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Adequacy in pre-dilution haemofiltration: Kt/V or infusion volume?

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Abstract. Kt/V is the main index of adequacy for diffusive and diffusive–convective methods of extracorporeal depuration, yet there exists no universally acceptable validation of an adequacy index for the solely convective methods such as haemofiltration (HF). The aim of the present study is to analyse which of the parameters of adequacy used in two multicentre HF studies, Kt/V for urea or infusion volume, correlate best with nutritional parameters and can therefore be utilized for the evaluation of treatment dose in on-line pre-dilution HF.

Twenty-three clinically stable patients were enrolled in the first study [3 months of haemodialysis (HD) + 3 months of HF]. In the second study, 24 stable patients were studied in three phases: 6 months in HF, 6 months in HD and a further 6 months in HF; in this study, a target of Kt/V = 1.2 in all three periods was pre-established: 15 patients completed the full study. In both studies, we utilized the same monitor (AK 100/200 Ultra, Gambro), the same membrane (polyamide) and the same on-line prepared ultrapure dialysis fluid and sterile infusion solution.

In both studies, we ensured that HF fulfilled the following parameters of adequacy: urea kinetics, cardiovascular and blood pressure stability (better in HF than in HD), common haematochemical and nutritional parameters, reduction in β_2-microglobulin levels, a good intra- and extra-session clinical outcome, and a good quality of life with morbidity and mortality rates no different from those of HD.

HF proved to be an efficacious method of ensuring adequate depuration and a good quality of life for uraemic patients. We have shown that in longer periods of HF, a notable correlation between Kt/V and normalized protein catabolic rate (nPCR) and an equally good correlation between total ultrafiltration (UF)/dry weight ratio and nPCR could be achieved. In both studies, the patients showed a good level of epuration adequacy when total UF per session was at least 1.3 times the dry body weight. The total UF/body weight ratio thus seems to be an easy method in HF because of its greater ease of predictability and measurement, also when it is used independently of the Kt/V index.

Key words: adequacy; Kt/V; on-line haemofiltration; pre-dilution haemofiltration

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Introduction

In the last 15 years, the concept of dialysis adequacy has been in continuous evolution. From the parameters of adequacy based on urea kinetics, such as Kt/V, normalized protein catabolic rate (nPCR), URR and TAC [1], there has been a progression to the evaluation of an adequate removal/reduced intra-dialytic production of solutes of greater molecular weight, such as middle molecules, parathyroid hormone (PTH), β_2-microglobulin, and, more recently advanced glycation end products (AGEs) [2–4]. In the last 8 years, the concept of the removal of toxic solutes has been broadened to the equally important one of the maintenance of a good nutritional status [5,6].

Dialysis adequacy also involves good control of the fluid and electroyte balance, the removal of fluids during the session also in asymptomatic states, and good control of arterial pressure during the treatment and in the inter-dialytical period [7]. Good control of the cardiovascular system, increasing care in the correction of uraemic acidosis [8] and a good quality of life [9] are equally important, not forgetting those parameters which based on epidemiological data have considerable impact on morbidity and mortality.

Although the above parameters are easily applicable to the diffusive or diffusive–convective methods, references in the literature are scant on the evaluation of adequacy in the purely convective treatments, especially those carried out in pre-dilution [10]. Still rarer in the literature are references to medium- and long-term clinical studies on the application of purely convective on-line methods [11].

The aim of this work was to look for a parameter, not necessarily a classical one, for the calculation of the dialysis dose applied to pre-dilution haemofiltration

(HF) evaluated in two different studies performed in a multicentre setting.

The first study was carried out in the following way: 3 months of haemodialysis (HD), followed by 3 months of on-line HF with the possibility of prolonging HF for another 3 months; in this first study, no Kt/V targets were pre-established exactly [11].

The second study consisted of an initial phase of HF (HF1) of 6 months, followed by a second phase of HD of 6 months and a further 6 months of HF (HF2); in this study, the patients were rigorously selected so as to maintain a constant Kt/V in all the phases and, if possible, with a target of 1.2 [12].

In both studies, the patients were in a stable clinical condition which enables a more adequate evaluation of the urea kinetic parameters.

Patients and methods

In the first study, we enrolled 23 patients of a mean age of 58.9 ± 9.5 years, undergoing dialysis treatment for 69.7 ± 50.5 months; of these, only 18 patients had the further 3 months of HF.

