Normalization of haemoglobin: why not?

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Abstract

It has been suggested that normalization of haemoglobin with epoetin in anaemic chronic renal failure (CRF) patients might result in even greater benefits than those currently achieved with partial haemoglobin correction. Four prospective randomized trials recently examined this hypothesis. The Scandinavian Multicentre Trial, which was completed in February 1998, included 416 haemodialysis, continuous ambulatory peritoneal dialysis and predialysis patients. Preliminary analysis of the data found no differences with respect to safety between patients treated to achieve subnormal haemoglobin (9.0–12.0 g/dl) and those in whom haemoglobin was normalized (13.5–16.0 g/dl). The Canadian Multicentre Trial included 159 haemodialysis patients with asymptomatic left ventricular (LV) dysfunction. In patients with a normal LV cavity volume at enrolment, the change in LV cavity volume at 48 weeks was significantly greater in the control group (target haemoglobin 9.5–10.5 g/dl) than in the intervention group (target haemoglobin 13.0–14.0 g/dl). The Normal Hematocrit Cardiac Trial in the US included 1233 haemodialysis patients with clinically evident ischaemic heart disease or congestive heart failure. The trial was stopped in 1996 after an interim analysis showed increased mortality in the intervention group (target haematocrit 42%) compared with the control group (target haematocrit 30%). The higher haematocrit values themselves, however, did not appear to be responsible for the differences in mortality, as the mortality rates within each group decreased with increasing haematocrit. Nonetheless, until evidence is available from other trials demonstrating a benefit of normalizing haemoglobin, it has been recommended that a target haematocrit value of 42% be avoided in haemodialysis patients with clinically evident ischaemic heart disease or congestive heart failure. Further studies are also required to determine whether increasing haemoglobin to normal may prove to be beneficial in other patient groups. The Spanish Quality of Life Study of 134 haemodialysis patients found a significant improvement in all quality-of-life parameters when haemoglobin was increased to a mean of 12.5 g/dl. The investigators suggested that in patients without severe co-morbidity, the target haemoglobin should be as close to normal as possible.

Key words: anaemia; cardiac disease; chronic renal failure; epoetin; haemoglobin; quality of life

Introduction

Numerous trials show that partial correction of anaemia with epoetin in haemodialysis patients with chronic renal failure (CRF) is associated not only with relief of anaemic symptoms, but also with partial regression of left ventricular hypertrophy (LVH) and improvements in quality of life (J. F. E. Mann, this volume). However, it is not yet clear whether full correction of anaemia will have further beneficial effects.

Moreover, despite more than a decade of clinical experience with epoetin, the optimal target haemoglobin must still be defined. The National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI™) guidelines currently recommend a target haemoglobin of 11–12 g/dl [1]. This recommendation was based on a review of the literature available at the time, which found an association between increased morbidity and mortality and a haemoglobin of ≤10 g/dl. However, as preliminary data from more recent trials show beneficial effects from increasing haemoglobin to normal, the NKF-DOQI guidelines acknowledge that a higher target haematocrit/haemoglobin may ultimately prove to be more appropriate in CRF patients.

There are reasons for supposing that normalizing haemoglobin may be beneficial. First, there is an intuitive belief that hormone replacement therapy—whether it be for diabetes or renal anaemia—should strive to achieve a normal physiological value. Haemoglobin concentrations at the currently recommended 11–12 g/dl are considerably less than the lower
limit of the normal range for males and post-menopausal females (13.5–17.5 g/dl) and less than or at the lower limit of normal for pre-menopausal females (12.0–16.0 g/dl). Second, indirect evidence from prospective and retrospective studies shows that the risk of LV dilatation, heart failure and premature death increases as the anaemia of CRF worsens [2–5]. These findings logically suggest that the more effectively anaemia is corrected, the greater the potential benefits in terms of symptom relief, regression and prevention of LVH, and improvements in quality of life. It might reasonably be predicted that mortality would also be reduced.

