission rate (days/patient-year)	1.50	3.79*	1.21	1.36	2.29	2.86	2.14	2.57

*p<0.05 (always compared to lfHD)
**Qb-blood flux

The same fluid electrolyte concentration was used for both haemodialysis and olHDF: sodium 140-144, calcium 1.25-1.75 and bicarbonate 30-34 mmol/l. The prescription of electrolyte fluid concentrations was individualised and adjusted monthly.

The temperature dialysate setting on the machine (35.5-36.0ºC) was kept relatively constant according to patient tolerability and hypotensive profile.

All hemofilters used for haemodialysis and olHDF were made of polysulfone. The blood flux target was 350-400 ml/min in both techniques and dialysis fluid flow was 500 ml/min and 800 ml/min for lfHD and olHDF, respectively.

The replacement fluid in olHDF was always infused after the dialyser (postdilution) and consisted of 10 litres/session until December 1998 and 20 litres/session thereafter.

All patients were dialysed four hours, thrice weekly. Our water treatment system integrates two reverse osmosis in series. Monthly disinfection of treatment system and water distribution net were always performed as well as bacteriological controls. Water and

dialysate endotoxins were also measured monthly. Our HD unit uses dry bicarbonate (Bibag®) and produces acid on-line with Fresenius Granudial AF (CDS).

The switch from conventional dialysis to olHDF was performed according to clinical criteria favouring older, diabetic or patients with dialysis-related amyloidosis (DA).

The criteria for intradialytic hypotension included any of the following:

- Reduction of blood pressure (BP) associated with one or more symptoms (nausea, vomiting, cramps, dizziness or loss of consciousness) that led to specific therapeutic procedures;
- Sudden dizziness, fainting sensation or loss of consciousness leading to specific interventions, even if it was not possible to record BP values;
- Systolic BP lower than 90 mmHg if accompanied by symptoms and/or needing therapeutic procedures.

The relevant specific intervention measures mentioned included Trendelenburg's position, increase of sodium dialysate, sodium chloride or hypertonic intravenous infusion, temporary reduction or abolition of ultrafiltration and suspension of the dialysis session.

Adjustments in dry weight, erythropoietin, antihypertensive drugs, vitamin D, phosphate binders and dialysate calcium concentration were performed according to our unit protocols. Pyrogenic reaction was diagnosed based on the presence of hyperthermia (axillary temperature above 38ºC) without any presumed infection. Hospital admissions were also evaluated as a marker of morbidity.

The majority of results are presented as mean and standard deviation except for CPR and iPTH, which are presented as median [minimum, maximum]. Continuous variables were compared using the t-test with the chi-square test used for categorical variables.

RESULTS

At the beginning of the study, the 14 patients enrolled were 62.4±11.3 years old and eight were female. They had heart failure (n=5), diabetes mellitus (n=3) and cerebrovascular disease (n=2). Their causes of end-stage renal failure were autosomal dominant polycystic kidney disease (n=4), unknown aetiology (n=3), diabetic nephropathy (n=2), tubulointerstitial nephritis (n=2), rapidly progressive renal failure (n=1), chronic glomerulonephritis (n=1) and urinary obstruction (n=1). They had been on lfHD for six years [1-10].

The predominant vascular access was the arteriovenous fistula (n=12). The remaining two patients had tunnelled dialysis catheters.

The clinical, biochemical and haematological parameters evaluated are specified in Table I.

Higher urea clearance (Kt/Vsp 2.05±0.48 *vs.* 1.67±0.25; p<0.05) on olHDF may be explained by the added convection and higher dialysate flux (Qd). Reduction of predialysis β2-microglobulin (24.7±4.7 *vs.* 33.6±9.5 mg/l; p<0.05) was significant after the first year on olHDF, when compared with conventional haemodialysis. Six of these patients already suffered from clinical carpal tunnel syndrome (CTS) before the beginning of olHDF. One patient underwent bilateral neurolysis of the median nerve before and other three patients had this surgery after the start of olHDF. Noticeably we registered two more cases of CTS after olHDF was implemented.

The earlier gains in intradialytic haemodynamic stability were lost over the years on olHDF, as shown by the increase of hypotensive episodes.

Haemoglobin values increased in olHDF (12.8±1.3 *vs.* 11.6±1.1 g/dl; p<0.05) without any counterpart increase in erythropoietin (EPO) dose. Transferrin saturation was higher in olHDF but serum ferritin remained stable.

In our patients serum aluminium level reduction (9.0±5.0 *vs.* 17.8±11.4 g/dl; p<0.05) preceded the decline of aluminium hydroxide use as phosphate binder suggesting these were independent factors and that olHDF might be superior to lfHD in terms of aluminium removal.

Triglycerides (182±66 *vs.* 125±47 mg/dl; p<0.05) and total cholesterol (179±53 *vs.* 154±32 mg/dl; p<0.05) decreased and HDL cholesterol increased

(41±9 *vs.* 52±21 mg/dl; p<0.05) with olHDF. Normalised Protein Nitrogen Appearance (nPNA) and C-reactive protein (CRP) remained stable during olHDF but albumin progressively decreased (3.93±0.32 *vs.* 3.32±0.29 g/dl; p<0.05).

