The modality of dialysis treatment: does it influence the response to erythropoietin treatment?

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Introduction

Over the last decade, the availability of recombinant human erythropoietin (rh-Epo) has led to the almost complete disappearance of the severe anaemia of end-stage renal disease (ESRD). However, despite an increase in the use and average dose of rh-Epo, a substantial percentage of patients do not achieve a haematocrit level of more than 30% [1,2]. Although iron deficiency is probably the main factor affecting the response to rh-Epo in most patients, occult blood loss, infection, inflammation, and dialysis adequacy are also important. Given that rh-Epo resistance is a clinically and economically relevant problem, it is important to understand to what extent the mode and/or the dose of dialysis can influence anaemia and the response to rh-Epo.

Dialysis dose and frequency

Adequate dialysis can contribute to correction of anaemia by removing hypothetical small, and possibly...
also medium/large molecules, that potentially inhibit erythropoiesis. However, the role of dialysis dose per se on the response to rh-Epo has been largely underestimated in the past and it has been only recently that more interest has been focused on this issue.

Large observational [3] and cross-sectional [4] studies indicate a correlation between dialysis dose, haematocrit levels and rh-Epo dose in haemodialysis patients. This association is stronger in patients receiving a low ‘dose’ of dialysis. However, these studies were not designed to discriminate the effect of adequacy from that of membrane biocompatibility, and haematocrit levels were also higher in patients treated with synthetic compared with non-synthetic membranes. Similar findings were obtained from smaller studies [5–7]. Certainly, patients receiving a very low ‘dose’ of dialysis benefit most from an increase in dialysis adequacy. Ifudu et al. [5] prospectively studied 135 patients and found that increasing the ‘dose’ of dialysis in patients receiving inadequate dialysis led to a significant improvement in their response to rh-Epo; however, interpretation of this result is difficult because patients were also changed to biocompatible and highly permeable membrane (high-flux polysulphone). It is possible that biocompatibility or permeability, or both, may have had an additive effect over and above increased ‘dose’ of dialysis on the correction of anaemia in these patients. In order to separate the direct effect of dialysis adequacy per se from the effects of dialysis modality and membrane biocompatibility, Movilli et al. [7] investigated the relationship between rh-Epo and dialysis ‘dose’ in 68 patients on conventional haemodialysis. By multivariate regression analysis, Kt/V was the only significant variable independently contributing to rh-Epo dose; the influence of dialysis adequacy on rh-Epo dose was also evident in patients receiving more adequate dialysis (Kt/V ≥ 1.2). This suggests that dialysis adequacy per se can influence anaemia, independently from a possible additive role of biocompatibility or permeability.

Dialysis adequacy could have an effect on anaemia not only in terms of dialysis dose, but also in terms of dialysis frequency and time. Some preliminary observations indicate that larger dialysis ‘dose’ in patients receiving inadequate dialysis led to a significant improvement in their response to rh-Epo; however, interpretation of this result is difficult because patients were also changed to biocompatible and highly permeable membrane (high-flux polysulphone). It is possible that biocompatibility or permeability, or both, may have had an additive effect over and above increased ‘dose’ of dialysis on the correction of anaemia in these patients. In order to separate the direct effect of dialysis adequacy per se from the effects of dialysis modality and membrane biocompatibility, Movilli et al. [7] investigated the relationship between rh-Epo and dialysis ‘dose’ in 68 patients on conventional haemodialysis. By multivariate regression analysis, Kt/V was the only significant variable independently contributing to rh-Epo dose; the influence of dialysis adequacy on rh-Epo dose was also evident in patients receiving more adequate dialysis (Kt/V ≥ 1.2). This suggests that dialysis adequacy per se can influence anaemia, independently from a possible additive role of biocompatibility or permeability.

