Percentage hypochromic red cells and the response to intravenous iron therapy in anaemic haemodialysis patients

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Abstract

Introduction. Iron deficiency is commonly encountered in haemodialysis (HD) patients and may be overcome by i.v. iron therapy. We have examined the percentage hypochromic red cells (%HRC) for predicting response to i.v. iron in subjects with a low serum ferritin.

Methods. Prospective study of i.v. iron saccharate (trivalent iron 200 mg/week for 8 weeks) in anaemic (Hb < 10 g/dl) HD patients with serum ferritin < 100 μg/l despite oral iron therapy. Response to i.v. iron was assessed by comparing Hb at 0 and 8 weeks according to %HRC at baseline (0–3%, 4–9%, ≥ 10%). Results are mean ± 1 SD.

Results. For all subjects (n=82), Hb and ferritin increased between 0 and 8 weeks (8.9 ± 1.0 to 10.1 ± 1.4, P < 0.0001; 55 ± 24 to 288 ± 126, P < 0.0001). Patients were stratified into three groups according to %HRC at baseline (0–3%, 4–9%, ≥ 10%). Hb increased significantly in all three groups. The mean increase in Hb was greater (0–3%, 0.6 ± 1.2; 4–9%, 1.2 ± 1.0; ≥ 10%, 1.6 ± 1.4; P < 0.02) and the proportion of patients showing a ≥ 1 g/dl increase in Hb was greater (0–3%, 27%; 4–9%, 57%; ≥ 10%, 67%; P = 0.02) in those with the largest %HRC pre-treatment.

Conclusion. Intravenous iron therapy is effective in improving Hb in anaemic HD patients with a low ferritin. However, the magnitude of this response and the proportion of patients responding is related to the percentage hypochromic red cells prior to treatment.

Key words: haemodialysis; intravenous iron; red cell hypochromia; erythropoietin

Introduction

The loss of response or resistance to erythropoietin (EPO) therapy during the management of anaemia in end-stage renal failure is most commonly due to iron deficiency [1]. The absence of an accurate marker of iron availability for erythropoiesis in EPO-treated patients is a major obstacle to assessment of iron deficiency. A combination of serum ferritin, transferrin saturation, and percentage of hypochromic red cells has been suggested [2]. However there is no current ‘gold standard’ test, other than the demonstration of a response to iron administration.

The predominant body iron pool is contained in circulating erythrocytes. Iron is otherwise stored in the reticuloendothelial system in an inert and slowly mobilized form, tissue ferritin. A small quantity of iron is present in the serum bound to transferrin. In normal subjects, serum ferritin is an accurate indicator of the reticuloendothelial or ‘tissue’ iron store [3]. Depletion of the body iron store will result in a low serum ferritin and ‘absolute’ iron deficiency. In subjects with renal failure, the threshold serum ferritin that defines iron deficiency has been set at a greater level than in normal subjects (50–100 μg/l; [4,5]).

There are two major difficulties with using serum ferritin as the main indicator of iron deficiency in dialysis patients. Firstly, ferritin is an acute phase protein and increases during any infective or inflammatory disorder. Secondly, during rapid erythropoiesis adequate tissue iron stores may be present, but complexed iron does not become available with sufficient speed to maintain an adequate iron supply for haemoglobin synthesis. In these circumstances a ‘functional’ iron deficiency is said to be present. The serum ferritin can be normal or high in these patients. A number of tests have been suggested that may give more information about the availability of iron for erythropoiesis. One such test is the percentage of hypochromic red cells (%HRC), the number of red cells with a decreased individual red cell haemoglobin concentration expressed as a percentage of the total number of red cells. %HRC has been reported to be a useful indicator of functional iron deficiency in haemodialysis patients, with 2.5% being the upper limit of the normal range and greater than 10% indicating iron deficiency [6].

