COMPARATIVE STUDY OF EFFICACY AND SAFETY BETWEEN ORAL IRON AND INTRAVENOUS IRON SUCROSE THERAPY IN ANAEMIA IN PREGNANCY

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ABSTRACT

BACKGROUND: Anaemia is a major health problem in the antenatal clinics all over the world. India has a very high incidence from 40%-80% in various set ups. Maternal morbidity and mortality are high in anaemia in pregnancy. Iron supplementation is the mainstay of treatment. It can be given in oral or parenteral forms. This study was conducted to study the effects of the two forms in pregnant women and to compare the effects, side effects and foetal outcomes. MATERIALS AND METHODS: This study was conducted on 100 cases of iron deficiency anaemia in pregnancy of 16–36 weeks with haemoglobin between 6-10 g/dl at S.S.G Hospital, Vadodara. Patients were randomly divided into two groups of 50 patients each for administration of oral or injectable iron. Patients were called for follow up after 3 weeks and 3 months. The primary outcome was haemoglobin concentration at 3 weeks and 3 months and the secondary outcomes were ferritin levels, serum iron levels, adverse effects and foetal birth weight. RESULTS: There was a clear increase in the haemoglobin from 7.87 g/dl to 10.69 g/dl after three months in injectable group and from 8.43g/dl to 9.84 g/dl in the oral group and this difference was statistically significant. There was a statistically significant increase in the ferritin level and serum iron in the injectable iron group. No major side effects were noted in either group and difference in birth weights were not statistically significant. CONCLUSION: Injectable iron is more efficient in replenishment of iron stores (ferritin). It is the treatment of choice as it has no serious side effects compared to oral iron supplementation.

Keywords: anaemia, pregnancy, morbidity, mortality, parenteral, ferritin

INTRODUCTION

Anaemia is one of the world’s leading cause of morbidity and one of the serious global public health problems.¹ Anaemia in pregnancy includes anaemia as a direct consequence of pregnancy or just an associated condition worsened or unmasked by pregnancy. Anaemia is an indirect contributor to a lot of pregnancy complications like ante partum and postpartum haemorrhage, preterm labour, Pregnancy Induced Hypertension (PIH) and foetal complications like prematurity, Intrauterine Growth Retardation (IUGR), prenatal morbidity and mortality.²,³ Iron supplementation is the mainstay of treatment of iron deficiency anaemia.

The objective of treatment is to restore the haemoglobin level to normal and to replenish the exhausted iron stores. Iron can be administered orally or parenterally. Oral iron is a safe, cheap and easily accepted mode of administration of iron without significant side effects. Oral iron is a less than ideal treatment, however, with gastrointestinal toxicity occurring in negligible to 31% of patients and a long course needed to resolve anaemia and replenish stores. Nonadherence to a prescribed course of oral iron is common, and even in adherent patients, poor intestinal absorption fails to compensate for iron need in the presence of ongoing blood losses.⁴,⁵,⁶ Intravenous iron administration has also been available for several years. In a small proportion of patients who either shows intolerance to oral iron, poor compliance to oral iron or in whom oral iron is contraindicated (post gastrectomy or other gastrointestinal disorders), injectable iron preparations are a feasible option.⁷,⁸ However, there remain concerns about the acute safety profiles of the few available preparations and the potential for long-term toxicity with their repeated administration. However with the availability of iron sucrose, these side effects
are almost negligible and there are excellent safety records. This lead us to compare the effects of the two modes of iron administration in terms of the effect on haemoglobin level, serum ferritin level, side effects and foetal outcome in terms of birth weight.

**MATERIALS AND METHODS**

This was a prospective study in which 100 women visiting the antenatal clinics or admitted to the obstetric ward of SSG Hospital, Vadodara were included after taking an informed consent. This study was carried out between June 2010 and October 2011. The inclusion criteria were pregnant women with gestational age between 16-36 weeks with haemoglobin level of 6-10 g/dl. Mean Corpuscular Volume <100 femtolitre and serum ferritin<50 microgram/litre. Exclusion criteria were patients having anaemia not linked to iron deficiency, asthma, cirrhosis of liver, viral hepatitis, multiple pregnancy, risk of premature birth, suspected acute infection, history of intolerance to iron derivatives or sickle cell disease. At inclusion, the patient’s haemoglobin, Mean Corpuscular Volume (MCV), serum iron levels, serum ferritin were measured. The patients who were selected were divided into two groups by randomisation table according to the mode of administration of iron: group A for oral iron and group B for injectable iron.

**Group A** consisted of 50 patients. They were given oral ferrous sulphate tablets.200 mg tablets (with 60 mg of elemental iron) were given two times a day: equivalent to 120 mg of elemental iron per day. Patients were carefully monitored for compliance.

