HAEMOFILTRATION WITHOUT SUBSTITUTION FLUID

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Summary

Haemofiltration at its best is able to give excellent clearances of solutes in a wide molecular weight range, but the need of large amounts of reliable substitution fluid makes this technique too expensive for more widespread application.

In order to give an ‘adequate’ treatment by a safe, well tolerated, effective and comparatively cheaper method, haemofiltration without substitution fluid (HWSF) has been carried out. This method, consisting of the regeneration of appropriate amounts of pure convected plasma water by highly permeable, high surface area dialysis membranes, has been utilised for several months in four patients, with encouraging clinical results.

Introduction

In 1975, according to the middle molecule hypothesis, Babb [1] and Funck-Brentano [2] claimed that a vitamin B₁₂ dialysis clearance of 30L/week (2.9ml/min) and a urea clearance of 69L/week (6.8ml/min) was sufficient to prevent or cure uraemia.

In 1979 Savazzi [3] demonstrated that signs of polyneuropathy were absent in conservative patients whose residual glomerular filtration rate (GFR) was equal to or greater than 13ml/min, while polyneuropathy was still seen in all dialysis patients despite a dialysis index equal to or greater than one. Teschan [4] has recently (1983) shown the disappearance even of the mildest ‘uraemic’ symptoms (neurobehavioural changes) in his patients receiving a dialysis prescription of 3000ml/week/L body water as total urea clearance, which corresponds to about 10 per cent of normal GFR.

High efficiency haemofiltration (HEHF) was proposed in 1983 by Civati [5] as the best method to clear solutes in the widest molecular weight range: by this prescription (3.3L/L body water/week) it was possible to achieve a urea clearance of 115.9L/week (11.5ml/min) and an inulin clearance of 86.6L/week.
(8.6ml/min). Using this technique Minetti [6] found a marked improvement of the peripheral uraemic polyneuropathy. The aim of our study was to test a new model of haemofiltration without substitution fluid (HWSF) evaluating the removal of various sized solutes, the haemodynamic stability, the acid-base equilibrium, the easy feasibility, safety and costs.

Patients, materials and methods

Four patients, all women aged 22 to 65 years (mean 45.7), body weight 47.5 to 82.5kg (mean 59.2 ± 15.7) have been treated thrice weekly for four hours by HWSF for a period of three to nine months (mean 6.1 ± 3.2). Maximum weight loss was between 2.2 per cent and 6.5 per cent of total body weight (mean 2.6 ± 1.06%). An average pure convective ultrafiltration rate of 180–200ml/min was obtained by an appropriate haemofilter (ASAHI PAN 250) with a blood flux of 500ml/min or more, transmembrane pressure of 400 ± 50mmHg, the mean Ht being 20.3 ± 3.4 per cent and total protein concentration 6.9 ± 0.9g/dl. This acellular and aproteic ultrafiltrate the composition of which is nearly identical to the plasma water, was then passed into a high surface area, highly permeable dialyser (2 TORAY B1L = 4.2m² PMMA) through which 600ml/min of dialysate (Na⁺ 140; K⁺ 1.5; Mg²⁺ 1.5; Ca²⁺ 4; Cl⁻ 107; Acetate 40mEq/L; Glucose 1g/L; mOsm 300/L) were flowing (Figure 1).

Figure 1. Haemofiltration without substitution fluid (HWSF). Clearances calculated as:

\[ C_l = \frac{Q_f (F_i - F_o)}{P} \]

where \(Q_f\) = ultrafiltration rate (ml/min) \(F_i\) = solute concentration at regenerator inlet; \(F_o\) = solute concentration at regenerator outlet; \(P\) = plasma solute concentration
Results

Plasma clearances

All data were calculated as the mean of three values, each of them being the average of duplicate samples at 15, 120, 240min from the start, for three consecutive runs. The mean ultrafiltration rate (QF) was 187.1 \pm 15.3ml/min. Average urea clearance was 188.8 \pm 3.7ml/min and creatinine clearance 182.6 \pm 3.3ml/min, while inulin (MW 5200) and \( \beta_2 \)-microglobulin (MW 11800) clearances were 70.2 \pm 3.8ml/min and 11.9 \pm 1.4ml/min respectively.

Plasma solute values and balances

The data are shown in Table I.

<table>
<thead>
<tr>
<th>Solute</th>
<th>Before</th>
<th>After</th>
<th>Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea g/L</td>
<td>1.5 \pm 0.3</td>
<td>0.6 \pm 0.2</td>
<td>-33.7 \pm 7.2g*</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>8.7 \pm 1.9</td>
<td>3.7 \pm 1.1</td>
<td>-1.1 \pm 0.1g*</td>
</tr>
<tr>
<td>Phosphate mg/dl</td>
<td>4.6 \pm 0.5</td>
<td>2.8 \pm 0.2</td>
<td>-0.6 \pm 0.05*</td>
</tr>
<tr>
<td>Calcium mg/dl</td>
<td>9.1 \pm 0.2</td>
<td>11.1 \pm 0.5</td>
<td>+0.3 \pm 0.06g†</td>
</tr>
<tr>
<td>Potassium mEq/L</td>
<td>4.9 \pm 1.1</td>
<td>3.3 \pm 0.3</td>
<td>-130 \pm 36mEq†</td>
</tr>
</tbody>
</table>

* Solute amount collected in the tank
† Solute supplied — solutes collected in the tank

Blood gas equilibrium

\( \text{PaO}_2 \) and \( \text{PaCO}_2 \) were quite similar in HWSF and in a pure convective method such as high efficiency haemofiltration (Figure 2), while the same did not happen in acetate dialysis where a fall of \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) was seen especially with large surface area dialysers.

