New strategies in haemodiafiltration (HDF): prospective comparative analysis between on-line mixed HDF and mid-dilution HDF

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Abstract

Background. Improvement in the uraemic toxicity profile obtained with the application of convective and mixed dialysis techniques has stimulated the development of more efficient strategies. Our study was a prospective randomized evaluation of the clinical and technical characteristics of two new haemodiafiltration (HDF) strategies, mixed HDF and mid-dilution HDF, which have recently been proposed with the aim of increasing efficiency and safety with respect to the standard traditional HDF infusion modes.

Methods. Ten stable patients on renal replacement therapy (mean age 64.7 ± 8.2 years) were submitted in randomized sequence to one mid-week session of mid-dilution HDF and one of mixed HDF with transmembrane pressure feedback control. All sessions were carried out under similar operating conditions and involved monitoring pressure within the internal dialyser compartments and calculating the rheological and hydraulic indexes. Efficiency in removing urea, phosphate and \( \beta_2 \)-microglobulin (\( \beta_2 \)-m) was tested.

Results. In mixed HDF, safer and more effective flux/pressure conditions resulted in better preservation of the hydraulic and solute membrane permeability (mean in vivo ultrafiltration coefficient 36.9 ± 3.9 vs 20.1 ± 3.3 ml/h/mmHg) and ensured higher volume exchange (38.7 ± 4.2 vs 35.3 ± 6.5 l/session, \( P = 0.02 \)) and greater efficiency in removing small and middle molecules (mean urea clearance: 274 ± 42 vs 264 ± 47 ml/min, \( P = 0.028 \); eKt/V: 1.78 ± 0.22 vs 1.71 ± 0.26, \( P = 0.036 \); mean phosphate clearance: 138 ± 16 vs 116 ± 45 ml/min, \( P = 0.2 \); mean \( \beta_2 \)-m clearance: 81 ± 13 vs 59 ± 13 ml/min, \( P = 0.001 \)).

Conclusions. Mixed HDF was the most efficient technique in the highest range of safe operating conditions. In mid-dilution HDF, high pressures generated inside the dialyser compromised membrane permeability and limited the total infusion rate, resulting in an overall reduction in solute removal.

Keywords: haemodiafiltration; membrane permeability; mid-dilution HDF; mixed HDF; phosphate; \( \beta_2 \)-microglobulin

Introduction

Several recent prospective studies have demonstrated that convective and mixed dialysis strategies may induce a sustained improvement in the uraemic toxicity profile, by reducing the level of small and middle molecular compounds which are recognized as risk factors and/or markers of severe uraemic complications, such as inflammation, amyloidosis, secondary hyperparathyroidism and accelerated atherosclerosis [1–5]. Even though not yet proven by a large prospective study, the combined routine use of ultrapure dialysate, highly biocompatible membranes and enhanced solute removal by convection could actually help to reduce the high mortality rate of dialysis patients. Support for this thesis may derive from the recently published Euro-DOPPS Study [6], which reported a significant 35% lower mortality risk in patients on haemodiafiltration (HDF) with high volume exchange of more than 15 l/session, compared with patients on low-flux haemodialysis (HD).

This state of affairs has greatly encouraged research into new and more efficient membranes and dialysis strategies. Thanks to the unlimited availability of sterile infusion fluid which is prepared cheaply by the dialysis machine, two new on-line HDF techniques, mixed HDF [7,8] and mid-dilution HDF [9,10], have recently been proposed with the aim of improving the efficiency and safety of HDF technique, while at the same time reducing the shortcomings and risks associated with the traditional HDF infusion modes. Indeed, in post-dilution HDF, haemoconcentration and high blood viscosity may cause filter clotting, high

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transmembrane pressure (TMP) and loss of membrane permeability, so limiting the effect of high ultrafiltration rates (Q_{UF}) on solute removal by convection [7,11]. The pre-dilution mode prevents the occurrence of these negative aspects, but at the price of reduced efficiency due to dilution of the solute concentration gradient across the membrane. Both mixed HDF and mid-dilution HDF claim better rheological and hydraulic conditions, and consequently, greater efficiency when compared with the traditional infusion modes. This study is a comparative analysis of the above aspects of the two novel HDF modes.

