

Original Article

Mid-dilution on-line haemodiafiltration in a standard dialyser configuration

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Abstract

Background. Mid-dilution haemodiafiltration (HDF) results in an improved middle molecule removal compared with standard HDF. The OLPurTM MD 190 haemodiafilter represents a new dialyser design exclusively for mid-dilution on-line HDF. Compared with standard haemodialysers, structural changes in the headers allow the infusion of high replacement fluid volumes after a first post-dilution and before a second pre-dilution stage.

Methods. We compared *in vitro* the new device [blood flow (Q_B) 400 ml/min, substitution flow (Q_S) 100 and 200 ml/min, dialysate flow (Q_D) 800 ml/min] with a conventional high-flux dialyser of the same surface area in haemodialysis (HD) (Q_D 500 ml/min) and post-dilution HDF (at Q_S 60, Q_D = 500 ml/min and at Q_S 100, Q_D = 800 ml/min) modes. Subsequently, we performed an initial clinical application of the new device in six mid-dilution HDF treatments of five end-stage renal disease patients (Q_B 400 ml/min, Q_S 200 ml/min, Q_D 800 ml/min, treatment duration 205 ± 23 min).

Results. *In vitro* urea and β_2 -microglobulin clearances in mid-dilution HDF were, respectively, 309.2 ± 5.5 and 144.4 ± 15.2 ml/min (Q_S 100) and 321.6 ± 4.1 and 204.9 ± 4.1 ml/min (Q_S 200), compared with 278.6 ± 17.2 and 94.0 ± 7.6 ml/min in HD, and 310.8 ± 10.2 and 123.0 ± 6.5 ml/min (Q_S 60) and 323.6 ± 11.2 and 158.0 ± 10.3 ml/min (Q_S 100) in post-dilution HDF. The *in vivo* trials showed the clinical utility of the device and confirmed the *in vitro* data: urea and β_2 -microglobulin clearances were, respectively, 324.6 ± 10.9 and 207.9 ± 29.3 ml/min, while reduction ratios were 75.0 ± 5.5 and $83.6 \pm 4.7\%$.

Conclusion. Our preliminary results need confirmation in a prospective cross-over study. However, the Nephros MD 190 haemodiafilter promises to be a true

technological step ahead in terms of improved β_2 -microglobulin removal.

Keywords: haemodiafiltration; haemodialyser design; middle molecules; mid-dilution; on-line substitution fluid

Introduction

Haemodiafiltration (HDF) is a form of renal replacement therapy that provides an improvement in middle molecule clearance compared with standard haemodialysis (HD) [1–3].

The most common forms of HDF use a standard high-flux dialyser [4]. Replacement of ultrafiltered plasma water is generally performed by infusing a substitution fluid into the blood either before the blood enters the dialyser (pre-dilution HDF) or after the blood exits the dialyser (post-dilution HDF), or a combination of both (mixed-HDF) [5]. The source of substitution fluid can be bags of sterile fluid, or it can be generated ‘on-line’ from dialysate, using appropriate filters and strict hygienic practices [6–8]. These diafiltration modes, however, have inherent limitations. For example, adding a substitution fluid in the pre-dilution mode negatively affects the clearance of small molecular weight toxins by reducing the concentration gradient between the blood and dialysate streams. In a post-dilution mode, the filtration rate of plasma water from blood is generally limited to <25% of the blood flow rate, due to haemoconcentration effects and the resulting high viscosity of blood as it passes through the dialyser.

To remove middle molecular weight toxins from uraemic blood, several investigators have evaluated configurations in which a second dialyser has been added to the blood circuit or configurations having multiple dialyser stages. Examples include ‘high-flux HDF’ [9], ‘paired filtration dialysis’ [10] and ‘modified

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on-line HDF' [11]. Though these systems have shown some promise, their increased complexity, compounded by doubled disposable dialyser costs, have limited their acceptance in the clinic. To bridge this gap, investigators continue to look for ways to design a single, cost-effective device that efficiently removes small molecular weight toxins such as urea [used for the kinetic modelling for the determination of dialysis adequacy, i.e. urea reduction ratio (URR) or Kt/V] while maximizing clearances of middle molecules [12].

