Evidence and implications of haemoglobin cycling in anaemia management

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Introduction

Treatment with erythropoietic-stimulating agents (ESA) has been a major advance for improving the lives of patients with chronic kidney disease (CKD). Treatment, however, differs greatly from normal erythropoietic biology. The ESA drugs are administered episodically, resulting in great fluxes in serum erythropoietin levels. While the erythropoietic efficacy of treatment is clear, there are aspects of pharmacological response that are important to consider if we are to optimize treatment. One such phenomenon recently described, haemoglobin (Hb) cycling, is the repeated, cyclical, up and down movement of Hb levels during ESA treatment. This review will describe the phenomenon of Hb cycling, highlighting potential contributing factors and discussing the possible clinical implications.

Evidence for Hb cycling

Results from a recent study suggest that Hb cycling is a common occurrence in ESA-treated patients on haemodialysis [1]. Hb cycling can be defined as oscillations over time in measured Hb levels in individual patients, with Hb levels decreasing or increasing over time, then reversing direction. The starting and ending Hb levels and rate of change in Hb level as it changes in opposite directions may differ. In our recent study, Hb cycling was defined as an oscillation in Hb of ≥1.5 g/dl over >8 weeks during which Hb levels increased or decreased and then reversed the initial trajectory. This phenomenon was investigated in 281 patients treated with epoetin-α at Winthrop-University Hospital Dialysis Centers between 1998 and 2003. Over the course of 1 year, Hb cycling was observed in >90% of the patient population. Patients experienced a mean of 3.1 Hb excursions (defined as half of one full Hb cycle) per year (Figure 1) and the mean amplitude of excursions was 2.5 g/dl.

Frequent Hb fluctuations were also observed by Macdougall et al. [2], in a 12-month study of 154 patients on haemodialysis receiving either epoetin-β or darbepoetin-β. On average, each patient experienced 3.2 excursions per year and 73% of patients had three or more Hb oscillations per year that were outside the target Hb range of 11–12.5 g/dl. Furthermore, 43.5% of patients had up to two Hb oscillations per year during which Hb levels were <10.3 g/dl.

In another study, Hb variability was analysed in 65,009 patients on dialysis, 98% of whom were receiving epoetin [4]. The proportion of patients with 3-month rolling average Hb levels within the target range of 11–12 g/dl appeared to be constant throughout the 1-year study at 38%; however, 29% of the patients moved from below to above the target range or vice versa during this period. It was estimated that the average patient would be expected to experience a fluctuation in 3-month rolling average Hb level of 1.4 g/dl/year. Substantial variability in Hb levels was also demonstrated in a longitudinal evaluation of 31,267 patients on haemodialysis receiving epoetin-α in the Fresenius Medical Care-North America database [5]. Only 5% of the patients...
Fig. 1. Distribution of the number of haemoglobin excursions per patient per year [10]. An excursion is defined as half of one haemoglobin cycle. Adapted by permission from Macmillan Publishers Ltd: *Kidney International* Fishbane S, Berns JS. Haemoglobin cycling in haemodialysis patients treated with recombinant human erythropoietin. copyright 2005: 68: 1337–1343.

who began the 6-month period with a mean Hb level of 11–12 g/dl remained within that range for six consecutive months.

**Factors affecting Hb cycling**

The cause of Hb cycling is not yet fully understood; however, it is highly likely this is multifactorial and a number of parameters have been proposed.

**ESA management practices**

ESA dose adjustment may be a major cause of Hb fluctuations. Indeed, epoetin dose adjustment was found to be the most important driver of Hb cycling in the Winthrop-University Hospital Dialysis Centers study [1]. A total of 84% of up excursions were associated with an epoetin dose increase and 62% of down excursions were related to dose reduction. In this study, frequent epoetin dose changes were required to maintain Hb levels within the target range of 11–12 g/dl then recommended in the NKF-K/DOQI guidelines [6], with an average of 6.3 dose changes per patient per year.

