A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin

John Stoves, Helen Inglis and Charles G. Newstead

Department of Nephrology, St James’s University Hospital, Leeds, UK

Abstract
Background. Correction of anaemia as a result of renal failure improves cardiovascular function and also provides significant cognitive and emotional benefits. The most appropriate route for iron supplementation has not been determined for patients with chronic renal failure who are not yet on dialysis.

Methods. Forty-five anaemic patients with progressive renal insufficiency (PRI) were prospectively randomized to receive oral (ferrous sulphate 200 mg tds) or intravenous (300 mg iron sucrose monthly) iron treatment. Erythropoietin (rHuEpo) was simultaneously commenced and the dose adjusted according to a pre-established protocol.

Results. There were no significant differences in baseline patient characteristics between the two groups. The average follow-up was 5.2 months. Three patients suffered possible allergic reactions to iron sucrose. Haemoglobin response and changes in red cell hypochromasia were similar in the two groups, but serum ferritin was significantly higher in the intravenous group. The starting dose of rHuEpo could be temporarily discontinued in 43% of patients on oral iron and 33% of patients receiving iron sucrose (NS). rHuEpo was increased after 3 months in 9% of patients on oral iron and 19% of patients receiving iron sucrose (NS). Final doses of rHuEpo were 33.5 (0–66) and 41.6 (0–124) U/kg/week respectively in the oral and intravenous groups (NS). Although gastrointestinal symptoms were more commonly reported in patients taking oral iron, these were mild according to scores on visual analogue scales. Dietary protein and energy intake were not significantly different in the two groups at 0, 3 and 6 months.

Conclusions. In pre-dialysis patients, the efficacy of monthly 300 mg iron sucrose given intravenously is not superior with regard to haemoglobin response and rHuEpo dose as compared with a daily oral dose of 600 mg of ferrous sulphate or equivalent. Where intravenous iron is preferred, lower doses may help to reduce the incidence of allergic or ‘free iron’ reactions, especially in patients with low body mass.

Keywords: anaemia; ferritin; haemoglobin; iron; iron sucrose; progressive renal insufficiency

Introduction
Anaemia increases cardiovascular risk in patients with chronic renal disease [1–3]. Left ventricular hypertrophy (LVH) is present in approximately three quarters of patients commencing dialysis and predicts mortality [4–6]. Correction of anaemia has been shown to improve cardiovascular function with partial reversal of LVH [7,8]. There are also cognitive and emotional benefits, which are reflected in improved quality of life scores [9,10].

Previous studies have demonstrated that recombinant human erythropoietin (rHuEpo) can improve anaemia in patients with progressive renal insufficiency (PRI) who are not on dialysis treatment [11,12]. The importance of adjuvant iron therapy has not been demonstrated as clearly as for dialysis populations [13–15], and there have been calls for more detailed studies, particularly comparative trials to ascertain the relative efficacy of different methods of administration [16]. We have examined the efficacy and tolerability of oral and intravenous iron in PRI by way of a prospective randomized controlled trial, comparing outcomes in patients receiving either regular oral iron or monthly infusions of iron sucrose (Venofer, Syner-Med) in combination with rHuEpo.

Subjects and methods
Regional Ethics Committee approval for the study was obtained. Computerized records of data for all patients who were receiving follow-up nephrological review in our
unit (a population of approximately 400 patients) were examined to identify individuals with PRI (defined as progressive deterioration in renal function with a serum creatinine of more than 250 μmol/l, not requiring dialysis) and worsening anaemia (defined as a progressive reduction in haemoglobin concentration to a value of less than 11 g/dl, irrespective of gender). Patients who had been treated with intravenous iron during the previous 6 months were excluded from the study. Other exclusion criteria are shown in a patient flow chart (Figure 1).

After obtaining informed consent, patients were assigned to one of two treatment schedules using a computer-based randomization method. One group received oral ferrous sulphate at a dose of 200 mg tds (or an equivalent dose of an alternative iron preparation which had been previously well tolerated), and the other group received infusions of iron sucrose (300 mg over 2 h, repeated monthly according to serum ferritin estimations). All patients commenced rHuEpo (Eprex pre-filled syringes, Janssen-Cilag) at an initial dose of 2000 U twice weekly. This was self-administered by subcutaneous injection in the majority of cases, but some patients were dependent on partners or regular visits by a District Nurse. The intended duration of follow-up was 6 months.

