Intravenous iron supplementation for the treatment of anaemia in pre-dialyzed chronic renal failure patients

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Abstract

Background. Intravenous iron is a recognized therapy of anaemia in chronic haemodialyzed patients, especially in those receiving erythropoietin (Epo), while its role in the anaemia of pre-dialyzed chronic renal failure (CRF) patients is much less clear. This study attempted to evaluate the effects of intravenous iron in anaemic pre-dialyzed patients.

Methods. Sixty anaemic (haemoglobin <11 g/dl) non-diabetic patients with moderate CRF [32 males, 28 females; mean age 52.2±12.5 years; mean glomerular filtration rate 36.2±5.2 ml/min], without iron deficiency, iron overload or inflammation, without concomitant erythropoietin treatment and without any previous iron therapy were enrolled. Intravenous iron was administered as iron sucrose, 200 mg elemental iron per month for 12 months, with 1 month pre-study survey and 1 month follow-up after the last iron dose.

Results. Intravenous iron supplementation was associated with a significant increase in haemoglobin (from 9.7±1.1 at the baseline to 11.3±2.5 g/dl after 12 months, a mean increase of 1.6 g/dl), a further 36% of patients reaching the target haemoglobin of 10 g/dl. There was a significant increase in serum iron from 73.9±17.2 to 101.8±12.2 μg/dl, in serum ferritin from 98.0 (24.8–139.0) to 442.5 (86.0–496.0) μg/l and in transferrin saturation from 21.6±2.6 to 33.6±3.2%.

No worsening of renal function, no increase in blood pressure and no other side effects were noted.

Conclusions. Intravenous iron therapy in pre-dialysis patients with no Epo seems often to ameliorate the anaemia, avoiding the necessity of Epo or blood transfusions in one-third of pre-dialyzed non-diabetic patients. Intravenous iron supplementation appears to be an effective and safe treatment for anaemia in pre-dialysis CRF patients.

Keywords: anaemia; chronic renal failure; iron therapy; pre-dialysis

Introduction

Intravenous iron supplementation is a recognized therapy of anaemia in chronic haemodialyzed patients, especially in those treated with erythropoietin [1,2]. The role of iron supplementation in pre-dialyzed chronic renal failure (CRF) patients is much less clear.

The pre-dialysis survey on anaemia management revealed that few pre-dialysis patients (32%) met the European best practice guidelines target for haemoglobin (Hgb) concentration of above 11 g/dl [1], despite regular nephrology care [3]. Data from the Romanian Renal Registry showed that 89% of patients starting renal replacement therapy (RRT) in Romania had Hgb levels lower than the recommended target of 10 g/dl [4].

Several studies have revealed iron deficiency as a very common cause of anaemia in pre-dialysis patients, even when assessed by reduced iron staining in the bone marrow [5–7].

In the pre-erythropoietin treatment era, the role of disturbances in iron metabolism in the pathogenesis of renal anaemia was considered to be minor. After recombinant human erythropoietin became the standard therapy of anaemia in renal patients, many studies were focused on the main causes of Epo-hyporesponsiveness, iron deficiency being one of the major ones [1,2,5–9]. The vast majority of pre-dialized CRF patients seem to be iron deficient, because of multiple interferences with all phases of iron metabolism: reduced iron intake (because of anorexia, as well as low protein diets, with low animal protein and iron content), reduced gastro-intestinal iron absorption (gastro-intestinal impairment in uraemia, use of phosphate binders, histamine 2-blockers or proton pump inhibitors), gastro-intestinal bleeding (uraemic gastro-enteropathy, platelet dysfunction,
prophylactic use of aspirin), urinary loss of iron in patients with heavy proteinuria and reduced haemato-
poietic utilization of the orally administered iron
[1,5,6,7]. Hepcidin was recently found to be involved in reduced iron availability by decreasing intestinal
iron absorption and, possibly, by favouring iron sequestration within cells of the reticulo-endothelial
system [10].