Dialysis adequacy could have an effect on anaemia not only in terms of dialysis dose, but also in terms of dialysis frequency and time. Some preliminary observations indicate that a more frequent schedule, daily haemodialysis (2 h × 6/week), could lead to better control of anaemia [8,9]. Furthermore, the duration of dialysis session may matter. Patients treated with long haemodialysis (8 h) in Tassin had much lower rh-Epo requirements for similar haematocrits than Swedish patients treated with shorter dialysis sessions (3–5 h) [10]. The patients in Tassin also had significantly higher mean Kt/V, however. So, it remains difficult to discriminate between whether the better control of anaemia was mainly due to a higher depuration rate or to a possible effect of dialysis time per se, independent from dialysis adequacy.

Altogether, these results further stress the importance of adequate dialysis, not only as a tool for reducing morbidity and mortality, but also for: (i) reducing the proportion of patients who need rh-Epo treatment; or (ii) optimizing response to rh-Epo.

Membranes and convective treatments

Conventional haemodialysis may have a significant role in removing low molecular-weight erythropoietin inhibitors. However, medium-large and high molecular-weight inhibitors have also been found in uraemic serum [11]. These inhibitors can only be removed by more permeable and/or highly porous membranes. Some preliminary observations indicate that large-pore membranes, and particularly the BK-F polymethylmethacrylate membrane, may improve the haematocrit and the response to rh-Epo [11–13]. However, a number of drawbacks (small sample sizes, no randomization, wide range of haematocrit levels, scanty information on iron status) prevent one from drawing definitive conclusions from these studies.

With the aim of obtaining controlled information to confirm this hypothesis, Locatelli et al. [14] performed a multicentre, controlled, and randomized study in 84 haemodialysis patients. The aim of the study was to examine whether haemodialysis with the high-flux BK-F polymethylmethacrylate membrane improved anaemia in comparison with conventional haemodialysis. An increase in haemoglobin levels was observed in the population as a whole, but this trend was not significantly different between the conventional and experimental groups [14] (Figure 1). In the experimental group, the haemoglobin level tended to increase progressively during the trial follow-up, but this was not significant, possibly because the period of observation was too short [14]. Indeed, other authors observed a significant improvement in

![Fig. 1.](Image)
haematocrit levels during a similar follow-up period [5,11]. In particular, Ifudu et al. [5] found an increase in haematocrit values as early as 6 weeks after the dialysis dose was increased. It is possible that, in this study [5], the observed improvement in anaemia was mainly due to the increase in dialysis dose in patients receiving a very inadequate dialysis at baseline rather than to the use of a high-flux biocompatible membrane.

There may also be other explanations why, in the study by Locatelli et al. [14], the effect of the experimental treatment on correction of anaemia was much less than expected. Certainly, the fact that the patients were all well-nourished, adequately dialysed ($Kt/V = 1.3$) and without other known factors affecting anaemia, may have reduced the power of the study. Moreover, there was an imbalance in the percentage of patients receiving iron therapy (higher in the conventional group) and a different distribution of underlying disease (polycystic kidney and diabetes mellitus) that may have favoured the conventional treatment.

Similar negative findings were obtained from the secondary analysis of a multicentre trial [15] comparing biocompatible and traditional membranes, as well as convective and diffusive treatment modalities in 380 patients. Haematocrit levels increased in the overall trial population (probably as a consequence of a trial effect), but this did not significantly differ among the four treatment modalities: cuprophane haemodialysis; low-flux polysulphone haemodialysis; high-flux polysulphone haemodialysis; and high-flux polysulphone haemodiafiltration (HDF) (unpublished data). However, a significantly higher increase in haematocrit was observed in patients on high-flux compared to those on low-flux treatments. It is possible that a difference in dialysis dose (higher in the HDF group) may partially explain this observation.

