On-line haemodiafiltration with high volume substitution fluid: long-term efficacy and security

Sir,

On-line haemodiafiltration (HDF) is a technique that combines diffusion with elevated convection in which the substitution fluid is produced directly from the dialysate [1]. The safety of this technique in terms of sterility and non-pirogenicity has been confirmed by several studies [2,3]. The activation of inflammatory systems has been associated with both short- and long-term complications of dialysis, namely: β2-microglobulin amyloidosis, accelerated atherosclerosis, cardiovascular calcifications and mortality, anaemia and malnutrition [4–6].

Several studies suggest that on-line convective therapies provide the most haemocompatible systems, thus reducing the bioreactivity of dialysis [1,2,4]. This is achieved by the use of synthetic, highly permeable membranes, ultra-pure dialysate and the optimization of convection which offers the greatest clearances for low- and high-molecular weight uremic toxins, and the best biological compatibility thus approaching the function of the normal kidney [4].

The use of HDF in the pre-dilution mode allows higher ultrafiltration rates permitting the highest middle molecule clearances. On the other hand, it has the theoretical disadvantage of reducing blood concentration, thus reducing the clearance of small molecules [7].

In a previous study, we were able to demonstrate that the potentiation, by on-line HDF, of the convective effect of high-flux (HF) polysulphone membrane optimizes their efficacy in terms of solute removal and probable reduction in chronic inflammatory response, as demonstrated by the decrease in the serum levels of inflammatory cytokines such as tumour necrosis factor-α (TNF-α) [5].

With the purpose of evaluating the long-term efficacy and security of on-line HDF with high substitution fluid load (pre-dilution, 250 ml/min; 60 l/session), we conducted an historical prospective study, in a group of prevalent and stable chronic haemodialysed patients.

Every 3 months, during an year (T0,T3,T6,T9,T12), we measured the removal of small molecules (urea equilibrated Kt/V); middle molecules (serum β2-microglobulin); heavy metals (serum aluminium) and several other biochemical parameters of 28 haemodialysed patients (19 male, mean age 54±13.1 years) submitted to pre-dilution HDF with a reposition volume of 250 ml/min. These patients were compared with a control group of 28 HF haemodialysed patients stratified according to time on dialysis, age, gender and presence of diabetes mellitus. The exclusion criteria were: infectious or inflammatory diseases, therapy with non-steroid anti-inflammatory drugs, corticoids or antibiotics.

Every patient was dialysed with high-flux polysulphone dialyser and volumetric monitors (HDF 4008-H) both from Fresenius Medical Care. We used ultra-pure water and the endotoxin level was evaluated by the Chromogenic Kinetic Limulus Amoebocyte Lysate (LAL) method.

Results were analysed by Student’s t-test. A P < 0.05 was considered statistically significant.

As shown in Figure 1, in the group submitted to HDF, serum C-reactive protein levels decreased significantly from the onset of the technique (T0–T3, \( P = 0.009 \)); and were maintained during the 12 months of study (\( P = 0.04 \)). This profile was not observed in the group submitted to high-flux dialysis.

The serum levels of aluminium showed a progressive and significant reduction in both groups (Figure 2).

Dialysis adequacy measured by eKt/V was maintained (HDF T0 = 1.44 ± 0.21 and T12 = 1.42 ± 0.25). Serum β2 microglobulin (HDF T0 = 17 283 ± 6518 ng/ml; HDF T12 = 16 355 ± 4944 ng/ml) and albumin (HDF T0 = 3.96 ± 0.31 g/dl; HDF T12 = 4.0 ± 0.37 g/dl) remained stable during the whole study. There were no significant differences in these parameters between pre-dilution HDF and HF dialysis.

Our results show, for the first time on a long-term basis, that convection optimization by on-line haemodiafiltration with very high volume substitution fluid (250 ml/min), is a safe technique, associated with a reduction in serum inflammatory markers, without compromising dialysis adequacy and the nutritional status of haemodialysed patients.

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**Albuminuria is an independent predictor of decreased serum erythropoietin levels in type 2 diabetic patients**

Sir,

Anemia occurs more commonly in patients with diabetic nephropathy than those with non-diabetic renal diseases [1]. Reduced erythropoietin (EPO) production has been implicated as a predominant cause of anemia in patients with diabetic nephropathy [1,2]. EPO is produced in peritubular fibroblasts in the renal cortex [3]; therefore, tubulointerstitial damage in diabetic nephropathy may contribute to EPO deficiency. Although previous studies demonstrated that decreased haemoglobin is associated with both reduced glomerular filtration rate (GFR) and increased albuminuria in diabetes [1,2], information is scarce regarding the independent effects of these parameters on serum EPO levels in diabetic patients with nephropathy. We, therefore, conducted this cross-sectional study to determine factors that contribute to decreased EPO levels in type 2 diabetic patients with albuminuria.

