

When should we start erythropoietin therapy?

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Introduction

Evidence has accumulated over the last decade linking anaemia with cardiac enlargement, cardiac failure, and death, in the haemodialysis population. Observational studies have suggested that these features may be part of a pathological cascade that frequently occurs with declining renal function. The starting point for this cascade, anaemia, begins well before the onset of end-stage renal disease in most patients. Typically, this process begins as glomerular filtration falls below 30 ml/min [1]. Despite the routine availability of recombinant human erythropoietin, our approach to renal anaemia has been one of delayed intervention and variable haemoglobin targets, which are, in general, below population levels.

Evidence from observational studies

Several recent studies with hard outcomes like cardiovascular events, hospitalization, and death have suggested that previously acceptable haemoglobin targets may place our patients at risk. In a cohort of patients starting dialysis therapy we found the following spectrum of abnormalities: concentric left ventricular hypertrophy in 39% of patients, left ventricular dilatation in 27%, and systolic dysfunction in 18%. The characteristic evolution of left ventricular morphology in this cohort was one of progressive dilatation with compensatory hypertrophy. Risk increased progressively as follows: normal, concentric left ventricular hypertrophy, left ventricular dilatation with intact systolic function, systolic dysfunction. During dialysis therapy the average haemoglobin level was 8.8 g/dl. Each 1 g/dl decrease in mean haemoglobin was associated with left ventricular dilatation on follow-up echocardiography, the development of *de novo* cardiac failure, recurrent cardiac failure and death [2–5]. Madore *et al.* [6] examined a cohort of 21 899 patients

receiving thrice-weekly haemodialysis in 1993. The adjusted 1-year mortality risk for patients with haemoglobin concentrations of less than 8 g/dl was twice that of patients in the 10–11 g/dl range. Ma *et al.* [7,8] studied a very large group of Medicare haemodialysis patients in the US. Haematocrit was averaged over 6 months. They observed a monotonic reduction in mortality and hospitalization as haematocrit rose into the 33–36% range.

There is relatively little epidemiological work examining the association of haemoglobin levels above 12 g/dl and subsequent outcome. The study of Levin and co-workers [1] demonstrated a clear association between modest declines in haemoglobin levels, from a baseline level of 12.8 g/dl, and progressive left ventricular growth in patients with early renal insufficiency. In the Spanish Co-operative Renal Patients Quality of Life Study, 156 haemodialysis patients received epoetin, which resulted in an increase in haemoglobin from 10.2 to 12.5 g/dl over 6 months. Non-diabetic patients without cardiovascular dysfunction were selected. Clear improvements in Sickness Impact Profile and Karnofsky scale scores were observed, associated with lower hospitalization rates [9]. Silverberg and co-workers [10] recently reported a very provocative though uncontrolled study in a group of patients whose primary problem was cardiac failure. The prevalence of anaemia, defined as a haemoglobin below 12 g/dl, increased with the severity of CHF, reaching 79.1% in those with New York Heart Association class IV. Twenty-six anaemic patients with maximal conventional anti-failure therapy were treated for a mean of 7.2 months with epoetin and i.v. iron. Haemoglobin levels rose from 10.16 to 12.10 g/dl, associated with increases in ventricular ejection fraction, reduced diuretic requirements, dramatically lower hospitalizations rates, and improvements in New York Heart Association class [10].

Target haemoglobin levels: recent controlled trials

The United States Normalization of Hematocrit Trial examined 1233 haemodialysis with symptomatic ischaemic heart disease or cardiac failure. The primary outcome was a composite of either myocardial infarction or death. These patients had the target risk factor, anaemia, for several years and were at high cardiovascular risk, illustrated subsequently by high event rates. Patients in the higher haematocrit group (42%)

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had a trend towards greater mortality than those in the lower haematocrit (30%) group, and a higher rate of vascular access thrombosis [11]. This study of late, aggressive intervention showed that normalization of haemoglobin, compared to current practice guidelines, was not protective in patients with well-established cardiac disease.