The objective of this study is to present the design and basic performance of a new haemodiafilter that has been optimized for removal of uraemic toxins across the molecular weight spectrum. This device integrates a mid-dilution HDF technology into a cost-effective, single fibre bundle cartridge.

Materials and methods

Haemodiafilter design

The OLpürTM MD 190 haemodiafilter (Nephros, Inc.) is shown in Figure 1. Its basic construction is similar to a typical hollow fibre dialyser, containing a cylindrical fibre bundle that has been 'potted' with polyurethane to form a fibre bundle tube sheet at each end of the device. The lumen of each hollow fibre is opened at each end by a polyurethane trimming operation. Prior to adding header caps at each end of the device, a circular groove is incorporated into the fibre bundle tube sheet at one end of the device. A two-port header cap (for blood inlet and outlet connections) is then attached to the device at the end that includes the groove. The header cap includes an internal wall that fits into the

circular groove, in effect creating two discrete but serially connected paths for blood: an outer or annular path (stage 1) and an inner or core path (stage 2). Incoming blood is restricted to the annular header region, which communicates with the hollow fibres of stage 1. Treated blood exiting the hollow fibres of stage 2 is collected into the inner header region, which directs blood toward the blood outlet port and back to the patient. The other end of the device has a single port header cap which is used to infuse substitution fluid in a mid-dilution mode. The volume of this single-port header cap is larger than that of a typical dialyser blood header cap, because it functions as a mixing chamber for the infused substitution fluid and the partially treated blood exiting the annular hollow fibres of stage 1. The blood and substitution fluid mixture then flows into the core hollow fibres of stage 2 in a reverse direction relative to the blood flowing through the annular hollow fibres of stage 1. Fresh dialysate enters the device at the end with the single-port (substitution) header cap and perfuses in and around the fibre bundle (outside the hollow fibers) in the same manner as a hollow fibre dialyser. Spent dialysate exits the device at the end with the two-port (blood) header cap.

In vitro study

To evaluate the performance of the mid-dilution haemodiafilter design, control dialysers with the same surface area and containing the same high-flux polyethersulfone membrane (DIAPES[®] HF800, Membrana GmbH, Wuppertal, Germany) as the OLpürTM MD 190 device were constructed using typical dialyser blood header caps. Measurements of urea and β_2 -microglobulin (β_2m) clearances were performed on the bench with bovine blood [$32 \pm 3\%$ haematocrit (Hct)] in a single pass configuration at a blood flow (Q_B) of

