A prospective crossover trial comparing intermittent intravenous and continuous oral iron supplements in peritoneal dialysis patients

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Abstract

Background. Concomitant iron supplementation is required in the great majority of erythropoietin (Epo)-treated patients with end-stage renal failure. Intravenous (i.v.) iron supplementation has been demonstrated to be superior to oral iron therapy in Epo-treated haemodialysis patients, but comparative data in iron-replete peritoneal dialysis (PD) patients are lacking.

Methods. A 12-month, prospective, crossover trial comparing oral and i.v. iron supplementation was conducted in all Princess Alexandra Hospital PD patients who were on a stable dose of Epo, had no identifiable cause of impaired haemopoiesis other than uraemia, and had normal iron stores (transferrin saturation >20% and serum ferritin 100–500 mg/l). Patients received daily oral iron supplements (210 mg elemental iron per day) for 4 months followed by intermittent, outpatient i.v. iron infusions (200 mg every 2 months) for 4 months, followed by a further 4 months of oral iron. Haemoglobin levels and body iron stores were measured monthly.

Results. Twenty-eight individuals were entered into the study and 16 patients completed 12 months of follow-up. Using repeated-measures analysis of variance, haemoglobin concentrations increased significantly during the i.v. phase (108 ± 3 to 114 ± 3 g/l) compared with each of the oral phases (109 ± 3 to 108 ± 3 g/l and 114 ± 3 to 107 ± 4 g/l, P < 0.05). Similar patterns were seen for both percentage transferrin saturation (23.8 ± 2.3 to 30.8 ± 3.0%, 24.8 ± 2.1 to 23.8 ± 2.3%, and 30.8 ± 3.0 to 26.8 ± 2.1%, respectively, P < 0.05) and ferritin (385 ± 47 to 544 ± 103 mg/l, 317 ± 46 to 385 ± 47 mg/l, 544 ± 103 to 463 ± 50 mg/l, respectively, P = 0.10). No significant changes in Epo dosages were observed throughout the study. I.v. iron supplementation was associated with a much lower incidence of gastrointestinal disturbances (11 vs 46%, P < 0.05), but exceeded the cost of oral iron treatment by 6.5-fold.

Conclusions. Two-monthly i.v. iron infusions represent a practical alternative to oral iron and can be safely administered to PD patients in an outpatient setting. Compared with daily oral therapy, 2-monthly i.v. iron supplementation in PD patients was better tolerated and resulted in superior haemoglobin levels and body iron stores.

Keywords: erythropoietin; ferritin; haemoglobins; iron economics; peritoneal dialysis; prospective studies

Introduction

The development of recombinant human erythropoietin (Epo) has resulted in substantial health benefits for patients with end-stage renal failure, including improved quality of life, reduced blood transfusion requirements, decreased left ventricular mass, diminished sleep disturbance and enhanced exercise capacity [1,2]. Unfortunately, a considerable proportion of such patients exhibit a suboptimal haematologic response to Epo, which in most cases is due to inadequate iron supply to the erythron [3]. Concomitant iron supplementation is, therefore, required in as many as 90% of Epo-treated individuals [3].

There has been much controversy as to whether such iron supplementation is best administered orally or intravenously, particularly in the pre-dialysis and peritoneal dialysis patients [3]. Numerous studies in haemodialysis populations, including a randomized controlled trial, have consistently demonstrated that i.v. iron supplementation is superior to oral iron replacement with respect to enhancing body iron stores, augmenting haemoglobin levels and reducing Epo requirements [3–5]. Comparable detailed data are lacking for peritoneal dialysis (PD) patients and have been limited to several small studies involving patients.
with very low transferrin saturation values [4,6]. Many authors [7–9] and clinical practice guidelines [10–12] have, therefore, recommended oral iron supplementation for PD patients in the first instance, because of its greater simplicity, the avoidance of repeated i.v. cannulation and the generally smaller iron losses in PD patients compared with haemodialysis patients. However, recent studies in Epo-treated PD patients have indicated that oral iron supplementation is insufficient to maintain a positive iron balance over medium- to long-term periods [3,13].