The Canadian Normalization of Haemoglobin study also compared normalization of haemoglobin to partial correction of anaemia in haemodialysis patients. One hundred and forty-six haemodialysis patients with either asymptomatic concentric left ventricular hypertrophy or left ventricular dilatation were randomly assigned to target haemoglobin levels of 10 or 13.5 g/dl. In the left ventricular dilatation group the change in cavity volume index was similar for both haemoglobin targets. In the concentric LV hypertrophy group the changes in left ventricular mass index were similar; those assigned to higher targets were less likely than controls to have progressive dilatation of the left ventricle. Patients in the higher haemoglobin arm had less depression and fatigue and improved relationships. There was no increase in the rate of dialysis access loss [12].

McMahon and colleagues examined the impact of normalization of haemoglobin on physical performance in haemodialysis patients. Fourteen patients with a mean baseline haemoglobin of 8.3 g/dl were randomly assigned to haemoglobin targets of 10 or 14 g/dl, using a cross-over design. Studies were performed at rest and during a maximal incremental exercise test. Both peak work rate and VO_2 peak were higher at a haemoglobin level of 14 g/dl [13]. In addition, normalization of haemoglobin was found to ameliorate left ventricular dilatation and improve quality of life [14]. Several ongoing trials are assessing the overlapping approaches of higher treatment thresholds, higher target levels, and earlier intervention. If chronic haemodynamic stress leads to higher rates of fibrosis and accelerated death of cardiac myocytes, as animal models suggest, the risk-benefit profiles of these proactive approaches should differ from current approaches.

Conclusion

It is likely that the left ventricular changes observed in uraemia may be partially preventable by early treatment of anaemia. The evidence in favour of a target haemoglobin of at least 11–12 g/dl is persuasive. Normalization of haemoglobin is very likely to be associated with enhanced quality of life and physical performance, but the safety and cost of this approach, and its impact on cardiovascular outcomes remain to

be determined. Incomplete evidence suggests that earlier intervention confers greater benefit than later intervention. The quality of life benefits of higher haemoglobin levels, which are considerable and consistent across studies, should be considered in the timing of anaemia interventions. Full correction of renal anaemia remains an open question. Several ongoing randomized trials should answer this question over the next 5 years.

References

- Levin A, Thompson CR, Ethier J *et al.* Left ventricular mass index in early renal disease. Impact of a decline in hemoglobin. *Am J Kidney Dis* 1999; 34: 125–134
- Foley RN, Parfrey PS, Harnett JD, *et al.* The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995; 5: 2024–2031
- Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 1996; 11: 1277–1285
- Foley RN, Parfrey PS, Kent GM *et al.* Long-term evolution of cardiomyopathy in dialysis patients. *Kidney Int* 1998; 54: 1720–1725
- Foley RN, Parfrey PS, Harnett JD *et al.* The impact of anaemia on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Am J Kidney Dis* 1996; 28: 53–61
- Madore F, Lowrie EG, Brugnara C *et al.* Anemia in hemodialysis patients: variables affecting this outcome predictor. *J Am Soc Nephrol* 1997; 8: 1921–1929
- Ma J, Ebben J, Xia H, Collins A. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 1999; 10: 610–619
- Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol* 1999; 10: 1309–1316
- Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F, for the Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. *J Am Soc Nephrol* 2000; 11: 335–342
- Silverberg DS, Wexler D, Blum M *et al.* The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000; 35: 1737–1744
- Besarab A, Kline Bolton W, Browne JK *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; 339: 584–590
- Foley RN, Parfrey PS, Morgan J *et al.* Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 2000; 58: 1325–1335
- McMahon LP, McKenna MJ, Sangkabutra T *et al.* Physical performance associated electrolyte changes after haemoglobin normalization: a comparative study in haemodialysis patients. *Nephrol Dial Transplant* 1999; 14: 1182–1187
- McMahon LP, Mason K, Skinner SL, Burge CM, Grigg LE, Becker GJ. Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. *Nephrol Dial Transplant* 2000; 15: 1425–1430