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Pre-dilution haemofiltration—the Sardinian multicentre studies: present and future

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Background

Several benefits of haemofiltration (HF) over haemodialysis (HD) have been well documented in the literature, such as better cardiovascular stability [1–3], lower morbidity [4,5], a higher survival rate in high risk patients [6,7] and better removal of high molecular weight metabolites such as β_2-microglobulin [8,9]. In spite of this, HF is used only to a limited extent; the main reason for the lack of widespread clinical application of HF is its limited efficiency for removal of urea and other low molecular weight substances, leading to long treatment times. HF with repletion offers the possibility of overcoming this limit [10] and maintains all the potential benefits of HF [11–13].

On-line pre-dilution HF needs a large amount of infusion in order to be efficacious in removing urea. For the above reasons, the system requires the on-line preparation of the substitution fluid.

At present, the urea clearance is the predominant parameter used to identify the dialysis dose with the normalized dose given by the Kt/V urea index. It has been found that there is a relationship between the dialysis dose quantified as Kt/V for urea and the nutritional state expressed as the normalized protein catabolic rate (nPCR) [14]; this relationship is believed to be different for dialysis with low-flux and high-flux membranes [14,15]. This difference could be due to the differences in biocompatibility and the different spectrum of catabolite removal between the membrane types.

The Sardinian Collaborative Group on pre-dilution HF on line carried out two prospective multicentre studies to compare a sufficient number of patients sequentially treated with high-flux HD with ultrapure bicarbonate fluid (HD) and pre-dilution HF with on-line prepared bicarbonate substitution fluid (pre-HF) using the same machines (AK 100 Ultra or AK 200 Ultra) and the same membrane (polyamide) [16,17].

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The first study

Twenty-three patients (13 males and 10 females) from eight Sardinian dialysis units were selected randomly to be included in the study [13]. Their mean age was 58.0 ± 9.5 years and they had been on renal replacement therapy for 69.7 ± 50.5 months. Inclusion criteria comprised the following:

(i) stable clinical conditions, with a diuresis <300 ml/day;
(ii) absence of chronic infection, malignancy, diabetes, liver insufficiency or active liver diseases, serious endocrine dysfunction and vasculopathies;
(iii) well functioning vascular access; and
(iv) body weight <85 kg.

Study design: methods

The study was divided into two phases: phase I, treatment with high-flux HD, lasting for 3 months; phase II, treatment with pre-dilution HF, lasting for 6 months. In both phases, the same monitor, AK 100 Ultra from Gambro AB, was used.

The same fluid electrolyte concentration was used for both HD and HF (mmol/l): sodium 138–140; potassium 1–2; chloride 108.0–109.5; calcium 1.50–1.75; magnesium 0.5; bicarbonate 30–34; acetate 3; and glucose 0–5.55.

The dialyser used for HD was a 1.4 m^2 polyamide filter (Polyflux 160 from Gambro AB). Blood (Q_b) and dialysis fluid (Q_d) flow rates were set to 300 and 500 ml/min, respectively. The mean treatment time was targeted to 4 h.

The haemofilter used for pre-HF was a 2.0 m^2 polyamide filter (FH 88H from Gambro AB). Q_b was 350–400 ml/min and the filtrate volume was aimed at 1.2 times the dry body weight.

HD was targeted to a Kt/V of 1.4 and HF was targeted

to a Kt/V of 1.0, these values being the values most often recommended in common clinical practice.

Clinical, haematological and adequacy monitoring, treatment parameters. During each treatment session, the following parameters were recorded: Q_b; infusion flow (Q_{inf}); rate of weight loss, infusion volume, treatment time and composition of the dialysis and substitution fluids.

Clinical parameters. Body weight, blood pressure (BP), heart rate and body temperature were monitored before and after each treatment.

Intra-treatment symptoms. The number of episodes of symptomatic hypotension and hypertension, cardiac arrhythmia, dyspnoea, fever, muscular cramps, headache, pruritus, nausea and vomiting were recorded during each treatment.

Inter-treatment symptoms. The patients were asked to record the presence of the following symptoms during the inter-treatment periods: hypotension, hypertension, arrhythmia, respiratory distress, pruritus, muscular cramps, arthralgia, headache, insomnia, fatigue, abnormal thirst, diarrhoea and constipation.

Urea kinetics. The urea kinetics were determined at the beginning of each treatment phase and subsequently every 2 weeks during the mid-week session. Pre- (C1) and post-session urea (C2) concentrations were determined in blood samples taken in the arm contralateral to the fistula. The sample for post-dialysis urea was taken 30 min after the end of the treatment. Kt/V was calculated using the Daugirdas formula [18] and nPCR using the formulae on which the Daugirdas nomograms are based. These formulae are validated for single-compartment variable-volume urea modelling for HD.