The aim of the present study, therefore, was to prospectively compare the relative effects of continuous oral vs 2-monthly, i.v. iron supplementation on iron status, haemoglobin concentration and Epo dosage in a prevalent cohort of stable PD patients. The 2-monthly i.v. iron regimen was designed to coincide with routine outpatient clinic appointments in order to facilitate ease of administration and to minimize the impact on patient lifestyle.

Methods

Patients

All iron-replete PD patients receiving Epo treatment at Princess Alexandra Hospital between February 1999 and August 1999 were eligible provided that they met the following inclusion criteria:

(i) stable on PD for a minimum period of 3 months;
(ii) no change to Epo dose for the preceding month;
(iii) absence of absolute or functional iron deficiency (ferritin > 100 µg/l and transferrin saturation > 20%);
(iv) ferritin ≤ 500 µg/l;
(v) normal or elevated serum B₁₂ and red blood cell folate levels;
(vi) CRP < 10 mg/l;
(vii) parathyroid hormone level < 100 pmol/l;
(viii) serum aluminium < 2 µmol/l;
(ix) absence of systemic haematological disease or known haemoglobinopathy;
(x) absence of recent major surgery, infection, chronic inflammation or malignancy within the last 3 months and,
(xi) absence of i.v. iron therapy or blood transfusion within the previous 6 months.

Informed consent was obtained from all patients prior to their participation in the trial and the study protocol was reviewed and approved by the Princess Alexandra Hospital Research Ethics Committee.

Study protocol

The study followed a prospective crossover design whereby patients acted as their own controls. For the first 4 months (oral phase), patients were prescribed oral iron therapy in the form of ferrous sulphate (Ferrogudumet®), Abbott, 350 mg twice daily, equivalent to 210 mg elemental iron per day). They were instructed to take the tablets on an empty stomach and at least 2 h apart from phosphate binder ingestion. At the end of the 4-month period, patients ceased their oral iron supplements and received an i.v. infusion of iron polymaltose (Ferrum H®, Sigma, 200 mg diluted in 100 ml normal saline). The infusion began at a rate of 40 ml/h for 75 min and was then increased to 120 ml/h for the remainder of the dose (total duration 1 h and 45 min). Medical staff and full resuscitation facilities were available for every iron infusion. This procedure was repeated 8 weeks later, thereby resulting in an average weekly i.v. iron dose of 25 mg during the second 4-month period (i.v. phase) of the study. At the end of the i.v. phase, patients were recommenced on oral iron supplements for an additional 4 months (oral phase).

Blood samples were collected at monthly intervals during the study for the determination of haemoglobin concentration, serum ferritin, and percentage transferrin saturation (serum iron divided by total iron binding capacity multiplied by 100). Measurements of iron stores were always performed at least 3 weeks following any i.v. iron infusions [11]. Epo doses were adjusted monthly to maintain the haemoglobin concentration between 95 and 125 g/l. The Epo dose was doubled if the haemoglobin concentration fell below 95 g/l and halved if the concentration exceeded 125 g/l. In accordance with the CARI clinical practice guidelines [11], iron supplements were withheld if serum ferritin concentrations exceeded 800 µg/l.

Patients were reviewed in the outpatients clinic every 2 months throughout the 12-month study period to monitor their medications, blood pressure and general well-being. They were questioned regarding their compliance with Epo and oral iron (during the oral phases) and about possible treatment-associated adverse reactions. The importance of taking all prescribed medications was emphasized heavily at each clinic visit and it is unlikely that a higher level of medication compliance could be achieved in routine clinical practice.

Statistical analysis

Results are expressed as mean ± SEM for continuous data and as frequencies and percentages for categorical data. Changes in haemoglobin concentrations, percentage transferrin saturations, serum ferritin concentrations and Epo dosages over the course of the study and between each of its phases were assessed by repeated-measures analysis of variance (RM-ANOVA). Allowing for a 33% attrition in the study population due to death, transfer to haemodialysis, renal transplantation, and blood transfusion (e.g. for acute haemorrhage), power calculations indicated that a minimum sample size of 25 patients was required to have an 80% probability of detecting a significant mean difference in haemoglobin concentration of 10 g/l (α = 0.05), assuming a population standard deviation of 10 g/l. Differences in the baseline characteristics between those patients who did and did not complete the study were assessed by Student’s t-test (continuous data) or χ² test (categorical data). Data were analysed using the software package Statview version 4.5 (Abacus Concepts Inc., Berkeley, CA, USA). P values < 0.05 were considered significant.

