A rationale for an individualized haemoglobin target

Norman Muirhead

University of Western Ontario, London, Ontario, Canada

Abstract
Despite the use of recombinant human erythropoietin (rh-EPO, epoetin) for more than a decade in treating renal anaemia, there is still considerable debate over optimal target haemoglobin (Hb) levels. Current European and North American guidelines that are based on decade-old trials aim for partial anaemia correction, with a subnormal target Hb concentration. More recent randomized clinical trials examining the effect of normalizing Hb levels have produced conflicting results. A study in the USA, in patients with existing congestive heart failure or ischaemic heart disease, showed an unexpected rise in cardiac mortality and haemodialysis access failure with higher Hb levels. In contrast, three other studies (in Australia, Spain and Canada) that normalized Hb levels in healthier dialysis patients observed improvements in quality of life and exercise capacity and a slower progression of left ventricular dilatation, without an unacceptable increase in the incidence of adverse effects. These studies indicate that, while higher Hb levels may be detrimental to patients with pre-existing cardiac disease, healthier patients benefit from normalized Hb levels. Thus, there is no clear scientific rationale for setting a single Hb target for all patients, and individualized treatment targets would appear to be a more logical and patient-centred approach.

Keywords: anaemia; dialysis; end-stage renal disease; erythropoietin; haematocrit; haemoglobin; vascular hypertrophy

Introduction
A normocytic, normochromic anaemia may occur during chronic renal failure (CRF) as a consequence of an inadequate renal production of erythropoietin [1,2]. This produces physiological problems, such as decreased oxygen delivery and utilization in tissues, leading to fatigue and reduced exercise capacity [2], decreased cognition [3] and impairment of the immune system [4,5]. Furthermore, cardiac abnormalities, such as increased cardiac output, cardiac enlargement, left ventricular (LV) hypertrophy, angina and congestive heart failure (CHF), may also occur as maladaptive compensatory mechanisms for the anaemia [5–8]. Indeed, cardiac disease is the most common cause of death in CRF patients.

The introduction of recombinant human erythropoietin (rh-EPO, epoetin) has revolutionized the care of patients suffering from renal anaemia. Epoetin stimulates erythropoiesis, thereby increasing haemoglobin (Hb) and haematocrit (Hct), and, ultimately, at least partially reversing the anaemia. Although epoetin has been used for more than a decade in the treatment of renal anaemia, there is still considerable debate concerning the optimal level to which Hb should be raised.

Normal concentrations of Hb are generally considered to be within the range of 13–15 g/dl for women and 14–16 g/dl for men. However, when treating anaemia, the US NKF-DOQI Clinical Practice Guidelines recommend a target Hb concentration of 11–12 g/dl and an Hct of 33–36% [2,9]. The European Best Practice Guidelines recommend a target Hb of at least 11 g/dl [10,11]. Clearly, these targets represent a subnormal correction of the anaemia. Furthermore, according to the European Survey in Anaemia Management, it would appear that significant proportions (40–50%) of patients are failing to reach even these modest targets [11,12].

The choice of Hb targets for treating patients with renal anaemia is still a matter of great debate. Are these subnormal targets ideal, or should Hb be increased further towards normal levels? Clearly, achievement of these subnormal levels does result in significant improvements in well-being, quality of life and exercise tolerance, with minimal adverse effects [13]. However, increasing Hb levels further may produce greater benefits, particularly as there seems to be a relationship between low Hb and increased cardiovascular disease in end-stage renal disease (ESRD) [6]. Additionally, further improvements in
quality of life may be derived from increasing Hb to normal levels [14]. On the other hand, raising Hb levels may increase the risk of adverse effects such as access failure, hypertension and mortality [13,15]. Therefore, we need to consider both the risks and the benefits of epoetin therapy and achieve a balance in order to select the most appropriate Hb level for individual patients. This highlights the need for individualized treatment targets in the management of patients with renal anaemia.

Why raise haemoglobin to only subnormal levels?