**Subjects and methods**

**Study design**

Two on-line HDF modalities were compared in this prospective randomized crossover study. Patients were submitted in randomized sequence to one mid-week session of mixed HDF and one of mid-dilution HDF. The study was approved by the local Ethic Committee and conducted in accordance with the principles of the Declaration of Helsinki and the rules of Good Clinical Practice. Written informed consent was obtained from all participants. Prospective-defined endpoints of the comparison were the extent of overall solute removal for each HDF modality, and the efficiency and safety of both the dialysers and the techniques in terms of hydraulic and solute membrane permeability, rheological conditions and hydrostatic pressures within the systems.

**Patients**

Ten patients (8 males, 2 females, mean age 64.7 ± 8.2 years), who had been on thrice weekly on-line HDF in our centre for at least 6 months were included in the study. Mean dialysis duration was 54.7 ± 63.6 months (median value 36.9, range 7.3–208.9). All patients had a permanent native or prosthetic vascular access capable of delivering an effective blood flow. Pre-treatment blood samples were drawn immediately after the end of the treatment session. During each session, the effluent dialysate was collected. Blood and dialysate flow counter-current in the descending U branch of the capillaries (1.1 m²), where post-dilution is performed and co-currently in the ascending, pre-dilution U branch (0.8 m²).

Treatment sessions to be compared were carried out in each patient using the same blood and dialysate flow, duration, anticoagulation protocol and dialysate/infusate composition. The initial infusion rate (Q_{inf}), which was the same for both techniques, was set in pilot sessions where maximal tolerance to ultrafiltration of the patient-machine system was tested. ‘Ultrapure’ dialysate was produced on-line, as per routine use, using a double reverse osmosis system for water treatment and a polysulphone ultra-filter (Diasafe plus, FMC) for subsequent filtration of the dialysate. A further stage of dialysate filtration was required for production of the infusion fluid. In our unit, both dialysate and infusion fluid are checked monthly to ensure that they are free of endotoxins (LAL test) and meet the standards of microbial purity recommended by the European Best Practice Guidelines.

Patients and treatment characteristics are summarized in Table 1.

**Data collection and laboratory analysis**

Pre-treatment blood samples were drawn immediately after needle insertion; post-treatment blood samples were taken from the arterial port using the slow flux technique. Separate blood samples from the arterial and vein ports were drawn 5 min after the beginning and 5 min before the end of the session. During each session, the effluent dialysate was sampled.

<table>
<thead>
<tr>
<th>Table 1. Patients–treatment characteristics</th>
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<tbody>
<tr>
<td>Mixed HDF</td>
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<tr>
<td>n = 10</td>
</tr>
<tr>
<td>Dry body weight (kg)</td>
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<tr>
<td>Body weight loss (kg)</td>
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<tr>
<td>Q_{eff} (ml/min)</td>
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<td>Q_{inf} (ml/min)</td>
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<td>Q_{UF start} (ml/min)</td>
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<td>Q_{O start} (ml/min)</td>
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<td>HD time (min)</td>
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<tr>
<td>Membrane</td>
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<tr>
<td>Surface (m²)</td>
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<tr>
<td>Wall thickness (µm)</td>
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<td>Inner diameter (µm)</td>
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<tr>
<td>Nominal K_{UF} (ml/h/mmHg/m²)</td>
</tr>
</tbody>
</table>

Abbreviations and definition of the parameters are in the text (section ‘Methods’). Data are means ± SD.

*Student's t-test for paired data.
collected with a proportional pump at a constant rate of 10 ml/h, following the partial dialysate quantification (DQ) method [14]. Blood and dialysate samples were analysed for urea, phosphate and β2-microglobulin (β2-m) using conductimetric, colorimetric and immunonephelometric methods, respectively. Haematocrit (Hct) and total plasma protein (TP) concentration were measured in arterial blood which was sampled 5 min after the beginning and 5 min before the end of the session.

The mass of solute removed during each session (MTDQ) was calculated from the effluent dialysate sample (~40 ml), which was representative of the entire effective volume of spent dialysate (Vd), as in:

\[ M_{TDQ} = C_d \times V_d \]  \hspace{1cm} (1)

where \( C_d \) is the dialysate concentration of the examined solute. The mean dialysate clearances of the session (KDO) were calculated with the following equation of the DQ method [14]:

\[ K_{DO} = \frac{M_{TDQ} \times \ln(C_i/C_f)}{t \times (C_f - C_i)} \]  \hspace{1cm} (2)

where \( C_i \) and \( C_f \) are the initial and end-session plasma water concentration of the examined solute and \( t \) is the session duration in minutes. Calculated as above, MTDQ and KDO underestimate the actual β2-m removal, due to the amount of solute absorbed on the membrane. However, this systematic and constant error is unlikely to affect the results of a comparison between the different procedures in the same patient and with a similar polysulphone-based dialyser membrane.