Results

Patients

Twenty-eight patients were enrolled in the study. Their baseline characteristics are depicted in Table 1. The
Table 1. Baseline characteristics of the total study population, patients who completed the 12-month follow-up, and those who were withdrawn during the course of the study; none of the differences between the completed and withdrawn groups achieved statistical significance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 28)</th>
<th>Completed (n = 16)</th>
<th>Withdrawn (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.8 ± 2.8</td>
<td>61.8 ± 2.8</td>
<td>57.2 ± 5.3</td>
</tr>
<tr>
<td>Female (%)</td>
<td>61</td>
<td>56</td>
<td>67</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>75</td>
<td>81</td>
<td>67</td>
</tr>
<tr>
<td>Automated PD (%)</td>
<td>21</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>39</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>ESRF duration (years)</td>
<td>1.5 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 1.0</td>
<td>27.9 ± 1.3</td>
<td>24.9 ± 1.5</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>107 ± 3</td>
<td>109 ± 3</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>24.2 ± 1.7</td>
<td>24.8 ± 2.1</td>
<td>22.7 ± 3</td>
</tr>
<tr>
<td>Epo dose (U/kg/week)</td>
<td>91.0 ± 10.0</td>
<td>82.4 ± 14.5</td>
<td>102 ± 13</td>
</tr>
<tr>
<td>Kt/V</td>
<td>2.38 ± 0.07</td>
<td>2.40 ± 0.10</td>
<td>2.34 ± 0.10</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>70.5 ± 3.0</td>
<td>73.0 ± 4.7</td>
<td>67.0 ± 3.0</td>
</tr>
<tr>
<td>Residual GFR (ml/min/1.73 m²)</td>
<td>1.47 ± 0.35</td>
<td>1.8 ± 0.5</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Serum aluminium (µmol/l)</td>
<td>0.38 ± 0.10</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>PTH (pmol/l)</td>
<td>50.6 ± 16.5</td>
<td>50.6 ± 16.5</td>
<td>44 ± 9.4</td>
</tr>
<tr>
<td>Serum B₁₂ (pmol/l)</td>
<td>388 ± 48</td>
<td>320 ± 41</td>
<td>470 ± 90</td>
</tr>
<tr>
<td>Red cell folate (nmol/l)</td>
<td>2250 ± 172</td>
<td>2015 ± 267</td>
<td>2520 ± 180</td>
</tr>
</tbody>
</table>

Causes of end-stage renal failure included chronic glomerulonephritis (n = 8), diabetes mellitus (n = 8), renovascular nephrosclerosis (n = 3), analgesic nephropathy (n = 2), reflux nephropathy (n = 2), cystic dysplasia (n = 1) and unknown (n = 4). Twelve patients did not complete the study due to transfer to haemodialysis (n = 4), urgent blood transfusion for gastrointestinal haemorrhage (n = 2), renal transplantation (n = 3), erythropoietin non-compliance (n = 2) and patient-requested withdrawal during the initial oral iron phase (n = 1). The baseline characteristics of these patients did not differ significantly from those who completed their 12-month follow-up, except for a tendency towards a longer duration on dialysis in the former (2.2 ± 0.7 vs 0.9 ± 0.2 years, respectively, P = 0.07).

**Haemoglobin response, iron studies and Epo dosages**

Mean haemoglobin levels rose significantly during the i.v. phase (+ 6 g/l) compared with the slight reductions seen during each of the oral phases (−1 and −7 g/l, P < 0.01) (Figure 1). Similar patterns were seen in percentage transferrin saturations (P < 0.05, Figure 2) and serum ferritin concentrations (P = 0.10, Figure 3), although the results for the latter just failed to achieve statistical significance. Iron supplements were withheld in the final month of the second oral iron phase in two (13%) patients as a result of serum ferritin concentrations exceeding 800 µg/l.

