Convection versus diffusion in dialysis: an Italian prospective multicentre study

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Abstract
The concept of dialysis adequacy has to be widened to include medium size and large molecule removal in addition to urea kinetics. The HEMO study found a non-significant trend toward a beneficial effect on mortality of high-flux dialysis compared with low-flux dialysis. In that study, the beneficial effect of convection could have been attenuated by the fact that ‘internal filtration’ in high-flux haemodialysis (HD) is lower than that expected by convection in haemofiltration (HF) or haemodiafiltration (HDF). To explore the putative beneficial effect of convection, this Italian multicentre study was planned, comparing on-line convective treatments (HF and HDF) with standard, low-flux HD. The enrolled patients will be evaluated prospectively on their usual treatment for 2 months (baseline period) and subsequently randomized to continue either with low-flux HD (50%) or to start on-line convective treatment (50%), HF or HDF according to a 1:1 ratio. The primary end point of the study will be cardiovascular stability and blood pressure control. As secondary aims of the study, the impact on symptoms, morbidity and mortality will be assessed. Feasibility and patient compliance during HF and HDF treatments will also be evaluated. The experimental phase of the study, of at least 2 years, is divided into a 3-month adaptation period and a subsequent evaluation period. A recruitment period of 1 year is planned. The study design has adequate power to detect an absolute reduction of 3% hypertensive episodes with the experimental convective treatments compared with standard low-flux HD.

Keywords: blood pressure; cardiovascular stability; morbidity; mortality; symptomatic hypotension

Study background and rationale
Over the last decade, several epidemiological studies based on large databases have suggested a possible superiority of convective treatments in terms of reducing morbidity and mortality of dialysis patients.
[1–6]. Despite conflicting results of prospective randomized controlled trials, they suggest that the concept of dialysis adequacy has to be widened to include, in addition to urea kinetics, medium-size and large molecule removal as well as biocompatibility. In a controlled randomized study involving 380 patients, Locatelli et al. [7] compared four treatment dialysis modalities [cuprophan dialysis, low-flux polysulfone dialysis, high-flux polysulfone dialysis and high-flux polysulfone haemodiafiltration (HDF)]. While no difference in terms of treatment tolerance and nutritional status was found, the authors demonstrated a difference in pre-dialysis β₂-microglobulin levels between convective and diffusive treatments (high flux vs low flux). Moreover, no difference in morbidity and mortality was found; however, the study was not powered to detect this difference. In an analysis of data from the Lombardy Registry patients [3], Locatelli et al. suggested a 10% reduction in mortality (not statistically significant) among patients on convective treatments compared with those on diffusive treatments.

Given the importance of this issue, two randomized, controlled clinical trials have been designed to assess the effect of high-flux membranes on mortality: the HEMO study [8] and the Membrane Permeability and ESRD patient Outcome (MPO) study [9]. The HEMO study started in the USA in 1995 and was concluded at the end of 2001. Using a 2×2 factorial design, patients were randomized to high or standard dialysis dose and to high-flux or low-flux dialysis membranes. The results of the primary analysis, recently published in the *New England Journal Medicine* [10], suggest that high dialysis dose and high-flux dialysis showed only small, non-significant beneficial effects on mortality. A non-significant 8% reduction in the relative risk of death (RR = 0.92, P = 0.23) was found for participants in the high-flux compared with those in the low-flux arm; similarly, a non-significant reduction in the relative risk of death (RR = 0.96, P = 0.53) was observed for the high dose vs standard dose arm. However, some limitations of this study have to be taken into account. One of the main methodological limitations was the inclusion of prevalent patients. In contrast, in the ongoing MPO study, designed to investigate the effect of membrane flux, only incident patients were included; additional differences between the HEMO and MPO studies are the longer duration of follow-up and the fact that dialyser reuse is not permitted in the latter. However, in the two studies, the beneficial effect of convection could be attenuated by the fact that its level in the experimental arm is low. In fact, solute transport obtained by internal filtration in high-flux haemodialysis (HD) is lower than that expected by convection in HDF or haemofiltration (HF). To maximize the putative beneficial effect of convection, systems for the on-line production of large amounts of ultrapure dialysate or substitution fluids are now available [11,12].