Age, gender, renal pathology and baseline biochemistry and haematology were recorded. Measures of haemoglobin (Hb), red cell hypochromasia (HRC), serum ferritin, creatinine, parathormone (PTH) and C-reactive protein (CRP) were repeated on a monthly basis. A 3-day diary of food intake was recorded before the start of the study and repeated after 3 and 6 months, as was a subjective visual analogue score of gastro-intestinal symptoms (indigestion, abdominal pain, constipation). Three stool specimens were checked for faecal occult blood after 3 months and whenever there was a clinical suspicion of gastro-intestinal haemorrhage.

Patients were assessed by a clinician each month, with additional clinic visits as necessary. They were withdrawn from the study if their treatment was either poorly tolerated or ineffective. rHuEpo treatment was discontinued if a haemoglobin concentration of 14 g/dl was exceeded, and then reintroduced at half-dose (1000 U twice weekly) if values below 12 g/dl were obtained with subsequent measurements. In cases where the haemoglobin response to treatment was delayed (arbitrarily defined as a failure to achieve values

![Flow chart for all patients with PRI and progressive anaemia (as defined in text).](image-url)
above 12 g/dl within 3 months of starting treatment), rHuEpo was increased to 4000 U twice weekly after the third month. A further increase to a maximal dose of 4000 U thrice weekly was made if monthly haemoglobin concentrations remained below 12 g/dl. Iron therapy was not interrupted unless the serum ferritin estimation exceeded 500 mg/l.

The study was designed to achieve a similar haemoglobin outcome in the two groups (by alteration of rHuEpo dose according to a pre-arranged protocol). The primary outcome measures were, therefore, serum ferritin and rHuEpo dose requirement. Taking the standard deviation (SD) of patient values at the start of the study, it was calculated that 26 patients would be needed for a power of 80% to show a difference in serum ferritin of 100 μg/l to be statistically significant (P < 0.05). In terms of rHuEpo (U/kg) requirement, there is no available information regarding the standard deviation (SD) of values in a pre-dialysis population. Assuming a SD of 15 U/kg/week, 30 patients were needed for a power of 80% to show a difference in rHuEpo requirement of 15 U/kg/week to be statistically significant (P < 0.05). Results from the two treatment groups were compared using χ²-squared and the Mann–Whitney test for non-parametric data.

**Results**

Fifty-nine patients under regular renal outpatient review with PRI and worsening anaemia (as defined previously) were identified from a systematic review of computerized records and case notes (performed at 3 monthly intervals over a period of 6 months). Of these, 10 were excluded and four were either unable or unwilling to give their informed consent (see Figure 1). Base-line characteristics of the remaining 45 patients are summarized in Table 1. Twenty-three patients were assigned to a group for which the randomized treatment was oral iron, and the remainder were assigned to a group for which the randomized treatment was monthly intravenous infusions of iron sucrose.

One patient continued to take weekly methotrexate (10 mg) with folic acid 5 mg on non-treatment days, and another received a single oral dose of cyclophosphamide for suspected reactivation of systemic lupus erythematosus. Both of these patients received intravenous iron.

The proportion of patients with diabetic renal disease was higher (22 vs 0%) in the oral iron group. There was a larger proportion of patients with autosomal dominant polycystic disease (9 vs 2%) in the intravenous iron group (Table 2). It is also relevant to note the more frequent use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin (AT) II receptor antagonists in patients taking oral iron (Table 1).