There is, however, a legitimate concern that increasing haemoglobin to normal might also be associated with unknown risks. Evidence from randomized, controlled trials in which adverse events can be assessed properly is therefore needed before the optimal target haemoglobin for patients receiving epoetin treatment can be determined.

Publication of four recent prospective studies of CRF patients will hopefully provide such evidence. These studies investigated the effects of normalizing haemoglobin with epoetin on cardiovascular outcomes and quality of life. The four study designs and preliminary trial results were reported and discussed during a workshop at the 2nd European Epoetin Symposium, Optimizing Anaemia Therapy in CRF. This article summarizes the information on these trials that was available at the time of the workshop, as well as the conclusions reached by the workshop participants based on the data presented.

Scandinavian Multicentre Trial

The Scandinavian Multicentre Trial was an open, randomized, controlled study of the effects of elevating haemoglobin from subnormal to normal values. Various efficacy and safety parameters were investigated, with an emphasis on cardiovascular function and quality of life. A total of 416 haemodialysis, continuous ambulatory peritoneal dialysis, and predialysis patients aged 18–80 years were included in the trial, which was conducted in Sweden, Norway, Finland and Iceland. The last patient completed the study in February 1998.

Patients were randomized to treatment with epoetin alfa, with the intention of either: (i) maintaining haemoglobin within the subnormal range (9.0–12.0 g/dl); or (ii) increasing haemoglobin to normal (13.5–16.0 g/dl), with the aim of increasing the haemoglobin by at least 25%. Following a titration period (usually 3–6 months), patients were kept at a steady-state haemoglobin for 12 months.

Physical, biochemical and haematological parameters, quality of life, iron status, chest X-ray, renal function, exercise capacity, epoetin alfa and iron dosing, hospitalizations and adverse events were monitored in all patients. In the haemodialysis patients, clotting of dialysers and heparin dose were also monitored.

To evaluate further potential benefits and adverse effects, several substudies were performed. These studies included echocardiography, rheology, renal function (in pre-dialysis patients), dialysis adequacy, coagulation parameters, iron dose, iron supplementation and serum transferrin receptor, and the results of renal transplantation of all transplanted patients.

In view of the early termination of the Normal Hematocrit Cardiac Trial in the US (see below), an interim analysis of cardiovascular adverse events was performed on two occasions during the present study. These analyses found no differences between the patient groups with normal and subnormal haemoglobin values with respect to safety.

Although the study data had not been analysed at the time of the symposium, the subjective impression was that a normal haemoglobin value would be of great benefit, particularly for pre-dialysis patients. Publication of the full trial results is expected in 1999.

Canadian Multicentre Trial

The Canadian Multicentre Trial investigated whether normalization of anaemia with epoetin alfa could improve LV geometry and quality of life in 159 anaemic haemodialysis patients with asymptomatic LV disease. Two sets of patients were randomized: patients with a normal LV cavity volume and LVH; and patients with an increased LV cavity volume. Patients with current symptoms of cardiac disease were excluded from the trial.

Patients from both sets were randomized to either: (i) an intervention group (epoetin alfa dose titrated upwards to achieve a target haemoglobin of 13.0–14.0 g/dl within 6 months, and maintenance of this target up to 48 weeks from study entry); or (ii) a control group (epoetin alfa given to maintain a haemoglobin of 9.5–10.5 g/dl).

Outcome measures were change in LV volume and LV mass. Both intention-to-treat and efficacy analyses were conducted, comparing echocardiograms performed at baseline with those taken 40 weeks after the start of the study.

