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Intravenous Iron Saccharate in Hemodialysis Patients Receiving r-HuEPO


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ABSTRACT. A study was undertaken to evaluate the safety and efficacy of iron saccharate in regular hemodialysis (HD) patients receiving r-HuEPO. A total of 109 patients (57 males, 52 females, mean age 34.1 ± 11.7 years) were included in the study, 64 of whom were iron deficient. The patients were divided into two groups. Group I (n = 58) received high dose iron saccharate (500 mg), intravenously (i.v.) (1-2 doses), and Group II (n = 51) received low dose iron saccharate (100 mg), i.v., thrice per week (5-10 doses). Results at four weeks showed a significant increment in hemoglobin (Hb), hematocrit (Hct), and serum ferritin in both groups. Two patients developed headache, fever and urticaria, and three patients developed fever in group I. None of the patients in group II developed any adverse reaction. Intravenous iron supplementation with iron saccharate in HD patients showing poor response to r-HuEPO, produced satisfactory Hct levels without major side effects and without the need to increase the dose of r-HuEPO. Commonly observed side effects were not seen with the low dose regimen.

Key words: Iron saccharate, Iron deficiency, Hemodialysis, Erythropoietin, r-HuEPO, Functional iron deficiency.

Introduction

Iron deficiency contribute significantly to the anemia in hemodialysis patients mainly because of blood loss (1-4) and inadequate iron supplement. Reasons for recurrent blood loss in hemodialysis patients include uremias associated bleeding tendency due to blood vessel and platelet dysfunctions (5-7), uremia related gastrointestinal abnormalities such a telangiectasia and hemorrhage (8,9), blood loss during dialysis (10-13) and iatrogenic (14). In uremic patients, oral intake of iron is often inadequate due to factors such as poor consumption of iron containing foods, side effects of oral iron preparations leading to non-compliance and finally, iron malabsorption associated with use of antacids given fo
phosphonate binding (15-17). Since recombinant human erythropoietin (r-HuEPO) became available for use in hemodialysis patients, blood transfusion, with its related iron overload and other adverse effects, is much less commonly undertaken (3,4,18,19). In order to induce erythropoiesis, r-HuEPO requires adequate iron supplement. Without adequate iron supplement, erythropoiesis becomes blunted, leading to unresponsiveness to r-HuEPO which improves only with adequate iron therapy (20-25). Routes of iron administration include oral, intramuscular, or intravenous. Oral iron administration to hemodialysis patients with iron deficiency is often insufficient, inconvenient, and usually results in delayed response and non-compliance (16,17,20,26). Intramuscular injections are relatively contraindicated in patients on hemodialysis because of the associated bleeding tendency. Besides, intramuscular administration of iron preparations may be associated with local malignancy (28-31). There are two forms of intravenous iron preparations generally available. First, iron dextran which is widely used (20,26,32,33). However, up to 30% of patients develop side effects which include anaphylaxis, urticaria, fever, headache, nausea, vomiting, severe arthralgia and meningism (16,34-38). The second preparation is iron saccharate which has minimal side effects and has been successfully used in hemodialysis patients, pregnant women and other conditions with iron deficiency (39-41).

In this study we present our experience with intravenous iron saccharate (Ferrosac®, SPIMACO, Saudi Arabia) in hemodialysis patients comparing two dosage forms, (i) high dose = 500 mg, once weekly (one to two doses) and (ii) low dose = 100 mg, thrice weekly (five to ten doses).

Patients and Methods

Adult regular hemodialysis patients were selected from the hemodialysis units at King Khalid University Hospital, Security Forces Hospital and King Fahad National Guard Hospital. There were 109 patients, 57 males and 52 females, aged 17-65 (mean 34.1 ± 1.7) years. All patients were on treatment with r-HuEPO (EPREX, Cilag AG International, Switzerland) for a minimum period of eight weeks. Patients who were iron deficient (ID), (n = 64), were given r-HuEPO up to 100 units/kg thrice weekly for at least eight weeks. Patients who were not iron deficient (NID) (n = 45), were given r-HuEPO 50 units/kg i.v. thrice/week for at least 8 weeks. In both ID and NID patients Hct levels remained below the target value of 35% (Table 1). Each patient underwent a meticulous medical evaluation to rule out causes of anemia other than renal failure and/or iron deficiency. Initial laboratory work-up included complete blood count, blood urea nitrogen (BUN), creatinine, electrolytes, liver functions, serum iron (Fe), total iron binding capacity (TIBC), ferritin, vitamin B12, serum and RBC folate, and serology for inflammatory disorders. Patients were excluded from the study if they had active bleeding, hemolysis, inflammation, infection, malignancy, or if they had any contraindication. Patients were divided into two main groups. Group I received a high dose iron saccharate, 500 mg in 250 cc normal saline, i.v., over 1-4 hours once, to be repeated at weekly intervals up to the total dose which was calculated as Hb difference (target Hb minus current Hb) x body weight (kg) x 3 in those who have iron deficiency. Group II received low, fractionated dose of 100 mg in 25 cc normal saline, i.v., over 5-10 min, thrice weekly for 5 to 10 doses. Vital signs and possible side effects such as anaphylaxis, urticaria, fever, headache, nausea, vomiting, severe arthralgia and meningism were monitored closely. The following blood tests were carried out at weekly intervals (while on treatment): complete blood count, serum iron, TIBC and ferritin.