There were no significant differences in Epo dosages during the period of the study. The mean Epo dosages at baseline and at the completion of the first oral, i.v. and second oral phases were 82.3 ± 14.5, 86.3 ± 15.7, 80.8 ± 16.1 and 84.0 ± 15.5 U/kg/week, respectively (P = NS).

![Fig. 1. Changes in haemoglobin concentration during three consecutive 4-month periods of oral, i.v. and then oral iron supplementation in PD patients (n=16). *P < 0.05 vs oral phases.](image)

**Adverse reactions**

Reports of gastrointestinal disturbances were significantly more common during the oral phase than the i.v. phase (46 vs 11%, P < 0.05). These mainly consisted of constipation (38 vs 11%, P = 0.08), with less frequent descriptions of nausea (19 vs 0%, P = 0.06) and abdominal pain (4 vs 0%, P = NS). No other adverse effects were reported during the period of the study. All i.v. iron infusions were well tolerated.

**Costs**

Oral iron supplementation cost $12.20 (AUD) during each of the 4-month oral phases. The equivalent
cost of i.v. iron supplementation for 4 months was $81.20 (AUD), which included Ferrum H® ($32.60), i.v. infusion consumables ($29.80) and nursing time ($18.80).

Discussion

The results of the present study demonstrated that second-monthly, low-dose (200 mg), i.v. iron infusion given to iron-replete PD patients in an outpatient setting represented a practical alternative to daily oral iron supplementation and resulted in improved body iron stores and an enhanced haemopoietic response to Epo. A subsequent significant reduction in Epo requirements was not able to be shown, but the follow-up period on i.v. iron supplementation (4 months) may have been too short for a significant effect to have become apparent. To our knowledge, this is the first prospective controlled study to have examined the relative merits of oral vs i.v. iron in PD patients.

A previous study by Ahsan [6] compared a single i.v. infusion of total dose iron (1000 mg iron dextran) in 13 PD patients with daily oral iron therapy (195 mg elemental iron) in another 12 individuals. After 6 months of follow-up, the i.v. iron group displayed significantly higher mean haematocrits and percentage transferrin saturations, despite a reduction in mean Epo dosage. However, the study was not adequately controlled as patients considered to have ‘adequate iron stores’ (serum transferrin saturation greater than 25%) were all assigned to the oral iron group, whilst the i.v. iron group was composed solely of patients who had a serum transferrin saturation less than 25% and had failed to achieve a target haematocrit of 35% after 3 months on oral iron. Thus, the differences in response between the two groups may have been accounted for by the fact that the i.v. iron group, but not the oral group, were iron deficient. Moreover, the groups were not comparable in their baseline demographic characteristics, as the patients receiving oral iron were significantly older and had spent a considerably longer period of time on dialysis. Thus, the trial was potentially confounded by the fact that variables other than the mode of iron supplementation could have contributed substantially to the differential haemopoietic response.

Silverberg and coworkers [5] similarly demonstrated that i.v. iron infusion (ferrous saccharate 100 mg fortnightly) in 64 haemodialysis and nine PD patients over at least 6 months engendered significant increases in serum haematocrit, ferritin, and percentage transferrin saturation, without adverse effects. However, the number of PD patients enrolled in the study was too small to draw conclusions regarding the role of i.v. iron supplementation in this population. In another study, Vychytil et al. [13] treated 17 stable PD patients over a period of 6 months with monthly i.v. iron saccharate (100 mg if transferrin saturation >20% or 200 mg if saturation <20%). Although the type of iron supplementation employed prior to the trial’s inception was not reported, a significant increase in transferrin saturation and decrease in Epo requirements were observed. However, serum ferritin and haematocrit did not significantly change and serious adverse reactions (vertigo, hypotension, lumbago and vomiting) were reported following 0.9% of the 100 mg applications and 5.9% of the 200 mg applications.

