An Effective Iron Repleting Protocol for Renal Anaemia in the Haemodialysis Population

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Abstract

Most patients on haemodialysis require erythropoietin therapy and iron repletion for correction of anaemia. The frequency of iron status measurements and guidelines for iron replenishment were modified to improve iron balance and erythropoiesis.

Intravenous iron polymaltose was administered in 40 haemodialysis patients over an eighteen-month period according to a specific intermittent intravenous protocol.

Haemoglobin levels were maintained at 12 g/dL with an initial rise (at 6 months) in serum ferritin to 486 ug/L and transferrin saturation to 30% from baseline values of 350 ug/L and 26%, and these levels were sustained throughout the study period. In the first 6 months of the study erythropoietin (Epoetin alfa) dosage was reduced from 9600 U/Wk to 9300 U/Wk when administered subcutaneously, and this reduction was maintained for the second 6 months of the study. The study's iron replenishment regimen successfully maintained haemoglobin with diminished need for erythropoietin and avoidance of iron overload.

Key Words
Erythropoietin, iron repletion, haemoglobin, ferritin, transferrin saturation, Epoetin alfa, cost effectiveness.

Introduction

Most patients on haemodialysis require erythropoietin (EPO) therapy and iron replenishment for the correction of their anaemia (Eschbach et al, 1987; Schaefer & Schaefer, 1992). However, the manner in which this is accomplished varies widely from unit to unit (Saltissi et al, 1998; Chow et al, 2005). Most renal units replete iron in a continuous manner but our unit has decided to give iron in an intermittent fashion in an attempt to limit the potential adverse effects of iron loading (Canavese et al, 2004).

The frequency of iron status measurements and guidelines for iron replenishment were modified with the intention of improving the effectiveness of iron replenishment by responding promptly to iron deficiency. We sought to restore iron balance in our dialysis patients who had either absolute iron deficiency or suspected of having functional iron deficiency by adjusting the iron dose with a set of infusion criteria based on serum ferritin and saturated transferrin levels. Adjustment in erythropoietin dose occurred when the cohort was converted from subcutaneous (SC) to intravenous (IV) administration of Epoetin alfa in the last 6 months of the study.

Methods

Forty patients were dialysed in an in-centre or satellite haemodialysis facility for the duration of the clinical study period. Period of dialysis and the number of treatments per week varied according to the treatment prescription. Only those patients who were being dialysed for the duration of the 18 month study and were receiving Epoetin alfa were included in the study (December 2001 to June 2003).

The monitoring of iron status in the haemodialysis population was altered with iron studies carried out every two months and ferritin alone measured in the intervening months. Prior to this the transferrin saturation (Tsat) had been measured on a three monthly basis. In addition, our guidelines for iron repletion were also modified (Table 1). Previously, iron repletion occurred if ferritin was less than 100 ug/L and Tsat less than 20%. The iron-study results, along with other monthly tests, were assessed within a week and acted upon. A test dose of iron was administered to reduce the risk of reaction to this medication by giving 25 mg iron polymaltose at the end of dialysis prior to the first dose. The first dose of iron polymaltose (500 mg in 250 ml of diluent) was given post dialysis

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Table 1 Intermittent protocol for iron dosing

Criteria	Treatment
Serum ferritin < 150 ug/L Transferrin saturation <25%	IV iron polymaltose (Ferrum H) 500 mgwith 3 consecutive dialysis treatments.
	Total 1500 mg.
Serum ferritin < 300 ug/L Transferrin saturation < 20%	IV iron polymaltose (Ferrum H) 500 mg with 2 consecutive dialysis treatments.
	Total 1000 mg.
Serum ferritin < 150 ug/L Transferrin saturation 25-40%	IV iron polymaltose (Ferrum H) 500 mg with 1 dialysis treatment.
	Total 500 mg.

and subsequent doses were infused over the last hour of dialysis (Table 1). Sodium ferric gluconate (Ferrlicit) and iron sucrose (Venofer) were also used for intravenous iron replacement in cases of suspected or proved allergy to iron polymaltose (Ferrum H or Ferrosig). In January 2003 all persons receiving SC Epoetin alfa were changed to the IV route as cases of pure red cell aplasia were reported in recipients of SC Epoetin alfa in other institutions (MacDougall, 2004). Our unit has not shared this experience.

Statistics

Data are presented as mean + SEM. Changes to mean haemoglobin, Epoetin alfa, ferritin or Tsat were analysed by paired t-tests. Changes to the proportion of patients with either Tsat or ferritin outcomes were analysed using the Cochran Q test.

Results

40 patients (17 female, 23 male); mean age 67 years; 37 Caucasians, 2 Asians, 1 Australian Aboriginal received haemodialysis over the entire study period (December 2001 to June 2003; Table 2).