With regard to phospho-calcium metabolism, the highlight was the increase of iPTH (80 [16-687] *vs.* 190 [15-1845] pg/ml; p<0.05) to the desired values and the stability of serum phosphorus. Calcium levels progressively decreased, due to the progressive reduction of calcium dialysate concentration and of calcium carbonate use as phosphate binder.

There was no pyrogenic reaction or significant variation in hospital admissions throughout the study.

DISCUSSION

olHDF removes medium molecular weight molecules. Nevertheless, there are few studies showing a progressive reduction of predialysis β2-microglobulin, including our short-term review[9]. Better removal of β2-microglobulin was achieved with olHDF due to the long course of convection and adsorption of hydrophobic substances such as β2-microglobulin to the surface of the dialysis membrane[11,12]. This latter mechanism takes place predominantly in the pores of the hydrophobic synthetic membranes and, to a lesser degree, in hydrophilic cellulose membranes. Carpal tunnel syndrome (CTS), one of the major clinical manifestations of dialysis-related amyloidosis (DA), can be delayed or even prevented by olHDF[13]. Six of our patients had CTS established before they began olHDF. One of them underwent surgery before and three during this technique. Nevertheless, we had only two more cases of CTS during the follow-up, suggesting a lower incidence of DA with olHDF.

Conflicting data exists concerning the relative effect of convective therapies on nutrition. Similarly to other studies[14,15], we found that olHDF was associated with an improvement of lipid profile expressed by an increase of HDL cholesterol and a reduction of total cholesterol and triglycerides. The increased clearance of a medium molecular weight lipoprotein lipase inhibitor[16] has been suggested as the major cause of this benefit. It does not seem that these patients were malnourished, because of their nPNA stability. Albumin level decrease might be explained in part by the increase of albumin loss due to the adsorption of olHDF. Nevertheless, it was proved that hfHD despite of its large pore size and sieving coefficient filters does not lose more dialysate amino acids than lfHD, which is around 5-8 g/dialysis in either hfHD and lfHD when dialysis dose and blood flow (Qb) were adjusted[17].

Anaemia is one of the major causes of ventricular hypertrophy in haemodialysis patients. Erythropoietin is used in 80 to 100% of those patients. In our own patients, haemoglobin values increased along the years without any variation in erythropoietin dose or iron stores. It is postulated that the great removal of uraemic inhibitors of erythropoiesis by convection may be responsible for this olHDF benefit[18,19]. Ultrapure water may also contribute by reducing the inflammatory state[20].

Serum aluminium level reduction in our patients was independent of the decreased aluminium hydroxide use as phosphate binder.

The haemodynamic benefit of olHDF could be related to higher clearance of vasodilator mediators, a negative thermal balance conditioned by the cooling of the extracorporal circuit, larger outlying vascular resistance and also to a lower sodium removal[21,22]. Our haemodialysis centre participated in a study conducted by Maggiore[23] which demonstrated that a lower dialysate temperature (35ºC) gives larger stability than the standard (37ºC). Donauer[24] explained this fact as being due to blood cooling along the extracorporal circuit. Better haemodynamic stability of this technique was described[21-24], but was not confirmed in our long-term study after the second year. In fact, hypotensive episodes were more frequent after two years, but we must take into consideration the low number of hypotensive episodes at our unit, the absence of a control group and the age of the patients.

As in most hospital-based HD units our patients were negatively selected in terms of comorbidity and age. These factors might have also contributed to the albumin reduction along the years, regardless of the lower inflammatory stimulus of this technique.

Hyperphosphataemia is a risk factor for mortality in haemodialysis patients[25]. olHDF removes a

larger amount of phosphate[26] that is not always expressed by phosphataemia reduction because of the slow efflux of phosphate from the large intracellular stores into the extracellular fluid during dialysis and subsequent rebound. In our study, phosphataemia remained stable and median iPTH reached the objective values of KDOQI[27] 2003. The reduction of calcaemia was possibly dependent on the decrease in dialysate calcium concentration and in calcium carbonate.

Bernard Canaud classified olHDF as the most biocompatible dialytic technique with the lowest inflammatory stimulus, demonstrated by the reduction of acute inflammation markers such as CRP[28]. In a recent prospective and randomised study this technique was even related to minimal endothelial lesion[29]. Ramirez and co-workers found that olHDF compared to hfHD significantly reduced endothelial dysfunction due to a lower inflammatory stimulus expressed by pro-inflammatory cells CD14+ CD16+ and endothelial progenitor cells reduction. They explained the lower inflammatory state of olHDF as due to its modulatory effect on inflammatory cells and/or the largest removal of uraemic toxins.

Pyrogenic reactions were absent during olHDF in our patients and none of them was excluded from this technique because of undesirable effects. Morbidity, evaluated by the number and duration of hospital admissions, remained stable.

Few studies with long-term olHDF results have been published to date. Our long-term experience in olHDF allowed us to present seven year results in fourteen patients.

olHDF was an effective technique in terms of dialysis dose, β2-microglobulin removal, lipid profile and anaemia control. It was also a safe dialysis modality as shown by the absence of pyrogenic reactions.

We consider olHDF to be more effective than conventional haemodialysis in terms of dialysis dose, metabolic control and patient safety. Despite the initial cardiovascular stability, we found no superiority of the technique in terms of intradialytic haemodynamics after the first two years.

Conflict of interest statement. None declared.

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