### On-line treatments

On-line HDF is a technique that combines diffusion with higher rates of convection than that provided by standard HDF. A dialysis fluid, free of toxins and pyrogens, is used as substitution fluid. It is possible that this technique may be more effective in achieving higher haematocrit levels by means of two mechanisms: (i) higher rates of removal of medium and large molecules (possibly containing bone marrow inhibitors); and (ii) less microbiological and pyrogenic contamination of the dialysate (maybe also important in causing or aggravating anaemia in haemodialysis patients by means of an enhanced production of cytokines).

Correction of anaemia was significantly improved, and the rh-Epo doses required were less, when patients were treated with on-line HDF [16,17]. However, some of the patients also experienced an improvement in dialysis dose during the on-line HDF period [16]. These observations were not confirmed by other studies [18,19]. In particular, on-line HDF had no effect on correction of anaemia in 44 patients who were randomized to undergo either low-flux polysulphone haemodialysis or on-line polysulphone HDF [19]. In this study, a number of confounding factors were eliminated (dialysis time and adequacy, membrane biocompatibility and permeability) and the same ultrapure dialysate was used in both groups. Consequently, this study suggests that the main factor accounting for the positive effect of on-line HDF on anaemia correction found in other studies may have been a reduced inflammatory stimulus from the dialysate. Favouring the importance of dialysate sterility on anaemia correction, a significant and sustained reduction of rh-Epo dose was found in patients switched from conventional bicarbonate haemodialysis (with potentially microbiologically contaminated dialysate) to a similar treatment modality using on-line-produced ultrapure dialysate [20].

Given that haemodialysis patients come into blood contact with approximately 120 l per dialysis session, i.e. 20 000 l each year, it is also important to remember that, in addition to microbiological contamination, chronic exposure to toxic substances in the dialysate, even if their concentrations may be extremely low, can cause a number of complications. Among these, one may be the development or the worsening of anaemia.

### Extracorporeal circuit

Last but not least, anaemia in haemodialysis patients can occur after haemolysis due to mechanical injury of erythrocytes from defects in the blood pump system, dialyser, connectors, occluded or kinked haemodialysis blood lines, or from faulty blood tubing sets. Even if these events are rare, it is worth remembering that in 1998 two patients died because of haemolysis caused by a faulty tubing lot [21]. Haemolysis can also occur when using small ago-cannulae at high blood flows. Large-diameter needles are thus recommended, and single-needle haemodialysis should be avoided as much as possible.

### Conclusions

Recombinant human erythropoietin-resistance is a clinically and economically relevant problem. Consequently, it is important to understand to which extent the mode and/or the ‘dose’ of dialysis can influence anaemia and the efficacy of rh-Epo treatment. Adequate dialysis may contribute to correction of anaemia by removing inhibitors of erythropoiesis. This effect appears to be much more prominent in patients receiving a very low dialysis dose and experiencing an increase of dialysis adequacy. Dialysis time per se, independently from dialysis adequacy, may have a role in the correction of anaemia, but this...
probably has never been tested properly. Given the possible presence of high-molecular weight erythropoietin inhibitors in uraemic serum, biocompatibility or permeability of membranes, or both, could have an effect on the correction of anaemia, in addition to increased dialysis dose.

However, in highly-selected, adequately dialysed patients without iron or vitamin depletion, this effect seems to be smaller than might be expected from the results of uncontrolled studies.

The possibility that on-line HDF/HF may achieve better control of anaemia is intriguing, but available results are conflicting. This is mainly because of differences in treatment modalities in control groups, small numbers of patients enrolled and because anaemia was not the primary outcome in any of the studies. Furthermore, on-line HDF achieved a higher dialysis dose than control treatments in many studies, further complicating the interpretation of these observations. Prospective randomized trials aimed at testing this hypothesis are awaited. Dialysate quality is also important in reducing haemolysis and pyrogen formation. On-line-produced ultra pure dialysate is probably a quality target to be reached in coming years in order to reduce bacterial contamination and the consequent chronic inflammatory response. This will probably improve anaemia correction, reduce rh-Epo dose requirements and partially compensate for extra costs of convective treatments.

References

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