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ORIGINAL ARTICLE

Evaluation of the efficacy of a medium cut-off dialyser and comparison with other high-flux dialysers in conventional haemodialysis and online haemodiafiltration

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Abstract

Background: Online haemodiafiltration (OL-HDF) has been shown to reduce all-cause mortality versus conventional haemodialysis (HD); however, it is not always available. In these situations, a novel class of membranes with a higher pore size, medium cut-off (MCO) dialysers, could be promising. The aim of this study is to evaluate the efficacy of an MCO dialyser in the removal of small and medium-size molecules and compare it with standard high-flux (HF) dialysers in HD and OL-HDF.

Methods: In this crossover study, 18 prevalent HD patients were studied in three single mid-week dialysis treatments during three consecutive weeks as follows: first week with OL-HDF with a standard HF dialyser, second week with conventional HD with a standard HF dialyser and third week with conventional HD with an MCO dialyser. Reduction ratios (RRs) of different-sized molecules and albumin losses were collected for the different dialysers.

Results: MCO HD provided a greater reduction of middle and larger middle molecules compared with standard HF HD [rate reduction (RR) β2-microglobulin 74.7% versus 69.7%, P=0.01; RR myoglobin 62.5% versus 34.3%, P=0.001; RR prolactin 60% versus 32.8%, P=0.001; RR α1-glycoprotein 2.8% versus −0.1%, P=0.01]. We found no difference in the clearance of small and larger middle molecules comparing MCO HD with OL-HDF. Albumin losses were 0.03 g/session with MCO HD and 3.1 g/session with OL-HDF (P=0.001).

Conclusion: MCO HD is superior to standard HF HD in the removal of middle and larger middle molecules and it is not inferior to OL-HDF in the clearance of small and larger middle molecules. Thus it could be an alternative in patients in which it is not possible to perform OL-HDF.

Key words: chronic haemodialysis, dialysis, dialysis adequacy, haemodialysis, uraemic toxins

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Introduction

Patients with end-stage renal disease (ESRD) undergoing chronic intermittent haemodialysis (HD) have a higher risk of cardiovascular (CV) morbidity and mortality. This could be explained by an ageing population with an increased prevalence of comorbid factors such as diabetes and hypertension [1] and also by risk factors due to uraemia itself, leading to chronic inflammation and mineral disorders. Uraemic toxins are classified into small (<500 Da), middle molecular (>500 Da) water-soluble solutes and protein-bound substances [2]. Retention of uraemic toxins in the middle molecular range, which are poorly removed by conventional HD modalities [3], has been associated with pathological features of uraemia and might play an important role in the adverse outcomes in dialysis patients due to CV disease [4]. Therefore, in recent decades, efforts have focused on improving the clearance of larger middle molecules in dialysis. High-flux (HF) membranes, which allow the clearance of middle molecules such as β2-microglobulin by convective transport, were introduced years ago. However, no clinical benefit of HF versus low-flux membranes was shown in two randomized clinical trials (the MPO and HEMO studies), except in subgroup analyses [5, 6]. The development of online haemodiafiltration (OL-HDF) techniques that combine diffusive and convective transport has resulted in markedly enhanced clearance of middle to large molecules. Its benefits to patient survival were first pointed out by retrospective studies [7–10] and afterwards confirmed by large randomized clinical trials like the Convective Transport Study CONTRAST study [11], the Turkish study [12] and the Estudio de Supervivencia de Hemodiafiltraciůn On-Line (ESHOL) [13] study, whose main conclusion was that high-efficiency post-dilution OL-HDF reduces all-cause mortality compared with conventional HD, especially when higher convective volumes are achieved. Unfortunately, OL-HDF techniques are not available for every patient for different reasons, including vascular access dysfunction, water treatment systems unable to provide ultrapure water or economic problems, even though OL-HDF can be considered cost effective compared with HF HD [14]. In these situations, a novel class of membranes with a higher pore size designed to increase the removal of larger middle molecules in conventional HD, called medium cut-off (MCO) dialysers, could be promising [15]. However, since they have been recently introduced, there is a lack of evidence on their use. There is only one study so far that compares the efficacy of MCO dialysers with HD and OL-HDF using contemporary HF dialysers, concluding that MCO HD removes a wide range of middle molecules more effectively than HF HD and even exceeds the performance of OL-HDF for large solutes [16].