The equilibrated Kt/V (eKt/V) for urea was estimated according to the Daugirdas 2nd generation equation [15]. Dialyser performance in middle molecule removal at different stages of the session was evaluated by calculating β2-m instantaneous plasma water clearances (\( K_I \)) at the start and the end of the session. The classic equations [16] were used to calculate plasma water flow (\( Q_{PW} \)) and \( K_I \):

\[ Q_{PW} = Q_{B,c} \times (1 - \frac{100}{100})F_p \]  \hspace{1cm} (3)

where \( F_p \) is the water fraction of plasma;

\[ K_I = Q_{PW} \left( \frac{C_{art} - C_{cen}}{C_{art}} \right) + Q_{UF} \frac{C_{cen}}{C_{art}} \]  \hspace{1cm} (4)

where \( C_{art} \) and \( C_{cen} \) are the solute concentrations at the arterial and venous port, respectively, and \( Q_{UF} \) is the ultrafiltration rate, in millilitres per minute.

On-line recording of the intra-compartmental pressures of the dialyser allowed for calculation of the instantaneous values for the mean TMP (mmHg), for the Resistance Index (RI, mmHg/ml/min), used to evaluate the pressure/flow conditions of the blood compartment, and for the in vivo ultrafiltration coefficients of the dialyser membrane (\( K_{UF, m2} \), ml/h/mmHg of TMP/m²), which was used as a proxy for changes in the hydraulic permeability of the dialyser during the sessions. The following equations were used:

\[ \text{mean TMP} = 0.5 \times [(P_{B,in} + P_{B,out}) - (P_{D,in} + P_{D,out}) - P_{\text{onc}}] \]  \hspace{1cm} (5)

where \( P_{B,in}, P_{B,out}, P_{D,in} \) and \( P_{D,out} \) are the pressures (mmHg) at the inlet and outlet blood and dialysate port, respectively and \( P_{\text{onc}} \) (mmHg), is the mean onotic pressure exerted by the plasma proteins, set by default to a constant value of 25 mmHg:

\[ RI = \frac{(P_{B,in} - P_{B,out})}{Q_{B,in}} \]  \hspace{1cm} (6)

where \( Q_{B,in} \) is the flow (ml/min) at the inlet blood port;

\[ K_{UF} = \frac{Q_{UF}}{\text{mean TMP/m²}} \]  \hspace{1cm} (7)

**Statistical analysis**

The descriptive analysis was based on the mean ± SD values of continuously normally distributed variables. The effects of the two procedures on parameters of treatment efficiency (\( K_{DO}, \) urea Kt/V and MTDQ) were compared with the Student’s t-test for paired data. A P-value < 0.05 was considered significant.