Historically, subnormal Hb targets were chosen based on the findings of decades-old trials that only aimed for partial correction of anaemia. However, restoration of Hb to these subnormal levels still produces clinical benefits with few adverse events and, therefore, there would seem to be little incentive to pursue higher Hb levels. There are several issues that need to be taken into account when considering a higher Hb target, including (i) iron deficiency; (ii) treatment costs; (iii) vascular access problems; and (iv) cardiac morbidity and mortality.

Iron is important for effective erythropoiesis, and iron deficiency may become a problem as Hb targets are increased. This is a concern for patients on haemodialysis (HD), where blood loss through the dialyser is a constant problem and, therefore, iron stores may be inadequate to maintain a normal Hb target. While administration of parenteral iron may be considered, it may increase the cost of therapy, as well as being logistically awkward for out-patients [2,16].

There may also be economic reasons behind low Hb targets. Renal anaemia is a long-term problem, persisting until death or a kidney transplant and, consequently, costs will accumulate. Raising Hb targets may therefore increase this financial burden. Indeed, a 2- to 3-fold increase in epoetin dose may be required to elevate Hb from subnormal towards normal levels [15]. However, less epoetin is required to maintain Hb levels when given subcutaneously, compared with intravenously [17]. Therefore, utilization of this route of administration may reduce the relative dosage and subsequent cost of epoetin associated with normalization of Hb. Consequently, while marketplace economics may dictate a low target for Hb correction, it appears that Hb may be normalized without unacceptable increases in dosage.

The choice of subnormal Hb levels has also been reinforced by safety concerns over higher Hb targets. As early as 1990, a concern over anaemia correction with epoetin has been an increase in the rate of vascular access thrombosis. In a multicentre study by the Canadian Erythropoietin Study Group, a placebo-controlled trial from the early 1990s, access loss increased in groups having anaemia corrected with epoetin [13].

Further apprehension about higher Hb targets developed when increased morbidity and mortality were noted in patients with pre-existing cardiac disease [15]. The US Normal Hematocrit Study, which was designed to address the issues surrounding normalization of Hb, selected subjects for study on the basis of having active cardiac disease, CHF and/or ischaemic heart disease. Patients had their Hct raised to 42% in the high Hct group and to 33% in the low Hct group. Those patients with a higher Hct had significantly improved quality of life and reduced probability of requiring a blood transfusion compared with patients with a low Hct. However, patients with the higher Hct were also at risk of a higher incidence of death or non-fatal myocardial infarction (risk ratio 1.3) than

![Fig. 1. Comparison of Kaplan–Meier estimates for death or a first non-fatal myocardial infarction between patients with a low and normalized Hct (adapted from the US Normal Hematocrit Study, Besarab et al. [15] with permission).](image-url)
those with a low Hct (Figure 1). The incidence of vascular access thrombosis was greater in the high Hct patients (39%) compared with low Hct patients (29%, $P = 0.001$). It was concluded from this study that normalization of Hct in patients with established cardiac disease could not be recommended. However, despite the fact that Besarab and colleagues suggested that their results may not be applicable to all patients, due to the selective population studied, this work has helped to deter the use of a normal Hb target in the treatment of renal anaemia.

**Benefits of higher haemoglobin targets**

While the US Normal Hematocrit Study has made nephrologists shy away from normalization of Hb levels, it should be emphasized that there are also numerous benefits. For example, from as early as 1990, a correlation between higher Hb levels and an improved quality of life has been shown [13]. An increase in quality of life at the higher Hb level was also apparent in the US Normal Hematocrit Study [15]. More recent studies have now shown that increasing the Hb target in certain patient populations can produce benefits without an unacceptable increase in adverse effects.

The first of these studies, the Canadian Multicenter Study, was published by Foley and colleagues [18]. The study investigated the effect of low (10 g/dl) and normalized (13.5 g/dl) Hb targets in HD patients with asymptomatic cardiomyopathy. They observed a slower progression of LV dilatation in patients with asymptomatic LV hypertrophy when on a higher Hb target. A 1 g/dl decrease in Hb led to a significant ($P = 0.009$) increase of 8 ml/m² in LV end diastolic volume (Figure 2). There was also a tendency towards a reduced LV mass, with a 1 g/dl decrease in Hb leading to a 6.94 g/m² increase in LV mass index, although this failed to reach significance ($P = 0.075$).