On-line HDF performed with substitution fluid reinfusion in pre- or post-dilution and pre-post-dilution is common clinical practice, since it provides a high dose of convection together with a powerful clearance of low molecular weight solutes [13,14]. On-line HF treatment potentially gives the highest amount of convection, but is less popular since it is less effective than HDF in low molecular weight molecule removal. Therefore, HF is usually reserved for treatment of haemodynamically unstable patients, and its use in clinically stable patients is limited [15].

Recently, two prospective clinical trials performed by the Sardinian Collaborative Group [16,17] compared the clinical effects of bicarbonate high-flux HD and pre-dilution on-line bicarbonate HF in clinically stable patients, with different (first study) [16] and similar eKt/V and treatment time (second study) [17] in HD and HF. In both studies, polyamide membranes, ultrapure fluid with similar electrolyte composition and the same dialysis machine were used. These studies demonstrated a better haemodynamic tolerance (both during treatment and in the inter-treatment periods) for HF compared with HD; using pre-dilution on-line HF, a better removal of high molecular weight solutes together with an adequate removal of urea was possible, thus maintaining a good nutritional status despite a lower urea removal in comparison with diffusive treatments [18].

A third prospective collaborative study performed by the same collaborative group compared HF with pre-dilution HDF treatment (unpublished data) in a group of 40 stable patients, after a run-in period of 6 months treatment on low-flux HD. HF was more effective in reducing the frequency of hypotension, while ePCR, albumin concentration and other nutritional parameters and intra- and inter-treatment symptoms were controlled satisfactorily in both treatments.

Based on the positive results of these relatively small Sardinian studies, and considering the theoretical premises of a beneficial clinical effect of high-flux dialysis, we used this model to design a new prospective multicentre Italian study, comparing standard low-flux HD with on-line convective treatments (HF and HDF) in order to evaluate the clinical effects of different doses of convection.

**Objectives**

The principal end point of the study will be the possible beneficial effect of convection compared with diffusion on cardiovascular stability and blood pressure control in chronic HD patients. Enrolled patients will be evaluated prospectively while maintained on their previous treatment for 2 months (baseline period). They will subsequently be randomized to continue standard dialysis treatment (50%) or to start on-line convective treatment (50%), HF or HDF according to a 1:1 ratio (Figure 1). If necessary for technical or clinical reasons or for reasons of non-compliance, patients will switch from HF to HDF, or from HDF to HF. The planned duration of the recruitment period is 1 year starting from July 1, 2003. The minimum planned duration of the experimental phase is 2 years,
divided into two periods: an adaptation period with a duration of 3 months and a subsequent evaluation period for comparison between the two groups. Secondary aims of the study will be the evaluation of symptoms, morbidity, and overall and cardiovascular mortality.

Study design

Treatment parameters similar in all patients
HD, HF and HDF machines must be provided with a dialysis fluid ultrafiltration system for the production of ultrapure dialysate and substitution fluid.

Total and bicarbonate conductivities and the same temperature will be maintained in order to follow as much as possible everyday clinical practice. The blood flow will be between 300 and 400 ml/min.

The treatment session will be three per week, with treatment times of ≈4 h for each session.

The lower limit of eKt/V will be 1.05 in all treatments.

Peculiar characteristics of the different treatments
(i) Bicarbonate HD. Membrane: low-flux membrane. The dialysate flow will be 500 ml/min.
(ii) On-line bicarbonate pre-dilution HF. Membrane: all synthetic high-flux membranes. The infusate flow will be kept near to 300 ml/min, aiming at an infusate/Qb ratio of 1:1.
(iii) On-line bicarbonate pre-dilution HDF. Membrane: all synthetic high-flux membranes. The infusate flow will be at least 60% of Qb, with a dialysate flow of 500 ml/min.

Inclusion criteria
At the time of randomization, patients must have been on thrice weekly HD for at least 6 months. Other inclusion criteria will be: age between 18 and 80 years, body weight not higher than 90 kg, and stable clinical conditions.