Intravenously administered iron which by passes the gastro-intestinal tract, could become immediately available for erythropoiesis in the bone marrow and could be converted into haemoglobin more rapidly and more efficiently than oral iron. Several reports suggested that intravenous iron corrects iron deficiency, augments response to erythropoietin and even allows for anaemia correction without Epo in a significant number of CRF patients [5–7].

Correction of renal anaemia in pre-dialyzed patients by intravenous iron alone is of particular interest in Romania, where, because of financial constraints, use of erythropoietin was restricted only to patients undergoing dialysis.

**Objective**

The objective of our study was to evaluate the effects of 1-year intravenous iron supplementation in pre-dialyzed CRF patients without absolute iron deficiency and not receiving concomitant erythropoie-
tin treatment.

**Study design**

We performed a longitudinal open-label, single arm, prospective study in a single nephrology centre. The total observation period was 14 months with a 1 month pre-study assessment period, 12 months of therapeutic intervention and one month follow-up after the last iron dose.

**Subjects**

Sixty non-diabetic patients with chronic renal failure, with stable renal function 1 month prior to the study (mean glomerular filtration rate, GFR, calculated using the Cockroft–Gault formula, of 36.2 ± 5.2 ml/min/1.73 m²), with haemoglobin level less than 11 g/dl and serum ferritin below 200 μg/l, with stable haemato logic and iron status 1 month prior to inclusion, and without any previous iron therapy were enrolled. The arterial blood pressure was well controlled with calcium channel blockers, beta blockers and/or ACEI.

Patients with previous Epo therapy, laboratory signs of absolute iron deficiency (serum ferritin level below 20 μg/l [1]), iron overload (serum ferritin level exceeding 500 μg/L [1]) or inflammation (CRP level greater than 5 mg/l), gastrointestinal bleeding, significant weight loss or evidence of folic acid and/or vitamin B12 deficiency were excluded.

There were 32 males and 28 females in our study, with a mean age of 52.2 ± 12.5 years (range: 33–78). The CRF was caused by primary glomerular nephropathies in 60%, by tubulo-interstitial diseases in 25%, by nephroangiosclerosis in 10% and by other renal diseases in 5%. The aetiology of CRF in investigated patients was similar to that reported by the Romanian Renal Registry for all the country [4].

**Parameters**

In all subjects, the parameters of erythropoietic response (haemoglobin, haematocrit), of iron status (serum iron, transferrin saturation and serum ferritin), of renal function (serum creatinine, glomerular filtration rate—GFR) and blood pressure were assessed monthly, with the exception of serum ferritin, which was evaluated only once every 3 months because of financial difficulties.

The haematologic measures were designated prior to the study as primary parameters, while the measures of iron status, of renal function and blood pressure were designated as secondary parameters. The percentage of patients achieving the target haemoglobin of 10 g/dl was prospectively set as the primary outcome parameter.

Haemoglobin, haematocrit, serum iron, serum ferritin, serum transferrin as well as serum creatinine levels were measured using standard laboratory methods.

The patients were also followed-up for the appearance of serious adverse reactions.

**Therapeutic intervention**

The therapeutic intervention consisted of monthly intrave-nous administration of 200 mg of iron sucrose (Venofer; Vifor, St. Galen, Switzerland). Two ampoules of iron sucrose, each one containing 100 mg elemental iron were intravenously administered in 500 ml saline solution in 2 h monthly for a period of 12 months for a total dose of 2400 mg. A test dose of 25 mg of iron sucrose in 100 ml saline solution in 60 min was administered before the first full dose in all patients.

**Statistical analysis**

The pre-study (T0) and post-treatment samples were obtained after 3, 6, 9 and 12 months of iron administration (T3, T6, T9, T12, respectively), the last blood sample being collected 1 month after the last iron dose. The pre-study and post-treatment values have been processed with descriptive methods (mean and standard deviation for the parameters with normal distribution, median and interquartile range for non-parametric data).

