Iron Therapy in Treatment of Iron Deficiency Anemia Before Delivery: Intravenous Versus Oral Route

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Ibrahim A. Abdelazim 1, Mohannad Abu-Faza 2, Vincent Joseph Sanchez 2

1 Ain Shams University, 2 Ahmadi Hospital, Kuwait Oil Company (KOC)


Abstract

Background and Objectives:

Anemia is one of the world’s leading causes of disability. Anemia is a cause of considerable perinatal morbidity and mortality. This study was designed to compare the efficacy and safety of intravenous versus oral iron in treatment of iron deficiency anemia during pregnancy and before delivery.

Patients and methods:

Sixty four (64) women between 24-30 weeks gestation with iron deficiency anemia during pregnancy and hemoglobin level below 10 gm/dl were randomized in this study to receive either; Iron Saccharate in intravenous group (IV group) or oral ferrous Fumarate in oral group (PO group). Laboratory investigations and complete blood count were done to assess treatment efficacy.

Results:

Hemoglobin concentration was significantly increased 30 days after treatment in both studied groups and the rise in hemoglobin was more significant in the IV group (from 9.13 ± 0.45 to 11.27 ± 0.56 gm/dl). Also, mean corpuscular volume (MCV) was significantly increased 30 days after treatment in both studied groups and the rise in MCV was more significant in the IV group (from 72.38 ± 5.9 to 92.8 ± 7.4 FL). Reticulocytes count was significantly decreased 30 days after treatment in IV group compared to PO group, also, serum ferritin level was significantly elevated in IV group, compared to PO group (p<0.05).

Conclusions:

Iron (III) Hydroxide Saccharate Complex (Iron Saccharate) appears to be a safe and effective treatment for iron deficiency anemia during pregnancy, to reduce the need for blood transfusion.

Citation

Introduction

Anemia is a major public health problem, defined by the World Health Organization as hemoglobin below 11 gm/dl. Anemia is one of the world’s leading cause of disability and thus one of the most serious global public health issues. Anemia affects all pregnant women in the world; 52% in developing countries compared with 23% in the developed world. The most common causes of anemia are poor nutrition, deficiencies of iron, micronutrients, malaria, hookworm infestation and schistosomiasis, HIV infection and hemoglobinopathies. Anemia is one of the most prevalent nutritional deficiency problems affecting pregnant females. High prevalence of iron deficiency anemia among women in developing countries is of concern and maternal anemia is still a cause of considerable perinatal morbidity and mortality. Anemia is responsible for adverse obstetric outcome in a large number of women in developing countries. Almost one thousand severely affected young women are reported to die every week because of inability to cope with the stress of childbirth. Anemia leads to increased risk of blood transfusion during the peripartum period. Iron therapy before delivery may reduce the blood transfusion rate for iron deficient women.

Patients and Methods

This randomized prospective study was conducted at the Kuwait Oil Hospital (KOC), Kuwait, from February 2013 to February 2014 after approval of the study by institute ethical committee. Ninety two (92) women were randomly assigned through a computer generated randomization sheet to receive either oral or intravenous iron therapy. The study was completed by Sixty four (64) women with iron deficiency anemia during pregnancy and hemoglobin level below 10 gm/dl after informed consent and assigned into two groups thirty two (32) women in each group by a randomization table (13 women were suffering from parasitic infestation, 9 women in oral group discontinued treatment because of side effects and 6 women did not continue IV therapy because of travelling and preterm labour). Complete blood picture (CBC), hemoglobin concentration (gm/dl), Mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCH), serum ferritin (ug/l) and reticulocytes count (106/mm3) were checked to confirm the diagnosis of iron deficiency anemia during pregnancy before inclusion in this study.

Women included in this study (inclusion criteria); were >18 years old, with a hemoglobin level between 8-10 gm/dl and pregnant between 24-30 weeks gestation. Pregnant women with anemia not related to iron deficiency, asthma, liver cirrhosis, viral hepatitis, multiple pregnancy, risk of preterm birth, suspected acute infection, intolerance to iron preparations, previous blood transfusion and/or current iron supplements were excluded from this study (exclusion criteria).