In the second study, we enrolled 24 patients of a mean age of 61.9 ± 8.7 years, undergoing dialysis treatment for 74.5 ± 59.2 months; the Kt/V target was pre-established at 1.2. Those patients who had achieved in the first semester of HF (HF1) a Kt/V >1.2 were required to maintain the same value in HD and in the third semester of HF (HF2); 15 patients were able to keep the pre-established parameters, completing the study in a total of 12 months of HF.

In both studies, we utilized a method of on-line pre-dilution HF with bicarbonate-containing fluid prepared by an AK 100/200 Ultra monitor (Gambro), using the same membrane (polyamide), with an area of 1.4 m^2 in HD and 2–2.1 m^2 in HF. High quality fluid, produced on-line, was utilized as dialysis fluid in HD and as infusion fluid in HF. The composition of the fluid was as follows (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.

At each phase of the study, the following parameters were registered:

(i) Blood (Q_b), dialysate (Q_d), infusate (Q_{inf}) and ultrafiltrate (Q_{uf}) flow rates, treatment time and variations in the composition of the fluids.
(ii) Clinical parameters during the session: episodes of arterial hypertension or hypotension, blood pressure (BP), heart rate, body weight and temperature, and any episodes of arrhythmia, dyspnoea, fever, muscle cramps, headache, itching or nausea/vomiting.
(iii) Clinical parameters in the inter-session period: episodes of hypertension or hypotension, arrhythmia, dyspnoea, fever, muscle cramps, headache, itching, nausea/vomiting, arthralgias, thirst, insomnia or asthenia.

Urea kinetics were studied with Kt/V equilibrated after 30 min from the end of the second session of the week in accordance with the formula and nomogram of Daugirdas [13].

Every 2 weeks, the patients underwent a pre-session haematological control during the first session of the week, with a host of analyses including the main routine parameters. As pharmacological control, the infusions of plasma expanders or saline solutions during the session and of the main drugs in the inter-session period were recorded. Each patient had 48 h of continuous BP monitoring with a Space-Lab device (ABPM), including the mid-week session and under the same climatic conditions [14]. Quality of life was assessed by means of two successive interviews during each treatment phase; some aspects of the quality of life of the patients were evaluated according to the method of Laupacis [15].

The statistical analysis was performed with Student's *t*-test for paired data. The correlations were made using Spearman's method.

Results

Urea adequacy

Table 1 illustrates the urea kinetic parameters in the first and in the second study. The means refer to a period of 3 months in the first study and of 6 months in the second study.

Convective adequacy

Table 2 illustrates the operative parameters utilized in HF in the two studies. In the second study, we wished to consolidate the ratio between volume of total ultrafiltration (infusion + weight loss) and dry weight, reaching a value of 1.3 times the body weight. We considered only the 18 patients who continued HF for 6 months in the first study and the 15 patients for a period of 12 months in the second study.

Blood analysis adequacy

Table 3 lists the principal biological reference parameters used in the two studies. In the second study,

Table 1. Urea adequacy

	First study (23 patients)		Second study (15 patients)		
	HD	HF	HF	HD	HF
Equilibrated Kt/V	1.41	1.08*	1.25	1.28	1.26
nPCR	1.19	1.13	1.23	1.18	1.19
URR, %	68.7	62*	64.6	65	64.8
Treatment time, min	238	211*	222	221	218

*$P < 0.001$.

Table 2. Convective adequacy

	First study (18 patients) 6 months	Second study (15 patients) 12 months
Q_b, ml/min	376 ± 39	421 ± 46
Q_{inf}, ml/min	323 ± 27	317 ± 33
Weight loss rate, ml/min	13.3 ± 3	12.8 ± 3
Infusion volume, l per session	67.2 ± 9.4	69.6 ± 9.8
Total UF, l per session	69.9 ± 9.5	72.4 ± 10.3
Session time, min	208 ± 27	220.2 ± 23.5
Total UF/dry weight ratio	1.17 ± 0.1	1.31 ± 0.1

pre-dialytic haemoglobin (Hb), haematocrit (Hct), urea and phosphate levels were improved, and there was also an improvement in the correction of metabolic acidosis.

Removal of β_2-microglobulin

It is well known that the convective methods offer the best β_2-microglobulin removal [16]. Control of β_2-microglobulin levels was made only in the first study. At the beginning of the study, the level of β_2-microglobulin was 27.1 ± 3.5 mg/dl, and at the end of the 6 months with HF this level significantly decreased to 22.4 ± 0.7 mg/dl ($P = 0.02$).