Clearance. *In vivo* plasma urea and creatinine clearances were determined at least twice during each treatment.

Blood analysis. A full blood analysis was carried out every 2nd week from samples taken before the first treatment of the week.

Infusion therapy and drugs. Intravenous dextran and hypertonic saline administration per session was recorded. The use of anti-hypertensive, anti-arrhythmic and cardiokinetic drugs, anti-aggregant-anticoagulant, anti-H_2 receptor, phosphate binders, calcitriol and derivates, tranquillizers, iron and erythropoietin during the inter-treatment period were registered.

Results

Eighteen out of 23 patients completed phase I and phase II of the study. Five patients dropped out during phase II for the following reasons: one patient underwent renal transplantation, and three patients dropped out for scheduling reasons and one because of prolonged treatment time on HF.

Treatment parameters and clinical relief. Q_b was significantly lower during HD than during HF (372 ± 27 *vs* 301 ± 49 ml/min) ($P < 0.001$). The treatment time was 238 ± 8 min during HF and 211 ± 27 min during HF ($P < 0.001$) (Table 1).

Pre- and post-session clinical parameters, including body weight, systolic and diastolic BP and heart rate, were similar during HD and HF. During HF, patients showed a lower frequence of hypotensive and hypertensive episodes, and less muscular cramps and nausea as shown in Table 2.

The better stability on HF was accompanied by a reduction in the intra-treatment infusion of hypertonic saline and plasma expander and a reduction in the percentage of patients who took anti-hypertensive drugs in the inter-treatment period.

Table 1. Treatment parameters and urea kinetics

	Phase I (HD)	Phase II (HF)	*P*
Q_b (ml/min)	301 ± 49	372 ± 37	<0.001
Q_{inf} (ml/min)		327 ± 31	
Infusion volume (l)		68.5 ± 8.8	
Treatment time (min)	238 ± 8	211 ± 27	<0.001
Equilibrated Kt/V	1.41 ± 0.26	1.08 ± 0.19	<0.001
nPCR	1.19 ± 0.23	1.13 ± 0.23	NS
Urea reduction ratio, %	68 ± 7	62 ± 8	<0.001

Between treatments, patients were less symptomatic on HF than HD: they experienced less muscular cramps (prevalence 13% on HF *vs* 22% on HD; $P = 0.07$), less arthralgia (17% *vs* 30%; $P = 0.03$), fewer headaches (24% *vs* 35%; $P < 0.07$) and less fatigue (24% *vs* 41%; $P < 0.001$).

The second study

The aim of the second prospective crossover study was to compare the clinical outcome of 24 stable patients, treated for three subsequent periods of 6 months each on HF–HD–HF [17]. The mean age of the patients was 61 ± 59.2 years. The patients were in stable clinical condition and were chosen using the same selection criteria as for study one.

In order to compare only patients with similar treatment dose, a difference of Kt/V of >0.1 between the treatment periods was considered a cause for exclusion of patients from the study. In addition, the treatment times were the same for HD and HF in all patients.

Results

Twenty out of 24 patients completed all three phases of the study. Four patients dropped out for the following reasons: successful renal transplantation in two patients; death after myocardial infarction in one patient; non-compliance in one patient. Additionally, five patients were excluded because their Kt/V values in HF and HD differed by 0.1 unit.

Treatment parameters and urea kinetics. Table 3 shows treatment parameters recorded during the three treatment phases HF1, HD and HF2. The average ultrafiltrate volume (infusion plus weight loss) corresponded during the two HF periods to 1.3 times the patients' dry body weight.

The main aim of the study was targeted; in fact, the urea C1 and C2 levels, Kt/V, nPCR and URR did not vary significantly during the three periods.

Clinical parameters. BP outcome recorded before and

Table 2. Intra-treatment symptoms

	Phase I (HD)	Phase II (HF)	*P*
Hypotension, %[a]	61	39	0.003
Hypotension episodes[b]	1.78 ± 2.8	1.17 ± 3.1	0.003
Muscular cramps, %[a]	33	17	0.02
Anti-hypertensive treatment, %[c]	47.8	36.9	0.05
Headache, %[a]	41	35	0.02
Nausea, %[a]	17	4	0.02

[a]Prevalence of patients showing one or more episodes per month.
[b]Average number of episodes per patient per month.
[c]Prevalence of patients taking any anti-hypertensive medication.