At the outset the mean haemoglobin was 12.0 g/dL, Epoetin alfa dose 9,600 IU/wk, ferritin 350 ug/L and Tsat 25.9%. In the first half of 2002, with the introduction of changes to iron management, ferritin and Tsat increased to 486 ug/L (paired t-test p=0.014) and 30.4% (paired t-test p=0.017) respectively with maintenance of haemoglobin (12.1 g/dL) and Epoetin alfa dose reduced by 300 IU/wk (Table 3, Figure 1). The remainder of 2002 produced similar values with haemoglobin 12.3 g/dL, ferritin 465 ug/L, Tsat 29.2% and weekly Epoetin alfa dose static at the reduced value of 9,325 IU/wk.

In the last 6 months of the study in 2003, 36 of the 40 dialysis patients were changed to IV Epoetin alfa (4 patients were already receiving IV Epoetin alfa) with the average weekly dose increasing significantly by 13.7% (from 9,325 IU/wk to 10,600 IU/wk, paired t-test p=0.014). Haemoglobin, ferritin and Tsat levels did not differ significantly from the previous half yearly period.

The percentage of patients with Tsat > 50% remained low throughout the study with values of 2.5% in December 2001 and 2.5% in June 2003 peaking at 5.0% (December 2002) (Cochran Q test p=0.84) and the percentage of patients with ferritin > 800 ug/L did not change significantly over the study with 5% in December 2001 and 10% in June 2003 and a peak value of 17.5% in December 2002 (Cochran Q test p=0.29). The percentage of patients with Tsat 25% or greater rose from just over 50% to a maximum of 70% in June 2002 with iron repletion, an increase not significant when tested (Cochran Q test p=0.43) (Figure 2). The cost of EPO therapy declined approximately 3% with iron repletion and SC Epoetin alfa administration but then increased by 13.7% with the need to administer IV Epoetin alfa.

Table 2 Age and Gender characteristics of study population

	Total	Male	Female
Mean Age	67.4 (2.3)	66.0 (3.2)	69.3 (3.6)
Minimum Age	26	26	42
Maximum Age	87	87	87
Number	40	23	17

Values represent Mean (SEM) Number of Caucasians 37, Asians 2, ATSI 1

Discussion

Haemodialysis patients become iron deficient through blood loss (dialyser and tubing, needling, blood sampling and gastrointestinal losses) and accelerated erythropoiesis with exogenous EPO administration (Locatelli et al, 2001; Schwartz et al, 2004). Hence the proper replenishment of iron is the key to optimising renal anaemia management in this population. In this study the

frequency of iron status measurement was increased and the unit's guidelines for intravenous iron replenishment on an intermittent basis were modified to minimise iron depletion and to allow administration of iron soon after the test results were available.

During the first 12 months, our study demonstrated the maintenance of haemoglobin levels at 12 g/dL with the concomitant reduction in Epoetin alfa dosage by 300 U/wk using the modified iron repletion guide. Maintaining haemoglobin at near normal and stable levels, especially in the range 11-13 g/dL, has been shown to assist greatly with the wellbeing of anaemic patients (Besarab et al, 1999; Crawford et al, 2002), restoring energy, physical activity and overall quality of life. Serum ferritin and Tsat levels were increased (486 ug/L and 30.4%, Table 3) from baseline values at study commencement and the percentage of patients with Tsat levels greater than 25% rose to 70% (Figure 2) indicating restoration of iron stores in these patients. These levels were maintained during the last 12 months of the study. Adequate iron repletion has been shown to assist not only with erythropoiesis but also with the immune response and resistance to infection via iron-dependent enzyme pathways required for normal neutrophil and macrophage function (Seligman et al, 1992).

Figure 1: Changes in haemoglobin and erythropoietin dosage during the study period.