When LV dilatation was already established, no benefit of a higher Hb level was observed. In this study, quality of life was also enhanced in patients with higher Hb levels, with symptoms of fatigue and depression showing improvements over those of patients with a low Hb target after 24 weeks. Foley *et al.* [18] also noted that there was no significant difference in the incidence of vascular access thrombosis, cardiac events or death between the two patient groups, although patients with higher Hb levels were more likely to require antihypertensive medication.

A study conducted in Australia investigated the effect of normalizing Hb levels in 14 HD patients (23–65 years old), who were in otherwise good health [14,19]. In this randomized, crossover study, patients were assigned Hb targets of 10 or 14 g/dl for 6 weeks before being switched to the alternative Hb target. Quality of life, assessed by the Sickness Impact Profile questionnaire, blood pressure and ECG parameters were measured throughout the study. In addition, patients underwent exercise testing to observe the impact of low and normal Hb levels on oxygen consumption and work rate. Patients with a high Hb target experienced significant improvements over lower target patients in cardiac output ($5.2 \pm 0.3$ vs $6.6 \pm 0.5$ l/min, for high vs lower targets, respectively, $P \leq 0.01$), LV end diastolic diameter ($4.8 \pm 0.2$ cm, $P \leq 0.01$) and quality of life (total Sickness Impact Profile score $6.5 \pm 1.7$ vs $13.4 \pm 3.0$, $P \leq 0.02$). In addition, LV mass index was significantly lower in patients with a high Hb target compared with baseline ($122 \pm 11$ vs $141 \pm 13$ g/m², $P \leq 0.02$). Furthermore those with the 14 g/dl Hb target could perform more work ($41.4 \pm 4.0$ vs $33.2 \pm 3.6$ kJ, $P \leq 0.01$) and consumed 18% more oxygen than those on the lower target (Figure 3). Due to the small cohort of patients in the study, caution should be used in interpreting these data. However, this study confirms the potential benefits of higher Hb for carefully selected patients.

---

![Fig. 2. Comparison of the change in LV cavity volume index in HD patients with LV hypertrophy (adapted from Foley *et al.* [18] with permission).](image-url)
Another recent study conducted in a greater number (156) of patients for a 6-month period corroborates the Australian study [20]. Here, HD patients, excluding diabetics, the elderly and patients with severe co-morbidities, achieved an increase in mean Hb levels from 10.2 to 12.5 g/dl. Raising Hb improved quality of life (Figure 4). In addition, compared with the previous 6 months, there was a 58% reduction in the number and 69% reduction in duration of hospitalizations in patients with the increased Hb target (Table 1). This decrease in the number and duration of hospitalizations may help offset the cost of the increase in epoetin required to normalize Hb levels. The incidence of discontinuations due to cardiovascular events (2%) and access thrombosis (5.7%) in this study compares favourably with other studies. There was also no significant increase in the incidence of arterial hypertension when Hb levels were increased. Thus, younger, healthier patients seem to gain significant benefits from higher Hb levels without experiencing an increase in adverse effects.

The case for individualization of treatment

Higher Hb targets may produce several benefits in patients with renal anemia. These include less LV hypertrophy and LV dilatation, with a subsequent potential benefit of protection against increased cardiac morbidity and mortality, together with improvements in quality of life and exercise tolerance. With the exception of the US Normal Hematocrit Study, which was performed in a highly selected and susceptible population, these advantages of a higher Hb level occur with an acceptable incidence of adverse effects. Thus, with these advantages in mind, the current guideline of a low Hb target seems an arbitrarily limited approach.

Raising Hb to a subnormal target of 11 g/dl improves quality of life, with minimal adverse events, in many patients. However, many other individuals may be capable of achieving even greater benefits. Thus, a single Hb target will not achieve maximal clinical benefit for all patients. The current blanket

---

Fig. 3. Comparison of peak oxygen uptake during exercise in HD patients with low or normalized Hb concentrations (adapted from McMahon et al. [14] with permission).