Adult type 2 diabetic patients with clinical albuminuria were recruited from the outpatient clinic of the Diabetes Centre, Tokyo Women’s Medical University Hospital, in Tokyo, Japan. Subjects were excluded if they had been treated with dialysis, and had received recombinant human EPO or oral/intravenous iron. At a regular visit, patients provided a first morning urine specimen. Non-fasting blood was drawn to determine serum EPO concentration as well as routine laboratory tests. Serum and urinary EPO levels were measured by radioimmunoassay, with a detection limit of 5.0 mU/ml. Urinary EPO levels <5.0 mU/ml were treated as 4.0 mU/ml. Albumin-to-creatinine ratio (ACR) was calculated from urinary albumin and creatinine concentrations; clinical albuminuria was defined as an ACR ≥300 mg/g Cr. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease Study group equation, refitted for Japanese individuals [4]. To determine which parameters are associated with serum EPO levels, simple correlational analysis and multivariate regression analyses with stepwise selection procedure were performed. For univariate correlation analyses, the Spearman’s correlation coefficient (R) was calculated. For multiple regression analysis, age, sex, haemoglobin A1C, urinary ACR, estimated GFR (GFR), and the usage of ACE inhibitors and ARBs were included as covariates; serum EPO, eGFR and urinary ACR were logarithmically transformed to improve normality. A P-value <0.05 was considered statistically significant.

We studied a total of 269 type 2 diabetic patients with clinical albuminuria, 71 women and 198 men, with a mean (±SD) age of 61 ± 12 years. Mean serum creatinine was 1.91 ± 1.42 mg/dl (range: 0.38–10.15) and blood haemoglobin was 11.9 ± 2.0 g/dl (8.0–17.3). Geometric mean eGFR, urinary ACR and serum EPO were 31.5 ml/min/1.73 m² (4.6–100.3), 1400.3 mg/g Cr (300–11 213.9), and 21.9 mU/ml (8.8–85.3). Among 269 patients, 81 patients were treated with an angiotensin-converting enzyme (ACE) inhibitor, 140 with an angiotensin receptor blocker (ARB), 150 with a diuretic and 55 with other antihypertensives.

In univariate correlational analyses, serum EPO correlated positively with age (Rₐ = 0.204, P = 0.001) and inversely with ACR (Rₐ = −0.188, P = 0.002). There was no significant correlation between serum EPO and eGFR (Rₐ = 0.107, P = 0.080) or blood haemoglobin (Rₐ = 0.052, P = 0.398). In the multiple regression analysis, age and logarithmic ACR remained in the model as variables significantly associated with logarithmic serum EPO, with the standardized partial regression coefficient of 0.198 (P = 0.002) for age and −0.127 (P = 0.049) for logarithmic ACR; the association between logarithmic eGFR and serum EPO was marginal (standardized partial regression coefficient: 0.109, P = 0.087). Urinary EPO was undetectable in 75% of patients. There was no significant correlation between urinary EPO and ACR (Rₐ = 0.0143, P = 0.834).

In this cross-sectional study, we demonstrate for the first time that lower serum EPO levels was independently associated with increased albuminuria but not with reduced GFR in diabetic patients. In glomerular diseases, increased protein filtration through the glomeruli, including filtration of cytotoxic cytokines, causes tubulointerstitial injury. We hypothesize that glomerular–proteinuria-induced tubulointerstitial damage, and the consequent reduced number of EPO-producing peritubular fibroblasts, may be responsible for decreased serum EPO levels, irrespective of GFR levels.

Another possibility for the decreased EPO levels may be due to increased glomerular filtration of EPO [5], which has a molecular weight of 30-400. Our present data do not support this hypothesis, as there was no relationship between urinary EPO and albuminuria, in accordance with an earlier study of children with nephrotic syndrome [6]. However, direct measurement of urinary EPO may be problematic due to conformational changes in EPO epitope following glomerular filtration.

In conclusion, we found that increased albuminuria was independently associated with decreased serum EPO levels in patients with type 2 diabetes regardless of GFR. Reduced EPO production of peritubular cells is most likely associated with lower EPO levels. Urinary loss of EPO should be investigated in patients with increased albuminuria.

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