Table 3. Treatment parameters and urea kinetics

	HF1	HD	HF2	Significance
Q_b (ml/min)	420.9 ± 47*	307.2 ± 37.9*	421.2 ± 46.3*	HD *vs* HF1, HF2
Q_{inf} (ml/min)	315.3 ± 34.8		319.3 ± 31.2	NS
Treatment time (min)	222.1 ± 27.8	221.6 ± 21.6	218.3 ± 18.5	NS
Urea reduction rate	64.6 ± 2.3	65 ± 2.5	64.8 ± 2	NS
Equilibrated Kt/V	1.25 ± 0.09	1.28 + 0.08	1.26 ± 0.06	NS
nPCR	1.23 ± 0.3	1.18 ± 0.1	1.19 ± 0.1	NS

*$P < 0.02$.

after treatment showed significant differences between the two treatment modes. The pre-session BP, systolic as well diastolic, was significantly higher during the HF periods than during the HD periods, while the intra-session weight gain was higher on HD than HF (Table 4).

When looking at the longitudinal BP changes, both systolic and diastolic mean BP progressively fell during the HD phase, rising again in the second period of HF treatment.

The 48 h systolic BP, the daytime systolic and diastolic BP, the night time systolic and diastolic BP and the first 24 h systolic and diastolic BP were all higher, but not significantly so, during the HF period than during the HD period (118.5 ± 22.7 mmHg on HF *vs* 113.9 ± 22.7 mmHg on HD). Only the mean systolic BP relative to the second day of ambulatory blood pressure monitoring measurement was significantly higher in the HF periods than in the HD period (110.7 ± 23.5 mmHg on HF *vs* 110.8 ± 18.4 on HD; $P = 0.04$).

Table 4. Blood pressure parameters

	HF1	HD	HF2	*P*
MAP before session, mmHg	96.7*	91.2*	92.8	0.003
MAP after session, mmHg	91.8*	85.9*	88.8	0.009
Δ MAP before/after session, mmHg	5.5	5.3	4.1	NS
Inter-treatment weight gain, kg	2.4	2.6*	2.4*	0.01

*Indicates elements which correlate; entity of correlations is indicated by the set of values under *P*.

The number of nocturnal dippers, defined as patients with a fall in BP of $\geqslant 10\%$ of the 24 h values, was low in both treatments (one out of 15 in HD, two out of 15 in HF). The dipping was larger, although not significantly so, during HF. The profile of the diastolic BP, although significantly higher for HF, was similar in both treatments.

Table 5 shows the incidence of intra-treatment symptoms. The prevalence of patients with hypotensive episodes during sessions increased significantly during phase 2 (HD), and decreased again during HF2.

In the inter-treatment period, patients experienced significantly less fatigue and muscular cramps on HF than on HD. The score obtained from the sum of the prevalence of the various inter-treatment symptoms progressively decreased during the three phases, reaching the nadir during third phase (HF1 score = 154; HD score = 220, HF2 score = 139, $P = 0.03$).

Table 5. Intra-treatment symptoms

	HF1	HD	HF2	*P*
Hypotension, %[a]	46.7	66.7	23.3	0.04
Hypotension episodes[b]	1.25	1.81	1.28	0.04
Anti-hypertensive treatment, %[c]	23.3	33.3	26.6	NS
Muscular cramps, %[a]	6.7	26.7	6.7	<0.03
Nausea prevalence, %[a]	13.3	6.7	0	NS

[a]Prevalence of patients showing one or more episodes per month.
[b]Average number of episodes per patient per month.
[c]Prevalence of patients taking any anti-hypertensive medication.

Figure 1 shows the frequency of episodes of intra-treatment hypotension and hypertension per patient per month throughout the 18 months. During the first phase on HF, the number of hypotensive episodes fell; a subsequent progressive rise during the HD period and a new fall during the second phase on HF was noted. The average dose of plasma expander during treatment sessions per patient per month increased although significantly only during the second quarter of the HD phase *vs* the second quarter of HF1. The administration decreased again during HF2 (Figure 1).

The third study

The Third Sardinian Multicentre Study on HF on line started in February 2000. The aim of this study is to treat 40 stable patients in three subsequent phases of treatment, of 6 months each, using the same dialysis machine (AK100 or 200 Gambro), the same membrane composition (polyamide), the same ultrapure, on-line produced fluids, the same treatment time and the same Kt/V values, but different doses of convection. The initial treatment will be low-flux HD for all patients (phase 1, convection dose limited to ultrafiltration), then all patients will be randomized to receive either haemodiafiltration (HDF) treatment (dose of convection ~25%) or HF (dose of convection 100%). In phase 3 of the study, all patients on HF will be crossed over to HDF and vice versa.

Discussion

The two Sardinian Collaborative Studies have confirmed that HF treatment caused fewer symptoms during the treatment sessions. This finding was particulary relevant in the second study in which HD and HF where both conducted under the same conditions, i.e. the same membrane, fluid composition, urea Kt/V and treatment time. Furthermore, the number of symptomatic hypotension episodes showed a progressive decrease during the first phase of HF, an increase during HD and a new decrease during the second phase of HF (Figure 1).