Fig. 4. Changes in Sickness Impact Profile scores of HD patients (adapted from Moreno et al. [20] with permission).
policy dictating a subnormal Hb target is inflexible and needs rethinking to allow individualization of treatment. A flexible approach that evaluates each patient and the relationship between their Hb levels and their symptoms will obtain the best results for each individual. The challenge for nephrologists is to identify the best Hb level for each patient and to tailor therapy accordingly.

Who needs higher Hb levels?

Pre-dialysis patients, and those with a short duration of ESRD represent a population that may benefit from a normal Hb concentration as they are less likely to have developed severe maladaptive conditions, such as LV hypertrophy. Anemia plays a role in the pathogenesis of LV hypertrophy [6], an established independent risk factor for fatal uremic cardiomyopathy, and preliminary findings indicate that early treatment of anemia decreases the incidence and severity of these problems in CRF [21–23]. Indeed, normalization of Hb prevents LV dilatation from worsening in HD patients who have not already developed this condition [18]. Little improvement in LV dilatation is observed in HD patients where LV hypertrophy or LV dilatation is already established [18]. Thus, pre-ESRD patients may gain the most from normalized Hb levels.

People who are active or are in full-time employment in a fairly strenuous job make more demand on their oxygen-carrying capacity and are more likely to notice its relative absence with a lower Hb concentration. Indeed, this reduced exercise tolerance may impact on their ability to work and exercise. McMahon et al. [14] have shown that exercise tolerance can increase when Hb levels are raised towards normal. Therefore, it would make sense that active people would benefit from a higher Hb level. Similarly, since the young are more physically active and have a longer life expectancy than the elderly, they would benefit more from normal Hb levels.

The health of an individual and the eventual presence of various disease states, such as coronary artery disease, may also dictate whether normalization of Hb is desirable. The findings of the US Normal Hematocrit Study indicate that patients with an existing cardiac disease should not have their target Hb raised to the normal range. In addition, as it appears that a high Hb level may exacerbate the risk of a vascular access thrombosis in some individuals [15], it may be advisable to aim for a lower Hb target in patients with a limited vascular access or a history of access problems.

Conclusions

In summary, studies concerning the normalization of Hb have shown conflicting results and it would appear that outcomes depend on the health status of the patients studied. For instance, while normalization of Hb may be detrimental to patients with pre-existing cardiac disease, healthier patients clearly benefit from higher Hb levels, achieving a better quality of life, improved exercise capacity and some protection against developing serious cardiac morbidities. Since these benefits are not offset by unacceptable increases in adverse events, there seems to be no clear scientific rationale for setting a single Hb target for all patients.

The continuing use of subnormal Hb targets is perhaps due to a lack of proper evaluation of individual patient needs, coupled to concerns regarding funding and potentially harmful effects of higher Hb levels. Such considerations could be eliminated by a return to individualized patient care, in which clear treatment goals are established for each patient receiving epoetin therapy. This flexible attitude towards treatment targets would appear to be a more logical and patient-centred approach and would significantly improve the lives of many HD patients.

References


Table 1. Influence of increased Hb levels on hospitalization (Moreno et al. [20])

<table>
<thead>
<tr>
<th></th>
<th>Baseline (6 months prior to study)</th>
<th>Study period (6 months)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of hospitalizations*</td>
<td>19</td>
<td>8</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Mean duration of hospital stay (days)</td>
<td>1.3</td>
<td>0.4</td>
<td>≤0.05</td>
</tr>
</tbody>
</table>

*Data for the previous 6 months were only available for 115 patients.

The total number of hospitalizations and length of hospital stay (mean days by patient) during the study period were compared with those occurring in the 6 months preceding the study in the same patients.
Individualized haemoglobin targets

23. Valderrabano F. Improvement and prevention of left ventricular hypertrophy in predialysis patients. 37th Congress ERA–EDTA, 2000, Nice