**Results**

**Hydraulic patterns**

Figure 1 shows the pressure profiles at the inlet and outlet blood and dialysate compartments of the dialyser, as recorded minute by minute throughout the two experimental procedures by the computer connected to the dialysis machine. Mean TMP for each session was calculated by elaborating the pressure values measured at the four points of the extracorporeal circuit using equation (5) and the software. The trend is shown in Figure 2, where the line labelled with the letter ‘t’ represents the TMP value displayed on the machine monitor. This value, here defined as two-point TMP, is calculated by the machine as the difference of two point-pressures recorded behind the blood and dialysate outlet ports. For technical reasons (lack of specific pressure sensors at the inlet blood and dialysate ports) Fresenius 4008 and Gambro systems use this two-point TMP as a proxy for the actual mean TMP, on the basis of an equation relating the two measures, which is not obtainable from the manufacturers. The two-point TMP calculated as above often provides an inaccurate estimate of the true mean TMP. Over- or under-estimation depends on the operational conditions. Particularly in the case of mid-dilution HDF, the two-point TMP greatly underestimates the actual TMP at different points of the dialyser, above all at the initial and middle part of the post-dilution section (Figure 2B). Widely different patterns were established in the two procedures. In mixed HDF, pressure in blood compartment was kept substantially constant for the duration of the session as an effect of the feedback device-controlling TMP. In general, loss of hydraulic membrane permeability occurs mainly in the first 15–20 min of an HDF session, as a consequence of haemoconcentration and protein layer formation on the membrane surface. This then requires the TMP to be progressively increased, sometimes up to dangerous values, in order to maintain the
programmed ultrafiltration. In mixed HDF, as in the present experimental setting, any TMP increase was prevented by the feedback TMP regulation through repeated small shifts of infusion fluid from the post-dilution to the pre-dilution site with no effect on the total infusion and ultrafiltration rate (Figures 2A and 3A). On the contrary, in mid-dilution HDF, very high pressure values were recorded right from the beginning of the sessions both at the inlet blood compartment and along its first part, the post-dilution section, up to the infusion site. As sessions progressed, further increase occurred and inlet blood pressure ($P_{Bi\,in}$) and infusion pressure ($P_{Bi\,mid}$) rose to dangerous levels despite attempts to reduce this effect with repeated manual reduction of the total infusion rate (Figure 3B). Mean TMP values achieved in the post-dilution section are shown in Figure 2B and the filtration pressure at different points along the capillaries is schematically depicted in Figure 4. The total volume exchanged during the mid-dilution HDF sessions was significantly lower than in mixed HDF sessions ($35.3\pm6.5$ vs $38.7\pm4.2$, $P=0.02$), as an effect of the necessary reduction of the infusion rate during the former procedure.

The resistance index during the two experimental procedures, depicted in Figure 5A, showed a more favourable flux/pressure ratio within the dialyser in mixed HDF. The trend of the in vivo ultrafiltration coefficient of the membranes (Figure 5B), after the expected initial reduction in both procedures, demonstrated that hydraulic membrane permeability was better preserved in the pre-dilution section of the
MD190 dialyser. It deteriorated during mixed HDF and even more during mid-dilution HDF in the post-dilution section, but only in the latter case were very high TMP values required to preserve the planned ultrafiltration flow.

Efficiency of the procedures

Baseline and end-session patient parameters of the two experimental procedures are reported in Table 2 and it can be seen that there was a significant difference only in initial and final β2-m levels.

Mixed HDF proved to be more efficient in removing small and middle-sized solutes. As reported in Table 3, urea clearance $K_{DQ}$ and equilibrated $Kt/V$ were significantly higher in mid-dilution HDF where there was a statistically significant higher clearance of low (urea) and middle molecular weight solutes (β2-microglobulin). In line with other studies [17], phosphate removal was in the high range with no statistical difference between the two techniques, even though the difference could be of clinical relevance, also in consideration that pre-dialysis phosphate concentration was well within the normal range, which was probably an effect of the high efficiency treatment prior to the study.

Data obtained by means of the pressure/flux monitoring system used in this study provided a plausible explanation of these results. In mid-dilution HDF, very high hydraulic pressures were recorded for the entire duration of each session within the blood compartment of the dialyser, especially in its first section where post-dilution takes place. The overall surface area of capillaries in this section is relatively low (1.1 m$^2$) and as depicted in Figure 5, this may...
create high resistance to the blood entering the dialyser and becoming progressively more concentrated along the fibres. Resistance is further increased by the infusion flow at the middle port of the dialyser, in spite of the pressure drop caused by ultrafiltration. Very high TMP values are set by the machine’s volumetric ultrafiltration control in an attempt to ensure the planned ultrafiltration and as a consequence, abnormally high pressures are also generated in the dialysate compartment. As can be seen in Figure 4, substantially different pressure and flux conditions were observed in the second section of the mid-dilution dialyser, this being an effect of the massive dilution of blood at the middle port. Under these circumstances, non-homogeneous distribution of the ultrafiltration flow is likely to take place, mostly in the small post-dilution section where there is a very high filtration pressure. It is well known that extremely high filtration pressures, besides creating a risk of capillary damage and rupture, also cause significant deterioration of the membrane due to the progressive depositing and thickening of the protein layer on its surface leading to a loss of hydraulic and solute permeability. In addition, in the second part of the dialyser, the efficiency of solute removal is likely to be significantly compromised by the massive dilution of blood, reducing the solute concentration available for diffusion and convection across the membrane, and by the co-current blood-dialysate flows, further reducing the gradient for solute diffusion into the dialysate flow.

