DOES LONG TERM HAEMOFILTRATION PROVOKE SECONDARY HYPERPARATHYROIDISM?

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Summary

One thousand nine hundred and forty-nine haemofiltration procedures have been performed since 1976; 4 different types of haemofilters have been tested in gravimetric and volumetric haemofiltration machines. Balance studies revealed a diminished calcium intake of about 1/3 of that found in conventional dialysis. Magnesium balance is negative and leads to decreasing serum Mg values. Inorganic phosphate is removed in similar quantity to dialysis. PTH levels increase during 3-18 months of treatment, whereas 25-OH-D₃ levels rapidly fell, gc-globulin- and HCT-levels did not change markedly. g-c globulin could be detected in filtrate samples in remarkable amounts, 25-OH-D₃ was found in traces. Radiologically no apparent alteration occurred. We recommend Vitamin D supplementation to compensate for the losses and thereby avoid development of secondary hyperparathyroidism.

Patients and Methods

Since 1976, 14 patients have been treated on a regular haemofiltration programme. Four patients have been discharged because of transplantation, normalisation of blood pressure response or movement to another city. All patients had a preperiod of chronic haemodialysis of 3 months to 7 years and were subjected to the haemofiltration treatment because of uncontrollable hypertension, severe polyneuropathy and marked signs of discomfort on regular haemodialysis [1]. By the end of May 78 we had performed a total number of 1949 haemofiltration procedures in a three times weekly schedule. Both types of haemofiltration system, the gravimetric and volumetric method were used to balance substitution fluid and haemofiltrate [2]. Four different haemofilters (Amicon Diafilter 30, Berghof capillary haemofilter, RP₆ and Sartorius haemofilter URF) were compared in clinical trials with respect to clearance values, sieving coefficients and membrane cut offs [2]. The replacement solutions were usually administered venously (‘postdilution’) and had
different electrolyte compositions (mEq/L):
Solution A: Na 135, K 2.0, Ca 3.75, Mg 1.5,
Cl 108.5, Lactate 33.75
Solution B: Na 140, K 2.0, Ca 4.25, Mg 1.5,
Cl 112, Lactate 35.75

Electrolytes in serum and filtrate samples were measured in a SMA 12 and
aca autoanalyzer, i-PTH was determined with a C-terminal sensitive RIA, 25-
OH-D by plasma ethanol extraction according to Belsey, g-c-globulin by radial
immuno diffusion (Beringwerke).

Results

During a single haemofiltration procedure a mean 23.17±1.31 L (N=81) of
plasma water were exchanged, the median fluid balance was -3.46±1.02 L
(L of replacement fluid minus L of haemofiltrate), weight loss averaged 2.2±
0.4 kg, whilst blood volume decreased 22% as determined by 5 measurements
with Indium-tagged erythrocytes [3].

Balance studies were undertaken, in order to determine net transfer rates
of Ca, Mg and phosphorus and compare the results with haemodialysis. Using
Sol A with a Ca concentration of 3.75 mEq/L we found in 32 procedures an
average net gain of 5.82±4.79 mEq/treatment, the mean fluid balance was
-3.2±1.1 L. Regression analysis showed a correlation coefficient r = 0.500457.
Using Sol B with a Ca concentration of 4.25 mEq/L, an average net gain of
9.62±4.80 mEq Ca occurred in 26 trials, correlating with the fluid balance
(coefficient r = 0.32904) which averaged -3.7±1.0 L. Comparing these results
with those won on haemodialysis with a dialysate Ca concentration of 3.5
mEq/L [4,5,6], the net gain in haemofiltration using Sol A is found to be
1/3 of that on haemodialysis (HF: mean: 116 mg/treatment, HD: mean: 300
mg/treatment). For Sol B the net gain nearly doubles. Despite these low Ca
intake rates compared with haemodialysis, total Ca serum values did not
decrease over the whole treatment period.

Both replacement solutions had a Mg concentration of 1.5 mEq/L, the Mg
loss averaged 14.38±5.15 mEq/treatment which correlates with the fluid bal-
ce (r = 0.597462), which averaged in these 39 trials -3.3±1.3 L. This neg-
ative Mg balance leads to decreasing serum Mg values. After 6 months of
haemofiltration treatment a 18.4% decrease was observed, followed by a fur-
ther decline of 28.9% after 18 months as compared with the starting point.

Phosphorus elimination in haemofiltration depends on serum phosphate
levels and the quantity of the filtrate. In 32 trials we found a mean net loss
of 846 ± 251mg of inorganic phosphate/treatment, which is not higher than
the phosphate elimination known in comparable conventional dialysers [7].
Aluminium hydroxide administration had to be maintained in the same quan-
tity as before in 4 patients, 3 had to take a lower and 3 a higher dosage. None
of our patients can be kept without Aluminium hydroxide in order to main-
tain serum phosphate levels between 4.5 - 7.5 mg%.

Long term observation showed an increase of PTH-levels determined by a
c-terminal sensitive radio-immunoassay in 8 of 10 patients using mainly the
Figure 1. Left side: Fluid balance plotted against the filtrate volume in 81 procedures. Mean ± SD is indicated. Right side: Decrease of body weight in a single treatment plotted against intravascular blood volume measured with Indium-tagged erythrocytes. Mean values of 5 procedures are indicated. (+)

Figure 2. Ca intake during a single haemofiltration procedure with replacement solution A (Ca 3.75 mEq/L) and Solution B (Ca4.25 mEq/L) related to fluid balance. Mean ± SD is indicated.
replacement solution A. The increase ranged from 11 - 144% after 3 - 18 months of treatment, whereas 25 OH-D values decreased rapidly to a minimum of 10% of starting values. The serum levels of the specific Vit-D-transport protein (g-c-glob) did not change directionally, as expressed by a mean of 99% after 3 - 18 months of treatment, alkaline phosphatase was in the normal range in all but one patient. During this period no Vit-D-supplements have been administered.