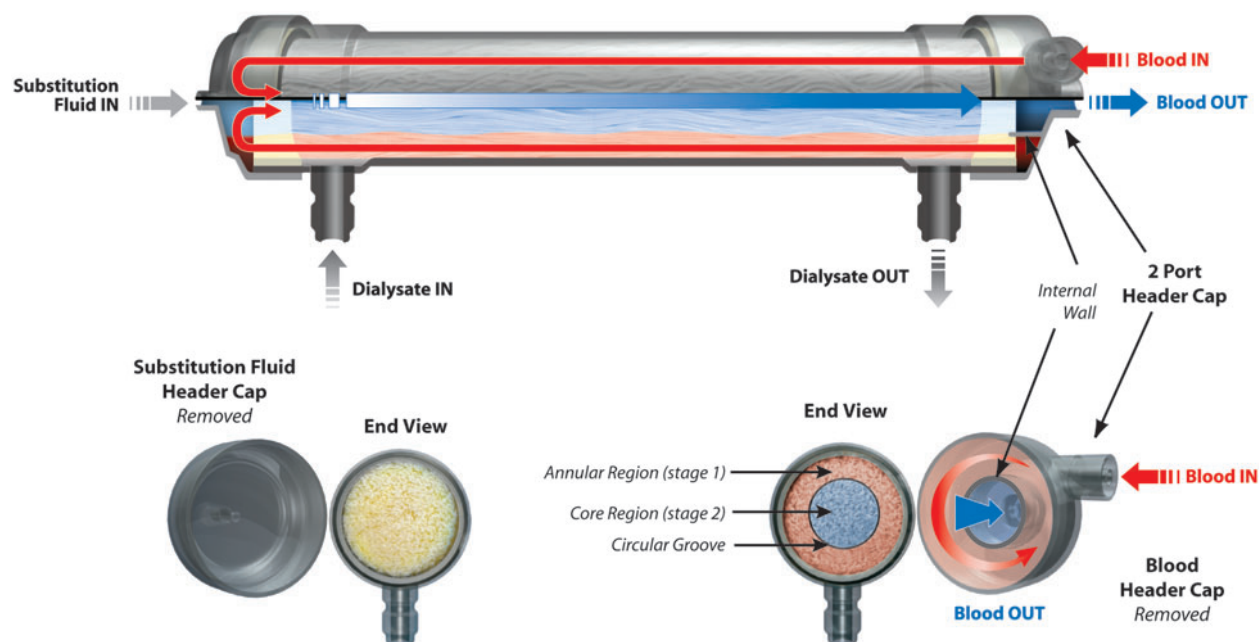


Fig. 1. Schematic illustration of the Nephros OLpürTM MD 190 mid-dilution haemodiafilter. Using a special two-port header cap, blood flows through the annular region of the fibre bundle (stage 1), mixes with substitution fluid at the other end, and flows in the reverse direction through the core region of the fibre bundle (stage 2) (courtesy of Nephros, Inc., NY).

400 ml/min. The control dialysers were tested under standard conditions at a dialysate flow (Q_D) of 500 µl/min and at substitution fluid flows (Q_S) of 0 ml/min (HD mode) and 60 ml/min (post-dilution HDF mode) and at a dialysate flow (Q_D) of 800 ml/min and at a substitution fluid flow (Q_S) of 100 ml/min (post-dilution HDF mode). The OLpürTM MD 190 devices were tested at substitution fluid flows (Q_S) of 100 and 200 ml/min in the mid-dilution HDF mode. Dialysate flow, which includes the substitution fluid flow, was set to 800 ml/min in order to account for the significant volume used to generate the on-line substitution fluid. Arterial, venous and dialysate outlet samples were drawn after an initial stabilization period. Clearance (K) was calculated as the average of the blood side (K_B) and dialysate side clearances (K_D), whereby red cell solute partition coefficients (SPCs) for urea and β_2m were assumed as 0.86 and 0, respectively, to account for differences between red cell and plasma concentrations. Whole blood clearances, blood side and dialysate side, were calculated by dividing the mass removed from the blood side or mass gained on the dialysate side by the whole blood solute concentration (C_B) computed as $C_B = C_P \times [(1 - Hct) + (SPC \times Hct)]$, where C_P is the plasma solute concentration. The average clearance was considered acceptable if the mass balance error [MBE = $(K_B - K_D)/K_B$] was $\leq \pm 10\%$ for urea and $\leq \pm 20\%$ for β_2m .

An *in vitro* assessment of albumin loss with mid-dilution HDF was performed by measuring albumin clearance using the closed loop clearance method. A fixed volume of human plasma (or bovine serum) was recirculated at a flow rate of 400 ml/min for 3 h. Substitution fluid was infused at a rate of 200 ml/min for mid-dilution HDF and 100 ml/min for post-dilution HDF. The total plasma volume (including that in the extracorporeal circuit) was small (<900 ml) and was kept constant such that changes in albumin concentration would be detectable using standard analytical techniques. Albumin clearance (K_{alb}) was calculated by multiplying total plasma volume by the slope of the regression line of the logarithm of albumin concentration *vs* time. An estimate of albumin loss (M_{alb}) was then calculated by multiplying clearance (K_{alb}) by a nominal patient albumin concentration (3.5 g/dl) and a nominal treatment time (4 h).

Patient characteristics

Five end-stage renal disease patients (three female/two male; 52 ± 22 years; 68.5 ± 27.5 kg) on thrice weekly renal replacement therapy (three HDF, two HD) for >3 months were included in a preliminary study after they had given informed consent. Three of them had arterio-venous fistulas and the other two double-lumen dialysis catheters, with no evidence of dysfunction. The underlying renal diseases were chronic glomerulonephritis (two), diabetes mellitus (one), tubulointerstitial nephritis (one) and unknown (one).