Exclusion criteria
Patients with clinically relevant infections, malignancies, active systemic diseases, active hepatitis or cirrhosis, unstable diabetes, diuresis > 200 ml/24 h or a malfunction of vascular access with a blood flow rate < 300 ml/min will be excluded from the study.

Follow-up monitoring and data registration

Patients will be asked to sign a detailed informed consent. All relevant anamnestic and clinical data will be recorded. Particular attention will be paid to nutritional and cardiovascular parameters and to general co-morbid conditions. Registration of all data will be performed by one or two nephrologists and one or two nurses, appointed as study monitors in each collaborative centre.

Laboratory parameters
The pre-dialysis levels of the following parameters will be registered monthly: haemoglobin, leukocytes, platelets, serum electrolytes (sodium, potassium, bicarbonate, calcium, phosphorus), BUN, creatinine, total protein and albumin. BUN, sodium, potassium, bicarbonate, calcium, phosphorus and total proteins will also be evaluated at the end of session. The following parameters will be determined every 3 months: iron, ferritin and transferrin. Cholesterol, triglycerides, intact parathyroid hormone, β2-microglobulin and C-reactive protein will be evaluated every semester. To take into account patients’ variable hydration status over the week, analysis of all blood samples will be done before each mid-week dialysis session.

Urea kinetics
Equilibrated Kt/V and ePCrN values will be calculated monthly using procedures and simplified equations described by Daugirdas [19]. The blood sample for the determination of the final plasma urea concentration will be drawn from the arterial line, 10 s after reducing the blood flow to 100 ml/min with dialysate flow in bypass and by clamping the venous line behind the venous bubble trap. In the absence of a steady-state condition, the determination of the Kt/V value will be postponed.

Clinical monitoring
All clinically relevant events occurring during the study period, in particular all co-morbid factors, hospital admissions, drop outs from treatments and their causes, will be recorded.
Intra-dialytic symptomatic hypotension will be defined as: rapid symptomatic fall of the systolic blood pressure that requires or does not require intervention.

Intra-dialytic symptomatic hypertension will be defined as a rapid symptomatic rise in systolic blood pressure.

Episodes of arrhythmia, dyspnœa, pruritus, cramps, headache, nausea and vomiting occurring during the session or up till 10 min after the sessions will be recorded.

Fever will be defined as an increase in body temperature beyond 37.8°C or an increase of at least 2°C from the beginning to the end of the session. Any other adverse or abnormal reaction will be recorded.

At the beginning of each session, a nurse or a doctor will interview patients about the occurrence of the following symptoms during the inter-treatment period: cramps, nausea and vomiting, hypotension and/or hypertension episodes.

The subjective patient’s evaluation of the intensity of fatigue and thirst will be recorded monthly using a 0–10 point scale (0 = absence of symptoms; 10 = maximum intensity of symptoms).

Operative data

The following data will be recorded during each session: filter type, blood flow, infusion flow and rate of total ultrafiltration (all expressed in ml/min), pre- and post-session body weight, dialysate and bicarbonate conductivities in mS/cm, and dialysate and infusate temperatures.

Therapy

For each session, the following parameters will be recorded: quantity and quality of saline infusions, dose of epoetin or equivalent drugs, iron and any other drug orally or i.v. administered during the session or in the immediate post-session period.

Inter-treatment therapy: any drug consumed by the patients will be recorded, with particular attention to anti-hypertensives, and oral calcium- and non-calcium-based phosphorus in binders.

Cardiovascular surveillance

At the start, after each hour and at the end of each session, blood pressure and pulse rate will be measured. Before the start and at the end of each session, the upright blood pressure and pulse rate will also be measured.