Clinical status and drugs during the session

In both the first and second study, some clinical parameters showed a notable improvement with HF. In particular, both studies reveal a significant reduction in the percentage of patients with episodes of hypotension (first study: HD 60.8%, HF 30.5%; $P < 0.01$; second study: HD 66.6%, HF 46.6%; $P < 0.04$) and of muscle cramps (first study: HD 32.6%, HF 11.1%; $P < 0.01$; second study: HD 26.6%, HF 6.6%; $P < 0.01$). A reduction in the prevalence of episodes of hypertension, nausea and arrhythmia was observed in the first study, but was not confirmed in the second. No change was recorded in either study in the incidence of dyspnoea, headache, itching or vomiting.

In the second study, in support of these findings, there was a significant reduction in the use of plasma expanders during the sessions of HF compared with those of HD (HF1 122 ml; HD 209 ml; HF2 156 ml; $P < 0.04$). No significant change was noted in either study in the dosages of heparin and erythropoietin between HD and HF.

Table 3. Blood analysis

	First study (18 patients)		Second study (15 patients)	
	HD 3 months	HF 6 months	HD 6 months	HF 12 months
Hb, g/l	10.0	10.1	10.9	10.6
Hct, %	31.7	31.3	35.1	34.8
Urea, mg/dl	84.7	97.4*	84.7	85.6
Creatinine, mg/dl	11.2	12.5	11.3	11.4
Uric acid, mg/dl	7.0	7.2	6.5	6.5
Potassium, mmol/l	5.7	6.1	5.6	5.8
Phosphate, mg/dl	5.3	5.7	4.9	4.9
Transferrin, mg/dl	214	223	221	215
Total cholesterol, mg/dl	170	163	165	164
Total protein, g/l	6.5	6.7	6.3	6.35
Albumin, g/l	3.9	3.9	3.7	3.7
pH	7.35	7.34	7.36	7.37
Bicarbonate, mmol/l	20.2	19.5	21.9	22.6
Intact PTH, μg/ml	288	213	198	231

*$P < 0.01$.

Clinical status and drug use outside the session

In both the first and second study, some clinical parameters notably improved with HF. In particular, both studies showed a significant reduction in the percentage of patients with asthenia, especially in the immediate post-session period (first study: HD 58.7%, HF 22.2%; $P < 0.01$; second study: HD 47%, HF 10%; $P < 0.01$) or episodes of muscle cramps, especially at night (first study: HD 21.7%, HF 8.3%; $P < 0.01$; second study: HD 13%, HF 1.7%; $P < 0.01$). A reduction in the prevalence of thirst was seen in the first study but was not confirmed in the second. In the second study, the patients reported a significantly lower incidence of hypotension episodes at home. No change was observed in either study in arrhythmia, dyspnoea, headache, itching or vomiting. We observed no change in the dosages of drugs habitually utilized by the patients at home (anti-hypertensive drugs, phosphate chelants, anti-arrhythmic drugs, H_2 antagonists).

Blood pressure monitoring assessment

In the first phase on HF of the second study, a progressive decrease in hypotensive episodes was observed and a subsequent rise during the HD period; the episodes of hypotension showed a new progressive fall during the second phase on HF.

The outcome of hypertension episodes per month during the session is of no significant difference in the three phases of the study. However, the incidence of intra- and extra-session hypotensive episodes was significantly different in the three phases ($P = 0.04$ and 0.01, respectively), with a trend towards improvement in phases HF1 and HF2 and a worsening in the HD phase.

The data relating to the monitoring of BP for 48 h in the second study do not reveal any particular differences: only the mean systolic BP in the 24 h preceding the session showed significantly more stable values in HF than in HD (120.7 ± 23.5 *vs* 110.8 ± 18.4 mmHg, respectively; $P = 0.04$).

Quality of life

The results of a double interview conducted in the three semesters of the second study using the method of Laupacis [15] showed a decreased psycho-physical discomfort expecially in the second semester of HF [12]. The following parameters greatly improved in the HF periods compared with the HD periods: fatigue, frustration and depression. In none of the two studies did we observe significant differences in morbidity and/or mortality rates between HF and HD periods.

Adequacy parameters

In the second study, in order to try to assess an optimal parameter of HF adequacy as an alternative to Kt/V, we made (for 12 months on 15 patients) a monthly correlation between the total UF/dry weight ratio and

nPCR. The correlation between Kt/V and nPCR was lower than that between the total UF/dry weight ratio and nPCR ($R=0.21$ and 0.32, respectively).