Acetate and bicarbonate equilibrium

In HWSF plasma acetate at 120min from the start (5.2 \pm 1.5mMol/L) was lower than that observed during a haemodialysis session with the same surface area and membrane type (6.4 \pm 1mMol/L). HWSF was well tolerated while sudden hypotension with a fall in \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) occurred during haemodialysis. During HWSF plasma bicarbonate never fell below starting values during the whole session, while they usually fell during haemodialysis. During HWSF, but also in a pure convective way, there is a characteristic pattern of acetate and bicarbonate (Figure 3).
Figure 2. Blood gas behaviour in HWSF and in HEHF (mean values of three consecutive sessions in four patients)

Figure 3. Behaviour of acetate (mMol/L) and bicarbonate (mEq/L) in HWSF at 0, 60, 120 and 240 minutes. Mean values of four experiments
HWSF is able to achieve very good clearances of small solutes. Average urea (MW 60) clearances (13.2ml/min = 132L/week) were identical to those obtained by HEHF, but creatinine (MW 113) clearances were somewhat lower (12.8ml/min = 129.6L/week). These data are as good as those obtained by conventional diffusive or convective methods.

According to Savazzi, Teshan and ourselves, this regimen could be ‘adequate’ and effective in preventing and curing neurobehavioural changes and peripheral polyneuropathy. The role of middle and larger molecules in the pathogenesis of uraemia is less clearly defined; but good removal of some of them (i.e. PTH and its fragments) must be of value. HWSF obtains a mean inulin (MW 5200) clearance of 5ml/min = 50L/week and $\beta_2$-microglobulin (MW 11800) clearance of 0.8ml/min = 8.6L/week. From this point of view HEHF seems still superior to HWSF, nevertheless the need for removal of such large solutes is not yet completely understood. On the other hand small clearances of $\beta_2$-microglobulin may not be disadvantageous because normally the kidney retains microproteins and free light-chains. Anyway neither a deficiency syndrome, nor a loss of significant amounts of albumin and globulins were seen in our patients.

In our experience HWSF was also a powerful tool for removing phosphates (mean = 625mg/session) and potassium (mean 130mEq/session), allowing patients to have a completely free diet. Calcium balance studies showed in our patients a mean gain of 310mg/session. These two latter features, together with PTH removal, could possibly slow the evolution of the uraemic osteodystrophy. Sodium balance of each HWSF session is precisely defined by the sodium concentration in the effluent dialysate per volume of weight loss, no other sodium escaping the system. Several factors may play a role in cardiovascular stability during HWSF sessions, where no significant change between pre and post mean arterial pressure (MAP) was recorded. First of all there is a small decrease of plasma osmolality, because the sodium saving effect of haemofiltration is fully maintained: no disequilibrium syndromes were seen in spite of the rapid decrease in urea even to one-third of the starting values. Moreover HWSF involves a bicarbonate saving effect and ensures blood gas stability and moderate acetate at the reinfusion site.

HWSF is a simple renal replacement therapy with no need of special equipment. We used commercial bags of pure salt, aluminium free (0.02 PPM) concentrate with deionised water. A Hospal Moniral machine with reliable control of weight loss at the effluent dialysate site and with a supplementary pump for convected ultrafiltrate was regularly utilised. No pyrogenic reactions were recorded; limulus amebocyte tests in affluent and effluent dialysate and in reinfused dialysed ultrafiltrate were always negative as well as cultures in the same samples and in blood. At least HWSF is cheaper than HEHF because no substitution fluid is required. Furthermore, regenerators can be utilised dozens of times without any problem at a very low price per session. Thus HWSF may be introduced as a routine procedure for ‘adequate’ and well tolerated treatment in end-stage renal failure.
Acknowledgments

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References

2. Funck-Brentano JL, Man NK, Sausse A. *Kidney Int 1975; Suppl 2: S52*

Open Discussion

ALBERTINI (Los Angeles) I think this is an elegant way of helping haemofiltration a little further. At the same time it seems to me that you are taking away one crutch to justify the treatment, which is the high molecular solute removal component, which in dialysis uses a purely diffusive transport mechanism. I also want to bring to your attention, as you will see in the next paper, if in your set up you left out the first step, which is the needles, you would double the efficiency of the whole treatment. You would have a blood flow of 500ml/min and you would get a clearance of about 440ml/min for urea.

CIVITI Yes, our philosophy in this kind of treatment was mainly to achieve a very good clearance of small and larger solutes. It could be done better by high efficiency haemofiltration with substitution fluid. We wanted to reduce the cost but maintaining the results in terms of stability and of acid base and bicarbonate equilibrium. This is the first clinical experiment in this field of regenerating ultrafiltrate. I think that we will improve this system when we can adapt as regenerators more compact membranes with higher cut off. This is a bioengineering problem.

SHALDON (Chairman) I think your goal of trying to achieve haemofiltration without fluid replacement is obviously the right way to go if one ever wants to achieve a transportable, portable or implantable artificial kidney. It seems to me that you have to produce 600ml per minute of dialysis fluid to achieve this goal. Have you considered looking at the sorbent field? A few years ago we published on the problems with aluminium but Dr Shapiro in New York has had quite encouraging results recently using a sorbent based system. What is your opinion on that?

CIVITI I think that the way of the sorbent is very hard. It is certainly harder than our method and I think is more expensive. I know the experiments you mention but I think that the method we have described is superior.