In vivo study

OLpürTM MD 190 devices containing 1.9 m² of high-flux polyethersulfone membrane (DIAPES[®] HF800, Membrana GmbH, Wuppertal, Germany) were selected for the preliminary evaluation of the new haemodiafilter design. The clearance measurements and the solute RRs of urea, creatinine, and β_2m (representative markers of small and

middle molecular weight uraemic toxins) were selected as the device's performance parameters.

A total of six mid-dilution HDF treatments were performed using a Fresenius 4008H dialysis machine with an Online PlusTM option, for the on-line generation of substitution fluid. Flow rates for blood and substitution fluid were set to 400 (Q_B) and 200 ml/min (Q_S), respectively. Dialysate flow (Q_D) was set to 800 ml/min. The patients were treated for an average of 205 min.

Instantaneous whole blood clearances were measured from arterial and venous blood samples collected at 45 min from the initiation of the treatment. RRs and standard spKt/V for urea were determined from blood samples drawn before and at the end of each treatment. To account for the haemoconcentration of β_2m at the end of a treatment, the post-dialysis β_2m level used to calculate the β_2m reduction ratio was adjusted for net fluid removal from the patient [13]. Albumin loss was not measured during this preliminary clinical assessment of the device.

Laboratory analysis

In vitro urea samples were analysed using an automated analyser (Hitachi 911, Roche Diagnostics). β_2m was determined using an immunological agglutination method with latex reaction enhancement. Albumin was analysed using the bromocresol green method. *In vivo* samples were analysed in the clinical laboratory of our hospital (CHU Montpellier), using an automated analyser for urea and creatinine and laser nephelometry for β_2m measurement.

Results

In vitro study

Mid-dilution HDF experiments were performed using bovine blood ($32 \pm 3\%$ Hct) in an open-loop, single-pass configuration at flow conditions similar to those used during the *in vivo* study ($Q_B = 400$ ml/min, $Q_S = 100$ and 200 ml/min and $Q_D = 800$ ml/min). The whole blood urea and β_2m clearances on representative OLpürTM MD 190 devices at $Q_S = 100$ ml/min ($n = 4$) were 309.2 ± 5.5 and 144.4 ± 15.2 ml/min, respectively; at the higher $Q_S = 200$ ml/min ($n = 6$), they were 321.6 ± 4.1 and 204.9 ± 4.1 ml/min, respectively (Table 1). The latter results were in good agreement with *in vivo* clearances (Table 2) performed at the same flow conditions. Urea and β_2m clearances of the control dialysers ($n = 5$), containing the same polyethersulfone membrane, were, respectively, 278.6 ± 17.2 and 94.0 ± 7.6 ml/min (HD mode at $Q_B = 400$ ml/min and $Q_D = 500$ ml/min) and 310.8 ± 10.2 and 123.0 ± 6.5 ml/min (post-dilution HDF mode at $Q_B = 400$ ml/min, $Q_S = 60$ ml/min and $Q_D = 500$ ml/min). At the higher substitution and dialysate flow rates (100 and 800 ml/min, respectively), urea and β_2m clearances were measured as 323.6 ± 11.2 and 158.0 ± 10.3 ml/min, respectively (post-dilution HDF mode). *In vitro* albumin loss over a simulated 4 h treatment session was estimated as 6.8 g for the

Table 1. *In vitro* performance of OLpür™ MD 190 (Q_B 400 ml/min)

Test device	Control dialyser (polyethersulfone)			OLpür MD 190	
	Haemodialysis Q _S = 0, Q _D = 500 (ml/min)	Post-dilution HDF Q _S = 60, Q _D = 500 (ml/min)	Q _S = 100, Q _D = 800 (ml/min)	Mid-dilution HDF Q _S = 100, Q _D = 800 (ml/min)	Q _S = 200, Q _D = 800 (ml/min)
Urea clearance (ml/min)	278.6 ± 17.2	310.8 ± 10.2	323.6 ± 11.2	309.2 ± 5.5	321.6 ± 4.1
β ₂ m clearance (ml/min)	94.0 ± 7.6	123.0 ± 6.5	158.0 ± 10.3	144.4 ± 15.2	204.9 ± 4.1
Albumin clearance ^a (ml/min)	—	—	0.54 ± 0.09	—	0.81 ± 0.36
Estimated albumin loss (g/4 h)	—	—	4.5	—	6.8