The main objective of the present study was to evaluate the efficacy of an MCO dialyser in the removal of small and medium-size molecules, as well as albumin losses. The second objective was to compare the efficacy of the MCO dialyser with HF HD and OL-HDF using contemporary HF dialysers.

Materials and methods

Design of the study

This transversal study was performed in patients with ESRD from the Dialysis Unit of Gregorio Marañon Hospital in Madrid, Spain. Informed consent was obtained. The study was conducted according to the Declaration of Helsinki.

Patients. Patients included were >18 years old, had no renal residual function and were on OL-HDF treatment for a period of >3 months before enrolment. They had to be clinically stable, defined as no hospitalization during the 3 months prior to inclusion. Exclusion criteria were patients who were not receiving OL-HDF, showed residual renal function, were not clinically stable or patients who declined to participate in the study.

Dialysis sessions. Treatments and dialysers were compared in a single mid-week treatment during three consecutive weeks: first week with OL-HDF with a standard HF dialyser, second week with conventional HD with a standard HF dialyser and third week with conventional HD with an MCO dialyser. In the rest of the sessions of the week, they received OL-HDF with their current prescription and dialysers.

The sessions were 4 h long and the dialysis treatments were based on their current prescription, with no restriction on blood flow. The OL-HDF sessions were performed in post-dilution mode with no restriction on the total convective ultrafiltration volume. In every session the ultrafiltration flow rate was adjusted to reach dry weight. Any individual anticoagulant treatment was continued as previously prescribed.

Dialysers and techniques

OL-HDF was performed using FX CorDiax 1000 dialyser (Fresenius Medical Care, Bad Homburg, Germany), HF HD was performed using FX CorDiax 80 dialyser (Fresenius Medical Care and MCO dialysis was performed using Theranova 500 dialyser (MCO, Gambro Dialysatoren, Hechingen, Germany, a subsidiary of Baxter International). Dialyser membrane characteristics are described in Table 1. Monitors used were models 5008 (Fresenius Medical Care), AK 200 Ultra (Gambro Baxter) and ARTIS (Gambro Baxter).

Samples. The efficacy of each treatment was analysed by measuring the reduction rates of substances with different molecular weights, which are shown in Table 2.

We obtained in each mid-week dialysis samples before and after the dialysis sessions. We estimated the rate reduction (RR) of small and medium-size molecules. The RR was calculated:

$$\mathrm{RR}\,(\%) = [1 - (C_{\mathrm{post}}/C_{\mathrm{pre}})] \times 100,$$

where C_{pre} and C_{post} are measured plasma concentrations of the solute before and at the end of study treatments, respectively.

Albumin losses were determined with MCO dialyser and in OL-HDF by measuring albumin levels in the dialysis fluid at 0, 5, 15, 30, 60, 120 and 240 min of the dialysis session with an inverse pump and measured albumin concentration using an autoanalyser (Dimension RXL, DADE, Siemens, Erlangen, Germany). The dialysate flux values were recorded at these time points. Thus, assuming that albumin losses decrease over time during the session, we estimated the minimum amounts of total leakage in each period:

$$\text{Rate of leakage} = \text{dialysate flux}\,(\mathrm{mL/min})\ 0 \times \text{Concentration}\,(\mathrm{mg/mL}).$$

We did not collect albumin losses from HF HD because of their small quantity. Serum, plasma and spent dialysate samples were collected and sent to our laboratory under standardized conditions.

Table 1. Characteristics of dialysis membranes in study dialysers

	Inner diameter (μm)	Wall thickness (μm)	Membrane polymer[a]	Effective surface area[a] (m^2)	UF coefficient[a] (mL/h/mmHg)	KoA_{urea}
Theranova	180	35	Polyarylethersulphone–PVP blend	2	59	
FX CorDiax 80	185	38	Polysulphone–PVP blend	1.8	64	1429
FX CorDiax 1000	210	35	Polysulphone–PVP blend	2.3	68	1421

[a]According to manufacturer's instructions for use.
KoA, urea mass transfer coefficient; PVP, polyvinylpyrrolidone; UF, ultrafiltration.