The change in cardiovascular stability resulting in a significantly higher and more physiological blood pressure profile during the two HF periods was progressive during each phase. This indicated that, in the absence of relevant change of body weight, the effect of the HF treatment in stabilizing the cardiovascular reactivity is progressive and long-term rather than immediate, as has been indicated previously. This is in apparent contrast to the acute effect attributed to lowering of the body temperature by HF rather than by HD [19–21].

The difference in blood pressure profile on HD and HF indicates that HF induces a more physiological response of the cardiovascular system to the stress caused by fluid removal during the treatment. As part of this response, there may be better refilling during HF than during HD [22].

The presence of greater nocturnal dipping (although not significant) in HF, the reaction of inter-treatment weight and the finding that HF causes less hypotension intra- and inter-treatment and less inter-treatment fatigue also favour the hypothesis that HF treatment has a more physiological effect on the cardiovascular system.

The stabilizing effect of HF in unstable patients has already been described [1–3]. However, our studies are the only prospective studies which describes a haemodynamically stabilizing effect of HF in a relatively stable group of patients with a low baseline prevalence of either hypertension or hypotension [16,17].

The reduced need for therapeutic interventions during the treatment (less plasma expanders and less saline infusions) and in the inter-treatment period is another argument supporting a more physiological cardiovascular profile.

Hypotensive therapy was used in 23.3 and 26.6% of the patients during HF1 and HF2, respectively, while 33.3% of patients needed this during HD (Table 5). Also, in the first study, 47.8% of patients were on hypotensive therapy at the end of phase I (HD) and only 36.9% at the end of phase II on HF (Table 2).

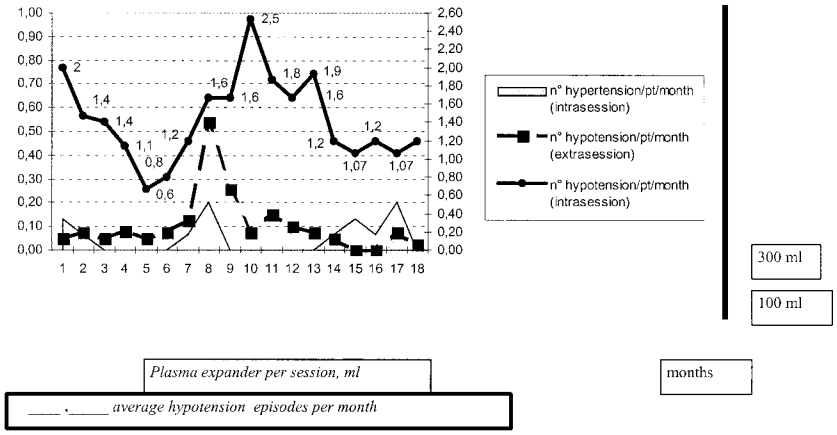

Fig. 1. Intra-treatment hypotension episodes and plasma expander infusions per session.

At present, it is not possible to establish which factors are responsible for the better cardiovascular stability of HF; our studies excluded that the better tolerance of HF was due to the better biocompatibility; in fact, the membrane, the fluid composition and the fluid quality were the same in both treatments. Different profiles during the intra- and inter-treatment periods and a lower prevalence of symptoms during the inter-treatment period on HF argue against the hypothesis that the better tolerance is due simply to a difference in temperature.

Usually, HF treatments are administered with a Kt/V which is lower than that in HD. In our first study, the nutritional parameters and the nPCR remained unchanged when patients were switched from an HD targeted at a Kt/V of 1.4 to an HF treatment targeted at a Kt/V of 1.0. The maintenance of a good nutritional status despite lower urea removal on HF was explained by some investigators as a consequence of the high removal of large molecular weight solutes influencing protein metabolism. In the second study, the urea removal indices were similar in the two treatment modes, with a targeted Kt/V of 1.2 in both modalities.

The use of highly permeable membranes in both modes certainly leads to some removal of medium to large solutes also during HD, although not as much as during HF, considering the large amount of convective transport in this mode. It is thus not clear if a difference in the solute removal profile between the two therapies could explain the better haemodynamic stability during HF in our study. Henderson [1] recently hypothesized that better removal of vasoactive mediators, such as calcitonin gene-related peptide (CGRP) during HF, could explain this difference.

When a new dialysis therapy is compared with other established therapies, it is desirable to demonstrate a decreased morbidity and mortality. Up to now, this has been done for HF only in retrospective studies [7,23]. Due to the fact that HF is used mainly in cardiovascularly unstable patients with high mortality and that there is a lack of prospective studies including a sufficient number of patients, it is impossible at present to establish what dose of HF is needed to reduce the morbidity and the mortality of patients in comparison with what is considered adequate treatment on HD.

The present study confirms the confidence in the use of on-line convective therapies, capable of obtaining adequate urea removal and keeping treatment times not substantially different from those of HD.

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