In intravenous group (IV group), the iron dose was calculated from the following formula; Total iron dose required (mg) = 2.4 × weight (kg) × (target hemoglobin – actual hemoglobin) gm/dl + 500 mg. The weight was the patient’s weight before pregnancy in kilograms, target hemoglobin was set at 12 gm/dl and actual hemoglobin in gm/dl was the patient's hemoglobin level on inclusion in this study. 2.4 is a correction factor that takes into account the patient’s blood volume and hemoglobin iron content, while the 500 mg is the quantity of stored iron in adults. The calculated IV iron dose was given through an intravenous infusion twice weekly. In each infusion 200 mg of Iron (III) Hydroxide Saccharate Complex (Iron Saccharate), (Fersosac, Spimaco, Al-Qassim Pharmaceutical, Saudi Arabia) was diluted with 200 ml of normal saline and given by intravenous slow infusion over one hour and the patient was monitored during the first 15 minutes for signs of intolerance, hypotension or anaphylaxis. The treatment was stopped once the total calculated dose was given. Iron (III) Hydroxide Saccharate Complex (Iron Saccharate), is a complex of poly-nuclear iron (III) hydroxide in sucrose for intravenous use. The poly-nuclear iron (III) hydroxide course is superficially surrounded by a large number of non covalently bond sucrose molecules resulting in a complex, with a molecular mass of approximately 60,000 Dalton, prohibiting renal elimination. The iron in the poly-nuclear cores is bound in a similar structure to that of physiologically occurring ferritin. The complex is stable and does not release ionic iron under physiological conditions. Following intravenous administration, iron sucrose is dissociated by the reticulo-endothelial system into iron and sucrose. Iron sucrose can be administered as intravenous injection or infusion. Iron sucrose does not contain dextran hence chances of anaphylaxis are negligible. Rate of iron delivery to the marrow is a major factor in regulation of marrow proliferation. Iron sucrose has an intermediate stability and strength. It is quickly cleared from the serum with a terminal half life of approximately 5-6 hours. It is more rapidly available for erythropoiesis. Oral treatment group (PO group) received; 350 mg oral ferrous Fumarate (Trihemic 600 tablets, Wyeth pharmaceutical company, Karachi, Sindh, Pakistan).
daily for 4 weeks. Patients were required to carefully note treatment compliance on a calendar provided for that purpose. In both studied groups; folic acid was systematically given in association with iron preparations to avoid an eventual folic acid deficiency and to avoid the influence of such deficiency on study results. The trihemic 600 tablets contain ascorbic acid, which forms a soluble complex with iron in the stomach and passes into the intestine. The effect of iron absorption inhibitors, which would normally bind to iron in alkaline pH of upper intestine is limited. 9 Two studied groups were monitored at each visit, adverse reactions related to iron preparations, especially intravenous iron were recorded (hypotension, tachycardia, arthralgia, abdominal or chest pain, headache, vertigo and skin eruptions). Laboratory investigations and CBC were done to assess the treatment efficacy by measurement of hemoglobin and reticulocytes on 15 and 30 days after treatment, also, serum ferritin, MCV, MCH were also done at inclusion in this study and 30 days after treatment.

Sample Size Justification

Using data of previous studies, G* Power software version 3.17 for sample size calculation (*Heinrich Heine Universität; Düsseldorf; Germany), setting the ?-error probability at 0.05, power (1- ? error probability) at 0.95 % and effective sample size (w) at 0.3. The effective size (w) was calculated as follows: w=\sqrt{\chi^2 / N} , where ?2 is the chi-square test and N is the total sample size. Number of participants needed to produce a statistically acceptable figure was 63 women.

Statistical Analysis

Statistical analysis was performed using statistical package for social sciences (SPSS) for Windows version 18.0 (Chicago Il, USA). Descriptive statistics for measured variables were expressed as mean and standard deviation. Differences between two groups were measured using paired and independent samples “ t ” test. The significance level was set at 0.05.