Table 2. Molecular weights of the different analysed substances

Substance	Molecular weight (Da)
Urea	60
Creatinine	113
Phosphate	30
β2-microglobulin	11 000
Cystatin C	13 000
Myoglobin	17 800
Prolactin	23 000
α1-glycoprotein	41 000

Statistical analysis

Analyses were performed using SPSS analysis software version 20.00 (SPSS, Chicago, IL, USA). Treatment effects were evaluated using a two-sided significance level of 0.05. The distribution of variables was analysed using the Kolmogorov–Smirnov test. Values are given as mean (SD) or median (interquartile range). Continuous variables were compared using statistics for repeated measurements (analysis of variance).

Results

Baseline characteristics

A total of 18 patients were included in the study. Patient and treatment characteristics are shown in Table 3.

Removal of small and middle molecules during HD and OL-HDF

RRs of medium- and small-size molecules in each treatment are shown in Table 4.

In our study, the MCO dialyser achieved a significantly higher mean RR of middle-size molecules, such as β2-microglobulin, cystatin C, myoglobin, prolactin and α1-glycoprotein ($P < 0.01$), compared with HF HD (Table 2). The RRs of small molecules such as urea, creatinine and phosphate were also higher with the MCO dialyser, yet the differences were not statistically significant.

Compared with HDF, removal of larger-size solutes such as α1-glycoprotein was greater with MCO HD (2.4 ± 0.08% versus 2.8 ± 0.18%), yet not significant ($P = 0.9$), whereas there was no difference in RRs of small molecules.

Albumin removal during MCO HD and OL-HDF

Albumin removal with MCO dialyser (0.03 ± 0.01 g/session) was significantly lower ($P < 0.001$) compared with OL-HDF (3.1 ± 0.6 g/session).

Safety

No adverse events were recorded among our population during the duration of the study or a 7-day period after each treatment.

Discussion

To our knowledge, this is one of the first studies that provides clinical experience with this novel class of dialysis membranes. The objective was to evaluate the efficacy of MCO dialyser in the removal of small and middle molecules and compare it with HD and OL-HDF using contemporary HF dialysers. The choice to compare with FX CorDiax dialysers was based on their wide use in Europe and reports indicating they achieve significantly greater middle molecule removal than other HF dialysers. Our results are strong, conclusive and similar in terms of efficacy to those obtained with OL-HDF.

Even though convective volumes reached during our OL-HDF sessions were 28 L on average, which has been shown to reduce all-cause mortality in the ESHOL study [13], probably because of an enhanced clearance of middle-size molecules, the results obtained with the MCO dialyser in conventional HD are comparable with those in OL-HDF. When we analysed the RRs of small-size molecules, such as urea, creatinine and phosphate, we found no significant differences between the MCO dialyser and OL-HDF. Regarding middle-size molecules, although the RRs of most of the molecules analysed were slightly but significantly higher with OL-HDF, there were no significant differences in the RRs of β2-microglobulin between the MCO dialyser and OL-HDF, which is the principal middle-size molecule whose levels predict mortality in dialysis patients, as shown in a *post hoc* analysis of the HEMO study [17].

Our RR of middle molecules obtained with MCO dialyser is comparable with those obtained by Kirsch *et al.* [16] in study 1 of their trial, in which mean dialysis time was 4 h (RR β2-microglobulin 71.5–72% in Kirsch *et al.*'s study versus 74.7% in our study; myoglobin 63.1–67% in Kirsch *et al.*'s study versus 62.5% in our study). The RRs obtained in study 2 of Kirsch *et al.*'s trial were higher because mean dialysis time was longer (4–5 h) and thus they cannot be directly compared with our results. Moreover, our patients reached higher convective volumes in OL-HDF compared with Kirsch *et al.*'s study (28 versus 21 L/session), which enhances the clearance of middle molecules. This explains that our RR of middle molecules with MCO dialyser, though comparable with those obtained by Kirsch *et al.*, are lower than those obtained with our OL-HDF. That could also explain the lower albumin losses with MCO HD compared with OL-HDF we found in our study. Nevertheless, we estimated the minimum amounts of total albumin leakage with each dialyser based on the albumin concentration in the dialysate fluid at different points and dialysate flow, but we did not correct by

Table 3. Baseline characteristics of the study population ($N = 18$)