Discussion

In the second study, which compared clinically and metabolically stable patients with homogeneous Kt/V, we wished to re-examine the data obtained in the first study [11]. In fact, in the second study, we were able to make correlations on long periods of treatment (for 12 months on 15 patients). Taking into consideration 180 determinations of Kt/V and nPCR in the space of the total 12 months of treatment in HF, we observed that in on-line pre-dilution HF, a purely convective method of epuration, there is a correlation (albeit a weak one) between Kt/V and nPCR (Figure 1); the same correlation was not found in the first study, probably because of the brief observation period (3 months).

The second study, however, revealed an equally important fact: there exists a better correlation between the UF/dry weight ratio and nPCR (Figure 2). Finally, again in the long term, we also found a good correlation between Kt/V and total UF (180 determinations made in the space of 12 months: $R -0.22$; $P=0.002$). This indicates that Kt/V and total UF per session can be correlated in the long term but could also be considered as parameters for the evaluation of adequacy independently of each other.

Both studies confirmed that on-line pre-dilution HF satisfies almost all the parameters of adequacy: fractional clearance of urea per session, nutritional status, a good control of the principal biological parameters, cardiovascular stability and an intra- and extra-session blood pressure control better than in HD, a greater removal and a lower production of β_2-microglobulin than with diffusive or mixed methods, and a more rapid recovery of well-being after treatment with favourable repercussions on the quality of life.

At this point, we feel able to propose an extremely simplified, easily measured parameter of convective adequacy in the evaluation of pre-dilution HF: the ratio between total UF volume and the dry weight of the patient. This ratio, with respect to the terms of adequacy, must be very near to 1.3 times the patient's dry weight: taking into account an average weight loss during each session of $\sim$4.5%, the volume of infusion in pre-dilution per session becomes 'adequate' if it is $>25\%$ (in l) of the patient's dry weight. At these levels of convective dose, the urea Kt/V also remains adequate in the long term.

It is thus possible that in the future of pre-dilution HF, reference parameters of adequacy can be used which differ from those of the Kt/V index.

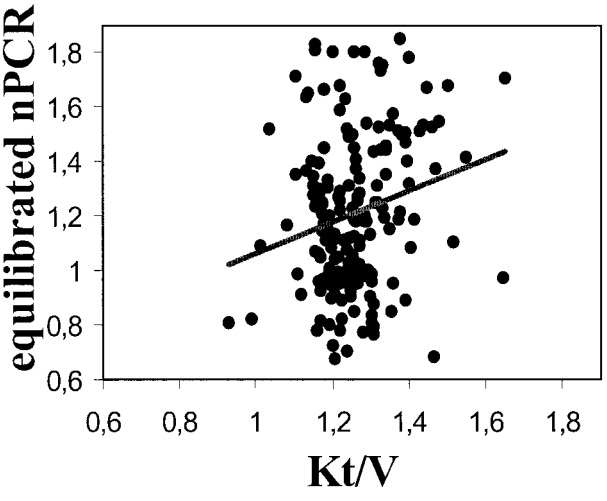

Fig. 1. Second study: correlation of Kt/V and nPCR in 180 samples during 12 months on HF on-line ($R=0.21$, $P=0.03$).

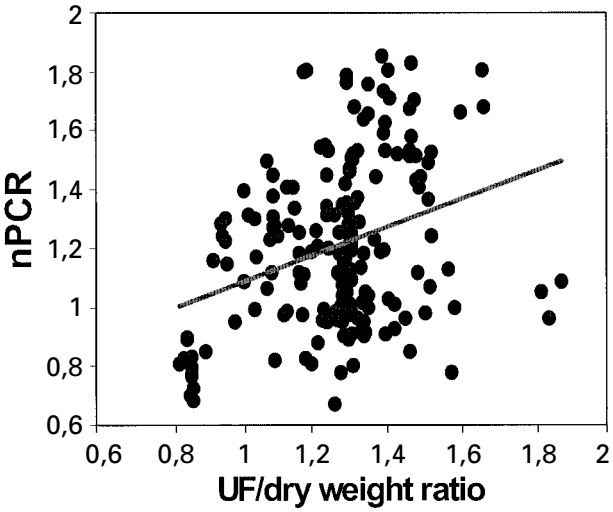

Fig. 2. Second study: correlation of UF/dry weight ratio and nPCR in 180 samples during 12 months on HF on-line ($R=0.32$, $P<0.01$).

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