**Group B** consisted of 50 patients who were given intravenous iron sucrose injection. Dose of iron sucrose was calculated according to the formula: Weight (kg) x (Target Hb-Actual Hb) x0.24 +500 mg Weight was the patient’s weight before pregnancy in kilograms, target haemoglobin was set as 11 g/dl based on WHO definition of anaemia in pregnancy, actual haemoglobin was patient’s haemoglobin level on inclusion in g/dl. 0.24 was a correction factor that took into account patient’s blood volume which was estimated at 7% of body weight and haemoglobin iron content and 500 mg is the quantity of stored iron in adults. A dose of 200 mg (2 ampoules) of iron sucrose was diluted in 200 ml normal saline and was given over 30 min in one sitting. Infusion was given with full facilities for acute emergency care. For the initial 10 minutes, the infusion was given slowly and patient was monitored for signs of intolerance such as hypotension or anaphylactoid reactions. The total calculated dose was divided and given as 2 ampoules on alternate days. Routine oral iron supplementation was withheld during the treatment schedule. 5 mg of folic acid was given to both the groups to prevent eventual folic acid deficiency. Both the groups were monitored clinically during the treatment schedule. In each group, adverse drug reactions such as nausea, vomiting, abdominal discomfort, diarrhoea and constipation with oral iron and hypotension, tachycardia, hyperthermia, arthralgia, sensation of chest tightness, headache, vertigo, skin eruptions, allergic reactions etc if any with injectable iron sucrose were noted at each visit. After completion of the total calculated dose, patients were called for follow up after 3 weeks and 3 months. The primary outcome measure was haemoglobin concentration at 3 weeks and 3 months after treatment. The secondary outcomes were serum ferritin level indicative of the iron stores, serum iron, recorded adverse drug reactions and foetal birth weight. Statistical package for social science (SPPS - 16) was used for statistical compilation and analysis. For statistical analysis of difference between groups, unpaired sample-t test was applied when appropriate. Statistical significance was accepted at $P <0.05$.

**RESULTS**

Hundred eligible women participated in the study between June 2010 to October 2011. They were randomly assigned to oral (n=50) and intravenous iron groups (n=49). One women was excluded from the intravenous group because of preterm delivery. There was a rise in haemoglobin from 8.43 g/dl to 9.84 g/dl in the oral iron group and from 7.87 g/dl to 10.69 g/dl after 3 months in the intravenous iron sucrose group. The rise of haemoglobin between the two groups was statistically significant (Table 1).

There was a rise in serum ferritin from 20.5 mg/l to 97.23 mg/l in the intravenous iron group and from 14.01 mg/l to 20.06 mg/l in the oral iron group three months after treatment. Thus there was a significant difference in the rise in the storage form of iron, that is, serum ferritin between the two groups three months after the treatment (Table 2), being significantly higher in the intravenous iron group. There was a rise in serum iron from 54.56 microgram/dl to 112 microgram/dl in the intravenous iron group and from 59.36 microgram/dl to 68.29 microgram/dl in the oral iron group three months after treatment. This shows that there was a significant rise in the serum iron levels in the parenteral iron group three months after treatment (Table 3). Only four out of 49 patients of the intravenous iron group developed minor side effects like low grade fever on the day of treatment. No other major side effects like anaphylactic reactions were noted. In the oral iron group,
majority of the patients experienced minor side effects like nausea, vomiting and constipation. There was also no significant difference in the mean birth weight of the babies delivered in the two groups. There was no significant difference in placenta weight, preterm labor, pre-eclampsia or gestational hypertension between the two groups.

Table 1: Comparison of mean values of haemoglobin in oral versus intravenous iron groups

<table>
<thead>
<tr>
<th>Time of Hb measurement</th>
<th>Group A on oral iron (g/dl)</th>
<th>Group B on intravenous iron (g/dl)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>8.43</td>
<td>7.87</td>
<td>0.01</td>
</tr>
<tr>
<td>3 weeks after treatment</td>
<td>9.02</td>
<td>9.69</td>
<td>0.0002</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td>9.84</td>
<td>10.69</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 2: Comparison of the mean values of ferritin in the oral versus intravenous iron groups

<table>
<thead>
<tr>
<th>Ferritin mean values (mg/l)</th>
<th>oral iron (mg/l)</th>
<th>intravenous iron (mg/l)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>14.01</td>
<td>20.5</td>
<td>0.0020</td>
</tr>
<tr>
<td>3 wks after treatment</td>
<td>17.56</td>
<td>61.27</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td>20.06</td>
<td>97.23</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 3: Comparison of the mean values of rise of serum iron in the oral versus intravenous iron groups