Two of the included subjects had previously commenced low dose rHuEpo (weekly doses of 2000 and

---

**Table 1. Baseline characteristics for treatment groups**

<table>
<thead>
<tr>
<th></th>
<th>Group receiving oral iron (n = 23)</th>
<th>Group receiving intravenous iron (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.9 ± 13.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>57.3 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender (M : F ratio)</td>
<td>15 : 8</td>
<td>10 : 12</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.7 (9.3–10.2)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.9 (9.2–10.6)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ferritin (μg/l)</td>
<td>74 (47–126)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (47–155)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Red cell hypochromasia (HRC%)</td>
<td>4 (1–10.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (3–13)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma parathormone (PTH, mg/dl)</td>
<td>186 (138–247)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>146 (69–194)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>C-reactive protein (CRP, mg/l)</td>
<td>6 (5–9)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (5–11)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calculated creatinine clearance</td>
<td>12 (11–19)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14 (10–21)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prevalence of ACE inhibitor/AII receptor blocker therapy (%)</td>
<td>52</td>
<td>23</td>
</tr>
<tr>
<td>Prevalence of pre-trial oral iron therapy (%)</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Proton pump inhibitor therapy (%)</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>H2-antagonist therapy (%)</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mean ± SD; <sup>b</sup>median + interquartile range.

**Table 2. Primary renal diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>Group receiving oral iron (n = 23)</th>
<th>Group receiving intravenous iron (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary glomerulonephritis</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Interstitial nephritis-pyelonephritis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease (ADPKD)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Other congenital-hereditary nephropathy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diabetic renal disease</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Other secondary nephropathy-vasculopathy-systemic disease</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Uncertain</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>
3000 U started approximately 4 months prior to enrolment). Both patients were randomized to receive oral iron treatment.

Patients were followed up for an average of 5.2 months. The reasons for early withdrawal from the study are summarized in Figure 1. One patient receiving intravenous iron suffered a sudden death in the community, which was presumed to have resulted from cardiovascular disease.

During the study period, a mean of 0.91 (0.84–0.98) infusions of iron sucrose per patient per month were administered. Three possible allergic reactions to intravenous iron occurred, all in women with a low body mass. Symptoms included urticarial rash, abdominal pain, arthralgia, myalgia, nausea, headache, paraesthesia and loss of consciousness. Two patients were not rechallenged with intravenous iron. The other (in whom the first infusion was associated with a mild reaction) received further infusions but experienced worsening symptoms that necessitated withdrawal of treatment. A ceiling ferritin of 500 mg/l was achieved in a single patient receiving iron sucrose.

Oral iron was discontinued in one patient who developed severe constipation, although this had been exacerbated by other factors. It was not necessary to alter the starting formulation of iron in any patients during the study period.

The overall response to therapy in the two study groups is illustrated graphically in Figure 2. No statistically significant difference in haemoglobin response was shown with any of the monthly analyses (e.g. 12.2 (10.6–12.8) vs 12.5 (11.6–13.3) g/dl at 6 months in the oral and intravenous groups respectively). A haemoglobin of 12 g/dl was achieved within the first 3 months of treatment in 70% of patients taking oral iron compared with 59% of patients receiving iron sucrose.

Serum ferritin estimations were significantly higher in those receiving intravenous iron from the second month of treatment (e.g. 95 (63–149) vs 330 (186–423) μg/l at 6 months, Figure 3).

The initial rHuEpo prescription of 4000 U/week could be temporarily discontinued in 43% of the oral iron group vs 33% of the intravenous iron group.

![Fig. 2. Haemoglobin response in the two study groups. The box indicates the lower and upper quartiles and the central line is the median. The points at the end of the 'whiskers' are the 2.5 and 97.5% values. The first three boxes (coloured grey) show data from 2, 4 and 6 months prior to study entry. The number of patients at each time point is indicated within the boxes.](image-url)
Fig. 3. Serum ferritin in the two study groups (months 0–6). The first three boxes (coloured grey) show data from 2, 4 and 6 months prior to study entry.

after mean intervals of 2.4 and 2.7 months, respectively (NS). rHuEpo was increased after 3 months in 9% of patients taking oral iron and 19% of patients receiving intravenous iron (NS). Of those who completed 6 months of treatment, median finishing doses of rHuEpo were 33.5 (0–66) U/kg/week and 41.6 (0–124) U/kg/week, respectively, in the oral and intravenous groups (NS), with higher mean and median values in the iron sucrose group for preceding months (Figure 4). For patients in whom rHuEpo was temporarily discontinued, the median fall in haemoglobin concentration in the first month after discontinuation for the study population as a whole was 1.1 (0.7–1.2) g/dl, with no significant difference between the two treatment groups.