The disparity in the incidence of adverse reactions to i.v. iron between our trial (no side effects from 36 infusions) and that of Vychytil et al. may partly relate to the nature of the i.v. iron preparation used (i.e. polymaltose vs saccharate). A randomized, prospective study comparing 200 mg infusions of three
different i.v. iron preparations (dextran, polymaltose and saccharate) in 43 dialysis patients [14] found that iron was released more rapidly onto transferrin with iron saccharate compared with the other two solutions, suggesting that ‘free iron reactions’ may be more problematic with the former preparation [15]. Despite this observation, the rate of adverse reactions following i.v. iron saccharate reported by Vychytil and colleagues still seemed to be unusually high. Although the number of PD patients in our study was somewhat small to effectively evaluate the safety of iron polymaltose, no such reactions have been observed following hundreds of such infusions at our centre. Similarly, anaphylactic reactions have not been witnessed following iron polymaltose infusions and appear to have so far been described almost exclusively in relation to iron dextran [3].

Recent epidemiological data linking i.v. iron therapy with an increase in bacterial infections [3] have additionally raised concerns about the possibility of iron overload following long-term i.v. iron infusions. However, it is uncertain whether this identified association represents a cause, effect, or epiphenomenon. In our short-term study, ferritin levels exceeded the upper limit of 800 µg/l, recommended by the CARI guidelines [11] and the European Best Practice Guidelines [10], in two patients (13%). Iron stores should, therefore, be carefully monitored in PD patients receiving i.v. iron.

The potential risks of i.v. iron therapy for PD patients must be weighed up against the adverse effects of oral iron supplements. In keeping with the findings of other studies [3,16], gastrointestinal intolerance occurred in a significant proportion of our study patients during the oral iron phases (46%). A recent, randomized, placebo-controlled trial of oral ferrous sulphate in 32 consecutive iron-replete dialysis patients revealed significant gastrointestinal side effects in 50% of patients treated with oral iron and were associated with a 20% decline in nPCR [16]. These findings raise the possibility that nutritional status may be adversely affected by oral iron supplementation.

In our study, the use of oral iron was also clearly inferior to i.v. iron with respect to maintaining iron stores and haemoglobin levels in Epo-treated PD patients. One possible weakness of this study is that compliance with oral iron supplements may have been incomplete, particularly in view of the higher prevalence of gastrointestinal disturbances during the oral phases. However, the importance of taking all prescribed medications was emphasized heavily at each clinic visit and it is unlikely that a higher level of medication compliance could be achieved in routine clinical practice. I.v. administration, therefore, appeared to offer the optimal route of iron supplementation.

Other parenteral routes of iron administration have been advocated in PD patients [3], but have been associated with potentially serious clinical problems. Suh and Wadhwa [17] reported that intramuscular (i.m.) iron dextran injections significantly decreased Epo requirements and increased haematocrit and serum ferritin in seven PD patients, but were associated with severe local pain in two patients and injection site discoloration in one patient. Muscle haematomas, sarcomas, and lipomyelodystrophy have also been reported following i.m. iron administration [18]. Mars and associates [19] investigated the efficacy of intraperitoneal (i.p.) iron dextran therapy (two 500 mg boluses 3–86 days apart) in 14 PD patients. Mean transferrin saturation and haematocrit were significantly increased and no adverse effects were observed over follow-up periods ranging between 1 and 7 months. However, long-term i.p installation of iron in animal PD models has been associated with peritoneal fibrosis and a reduction in peritoneal small solute transport rates [20]. It is, therefore, unlikely that these novel iron delivery strategies will ultimately be preferred to i.v. infusion.

A key advantage of the i.v. iron regimen utilized in this study was that it was simple, practical and readily able to be employed in an outpatient clinic setting. The protocol was designed specifically to minimize costs and patient inconvenience by administering i.v. iron at the time of the visit to the physician.

In summary, 2-monthly i.v. iron infusions represent a practical alternative to oral iron supplements and can be safely administered to PD patients in an outpatient setting. Compared with daily oral iron therapy, i.v. supplementation resulted in superior haemoglobin levels and body iron stores in Epo-treated PD patients, whilst at the same time reducing their total oral medication burdens and risk of gastrointestinal disturbance. Although further studies are required to document its long-term safety, i.v. iron infusion should be considered more often as a first-line supplementation strategy for Epo-treated PD patients.

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References


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