The use of i.v. iron therapy is becoming common-
place in dialysis units. Intravenous iron is more expensive than oral iron and its administration is not without potential hazard. We have investigated the utility of percentage hypochromic red cells in haemodialysis patients that would be expected to respond to i.v. iron, that is those with a ‘low’ serum ferritin.

Methods

The introduction of i.v. iron saccharate was studied in chronic haemodialysis patients with persistent anaemia (haemoglobin <10 g/dl) and serum ferritin <100 µg/l despite a maximum tolerated dose of oral iron (usually ferrous sulphate 200 mg three times a day). A weekly i.v. infusion of 200 mg of trivalent iron given as iron saccharate, Venoven® (Vifor International Inc., Switzerland) diluted in 50 ml of normal saline, was administered during haemodialysis. At first administration a test dose was given (infusion rate 25 ml/h for 15 min). Subsequent doses were administered over 1 h. Haemoglobin (Hb) and percentage hypochromic red cells (%HRC) were measured on a Technicon H*2 automated blood count analyser at 0, 4, and 8 weeks. Serum ferritin was measured by immunoassay (Bayer Immuno-1) at the same time intervals. The response to i.v. iron was assessed for all patients and according to three groups defined by %HRC (approximate tertiles, 0–3%, 4–9% or >10%) at baseline. Intravenous iron was discontinued if serum ferritin exceeded 250 µg/l. EPO dose was not adjusted during the follow up period. All data are expressed as mean ± standard deviation with the exception of %HRC (median and 25th, 75th centiles). Results at 0 and 8 weeks within groups were compared by paired t-test (haemoglobin and ferritin) or Wilcoxon rank test, †P<0.01, ‡P<0.001. Data between groups were compared by ANOVA. *P=0.02.

Results

Ninety-eight chronic haemodialysis patients received i.v. iron. Sixteen were excluded from analysis (13 received blood transfusion for symptomatic anaemia, two were transplanted prior to completing the study, and one patient had a possible anaphylactoid to the first dose of iron). No subject had abnormal Hb electrophoresis nor an elevated random serum aluminium. In keeping with the protocol, i.v. iron was discontinued after 4 weeks in 37 patients.

Data from 82 patients were available for analysis (Table 1). At baseline 71 were receiving erythropoietin and mean dose was 55.8±43.0 U/kg/week (3439±2465 U/week). Mean haemoglobin was 8.9±0.98 g/dl, ferritin 55.4±24.1 µg/l and median %HRC 7% (3–14). The response to i.v. iron is shown in Table 1 for the whole group and according to %HRC at baseline. For the whole group, Hb and serum ferritin increased significantly between 0 and 8 weeks (both \( P<0.001 \)). The %HRC did not change.

At baseline, there was no difference in EPO dose, Hb or ferritin according to %HRC. Serum ferritin increased significantly \( (P<0.001) \) in all subgroups defined by %HRC (Table 1). Mean Hb increased between 0 and 8 weeks in all groups, but the mean increase in Hb was greater with increasing %HRC at baseline \( (0–3%, 0.6±1.2; \ 4–7%, 1.2±1.0; \ >10%, 1.6±1.4; \ P=0.02, \text{ANOVA}) \). Median %HRC increased in the 0–3% group and decreased in the >10% HRC group.

The proportion of patients demonstrating a greater than 0.5 g/dl and a greater than 1.0 g/dl increase in Hb in response to i.v. iron is shown in Table 2. The proportion of patients with a >1 g/dl increase in Hb was greater as baseline %HRC increased \( (P=0.02) \).