<table>
<thead>
<tr>
<th>Serum iron mean values (microgram/dl)</th>
<th>Oral iron (microgram/dl)</th>
<th>Intravenous iron (microgram/dl)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>59.36</td>
<td>54.56</td>
<td>0.1128</td>
</tr>
<tr>
<td>3 wks after treatment</td>
<td>64.89</td>
<td>87.02</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td>68.29</td>
<td>112.00</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

DISCUSSION
Iron deficiency anaemia during pregnancy is common and deserves special attention due to its potential consequences. In this study, the efficacy, safety and tolerability of intravenous iron sucrose in treating pregnancy associated iron deficiency anaemia was compared with oral iron therapy. In our study, there was a significant difference in the rate of rise of haemoglobin in the two groups. Also, intravenous iron sucrose restored the iron reserves that is, serum ferritin, much better than oral iron at any time after the treatment. There were no significant adverse effects noted in either of the groups. Comparison with other studies is difficult because of different cut-offs used for laboratory parameters. Oral iron preparations used are also different. But the results from various studies are quite similar. Al Rapig et al conducted a randomised study to compare the efficacy of intravenous and oral iron in 90 women with Hb of 8-10 g/dl and serum ferritin <50 microgram/l was carried out by Francoise Bayoumeu et al in which there was a statistically significant difference in the ferritin levels between the intravenous and oral iron groups but no statistically significant difference in the rise of haemoglobin. Al Rapig et al conducted a randomised study to compare the efficacy of intravenous and oral iron in 90 women with Hb of 8-10.5 g/dl. The results showed that the change in haemoglobin from baseline was significantly higher in the intravenous group than the oral group. Ferritin levels were also higher in the intravenous group. Once oral iron is started, it takes about 3 weeks for haemoglobin to start rising and about 6-8 weeks if stores are exhausted and need to be replenished. Replenishment of the iron stores begins only after the haemoglobin returns to normal. This is a very slow process and takes about...
3-4 months with oral iron therapy. However there is rapid replenishment of stores with intravenous iron sucrose therapy as shown in our study. Increase in ferritin is not because of direct intravenous injection of iron complex; rather, it is because the intravenous iron sucrose complex releases iron rapidly to endogenous iron binding proteins with no deposition in the parenchymal tissue. Furthermore, even though oral iron supplements iron using the body’s normal absorption mechanism, the amount of iron absorbed is so small that replenishing iron orally would take a very long time and affect compliance of the patients. Intravenous iron sucrose has the potential of solving this problem because it overcomes the problem of compliance and absorption and has an excellent safety record. According to Van Wyck et al, the side effects of parenteral iron preparation are: life threatening anaphylaxis-0.002%, hypersensitivity reactions-0.005% and mild adverse reactions around 35%. However, these side effects are negligible with intravenous iron sucrose therapy. Mild adverse effects like vomiting, rashes and giddiness following first dose of iron sucrose administration reported in other studies were not observed in the present study. In our study only 8.16% women developed minor side effects like low grade fever after intravenous iron sucrose administration. Because there were no serious adverse drug reactions and no episodes of anaphylaxis, we feel that it is safe for anaemia in pregnancy. There is no increased risk of preterm delivery after iron supplementation. There are concerns over the release of free iron during intravenous iron therapy which would contribute to oxidative stress in the body. But according to the study by Van Wyck et al, no intravenous iron sucrose compound has generated any detectable free iron. Thus iron sucrose is safe, effective and highly reliable form of treatment for iron deficiency anaemia. It corrects anaemia at short duration and replenishes iron stores better than oral iron supplementation. It seems to be the treatment of choice with no serious side effects indicated in rapid correction of anaemia in pregnancy or restoring maternal iron stores especially because the total dose can be administered over a short period. The only limitation of iron sucrose is that it is costlier than oral iron and requires a hospital setting for administration. The limitations of this study were that although intravenous iron sucrose increased serum ferritin significantly, patients were not followed-up in the post-natal period to determine whether haemoglobin levels were maintained during lactation because of higher stores. We did not repeat serum ferritin at the end of pregnancy nor during the post-natal check-up to see how long the stores last.

CONCLUSION

We conclude that oral iron increases haemoglobin comparably with intravenous iron sucrose, but does not replenish iron stores as much. This is significant in our country where women may become anaemic again during lactation, especially when their iron stores have not been corrected. However, oral iron is cheaper and is easy to take. Though oral iron supplements iron following the normal body mechanism, it is possible to treat iron deficiency anaemia in a much better way by the use of intravenous iron sucrose therapy as it is highly reliable, safe and effective form of iron therapy. Moreover, intravenous iron sucrose is considered in patients with intolerance, unresponsiveness or non compliance to oral iron or in patients near term with moderate-severe anaemia thus avoiding the need for blood transfusion.

REFERENCES

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