A narrow target range may perpetuate Hb cycling, such that clinicians respond to a Hb fluctuation outside the target range with a change in ESA dose, only to find at the next Hb measurement that the Hb trajectory has changed direction, necessitating further dose adjustment. A number of studies have demonstrated the difficulties involved in maintaining Hb levels within a narrow target range [5,7]. In a study of 987 patients on haemodialysis receiving epoetin, Hb variability was investigated by calculating 1-month and 2- to 6-month rolling average Hb levels [7]. From a single month, the width of the range that included the middle 50% (25th–75th percentile), 80% (10th–90th percentile) and 90% (5th–95th percentile) Hb values was 1.7, 3.3 and 4.4 g/dl, respectively. A progressive narrowing in the range of Hb values encompassed by each percentile grouping was observed as longer rolling intervals were used; however, fewer than 50% of patients had Hb levels within the range of 11–12 g/dl even when a 6-month rolling average was applied.

Hb cycling may also be exacerbated by the use of inflexible ESA dose adjustment protocols that do not account for patient-specific responsiveness [1]. Patient responsiveness to ESA treatment is highly variable, with some patients responding with great sensitivity while others may be highly resistant [8,9]. Most haemodialysis units use rigid ESA dose adjustment protocols that do not account for the great variability in patient response. A 25% increase in dose when Hb is <11 g/dl may lead to a rapid increase in Hb in some patients and almost no change in others. We found that patients who were highly responsive to epoetin had a greater degree of Hb cycling (>2 full cycles per year) compared with less responsive patients (P = 0.02) [1]. In practice, there have not generally been efforts to characterize individual patient ESA-responsiveness and use this to prospectively manage ESA therapy.

Another ESA management practice that likely contributes to cycling is the over reliance on a single Hb test result. Individual Hb measurements may be subject to significant variation. In part, this may relate to fluid gain in haemodialysis patients, but the phenomenon is seen in non-uraemic patients as well. In haemodialysis patients, reliance on pre-dialysis Hb samples means that the measurement is vulnerable to dilution from interdialytic fluid weight gain. Since there may be great variability in weight gain from treatment to treatment, individual Hb levels may be disproportionately affected. A more rational practice is to base ESA dose adjustments not just on a single test result, but rather on recent trends in Hb movement.

**Illness and Hospitalization**

Intercurrent illness is a remarkably common problem for patients on dialysis, as well as patients with non-dialysis CKD. Most illnesses in these patients are associated with induction of inflammation, which has a profound negative effect on erythropoiesis. It is our opinion that these frequent illnesses, even when not requiring hospitalization, contribute greatly to Hb cycling.

Hospitalization is a key factor associated with Hb cycling [1,3]. In the study conducted at Winthrop-University Hospital Dialysis Centers, the relationship between Hb cycling and a variety of demographic and clinical factors was studied [1]. Hospital admission was often found to predate and initiate an Hb cycle or to reset an existing cycle; 14% of down excursions were associated with hospital admission. A downward shift in Hb trajectory was seen in the 4 weeks prior to ~40% of all hospital admissions. Furthermore, after hospitalization, many patients had a substantial upward trajectory of Hb, with 36% of up excursions being related to hospital discharge within the last 30 days.
The association between hospitalization and Hb cycling may relate to the detrimental effect of infection, bleeding and inflammation on erythropoiesis. Indeed, catheter insertions and vascular access infections have been associated with temporary relative resistance to epoetin treatment [10]. It should be noted that ESA responsiveness varies over time. It is likely that periods of obvious or occult inflammation might contribute to periods of relative hyporesponse. Other factors related to hospitalization that may exacerbate Hb cycling include missed or changed epoetin dose, surgical or other invasive procedures with blood loss, and increased blood sampling for laboratory tests.

Fluid balance

Changes in fluid balance caused by interdialytic fluid weight gain can also affect Hb levels. Variations in interdialytic fluid weight gain can lead to inconsistent and inaccurate Hb measurements, particularly when pre-dialysis samples are used for monitoring anaemia [11,12]. For the same level of red cell mass, the Hb level may appear quite different after an interdialytic period with minimal fluid gain compared with a period with 3–5 kg of accumulation. The rate of intradialytic plasma refilling also affects the change in Hb level during a dialysis treatment. Despite plasma refilling, Hb levels may increase by 1–3 g/dl during haemodialysis treatments due to intradialytic ultrafiltration [13].