Sample size calculation

The sample size was calculated considering the between-group difference in percentage frequency of intra-dialytic symptomatic hypotension as the main variable, and a reduction of this frequency with convective-only treatment (HD) or mixed with diffusion (HDF) compared with standard HD. An absolute reduction of 3% of the dialysis sessions with intra-dialytic symptomatic hypotension (from 15 to 12%) is considered as clinically relevant. The calculated sample size of at least 246 patients is based on a significance level (α error) of 0.05, a β error of 0.1, a power (1 – β) of 0.9 with an estimated drop out rate of 30%. To rule out bias due to adaptation to the new technique and any possible carry-over effects of previous treatments, the sessions considered in the analysis will include all the sessions following the first 3 months of follow-up of the experimental phase (adaptation phase). Thus patients who drop out from the study before the planned duration of the study (2 years) will also be considered for the analysis on the intention to treat basis, if their follow-up in the experimental phase is longer than 3 months. In the primary analysis, the difference in hypotension frequency between the evaluation period and the baseline period of 2 months for each patient will be used.

Statistical analysis

The descriptive analysis will be based on the mean values and standard deviations for normal distribution of continuous variables (e.g. blood pressure levels). Differences in clinical and laboratory variables at baseline between the two groups will be tested using the Student independent t-test for normally distributed continuous variables, the non-parametric Mann–Whitney U-test for not normally distributed continuous variables, and the χ² test for categorical variables.

Blood pressure will be evaluated at five levels: (i) change of the frequency of intra-dialytic symptomatic hypotension from baseline to the experimental evaluation phase; (ii) change of pre-dialysis blood pressure values from baseline to the experimental evaluation phase; (iii) change in intra-dialytic blood pressure values in the same periods; (iv) change of anti-hypertensive treatment score; and (v) effect of a recumbent position before dialysis and a standing position at the end of dialysis on the variation in blood pressure and heart rate values. Univariate logistic regression of intra-dialytic symptomatic hypotension (level i) will be used to test the effect of experimental treatment compared with the reference HD treatment and to find the possibly relevant predictors related to symptomatic hypotension. Sensitivity (the percentage of true positives among the dialysis sessions with real symptomatic hypotension), specificity (the percentage of true negatives among dialysis sessions without hypotension) and accuracy (the percentage of the sum of true positives and true negatives among all dialysis sessions) will be used to evaluate the model performance. The general linear model for repeated measures of analysis of variance will be used for the other variables (levels ii–v). The main between-subject factor is the group. The
statistical analysis will be performed considering the evolution of blood pressure before and during dialysis as the main response variable. The group effect will be tested using the group \* time of dialysis interaction.

The study will check differences between groups for other relevant response variables, such as possible different evolution of clinical, laboratory and nutritional variables, mortality (number of hospital admissions per year and number of hospitalization days per year), and total and cardiovascular mortality.

All statistical analyses will be performed using SPSS for Windows, Release 11.5.

Discussion

Despite the increased survival over recent years, the quality of life is still low and the morbidity and mortality of dialysis patients are still high, mainly because of dialysis inadequacy. The concept of dialysis adequacy has to be widened to include, besides urea kinetics, removal of medium size and large solutes as well as biocompatibility. Several epidemiological studies based on large database registries have suggested a possible superiority of convective treatments on reduction of morbidity and mortality in these patients. The USA-based HEMO study concluded that there was a non-significant trend toward a beneficial effect on mortality of high-flux dialysis compared with low-flux dialysis. The MPO study, currently running in Europe, is comparing high-flux low-flux dialysis. The MPO study, currently running in Europe, is comparing high-flux low-flux dialysis. The MPO study, currently running in Europe, is comparing high-flux low-flux dialysis. The MPO study, currently running in Europe, is comparing high-flux low-flux dialysis. However, in the two studies, the possible beneficial effect of convection could be attenuated by the fact that internal filtration in high-flux HD is lower than that expected by convection in HDF or HF.

To maximize the putative beneficial effect of convection, we planned this Italian multicentre study, comparing on-line convective treatments (HF and HDF) with standard low-flux HD in order to evaluate the clinical effects of very different doses of convection.

Since prospective studies comparing HD, on-line HF and HDF, including patients from a wide spectrum of Italian dialysis facilities, have not yet been published, we hope that the present study will be particularly useful in assessing the possible clinical differences in convective treatments compared with standard HD.

Another important point is the evaluation of the feasibility and patient compliance during HF and HDF treatments. This is particularly important in HF where, in patients with high protein intake, as the possibility of drop out may be higher because of lower small molecular weight solute clearance.

References