There was no significant difference in red cell hypochromasias between the groups at any stage of follow-up, although there was a wider range of values in patients receiving intravenous iron (Figure 5).

Other factors known to affect response to erythropoietin (calculated creatinine clearance, CRP, PTH) were not significantly different in the two groups. The rates of decline in renal function during the study varied between individuals, but the average monthly values of estimated creatinine clearance did not differ significantly between the two groups.

Faecal occult blood testing after 3 months gave uniformly negative results for the 31 patients who provided a sample.

Although gastro-intestinal symptoms were more commonly reported in patients taking oral iron, these were of mild severity according to scores on visual analogue scales. Dietary protein and energy intake were not significantly different in the two groups at 0, 3 and 6 months.

Discussion

Early correction of renal anaemia is desirable, although the evidence base for recommending a ‘target’ haemoglobin, and a means of achieving it, has not been firmly established [4,17]. Previous studies have reported a good response to rHuEpo in pre-dialysis patients, but evidence of iron deficiency has emerged in populations not receiving supplements [12].

It has previously been reported that intravenous iron has a greater additive effect with rHuEpo than
has oral iron, perhaps as a result of reduced iron absorption from the gut [18] and poor patient compliance with oral medication. Silverberg et al. [19] reported a mean rise in haematocrit of 1.9 vol% (0.6 g/dl) for undialysed patients not receiving rHuEpo in whom iron sucrose (200 mg monthly for 5 months) was substituted for oral iron. A later study showed that approximately one third of patients with moderate or severe chronic renal failure achieved a haematocrit of 35% using iron sucrose without rHuEpo [20]. Individual response to iron could not be predicted from laboratory measurements such as serum creatinine, ferritin or iron saturation. The same group have administered more than 20000 infusions of iron sucrose without complication. Other groups have reported infrequent symptoms with doses of 100 [21] and 200 mg [22] of iron sucrose, including chest pain, loin pain and bronchospasm.

The aim of this prospective, randomized study was to directly compare the efficacy and tolerability of oral and intravenous iron as adjuvant therapies for rHuEpo-treated anaemic patients with PRI.

The haemoglobin response to rHuEpo and iron was similar with oral and intravenous iron, a finding that runs contrary to the aforementioned reports but is consistent with the observations of Anastassiades et al. [23]. This was despite there being a greater proportion of diabetic patients, and more frequent use of ACE inhibitor and AT II receptor antagonist medications, in the oral iron treatment group.

Red cell hypochromasia, a measurement which is regarded as one of the most direct ways of assessing the adequacy of iron supply to sites of erythropoiesis [24], did not increase in either treatment group. The wider range of values seen in the intravenous iron group might reflect the rather unphysiological method of administration, with significant proportions of delivered iron being committed to, and subsequently retained as, body stores. There was certainly a tendency for iron stores (measured by serum ferritin) to increase in those receiving iron sucrose.

We conclude from this study that, for the majority of patients with PRI, the dose of adjuvant iron which is necessary to ensure optimal erythropoiesis can be delivered by way of oral supplements. Where intravenous iron is judged to be necessary, lower doses may help to reduce the incidence of allergic or ‘free iron’ reactions, especially in patients with low body mass.
Fig. 5. Red cell hypochromasia in the two study groups (months 0–6). The first three boxes (coloured grey) show data from 2, 4 and 6 months prior to study entry.

Acknowledgements. We are indebted to Dr E. J. Will and Professor A. M. Davison for helpful discussion and advice, Susie Stirling and Nicola Stewart for their dietary assessment of the completed 3-day food diaries, Cherry Bartlett for IT support, and Victoria Core for the early running of the study. We thank Jannsen Cilag and Syner-Med for their sponsorship of the study. JS is supported by the Yorkshire Kidney Research Fund.

References


Received for publication: 16.6.00
Accepted for publication: 21.11.00