^aTest performed at Q_D = 500 ml/min.

mid-dilution HDF mode, based on a measured albumin clearance of 0.81 ± 0.36 ml/min (*n* = 17). For the control dialysers, operated in a post-dilution HDF mode (Q_S = 100 ml/min), the estimated albumin loss was 4.5 g, based on a measured albumin clearance of 0.54 ± 0.09 ml/min (*n* = 5).

In vivo study

The preparation and handling of the new OLpür™ MD 190 haemodiafilter appeared to be only slightly, if at all, more complicated than the procedures for conventional HDF. The blood and effective dialysate flow rates during the study were 400 and 800 ml/min, respectively. The patients were treated for an average of 205 min (range 180–240) and required an average net fluid removal of 2.21 (range 1.0–3.3). Together with the 200 ml/min substitution fluid flow, this resulted in a total volume exchange over the course of the treatment of 43.21 (on average, range 38–50). All on-line mid-dilution HDF treatments were well tolerated without any side effects.

The instantaneous whole blood clearances and RRs from the *in vivo* study are summarized in Table 2. The clearances (mean ± SD) of urea, creatinine and β₂m were measured as 324.6 ± 10.9, 272.0 ± 17.1 and 207.9 ± 29.3 ml/min, respectively. In addition, for urea, creatinine and β₂m, solute RRs (mean ± SD) were measured as 75.0 ± 5.5, 68.8 ± 5.4 and 83.6 ± 4.7%, respectively.

Treatment adequacy, spKt/V, was calculated using the natural log formula for ultrafiltration (DOQI Guidelines). The spKt/V achieved *in vivo* with the MD 190 device was 1.64 ± 0.24.

Discussion

Current best-practice guidelines for HD recommend a minimum delivered dialysis dose (spKt/V, urea) of between 1.2 and 1.4 [14,15]. The European guideline extends 'haemodialysis adequacy' to include removal of middle molecules, such as β₂m, and recommends using a synthetic, high-flux membrane with a 'convective component' to maximize middle molecule removal [15]. The preliminary clinical

Table 2. *In vivo* performance of OLpür™ MD 190

Test solute	Solute clearance (ml/min)	Solute RR
Urea	324.6 ± 10.9	75.0 ± 5.5
Creatinine	272.0 ± 17.1	68.8 ± 5.4
β ₂ m	207.9 ± 29.3	83.6 ± 4.7

Mid-dilution HDF mode: Q_B = 400 ml/min, Q_S = 200 ml/min, Q_D = 800 ml/min.

results of the Nephros OLpür™ MD 190 device demonstrated that patients received a 'dialysis dose' of spKt/V = 1.64 ± 0.24 (URR = 75.0 ± 5.5%) and β₂m clearance (whole blood) was 207.9 ± 29.3 ml/min (β₂mRR = 83.6 ± 4.7%). Based on the measured performance, clearly the MD 190 device delivered a 'dialysis dose' well above current best-practice guidelines. Furthermore, our *in vitro* results, which were confirmed by *in vivo* applications, demonstrated a far better β₂m clearance than conventional post-dilution HDF.

In a comparison of the performance of the MD 190 at a reduced substitution rate (Q_S) of 100 ml/min, urea and β₂m clearances were slightly lower than that of a control dialyser (same membrane and surface area) configured for post-dilution HDF at the same substitution rate of 100 ml/min. This result is not unexpected when one considers that (i) post-dilution HDF is known to be the most efficient extracorporeal renal replacement therapy mode available so far; (ii) the MD 190 design combines the elements of pre-dilution and post-dilution HDF in a single device; and (iii) these tests were performed at one substitution fluid flow rate. The real benefit of the MD 190 design is that it can operate at a much higher substitution rate than post-dilution HDF. The result is that a mid-dilution HDF device under normal operating conditions clears middle molecules more efficiently than one operated in post-dilution HDF mode at its operational limit.