Results

At the beginning of this study 92 women were randomly assigned through a computer generated randomization sheet to receive either oral or intravenous iron. This study was completed by 64 women as 13 women were suffering from parasitic infestation, 9 women in oral group discontinued treatment because of side effects and 6 women did not continue intravenous iron therapy because of travelling and preterm labor. On inclusion the two studied groups were matched regarding; mean age (24.2 ± 4.3 in the IV group versus 25.3 ± 4.5 years in the PO group), parity (1.8 ± 1.2 in the IV group versus 1.9 ± 1.3 in PO group) and weight (66 ± 10.8 in the IV group versus 68 ± 11.6 Kg in PO group). Also, there were no statistical difference between the two studied groups regarding; the mean gestational age (26.6 ± 0.7 in IV groups versus 26.8 ± 1.3 weeks in PO group) and mean premedication hemoglobin (9.13 ± 0.45 in the IV group versus 9.17± 0.47gm/dl in PO group). (Table 1)

The hemoglobin concentration was significantly increased 30 days after treatment in both studied groups (from 9.13 ± 0.45 to 11.27 ± 0.56 gm/dl in IV group and from 9.17± 0.47 to 10.32 ± 0.56 gm/dl in PO group) and the rise in hemoglobin was more significant in the IV group compared to PO group (p<0.05). Mean corpuscular volume (MCV) was significantly increased 30 days after treatment in both studied groups (from 72.38 ± 5.9 to 92.8 ± 7.4 FL in IV group and from 71.98 ± 5.5 to 88.17 ± 6.3 FL in PO group) and the rise in MCV was more significant in IV group compared to PO group (p<0.05), Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>IV group (n = 32) Mean ± SD</th>
<th>PO group (n = 32) Mean ± SD</th>
<th>P value “t” test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.2 ± 4.3</td>
<td>25.3 ± 4.5</td>
<td>0.297* (&gt;0.05)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>66.2 ± 10.8</td>
<td>68.4 ± 11.6</td>
<td>0.596* (&gt;0.05)</td>
</tr>
<tr>
<td>Parity</td>
<td>1.8 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>0.701* (&gt;0.05)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>26.6 ± 0.7</td>
<td>26.8 ± 1.3</td>
<td>0.596* (&gt;0.05)</td>
</tr>
</tbody>
</table>
MCV was more significant in IV group compared to PO group. The only adverse reaction reported by women received intravenous MCV was more significant in IV group compared to PO group, also, MCV was significantly increased 30 days after treatment in both studied groups (from 72.38 ± 5.9 to 92.8 ± 7.4 FL in IV group and from 71.98 ± 5.5 to 88.17 ± 6.3 FL in PO group) and the raise in hemoglobin was more significant in IV group compared to PO group, also, MCV was significantly increased 30 days after treatment in both studied groups (from 9.3 ± 2.76 to 130.5 ± 4.4 ug/l, compared to PO group (elevated from 9.1 ± 2.4 to 26.83 ± 4.7 ug/l), (p<0.05), Table. 01. The mean corpuscular hemoglobin (MCH) was increased 30 days after treatment without any significant difference between two groups (from 21.73 ± 4.1 to 25.8 ± 2.8 pg in IV group and from 22.25 ± 4.0 to 25.4 ± 2.9 pg in PO group), (p>0.05). Reticulocytes count was significantly decreased 30 days after treatment in the IV group from 3.87 ± 1.5 to 0.096 ± 0.04 106/mm3 compared to PO group (decreased from 3.86 ± 1.6 to 0.1 ± 0.03 106/mm3), also, serum ferritin level was significantly elevated in IV group from 9.3 ± 2.76 to 130.5 4.4 ug/l, compared to PO group (elevated from 9.1 ± 2.4 to 26.83 ± 4.7 ug/l), (p<0.05), Table. 01. The only adverse reaction reported by women received IV iron was an unpleasant metallic taste during injection, no other serious or major side effects were recorded by women received intravenous iron and patients’ compliance recorded by the investigators was excellent. Nine (9) women discontinued oral iron therapy because of gastrointestinal symptoms in form of epigastric discomfort, nausea and vomiting and were excluded from this study.