ANOVA, chi-squared and the Mann–Whitney tests were used to compare results. A P-value of less than 0.05 was considered statistically significant.

**Results**

Fifty eight patients completed 12 months of study. Two patients were excluded: one patient refused study continuation for personal reasons and the other was lost to follow-up. Statistical analysis included only the 58 patients completing the 12 months of
Intravenous iron therapy was associated with a significant erythropoietic response, reflected by a significant, continuous, and progressive increase in haemoglobin. After 12 months of treatment, the mean increase in haemoglobin level was 1.6 g/dl, 16.5% above the baseline value, 58% of patients experiencing a rise in haemoglobin greater than 1 g/dl (Table 2).

There was an increase in serum iron, statistically significant only after 6 months of treatment. The transferrin saturation also significantly and continually increased, a progressively greater percentage of patients achieving the target (defined as values between 20% and 50% [1]) during the study period. The transferrin saturation remained far below the accepted upper limit of 50% for all the patients [1], but still remained below the accepted upper limit of 500 μg/l [1].

At the beginning of the study, only 44% of patients had haemoglobin levels above the Romanian recommended target of 10 g/dl. After 1 year of treatment, 80% of them achieved this level. Thirty six percent of patients not initially at target reached the above-mentioned recommended level of haemoglobin, without Epo treatment (‘iron-responders’), revealing that intravenous iron administration alone permitted anaemia correction in an important percentage of patients (Table 2).

A target haemoglobin level of 11 g/dl, as recommended by the European [1] and by the American Guidelines [2]. None of the enrolled patients had haemoglobin above this level at the study initiation. Intravenous iron administration was associated with a significant and progressive increase in the percentage of patients with haemoglobin greater than 11 g/dl, 55% of the enrolled patients reaching this target after 12 months of iron treatment, without any erythropoietic stimulating agent (Table 2).

At the end of the study, 76% of patients achieved the recommended target iron status of serum ferritin greater than 100 μg/l and transferrin saturation exceeding 20% [1], a significantly greater percentage than at the inclusion (Table 2).

There were no differences in any of the studied parameters between ‘iron-responders’ and ‘non-responders’ at the initiation of the study (Table 3).

There was no decrease in renal function, as described by serum creatinine level and by the GFR.

There were no significant differences in blood pressure and no serious adverse reactions to intravenous administration of iron sucrose were noted during the study.

Table 1. The investigated parameters during the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 month</th>
<th>3rd month</th>
<th>6th month</th>
<th>9th month</th>
<th>12th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.7±1.1</td>
<td>10.5±0.6</td>
<td>10.9±1.2</td>
<td>11.1±2.1</td>
<td>11.3±2.5</td>
</tr>
<tr>
<td>Serum iron (μg/dl)</td>
<td>73.9±17.2</td>
<td>74.8±13.8</td>
<td>84.2±9.4</td>
<td>97.8±13.5</td>
<td>101.8±12.2</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>21.6±2.6</td>
<td>24.9±5.3</td>
<td>28.6±5.6</td>
<td>27.8±4.4</td>
<td>33.6±3.2</td>
</tr>
<tr>
<td>Serum ferritin (μg/l)</td>
<td>98.0 (24.8–139.0)</td>
<td>156.0 (71.0–296)</td>
<td>229.5 (86.0–398.0)</td>
<td>259.0 (85.5–455.3)</td>
<td>442.5 (86.0–496.0)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.7±0.8</td>
<td>2.8±0.7</td>
<td>2.8±0.9</td>
<td>2.7±1.0</td>
<td>2.7±0.9</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>36.2±5.2</td>
<td>36.3±7.3</td>
<td>35.7±8.2</td>
<td>37.1±6.3</td>
<td>37.2±0.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>140±32</td>
<td>140±19</td>
<td>138±22</td>
<td>139±23</td>
<td>135±25</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82±20</td>
<td>80±12</td>
<td>81±14</td>
<td>80±18</td>
<td>80±21</td>
</tr>
</tbody>
</table>

1Statistical analysis included only the 58 patients completing the 12 months of therapeutic intervention.