Radiological assessment of renal osteodystrophy revealed no significant variation according to the Barnett-Nordin-Index [8,9], which was compared pre-haemofiltration treatment and 6 - 22 months later. In none of the patients did acro-osteoysis develop or when present, deteriorate. Subperiosteal resorption increased in one case, cortical striation in 4 cases but improved in one,

![Graphs showing changes in serum values of g-c-globulin, 25-OH-D, PTH and HCT.](image)

Figure 3. Changes in pre-treatment serum values of g-c-globulin, 25-OH-D, PTH and HCT during chronic haemofiltration treatment.
Figure 4. Changes in Barnett Nordin Index determined with 6 x ocular at basal phalanx III of right and left hand at onset of haemofiltration and 6 - 22 months later.

Endosteal resorption and periarticular calcification increased in 2 cases and improved in one. Thus the period of observation probably is too short to detect radiological variation of osteodystrophy with haemofiltration treatment.

For a 4 week period we gave supplements of 10,000 units of Vitamin D/day orally and detected an increase of 25-OH-D levels into the normal range. PTH slightly decreased in 8 of 10 patients indicating at least partial suppression of hyperparathyroidism, whereas total Ca values did not change pre- or post-treatment. Inorganic phosphate values, however, fell pre-treatment and to a larger extent post-treatment without any change in the haemofiltration procedure, the patients nutrition or the dose of aluminium hydroxide ingested. We think this might be caused by a Vitamin D effect forcing phosphate deposition in the bones [10].

Discussion

As the long term observation detected a marked decrease of 25-OH-D serum levels, we analysed filtrate samples, but found only traces of Vitamin D, probably because the levels are too low for the sensitivity of the assay. Seasonal variations of 25-OH-D levels also could be involved, as the last determinations were carried out in November 77. Changes in the rate of hepatic hydroxylation of Vitamin D might lead to decreasing serum levels. Despite the high molecular weight of about 56,000 Daltons, g-c-globulin could be detected in the filtrate in appreciable amounts by a 3H-labelled 25-OH-D binding assay.
Figure 5. Alteration of PTH, 25-OH-D, alkaline phosphatase (AP) and pre and post treatment total serum Ca and inorganic phosphate before and after treatment with 10,000 units of Vitamin D/day orally. Mean values ± SD are indicated. Note that there were no changes in haemofiltration treatment, patients’ nutrition nor the dose of aluminium hydroxide.

As mean serum values of g-c-globulin remained nearly stable, adequate synthesis must be implied, though serum albumin fractions were found to decrease from a mean of 58.6 rel% to 55.5 rel% after 6 - 22 months of haemofiltration treatment. PTH levels increase, though PTH and its biologically active and inactive fragments are filtrable and detectable in filtrate samples [11]. We think this increase is related to the low net intake of Ca, which is dependent upon the individual fluid balance. As total serum Ca levels did not change over the whole period of treatment, we suspected Ca depletion from the skeleton though radiologically no apparent signs could be detected. The decrease of the serum Mg values towards the normal range might be implicated in this development, yet the literature reveals contrary opinions [12,13,14].

In conclusion we believe that to avoid the development of secondary hyperparathyroidism in long term haemofiltration requires:
a) adequate calcium intake via the replacement solution. We recommend a Ca concentration of 4.0 - 4.25 mEq/L dependent upon individual fluid balance.
b) Vitamin D supplements to compensate for any loss, and thereby to avoid stimulation of parathyroid secretion.

Acknowledgements

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Open Discussion

FUCHS (Göttingen) I would like to ask you what kind of membranes you used in your investigation, especially in respect of the vitamin D results.

SCHNEIDER We used all membranes that were available, mainly RP6 and Amicon.

FUCHS Actually we could not find any changes in vitamin D during a five month period. I agree with you that probably the time when you were measuring vitamin D is much more important for explanation of your results because as I understood you were measuring the vitamin D concentrations in Winter time.

SCHNEIDER Yes we did. We did it to prove that.

KANIS (Oxford) Am I right in remembering that you did not see any change
in plasma alkaline phosphatase at all?

SCHNEIDER  Yes.

KANIS  I am just wondering whether you have done any chromatographic studies of the PTH that seems to be eluted during the haemofiltration and whether you might for example be removing biologically active fragments and retaining the rather larger, perhaps inactive, fragments and in fact you aren't increasing secondary hyperparathyroidism, you are just having an appropriate response to a further loss of biologically active PTH and are retaining further inactive products. Chromatography might help in this situation.

SCHNEIDER  Maybe. Dr Sheil from Berlin, measured PTH levels by N-terminal radioimmune assays and he found no increase, he found relatively stable values, so you might be right.

MADSEN (Copenhagen)  I may have missed it, but how can you be sure that the changes you describe for parathyroid hormone are significantly different from what we see when we give ordinary haemodialysis treatment?

SCHNEIDER  I don't know if there are significant changes compared with haemodialysis treatment. The purpose of this work was to see what haemofiltration does to hyperparathyroidism.