Laboratory Tests

Hematologic parameters were obtained by using a Coulter S-Plus electronic blood counter (Coulter Electronics, USA), serum iron and iron binding capacity (TIBC) using Synchron CX system (Beckman Instruments, Inc, USA) and serum ferritin was estimated by ELISA technique using Enzymun-Test Ferritin (Boehringer Manheim GmbH Diagnostics, Germany).
Table 1. Comparison between hematological and iron parameters before and four weeks after initiation of iron saccharate therapy

<table>
<thead>
<tr>
<th>Test (units)</th>
<th>Group I (n=58)</th>
<th>Group II (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ID (n=42)</td>
<td>ID (n=22)</td>
</tr>
<tr>
<td></td>
<td>NID (n=16)</td>
<td>NID (n=29)</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>A 8.3</td>
<td>A 8.5</td>
</tr>
<tr>
<td>(M:14-18 F:12-16)</td>
<td>±0.7 11.0*</td>
<td>±1.0 11.1*</td>
</tr>
<tr>
<td></td>
<td>B 8.8</td>
<td>B 8.5</td>
</tr>
<tr>
<td></td>
<td>±0.6 11.6*</td>
<td>±0.8 11.2*</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>A 24.9</td>
<td>A 25.7</td>
</tr>
<tr>
<td>(M:45-52 F:37-47)</td>
<td>±2.3 33.0*</td>
<td>±2.8 33.4*</td>
</tr>
<tr>
<td></td>
<td>B 26.5</td>
<td>B 2.8</td>
</tr>
<tr>
<td></td>
<td>±1.9 35.0*</td>
<td>±2.6 34.1*</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>A 71.7</td>
<td>A 75.4*</td>
</tr>
<tr>
<td>(78-92)</td>
<td>±4.7 81.4*</td>
<td>±4.4 84.7</td>
</tr>
<tr>
<td></td>
<td>B 83.7</td>
<td>B 85.2</td>
</tr>
<tr>
<td></td>
<td>±3.0</td>
<td>±4.2</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>A 24.5</td>
<td>A 28.4*</td>
</tr>
<tr>
<td>(27-33)</td>
<td>±1.5 30.9*</td>
<td>±1.5 32.1</td>
</tr>
<tr>
<td></td>
<td>B 31.4</td>
<td>B 31.9</td>
</tr>
<tr>
<td></td>
<td>±0.9 31.1</td>
<td>±0.8 31.2</td>
</tr>
<tr>
<td>Fe (umol/L)</td>
<td>A 11.0</td>
<td>A 15.2*</td>
</tr>
<tr>
<td>(14-32)</td>
<td>±2.9 18.7*</td>
<td>±2.4 19.9</td>
</tr>
<tr>
<td></td>
<td>B 19.8</td>
<td>B 21.1</td>
</tr>
<tr>
<td></td>
<td>±2.8 21.6</td>
<td>±3.2 23.4</td>
</tr>
<tr>
<td>TIBC (umol/L)</td>
<td>80.4 57.9*</td>
<td>±3.2 55.5*</td>
</tr>
<tr>
<td>(45-75)</td>
<td>±5.3 50.8</td>
<td>±9.4 55.5</td>
</tr>
<tr>
<td></td>
<td>±5.6 48.7</td>
<td>±8.1 47.6</td>
</tr>
<tr>
<td>Fer. (ng/ml)</td>
<td>A 18.6</td>
<td>A 88.7*</td>
</tr>
<tr>
<td>(18-300)</td>
<td>±11.8 52.2*</td>
<td>±10.7 107.5</td>
</tr>
<tr>
<td></td>
<td>B 165.0</td>
<td>B 6.0</td>
</tr>
<tr>
<td></td>
<td>±25.3 38.3</td>
<td>±23.0 38.5</td>
</tr>
<tr>
<td></td>
<td>±46.3</td>
<td>±66.3</td>
</tr>
</tbody>
</table>

Group I = patients who received high dose iron saccharate (300mg, 1 to 2 doses).
Group II = patients who received low dose iron saccharate (100 mg, thrice weekly, 5 to 10 doses).
A = before iron saccharate therapy, B = 4 weeks after initiation of iron saccharate therapy.
ID = iron deficient, NID = non-iron deficient. *P value < 0.001

Statistical Analysis

Paired Student's 't' test was used to compare hematological and iron parameters before and four weeks after initiation of iron saccharate therapy.

Results

The results are shown in table 1. Group I (n=58) consisted of 42 iron deficient and 16 non-iron deficient patients. Group II (n=51) consisted of 22 iron deficient and 29 non-iron deficient patients. All patients from both groups showed a significant rise in their hemoglobin, hematocrit and serum ferritin at the fourth week of initiation of iron saccharate administration, although the NID patients were receiving only smaller dose of r-HuEPO (50 units/kg). In addition, ID patients from both groups showed a significant increase in MCV and MCH. The dose of r-HuEPO in ID patients also could be brought down to about 50 units/kg to sustain Hct at the target level.

Side Effects

Two patients in Group I developed fever, headache, nausea, hypotension, and urticaria after the completion of the iron saccharate infusion. They responded to treatment with antihistamines and hydrocortisone and the reaction disappeared in a few hours. Three patients developed headache, nausea, and skin discomfort after 2 hours during the infusion. The symptoms disappeared when the infusion was stopped and no specific treatment was needed. Four of the patients who developed reactions previously received smaller doses subsequently (i.e., 100 mg, similar to Group II) without any further adverse reactions. Group II patients did not show any adverse reactions.

Discussion

This study clearly indicates the usefulness of parenteral iron supplement in hemodialysis patients for obtaining rapid response of Hct while on treatment with r-HuEPO. In most
Use of iron saccharate in small frequent doses is associated with fewer side effects.

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References