Based on the preliminary trial results, it was concluded that, compared with partial correction of anaemia, normalization of haemoglobin with epoetin may prevent progressive LV dilation in haemodialysis patients with a normal LV volume. However, it does not induce regression of concentric LVH or of LV dilatation in patients with pre-existing LV dilatation. As these results suggest that the adverse effects of anaemia on the heart can be prevented, but not reversed, early normalization of haemoglobin may prove to be the most beneficial strategy.
**Normal Hematocrit Cardiac Trial**

The aim of the Normal Hematocrit Cardiac Trial in the US was to examine the risks and benefits of normalizing hematocrit in hemodialysis patients with cardiac disease. A total of 1233 hemodialysis patients with clinically evident congestive heart failure or ischaemic heart disease were included in the trial [6]. Patients were randomized to one of two groups: a normal hematocrit group (n=618), in which patients received doses of epoetin sufficient to achieve and maintain a hematocrit of 42 ± 3%, and a low hematocrit group (n=615), in which patients received doses of epoetin sufficient to maintain a hematocrit of 30 ± 3%. The primary end point was time to death or a first non-fatal myocardial infarction.

The study was stopped prematurely after an interim analysis at 29 months showed 183 deaths and 19 first non-fatal myocardial infarctions in patients randomized to the normal hematocrit group vs 150 deaths and 14 first non-fatal myocardial infarctions in those randomized to the low hematocrit group (risk ratio normal vs low hematocrit: 1.3; 95% repeated confidence interval: 0.9–1.9). Although the difference in event-free survival between the two groups did not reach the pre-specified statistical stopping boundary, the study was halted because of safety concerns and because it was considered that an attempt to prove benefit for the higher hematocrit group would be futile.

The differences in outcomes in the two groups could not be explained by 11 prespecified baseline characteristics, because adjustment for these factors in a Cox regression analysis did not change the risk ratio for patients randomized to the normal- vs the low-hematocrit group. Although it remains unclear why patients randomized to the normal-hematocrit group fared less well than those assigned to the low-hematocrit group, it is important to note that the mortality rates decreased with increasing hematocrit in each group. When ‘group assignment’ was replaced in the analysis by ‘average hematocrit’, the risk ratio was 0.7 (95% confidence interval: 0.6–0.8, P<0.001), indicating a 30% reduction in the risk of death or myocardial infarction for a 10 point increase in hematocrit. This suggests that the increased mortality in patients randomized to the normal hematocrit group was not due to hematocrit itself. The causes of death in the two groups were similar. Post-hoc analyses suggest that two other factors may have contributed to the disparate outcomes in this trial. First, patients randomized to the normal hematocrit group showed a decline in the adequacy of dialysis during the study (lower Kt/V values), whereas Kt/V values increased in patients randomized to the low hematocrit group. Second, intravenous (i.v.) iron was administered more frequently and at higher doses to those patients randomized to the normal hematocrit group, and was associated with an increased risk of death. Whether the administration of i.v. iron supplements could be linked to an increased risk of complications, however, is a question that remains unresolved [8].

**Spanish Quality of Life Study**

This study was designed to measure the effects of increasing hematocrit with epoetin on quality of life. The aim was to increase hematocrit by ~5 percentage points. Quality of life was measured before the study, and at 3 and 6 months, using the Karnofsky Scale and the Sickness Impact Profile. The study included only stable hemodialysis patients under 65 years of age, who were already receiving epoetin and who had hematocrits of 30–35%. Diabetic patients as well as patients with a history of cerebrovascular accident, seizures, severe arterial hypertension, vascular access malfunction and severe co-morbidity were excluded.

A total of 134 patients were enrolled, 115 of whom completed the 6 months of follow-up. Ten of the 134 enrolled patients were excluded from the study, nine (6%) because of thrombosis of the vascular access and one because of uncontrolled arterial hypertension. There were no deaths during the study.

The mean hematocrit increase in the 115 patients who completed the study was 7.8. The mean hematocrit achieved was 39 ± 2.1, equivalent to a mean haemoglobin of 12.5 ± 1 g/dl.

All tests used demonstrated a significant improvement in quality of life. The global score of the Sickness Impact Profile decreased from a mean of 7.8 to 5.7 (P<0.0001) (the lower the score, the better the quality of life). The physical dimension score decreased from a mean of 5.3 to 3.9 (P<0.005) and the psychosocial dimension score decreased from 8.8 to 6.1 (P<0.0001) (Figure 1).