Iron status and therapy

As a result of the complex relationship between Hb and iron levels, iron status may have an impact on Hb fluctuations. In the Winthrop-University Hospital Dialysis Centers study, changes or initiation of intravenous (IV) iron were an independent predictor of Hb cycling ($P < 0.05$), and were responsible for 27% of Hb up excursions [1]. Furthermore, after the initial increase in serum ferritin following IV iron administration, serum ferritin levels decline and this may precipitate a downward Hb fluctuation. Hb cycling, however, was found not to be statistically significantly affected by stable weekly maintenance IV iron therapy. Therefore, maintenance iron therapy might have potential for reducing the impact of Hb cycling.

Clinical consequences of Hb cycling

The impact of Hb cycling on patients’ health is not known. Under normal conditions of homeostasis, steady Hb levels are maintained to ensure consistent and adequate oxygen delivery to tissues. With Hb cycling, oxygen carried in the circulation and delivered to tissues may fluctuate [14]. These repeated episodes of relative ischaemia could potentially result in organ dysfunction or injury [15]. The heart could be particularly affected by Hb cycling as it attempts to compensate for periods of reduced oxygen delivery, leading to disordered activation and resetting of cardiac growth signals. This could lead to the development of pathological changes, such as left ventricular dilatation or hypertrophy. In addition, other tissues and organs may be sensitive to injury related to variability in Hb levels and oxygen delivery. Since the possibility of tissue injury related to Hb cycling is hypothetical, research into this possibility should be encouraged.

Preliminary evidence derived from analysis of Fresenius Medical Care patient data indicate that Hb variability, after adjustment for important covariates and for time-dependent confounders, was associated with a 30–45% increase in mortality, depending on the method of analysis [16]. Similarly, Ebben, et al. [3] in the recently reported aforementioned study, found that both mortality and hospitalization risk were associated with high amplitude Hb swings (complete traverses of the Hb target range). Regidor et al. [17] studied changes in Hb over time in 2668 haemodialysis patients. Decreasing levels were associated with increased risk of death, but increasing Hb was associated with reduced risk. Taken together, these studies offer a first glimpse at the association of Hb cycling and mortality risk. The observational nature of the analysis makes it impossible to know if the role of Hb cycling is causal. We would encourage further research in this area.

Hb cycling may hypothetically lead to disturbance of iron homeostasis. As Hb levels fall, iron is transferred from the erythron to storage tissues, and when Hb levels rise, the reverse occurs. As a result, as Hb levels cycle, serum ferritin may cycle in the reverse direction. It is possible that the resulting fluxes in tissue iron stores could have adverse consequences. Further investigation of the tissue and organ effects of Hb and iron cycling would be of interest.

Implications and future directions

Hb fluctuations and subsequent ESA dosage adjustments increase the workload required to maintain Hb levels within target ranges. This burden is expected to increase with the forecasted escalation in numbers of patients with CKD who may require treatment with ESAs [18–20].

Although current anaemia management appears to contribute towards Hb cycling, there are a number of approaches that may help to improve current practice, and thus reduce the burden on already hard-pressed nephrology units. The narrow target Hb range previously recommended in NKF-K/DOQI guidelines [6] led to frequent dose adjustments. The 2006 revised KDOQI anaemia guidelines [21] recommend maintaining Hb >11 g/dl while avoiding Hb levels >13 g/dl. This wider target range may reduce the need for dose adjustments and thus help to prevent Hb cycling. However, recently published clinical trials showed no benefit or potential harm when Hb levels
Hb cycling is common in patients treated with currently available ESAs and several anaemia treatment practices may contribute towards the phenomenon. Further study is necessary to understand the clinical consequences of Hb cycling and to establish optimal treatment practices for the use of erythropoietic agents in patients with anaemia.

Conflict of interest statement. Dr Fishbane consults for Amgen, Roche, Watson and Affymax.

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