Discussion

Oral iron therapy is cheap, easily available, and has been reported to provide sufficient quantities of iron to maintain erythropoiesis during erythropoietin therapy [7]. However, poor tolerance leading to non-compliance [8] and, in haemodialysis populations, chronic blood loss and interference with iron absorption, may result in an inadequate iron supply. In a prospective, randomized study of 37 patients commencing erythropoietin, there was no difference in the haemoglobin response with oral iron supplementation (ferrous sulphate 200 mg tds) as compared to no iron supplementation, whilst those receiving i.v. iron dex-
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Intravenous iron therapy has been shown to be effective in improving haemoglobin levels and reducing the need for recombinant human erythropoietin (rHuEPO). The decision to discontinue i.v. iron therapy is important and should be guided by a high serum ferritin level (>1000 µg/l) and a low haemoglobin concentration. A low ferritin indicates absolute iron deficiency, but a normal hypochromic red cell count predicts a greater likelihood of iron deficiency.

The measurement of iron stores in haemodialysis patients has been controversial. Serum iron, transferrin, and transferrin saturation show marked diurnal variation and have a low specificity for diagnosing iron deficiency in haemodialysis patients. Serum ferritin reflects reticuloendothelial iron stores, but is also an acute phase reactant, increasing in a number of inflammatory/infective conditions. A low ferritin indicates absolute iron deficiency, but a normal or high serum ferritin may be present in functional iron deficiency, where erythropoiesis is occurring too rapidly to allow mobilization of stored iron. Modern automated technology allows measurement of individual red cell haemoglobin concentration. The number of cells with a low haemoglobin (<28 g/dl) can be expressed as a proportion of the total number of red cells, that is the percentage hypochromic red cells. This measure has been suggested as an accurate marker of iron deficiency at the red cell level, and is sensitive to iron deficiency in dialysis patients. Administering EPO without iron supplementation has been shown to increase the percentage of hypochromic red cell and this is reversed by i.v. iron. In another study of haemodialysis patients with a well maintained haemoglobin (>10 g/dl), i.v. iron allowed a reduction in EPO dose with maintenance of haemoglobin concentration. The reduction in EPO dose was proportional to %HRC (dose reduction of 8.5%, 11.3%, and 23.4% for a %HRC of ≤5%, 5–10%, and ≥10% respectively).

In the current study, subjects with apparent absolute iron deficiency (serum ferritin <100 µg/l) were examined. The introduction of i.v. iron resulted in a significant increase in the serum ferritin and in the mean haemoglobin concentration. All patients had previously received oral iron at a maximum tolerated dose. While patient compliance cannot be certain, this finding supports an additional benefit of i.v. over oral iron. In this ‘iron deficient’ group, not all patients responded to i.v. iron and the percentage of hypochromic red cells predicted the response. The mean increase in haemoglobin and the proportion of patients responding was greater as %HRC at baseline increased. Greater than 10% HRC has been suggested as a threshold for demonstrating iron deficiency in haemodialysis patients. In this study, 57% of subjects with 4.9% HRC had a greater than 1 g/dl Hb response, suggesting that this value is too high. Indeed the sensitivity and specificity of 10% HRC for demonstrating iron deficiency have previously been reported as 42 and 80% respectively.

The decision to discontinue i.v. iron if ferritin exceeded 250 µg/l resulted in a significant number of patients stopping iron before the end of the study. It could be argued that this value of serum ferritin was too low and that iron should have been continued until values exceeded 800–1000 µg/l. Some subjects may therefore have remained iron deficient at this serum ferritin. However, values were equal between groups suggesting that this did not influence the results.

Intravenous iron was well tolerated, with a possible adverse reaction in only one subject. This patient developed wheeze during the first few minutes of infusion. Prompt resolution followed the administration of hydrocortisone and chlorpheniramine. Low dose iron saccharate (10–40 mg i.v. bolus) has previously been reported to have a low incidence of side effects.

In summary we conclude that an increased % hypochromic red cells predicts a greater likelihood and magnitude of response to i.v. iron therapy in maintenance haemodialysis patients with a low serum ferritin. Even so, 27% of patients with ≤3% hypochromic red cells still responded. This test may be useful in directing iron therapy toward the patients most likely to benefit, thus maximising the risk:benefit ratio. It does not however identify all possible responders.

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References


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