### Table

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<th>PO group (n = 32) Mean ± SD</th>
<th>P value “t” test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication hemoglobin (gm/dl)</td>
<td>9.13 ± 0.45</td>
<td>9.17 ± 0.47</td>
<td>0.13* (&gt;0.05)</td>
</tr>
<tr>
<td>15 days post-medication hemoglobin (gm/dl)</td>
<td>10.3 ± 0.48</td>
<td>9.77 ± 0.45</td>
<td>0.001** (&lt;0.05)</td>
</tr>
<tr>
<td>30 days post-medication hemoglobin (gm/dl)</td>
<td>11.27 ± 0.56</td>
<td>10.32 ± 0.56</td>
<td>0.001** (&lt;0.05)</td>
</tr>
<tr>
<td>Premedication reticulocytes (106/mm3)</td>
<td>3.87 ±1.5</td>
<td>3.86 ±1.6</td>
<td>0.817* (&gt;0.05)</td>
</tr>
<tr>
<td>15 days post-medication reticulocytes (106/mm3)</td>
<td>0.096 ± 0.04</td>
<td>0.12 ± 0.04</td>
<td>0.001** (&lt;0.05)</td>
</tr>
<tr>
<td>30 days post-medication reticulocytes (106/mm3)</td>
<td>0.092 ± 0.03</td>
<td>0.1 ± 0.03</td>
<td>0.001** (&lt;0.05)</td>
</tr>
<tr>
<td>Premedication ferritin (ug/l)</td>
<td>9.3 ± 2.76</td>
<td>9.1 ± 2.43</td>
<td>0.486* (&gt;0.05)</td>
</tr>
<tr>
<td>30 days post-medication ferritin (ug/l)</td>
<td>130.5 ± 4.4</td>
<td>26.83 ± 4.7</td>
<td>0.001** (&lt;0.05)</td>
</tr>
<tr>
<td>Premedication MCV (FL)</td>
<td>72.38 ± 5.9</td>
<td>71.98 ± 5.5</td>
<td>0.37* (&gt;0.05)</td>
</tr>
<tr>
<td>30 days post-medication MCV (FL)</td>
<td>92.8 ± 7.4</td>
<td>88.17 ± 6.3</td>
<td>0.001** (&lt;0.05)</td>
</tr>
<tr>
<td>Premedication MCH (pg)</td>
<td>21.73 ± 4.1</td>
<td>22.25 ± 4.0</td>
<td>0.071* (&gt;0.05)</td>
</tr>
<tr>
<td>30 days post-medication MCH (pg)</td>
<td>25.8 ± 2.8</td>
<td>25.4 ± 2.9</td>
<td>0.231* (&gt;0.05)</td>
</tr>
</tbody>
</table>

n = Number, MCHC = Mean Corpuscular Hemoglobin Concentration, MCV = Mean corpuscular volume, * = Non significant, ** = Significant.

Also, mean corpuscular hemoglobin (MCH) was increased 30 days after treatment without any significant difference between two studied groups (from 21.73 ± 4.1 to 25.8 ± 2.8 pg in IV group and from 22.25 ± 4.0 to 25.4 ± 2.9 pg in PO group), (p>0.05). Reticulocytes count was significantly decreased 30 days after treatment in the IV group from 3.87 ± 1.5 to 0.092 ± 0.03 106/mm3 compared to PO group (decreased from 3.86 ± 1.6 to 0.1 ± 0.03 106/mm3), also, serum ferritin level was significantly elevated in IV group from 9.3 ± 2.76 to 130.5 4.4 ug/l, compared to PO group (elevated from 9.1 ± 2.4 to 26.83 ± 4.7 ug/l), (p<0.05), Table. 01. The only adverse reaction reported by women received IV iron was an unpleasant metallic taste during injection, no other serious or major side effects were recorded by women received intravenous iron and patients’ compliance recorded by the investigators was excellent. Nine (9) women discontinued oral iron therapy because of gastrointestinal symptoms in form of epigastric discomfort, nausea and vomiting and were excluded from this study.

### Discussion

Iron deficiency anemia is common during pregnancy and deserves special attention because of its potential consequences. Moreover, some pathologic situations during pregnancy increase the risk of hemorrhage and require a rapid restoration of iron stores. In this study, the hemoglobin concentration was significantly increased 30 days after treatment in both studied groups (from 9.13 ± 0.45 to 11.27 ± 0.56 gm/dl in IV group and from 9.17± 0.47 to 10.32 ± 0.56 gm/dl in PO group) and the raise in hemoglobin was more significant in IV group compared to PO group, also, MCV was significantly increased 30 days after treatment in both studied groups (from 72.38 ± 5.9 to 92.8 ± 7.4 FL in IV group and from 71.98 ± 5.5 to 88.17 ± 6.3 FL in PO group) and the raise in MCV was more significant in IV group compared to PO group. The only adverse reaction reported by women received intravenous...
(IV) iron in this study was an unpleasant metallic taste during injection, no other serious or major side effects were recorded by the patients and patients’ compliance recorded by the investigators was excellent. Al Momen and colleagues used centrifugal blood transfusion therapy to treat iron deficiency anemia during pregnancy. Al Momen and colleagues found that the intravenous iron sucrose complex group achieved significantly higher hemoglobin levels (12.85 ± 6.6 versus 11.14 ± 12.4 g/dL in the oral group). Also, they found that the intravenous iron sucrose complex group showed no major side effects, while 6% of the oral group could not tolerate oral ferrous sulfate, 18% (30%) complained of disturbing gastrointestinal symptoms and 18% (30%) had poor compliance. Al Momen and colleagues concluded that iron sucrose was a safe and effective alternative in treatment of iron deficiency anemia during pregnancy.