The above considerations provide an explanation of why, in the present study, we were unable to maintain the planned initial mean infusion rate of approximately 101/h during the session, even when we tolerated excessive internal pressure within the blood compartment, in respect of the reference limit ($P_{inf} < 650$ mmHg) suggested by the producer. However, in our opinion, this limit is neither advisable nor safe for applications in routine clinical setting.
Indeed, even below this value, dangerous transmembrane and blood inlet pressure can result, as shown in our study. Neither is the TMP control alarm displayed on the machine monitor (the two-point TMP) of any help as, for the reason explained above, it greatly underestimates the actual pressure at different points of the dialyser. This problem was apparently disregarded in the main report published on mid-dilution HDF [9]. In this study, in which excellent results in terms of efficiency are reported, the safety protocol is provided for a reduction of the infusion rate of 20 ml/min if TMP rose above 400 mmHg. Internal pressure monitoring was not performed but, according to our results, such two-point TMP values necessarily imply an internal pressure regimen which is even higher than that observed in our study. In that setting, coagulation of the extracorporeal blood circuit in one mid-dilution HDF session [9] and sustained albumin leakage were predictable complications.

Mixed HDF is an experimental HDF technique which has been performed in our centre on a modified 4008 Fresenius system since 1998 [7,8]. The basic concept is that splitting the infusion between pre- and post-filter guarantees the best possible rheological and hydraulic conditions within the dialyser at the highest fluid exchange rate and with the most solute removal by convection. Application of a TMP feedback control system and implementation of the new 5008 Fresenius machine has greatly improved the performance and safety of this technique. The TMP feedback control acts by modulating the ratio between pre- and post-dilution in order to gradually achieve and then maintain an optimal and safe TMP value for the entire session. This ensures maximal convection while better preserving dialyser membrane permeability. The characteristics and clinical results of mixed HDF have already been reported in previous publications [12,13,18]. The resistance index and in vivo ultrafiltration coefficient monitored throughout the sessions and shown in Figure 5 also demonstrated that the hydraulic characteristics of the dialyser are better preserved in mixed HDF. This is probably the main explanatory factor for the clear difference in efficiency between the two strategies examined in this study. In fact, for this reason, in mixed HDF it was possible to achieve greater exchange volume and thus, higher ultrafiltration flux, which resulted in significantly higher convective removal of β2-microglobulin. Our view is supported not only by our experience [18], but also by the results of a study in pre-dilution HDF [19], which showed that higher β2-microglobulin removal and minimal albumin loss resulted from a profiled filtration mode, planned to gradually increase the ultrafiltration rate from an initial low level. In mid-dilution HDF, the in vivo ultrafiltration coefficient showed acceptable values only in the second compartment of the dialyser, where safer pressure/flux conditions occurred, but only as a result of extreme and unfavourable blood dilution.

The same anticoagulation therapy was applied during the sessions of both techniques in the study, based on the fact that published works on mid-dilution HDF do not indicate any necessity to modify the heparin dose [10]. However, in consideration of the high internal pressure observed in the mid-dilution dialyser and the fact that major pro-coagulatory activity may result in the presence of a very high ultrafiltration flux [20], we conducted additional trial sessions with a 50% increase of heparin. Results in terms of pressure, flux and efficiency did not change in the tested patients.

In conclusion, both techniques demonstrated significant removal of small and medium sized uraemic compounds. However, in the case of mid-dilution HDF, these results were obtained only by tolerating unsafe operational conditions in terms of hydraulic pressure within the dialyser. Lack of an efficient pressure control system is particularly worrisome for safety in routine clinical applications. Improvements in this technique should include reconsidering the dialyser geometry and surface. The superior performance of mixed HDF is based fundamentally on the capacity to better preserve the hydraulic and solute membrane permeability and thus, to ensure maximal removal by convection of middle molecular toxic compounds, thanks to the efficient and safe flux/pressure conditions which are guaranteed by the strict control of the TMP feedback device. This device, implemented on a new dialysis machine, works inexpensively and automatically adapts the operational conditions to the patient and dialyser parameters (blood flow, haematocrit, coagulation status, surface and membrane permeability).

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Conflict of interest statement. L.A.P. has, presently, a temporary consultancy agreement with Fresenius Medical Care, Bad Homburg, Germany. The other authors declare no conflict of interest.

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