*Mean±SD.
†Statistically significant vs baseline (P<0.05).
*Statistically significant vs previous (P<0.05).
‡Median (interquartile range).

Table 2. Patients achieving the targets for haemoglobin and iron status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 month</th>
<th>3rd month</th>
<th>6th month</th>
<th>9th month</th>
<th>12th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Hb &gt;10 g/dl (%)</td>
<td>44</td>
<td>47</td>
<td>62*</td>
<td>65*</td>
<td>80*</td>
</tr>
<tr>
<td>Patients with Hb &gt;11 g/dl (%)</td>
<td>0</td>
<td>34*</td>
<td>51*</td>
<td>53*</td>
<td>55*</td>
</tr>
<tr>
<td>Patients with the rise in Hb &gt;1 g/dl versus baseline (%)</td>
<td>–</td>
<td>15</td>
<td>35</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Patients with serum ferritin &gt;100 μg/l (%)</td>
<td>50</td>
<td>64</td>
<td>67</td>
<td>71*</td>
<td>76*</td>
</tr>
<tr>
<td>Patients with transferrin saturation ferritin &gt;20% (%)</td>
<td>59</td>
<td>62</td>
<td>73</td>
<td>95*</td>
<td>97*</td>
</tr>
<tr>
<td>Patients with target iron status (%)</td>
<td>49</td>
<td>59</td>
<td>65</td>
<td>70*</td>
<td>76*</td>
</tr>
</tbody>
</table>

*Statistically significant vs baseline (P<0.05).
In our study, intravenous iron administration alone was followed by a significant haematological response, as reflected by the constant and continuous increase in haemoglobin and haematocrit levels, in patients with low but not consistently iron-deficient indices (mean transferrin saturation was 21%). This suggests a significant role of functional iron deficiency in the pathogenesis of renal anaemia in pre-dialyzed chronic renal failure patients.

It is important to note that there were no diabetic patients in our study group. The aetiology of CRF in the studied group was similar to that reported for RRT patients in Romania, where only 6.6% of patients have diabetes mellitus, a significantly smaller percentage than in Western European countries and in the USA [4]. Several studies reported an almost double prevalence of anaemia in diabetic patients for each level of renal function than in non-diabetics [11]. Moreover, iron deficiency seemed to be a much more common cause of anaemia in diabetes than is generally recognized [11], although the role of intravenous iron therapy in these patients was less investigated. Thus, the non-diabetic status of our patients might influence the described pattern of therapeutic response. Our results showed that intravenous iron alone allowed for anaemia correction in 36% of patients (‘iron-responders’). Since 44% were already at target haemoglobin levels before the study, this means that only 20% of the enrolled patients failed to achieve the target haemoglobin, despite iron-deficiency correction, without any differences in the studied parameters between ‘iron-responders’ and ‘non-responders’ at the initiation of the study.

More relevant, after 12 months of intravenous iron administration and without any erythropoietic stimulating agent, 55% of the enrolled patients reached even the European [1] and the American recommended target haemoglobin of 11 g/dl [2], none of them starting the study above this haemoglobin level (Table 2).

Initiation of intravenous iron therapy, like all treatment decisions, involves the weighing of benefits and risks. The benefits of iron treatment relate to achieving the target haematocrit level and consequently could improve survival, reduce hospitalization and improve quality of life. Above and beyond these effects, iron is vital for normal cell energy production.

On the other hand, iron could be toxic, causing oxidative tissue damage, accelerated atherosclerosis and enhanced bacterial growth [1,12–14]. Experimental data suggest that all intravenous iron preparations could increase the risk of endothelial cell injury, accelerating the progression of kidney disease [13,15]. There was no significant change in GFR in our study, suggesting no deleterious effect of intravenous iron therapy on the renal function.