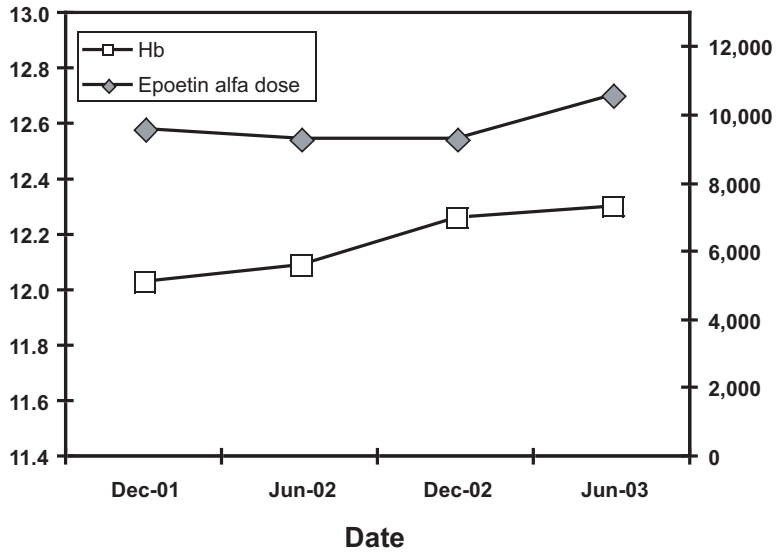
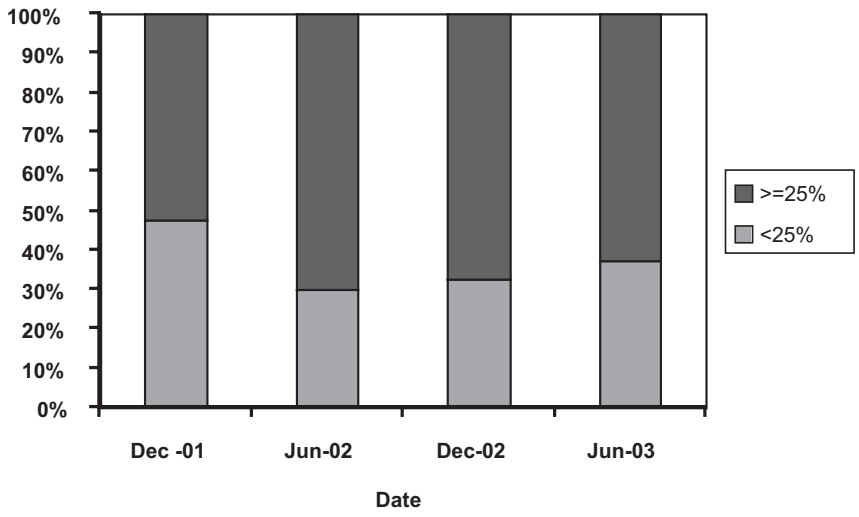


Figure 2: Distribution of patients with Tsat less than or greater than 25%



In our study, no significant change was observed in the number of patients with a ferritin greater than 800 ug/L or Tsat greater than 50%. The intermittent administration of intravenous iron rather than continuous supplementation, along with frequent iron status measurement, leads to a restoration of iron without resultant iron overload. Iron overload weakens macrophage function and erythrocyte viability (de Sousa, 1989) and has been associated with an increased risk of cardiovascular disease, infection and cancer (Brock, 1994; Weinberg & Weinberg, 1995; Weinberg, 1995; Tuomainen et al, 1998; Gasche et al, 2004). Furthermore, excessive iron can induce resistance to EPO therapy. A study by El-Reshaid et al. (1994) demonstrated that the EPO dose required was nearly twice as large in iron-loaded patients. This resistance could be overcome by ascorbic acid administration (Gastaldello et al, 1995; Petrarulo & Gianscaspro, 2004). Replacing iron as required will guard against chronic iron overload and its potential consequences.

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Table 3 Haemoglobin, Epoetin alfa, Ferritin and TSAT Outcomes

Measurement	Units	Dec-01	Jun-02	Dec-02	Jun-03
Haemoglobin	g/dL	12.0 (0.2)	12.1 (0.2)	12.3 (0.2)	12.3 (0.2)
Epoetin dose	IU/Wk	9,600 (850.9)	9,300 (677.7)	9,325 (750.5)*	10,600 (772.8)
Ferritin	ug/L	350.1 (38.0)*	486.0 (50.4)	465.3 (52.3)	459.5 (43.0)
TSat	%	25.9 (1.5)*	30.4 (1.7)	29.2 (1.9)	27.9 (1.5)

Values are Mean (SEM) N=40 * Significant paired t test

subcutaneous Epoetin alfa (MacDougall, 2004) necessitated a shift in the route of Epoetin alfa administration to the intravenous route. Consequently, it was found that in order to maintain haemoglobin levels at 12 g/dL, the Epoetin alfa dose increased significantly to 10,600 IU/Wk (13.7% increase). This attenuated haemoglobin response to IV Epoetin alfa has been previously documented by others (Leikis et al, 2004).

Guidelines for parenteral iron administration in haemodialysis patients remain contentious but this study has demonstrated that intermittent iron boluses delivered promptly can sustain optimal erythropoiesis and guard against iron overload.

Declaration

Ann Kruger is the renal anaemia co-ordinator at Flinders Medical Centre (funded by Janssen-Cilag) and Jeff Barbara is a member of the Australian Renal Anaemia Group (Janssen-Cilag).

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