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*Although the full results of the Normal Hematocrit Cardiac Trial were not available at the time of the workshop, they were published four months later [6] and the text reviewing this trial has been updated accordingly. It is important to note, however, that there is wide debate regarding interpretation of the methodology and statistical analyses used (for a discussion of the limitations and criticisms of this trial, see [7]).*
It was concluded that quality of life improved significantly when haematocrit was increased, despite the fact that the patients were already stable on epoetin prior to the study. The incidence of adverse effects in this study was negligible, but it is important to note that patients were screened rigorously to exclude diabetic patients and those with severe hypertension or other severe co-morbidity. Although the investigators acknowledged that individualization of target haematocrit is necessary, they suggested that it should be as close to normal as possible in patients without severe co-morbidity.

**Should haemoglobin be normalized?**

Full correction is often advised in, for example, iron-deficiency anaemia, vitamin B₁₂-deficiency anaemia and thalassaemia. In addition, in hormone-deficient states such as Addison’s disease, hypothyroidism, oestrogen deficiency and diabetes mellitus, the aim of hormone replacement therapy is to emulate the physiological effects of normal hormone concentrations. Yet, full correction of the anaemia of CRF, which is also a hormone-deficient state, is still a controversial issue.

The available evidence indicates that quality of life, exercise capacity and cardiac output are likely to improve as haemoglobin approaches normal. The preliminary data from the Canadian Multicentre Trial suggest that normalizing anaemia with epoetin alfa prevents progressive LV dilatation in patients who have not yet developed this adverse cardiac effect as a result of prolonged anaemia. Thus, early normalization of haemoglobin, probably starting in the pre-dialysis period, would seem to be a logical strategy for protecting the heart.

Normalisation of haemoglobin does not appear to have any negative impact on blood pressure stability, nor does it seem to increase the likelihood of thrombotic events [6,9–11]. Although an increase in the need for antihypertensive medication is seen in ~20% of patients receiving epoetin therapy for the anaemia of CRF, blood pressure can usually be controlled with appropriate clinical care [1].

There was no evidence of increased mortality or other serious adverse events in the normalized haemoglobin groups in the Scandinavian or Canadian trials (though neither of these trials was set up to examine mortality as an end point).

In the Normal Hematocrit Cardiac Trial, mortality was marginally greater in the normal haematocrit group. It is important to bear in mind, however, not only that all patients in this trial had documented ischaemic heart disease or congestive heart failure, but also that mortality decreased with increasing haematocrit in both the normal and the low haematocrit groups, indicating that the higher haematocrit values themselves were not responsible for increased mortality.

In the Canadian and Scandinavian trials, normalization of haemoglobin did not appear to have adverse cardiovascular effects. However, the Scandinavian Multicentre Trial initially included fewer patients with severe cardiac disease and, in response to early termination of the Normal Haematocrit Cardiac Trial, any such patients were withdrawn from the study at the first interim analysis. The Canadian Multicentre Trial excluded patients with cardiac symptoms from the outset, though all had evidence of asymptomatic LV disease.

It is possible, therefore, that the difference between the study populations in these three trials might explain the differences in the trial results with regard to safety.

**Conclusions**

On the basis of the Normal Hematocrit Cardiac Trial findings, and pending the results of other trials, the workshop suggested that normalization of haemoglobin in patients with CRF be avoided in the presence of documented ischaemic heart disease or congestive heart failure. It is hoped that publication after peer-review of the full results of the Scandinavian, Canadian and Spanish multicentre trials will help to quantify as well as qualify the potential benefits and risks of normalizing haemoglobin in CRF patients.

There was agreement among the workshop participants that increasing haemoglobin to normal may be beneficial in selected groups of CRF patients. Further studies, with clear and robust end points, are required not only to identify more precisely which patients would benefit most, but also to explore the impact of early normalization of haemoglobin, with a view to preventing the long-term complications of renal anaemia.

**References**


7. Macdougall IC, Ritz E. The Normal Haematocrit Trial in dialysis patients with cardiac disease: are we any the less confused...