Abhilashini et al. compared the efficacy and safety of intravenous iron sucrose and oral iron administration for treatment of iron deficiency anemia in pregnancy. They found that gastrointestinal side effects were not seen in women on intravenous iron therapy and Forty four percent (44%) of patients in oral iron group had gastrointestinal side effects.

Mishra et al. concluded that parenteral iron therapy in iron deficiency anemia is recommended in patients where oral iron therapy is ineffective due to malabsorption states and noncompliance. They also, concluded that intravenous iron results in much more rapid resolution of iron deficiency anemia with minimal adverse reactions compared to oral iron. Iron sucrose has a favorable safety profile and is an alternative to other forms of parenteral iron therapy in correction of iron stores depletion.

Also, Shafi et al. concluded that the hemoglobin level elevated and iron stores restored rapidly when women with iron deficiency anemia during pregnancy was treated parenterally with iron sucrose compared to oral ferrous ascorbate. In this study, serum ferritin level was significantly elevated in the IV group from 9.3 ± 2.76 to 130.5 ± 4.4 ug/l, compared to PO group (elevated from 9.1 ± 2.4 to 26.83 ± 4.7 ug/l in PO group), (p<0.05). Although, Benoai et al. compared the efficacy and safety of intravenous iron sucrose to oral ferrous sulfate and found that there was no significant difference between the two studied groups regarding the post-treatment hemoglobin and the depleted iron stores were significantly increased in oral group compared to intravenous group.

Fifty (50) women were included in Bayoumeu et al. study and the intravenous iron sucrose was compared with oral ferrous sulfate. Bayoumeu et al. found that the hemoglobin level was increased 9.6 ± 0.79 to 11.11 ± 1.3 g/dL in intravenous group and from 9.7 ± 0.5 to 11 ± 1.25 g/dL in oral group 30 days after treatment which was insignificant. They also found that the serum ferritin values were significantly higher in intravenous group than oral ferrous sulfate, on day 30 after treatment and at delivery. Also, Al Ragip et al. compared intravenous iron sucrose with oral iron polymaltose complex (300 mg elemental iron per day) in women with iron deficiency anemia. They found that the change in hemoglobin from baseline was significantly higher in intravenous group than oral group on day 14th and 28th after treatment. Also, Al Ragip et al. also found that the serum ferritin levels were significantly higher in intravenous group compared to oral group (28 ± 26 ug/l versus 11 ± 11 ug/l; respectively) at the fourth week of treatment and at birth (23.7 ± 13.8 ug/l versus 18.1 ug/l; respectively).

Iron (III) Hydroxide Saccharate Complex (Iron Saccharate) seems to be treatment of choice without serious side effects for iron deficiency anemia during pregnancy to avoid risks of blood transfusion. Dose of Iron (III) Hydroxide Saccharate Complex (Iron Saccharate) to be calculated according to the ideal patients’ weight and to the depleted iron stores evaluated by serum ferritin level. Further studies are needed to evaluate the effect of Iron (III) Hydroxide Saccharate Complex on the size and weight of the fetuses.

Conclusions
Iron (III) Hydroxide Saccharate Complex (Iron Saccharate) appears to be an effective treatment for iron deficiency anemia during pregnancy, which produces a rapid increase in hemoglobin concentration and serum ferritin levels without serious side effects indicated in women who cannot tolerate oral iron preparations and for replacement of depleted iron stores. Iron (III) Hydroxide Saccharate Complex (Iron Saccharate) is a safe, effective alternative for treatment of iron deficiency anemia during pregnancy, being given in outpatient settings and able to reduce the need for blood transfusion.

References