Age (years), mean ± SD	65 ± 13		
Sex (M/F), *n*/*n*	9/9		
CKD aetiology (%)			
Glomerular	44.4		
Diabetes mellitus	33.3		
Policystic disease	16.7		
Tumoural	5.6		
Vascular access (AVF) (%)	88.9		
Dialysis vintage (months), median (IQR)	75 (35–108)		
Predialysis haematocrit (%), mean ± SD	32.2 ± 6.4		
Effective dialysis time (h), mean ± SD	4 ± 0.05		
Blood flow at 30 min (mL/min), mean ± SD	450 ± 80		
Kt/V per session, mean ± SD	FX1000	FX80	Theranova
	1.9 ± 0.6	1.8 ± 0.4	1.9 ± 0.4
Ionic dialisance per session (mL/min), mean ± SD	284 ± 40	266.1 ± 23	277.8 ± 33
Convective volume during OL-HDF sessions (L/session), mean ± SD	28 ± 8		
Interdialytic weight gain (kg), mean ± SD	1.8 ± 0.7		
Ultrafiltration volume (L/session), mean ± SD	2.1 ± 1.2		

CKD, chronic kidney disease; AV, arteriovenous fistulae; IQR, interquartile range.

Table 4. Comparison of RR with each molecule using HF HD with FX80 dialyser, HD with MCO Theranova dialyser and OL-HDF using FX1000 dialyser

Substance	FX80 HD	Theranova HD	FX1000 OL-HDF	P-value
Urea	82.3 (4.39)	83.5 (7.15)	85.4 (3.91)	ns
Creatinine	74.8 (4.92)	75.7 (7.47)	77.4 (5.90)	ns
Phosphate	58.8 (10.63)	60.5 (11.62)	61.4 (11.62)	ns
β2-microglobulin	69.7 (6.57)	74.7 (8.09)*	81.2 (4.29)*	<0.001
Cystatin C	63.8 (4.79)	71.6 (7.45)**	78.9 (4.87)*	<0.001
Myoglobin	34.3 (7.88)	62.5 (8.66)*	72.4 (7.31)*	<0.001
Prolactin	32.8 (9.79)	60 (8.20)*	69.2 (9.13)*	<0.001
α1-glycoprotein	−0.1 (6.85)	2.8 (18.79)**	2.4 (7.98)*	0.02

All values presented as mean (SD).
*$P < 0.001$ versus HD.
**$P < 0.05$ versus HD.
ns, non-significant.

ultrafiltration volume, which could explain the difference between our results and those obtained by Kirsch *et al.*

The RR of larger middle molecules such as α1-glycoprotein was higher with the MCO dialyser than with OL-HDF, although the differences did not reach statistical significance, probably due to the reduced population included in our study. On the other hand, when we compared the RR between MCO dialyser with a standard dialyser in conventional HD, we found greater clearance of small, middle and larger middle molecules with MCO dialyser, which was statistically significant for middle and larger middle molecules, including β2-microglobulin, cystatin C, prolactin, myoglobin and α1-glycoprotein.

Our findings agree with those obtained by Kirsch *et al.* [16] in a randomized clinical trial and show that this novel class of membranes offers an opportunity to improve the removal of uraemic toxins in every HD patient, not only in candidates for OL-HDF.

In recent years there has been controversy concerning the benefits and risks of increasing convective volumes in OL-HDF because, due to their inner diameter and pore size, the enhanced pressures required for reaching these volumes may cause the leakage of certain substances such as albumin [18, 19]. Nevertheless, there is yet no evidence on the clinical impact of these losses [20]. We analysed albumin losses with MCO dialyser, as the higher pore size could lead to increased leakage, but instead we found significantly lower albumin losses compared with OL-HDF. Thus this potential but questionable limitation of OL-HDF concerning albumin losses should not represent a problem when using MCO dialysers.

A limitation of this study was the small sample size, which could explain why some of our results, although clinically relevant, did not reach significant differences. Moreover, we performed just one session with each dialyser, as it was designed as a transversal study, although follow-up could have added more information in terms of CV events and survival. This could also explain the fact that we found no adverse events in our population, differing from the results provided in Kirsch *et al.* [16], where adverse events were recorded in >50% of patients. However, our results are positive, strong and promising, especially for patients who are not candidates for OL-HDF.

To conclude, in light of the results of this study we can say that MCO dialyser is superior to conventional HD with standard HF dialysers in the removal of middle and larger middle molecules and it is not inferior to OL-HDF in the clearance of small and larger middle molecules. Thus it could be an alternative in patients in which it is not possible to perform OL-HDF.

Conflict of interest statement

None declared.

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