There were no adverse reactions to intravenous administration of iron sucrose complex: the safety in administration was remarkably good in the doses prescribed. Moreover, there was no evidence of hypertension (no increase in blood pressure and no need for any change in the initial antihypertensive treatment), as there might have been with erythropoietin therapy [9,10,16,17], and there was no evidence of accelerated renal damage after substantial doses of intravenous iron. In our patients, the benefits of intravenous iron therapy seemed to outweigh any theoretical risk.

Similar results were reported in a study on 90 pre-dialyzed CRF patients, showing that intravenous iron associated or not associated with Epo therapy corrects iron deficiency, augments the response to Epo and even permits anaemia correction without Epo in one-third of patients [7].

Compared to the previous studies using intravenous iron [5,6,7,18] for anaemia in pre-dialyzed patients, our study enrolled more patients receiving intravenous iron, had a longer duration, used higher cumulative iron doses and, moreover, excluded erythropoietin therapy, thus allowing us to isolate the iron effect.

Designed as single arm, thus assuming the lack of a control group, this study did not allow for strong conclusions. Despite this weakness, our results sustain the need for future randomized controlled trials in this field of wide clinical interest.

The possibility of correcting anaemia in pre-dialyzed CRF patients with intravenous iron alone opens new perspectives in the therapeutic approach to these subjects especially in Romania, where economic

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders (n = 46)</th>
<th>Non-responders (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.9 ± 1.2</td>
<td>9.3 ± 0.6</td>
<td>0.12</td>
</tr>
<tr>
<td>Serum iron (μg/dl)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>74.5 ± 16.8</td>
<td>71.4 ± 19.9</td>
<td>0.58</td>
</tr>
<tr>
<td>Transferrin saturation (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21.6 ± 2.6</td>
<td>21.9 ± 2.7</td>
<td>0.66</td>
</tr>
<tr>
<td>Serum ferritin (m/dl)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>114.5 (31.3–156.0)</td>
<td>84.0 (24.0–126.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.6 ± 0.9</td>
<td>2.7 ± 0.8</td>
<td>0.74</td>
</tr>
<tr>
<td>GFR (ml/min)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36.5 ± 4.2</td>
<td>36.0 ± 5.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>141 ± 33</td>
<td>139 ± 30</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82 ± 18</td>
<td>83 ± 19</td>
<td>0.47</td>
</tr>
</tbody>
</table>

‘Responders’—patients who achieved the local recommended target haemoglobin of 10 g/dl at the end of the study; ‘Non-responders’—patients who failed to achieve the haemoglobin level of 10 g/dl at the end of the study.

<sup>a</sup>Mean ± SD.

<sup>b</sup>Median (interquartile range).
reasons make recombinant human erythropoietin unavailable for anaemia treatment before initiation of renal replacement therapy.

Moreover, correction of anaemia could improve the cardiac function, interrupting the vicious circle of heart failure, renal failure and anaemia, the so-called ‘cardio-renal-anaemia syndrome’ [11,19,20]. Amelioration of the haematological status and of the cardiac function could reduce the rate of decline of glomerular filtration rate, postponing the need for renal replacement therapy and could improve the outcome in dialysis, as it is well-known that the fate of the dialysis patient is cast in the pre-dialysis period [5,6,19,20].

Conclusions

Intravenous iron administration in pre-dialyzed patients without Epo therapy seems to improve the renal anaemia and iron status, as haemoglobin, serum ferritin and transferrin saturation levels significantly increased. Moreover, intravenously administered iron alone permitted anaemia correction in about one-third of these patients. There was no worsening of renal function and no increase in blood pressure. No other side effects were noted.

Intravenous iron supplementation appears to be an effective and safe treatment for the anaemia in pre-dialyzed CRF patients without signs of iron overload, avoiding the necessity of erythropoietin or blood transfusions.

Conflict of interest statement. None declared.

References


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