Comparisons of morbidity and mortality between ESRD patients on 'convective' and 'diffusive' therapies have been performed in several large studies. An observational study of 6444 patients, who were followed between 1983 and 1995 on the Dialysis and Transplant Lombardy Registry, concluded that patients treated

by HDF or haemofiltration (HF) showed a non-significant trend toward improved survival compared with patients on HD [16]. In addition, the data indicated that in the first two groups there was a significant reduction in the relative risk of requiring surgery for carpal tunnel syndrome, after adjusting for age and diabetic status. A more recent analysis of 4505 patients, followed between 1998 and 2001 as part of the DOPPS European database, showed a lower crude mortality rate in HDF patients (11.9 deaths/100 patient years) compared with HD patients (14.2 deaths/100 patient years) [17]. After adjusting for patient demographics and co-morbid conditions, patients receiving HDF had a 23% lower relative risk of dying (0.77, $P=0.02$) compared with patients receiving HD. Published data from the HEMO study, a prospective, randomized, 2×2 factorial design study using low-flux dialysers ($\beta_2\text{m}$ clearance = 3 ± 7 ml/min) and high-flux dialysers ($\beta_2\text{m}$ clearance = 34 ± 11 ml/min), has shown a statistically significant correlation between pre-dialysis $\beta_2\text{m}$ levels and mortality (13% higher relative risk per 10 mg/dl increase in $\beta_2\text{m}$; $P < 0.001$) [18]. Given the high $\beta_2\text{m}$ clearance of the MD 190 device and the expected higher removal of other middle molecular weight uraemic toxins, the acceptance of convection-based therapies may be accelerated as they provide an even further separation than conventional HD therapy.

One consequence of any convection-based therapy using a more open dialyser membrane is the potential to lose more albumin than with standard HD. What is considered an acceptable loss of albumin is, however, still under debate [19]. There are reports in the literature of albumin losses ranging between 1 and 25 g per treatment with several high-flux and super-flux dialysers operating in post-dilution HDF [20]. Also, the albumin losses of continuous ambulatory peritoneal dialysis (CAPD) patients have been reported as 5.2 ± 0.5 g per day (total protein losses of 10.5 ± 1.2 g/day), which is ~ 36 g/week [21–23]. It has been speculated that the removal of some albumin may actually be beneficial to the patient, as it provides a means to remove protein-bound uraemic toxins and other advanced oxidation protein products. For the present experimental device, the observed *in vitro* albumin loss appears to be within an acceptable range for HDF, and it is clearly below what would be considered an acceptable weekly loss for CAPD patients. It is recognized that albumin loss may vary during a given treatment, and that a higher loss is associated with the first 30–60 min of a treatment. The method for estimating albumin loss from an average clearance value measured over a 3 h period certainly takes this into account (and may in fact overestimate the albumin loss). For example, continuing the experiment through an additional fourth hour, where the albumin loss is not as great as during the first hour, one would expect the slope of the log of albumin concentration *vs* time to be less than that measured over the 3 h period. This translates into a lower albumin clearance and hence a lower estimated albumin loss. As with the clearance data, *in vitro*

albumin loss must be confirmed *in vivo* in a prospective clinical trial.

Conclusion

The unique configuration that we report transforms a high-flux dialyser with a standard dialyser construction into a device optimized to deliver high-efficiency, on-line HDF. It offers a significant improvement over both standard high-flux HD and conventional post-dilution HDF methods. The mid-dilution design of the device has the ability to support substantially higher ultrafiltration rates and, as such, results in the removal of substantially higher amounts of $\beta_2\text{m}$. Despite having an internal co-current dialysate flow and a pre-dilution element associated with the second stage of the device, the device achieves a high clearance of urea and other highly diffusible toxins. This optimized HDF performance may now be provided at a cost comparable with conventional HDF, and as such it may become the new standard for renal replacement therapy.

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Conflict of interest statement. None declared.

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