Intravenous Iron Versus Oral Iron in Antenatal Women with Iron Deficiency Anemia in Sub-Himalayan Settings

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Abstract: Objective: Compare Intravenous Iron sucrose and Oral Ferrous sulphate in the treatment of iron deficiency anaemia during pregnancy. Method: 100 sub-himalayan antenatal women between 12 to 36 weeks gestation from Central Referral Hospital with Iron deficiency anemia; hemoglobin 6–9 gm/dl, MCV<78fl, MCH <30pg, and serum ferritin <15µg/l; were randomized to receive either 200mg ferrous sulphate tablet twice daily for 6 weeks or receive intravenous ferric hydroxide sucrose complex in water after calculating Total dose infusion. The primary outcome measure was change in hemoglobin, RBC indices, serum ferritin and total serum iron. Results: The mean increase in total serum iron following iron sucrose was 40.20±5.11µg/dl compared to a increase of 33.56±3.39 µg/dl with oral ferrous sulphate, which was statistically highly significant (P< 0.0001). Similarly, the mean increase in serum ferritin with iron sucrose was 31.72±10.74µg/dl and with ferrous sulphate being 23.31±4.06 µg/dl which was also statistically highly significant (P<0.001). There was no difference in the increase in hemoglobin, MCV and MCHC between the two groups. Conclusion: Though increase in hemoglobin and RBC indices were not significantly higher with iron sucrose, the main highlight of the study was that iron sucrose significantly increased serum ferritin and serum iron, suggesting that it replenishes iron stores much better than oral iron. Iron sucrose also had a more favourable improvement in clinical features with fewer side-effects, and more effective in later months of pregnancy. This may be of relevance to pregnant mothers residing in difficult Sub- Himalayan terrain.

Keywords: Ferrous sulphate, Iron deficiency anemia, Iron sucrose, Serum Ferritin, Serum Iron.

Introduction: The WHO Global Database on Anaemia for 1993–2005, covering almost half the world’s population, estimated the prevalence of anaemia worldwide at 25 percent.¹ Although the prevalence of anaemia is estimated at 9 per cent in countries with high development, in countries with low development the prevalence is 43 percent.² In absolute numbers anaemia affects 1.62 billion people globally with about 293 million children of preschool age, 56 million pregnant women, and 468 million non-pregnant women estimated to be anaemic.¹ India is one of the countries with very high prevalence of anaemia in the world. Almost 58 per cent of pregnant women in India are anaemic and it is estimated that anaemia indirectly is the underlying cause for 20–40 per cent of maternal deaths in India. India contributes to about 80 per cent of the maternal deaths due to anaemia in South Asia.³ Nutritional anaemia is a major public health problem in India and is primarily due to iron deficiency. The National Family Health Survey-3 (NFHS-3) data suggests that anaemia is widely prevalent among all age groups, and is
particularly high among the most vulnerable—nearly 58 per cent among pregnant women, 50 per cent among non-pregnant non-lactating women, 56 per cent among adolescent girls (15–19 years), 30 per cent among adolescent boys and around 80 per cent among children under 3 years of age.

Pregnancy causes a state of hydraemic plethora. Due to disproportionate increase in plasma volume there is apparent reduction in haemoglobin, RBC count and haematocrit. This haemodilution is maximum in second trimester that is why early in pregnancy and again near term, the hemoglobin level of most healthy women with adequate iron stores is 11g/dl or higher. For these reasons, the centers for Disease Control (1990) defined anaemia as less than 11g/dl in the first and third trimesters, and less than 10.5g/dl in the second trimester.²

The first choice in the treatment of iron deficiency anemia for almost all patients is oral iron replacement because of its effectiveness, safety, and lower cost. Intravenous iron therapy is reserved for a small number of patients in whom oral treatment fails or for whom iron loss exceeds intake that cannot be met by oral therapy. Severe systemic adverse effects associated with iron dextran and iron gluconate limited the use of intravenous iron. Both iron dextran and iron gluconate cause unpredictable anaphylactic reactions and require a test dose before the first administration for treatment. However, iron sucrose is reported to be safe and effective for the management of anemia, and it can be administered without a test dose.⁴,⁵,⁶ Total dose iron offers a single ministration where compliance is questionable.

**METHODS:** This prospective controlled-randomized study included 100 non blinded, pregnant women with iron deficiency anemia from Central Referral Hospital, the teaching hospital of Sikkim Manipal Institute of Medical Sciences, Gangtok from January 2010 to June 2011. Randomisation was doing by simple randomisation using computer generated sequence. To detect the 15% difference of Hb change between two groups during the study period with α=0.05 and β=0.2 (power=80%), sample size was calculated to hundred. Approval of Institutional Ethics committee was obtained before commencing the study. Written informed consent was taken from the patients prior to inclusion in the study.

Antenatal women with singleton pregnancy, gestational age between 12 to 36wks and Hemoglobin concentration between 6 to 9 gm/dl were included in the study. However, antenatal women with any obstetrical complicating factors like Pre-eclampsia, Gestational Diabetes, any other medical disorder like tuberculosis, diabetes, peptic ulcer, history of Ante-Partum Hemorrhage, history of allergy to iron containing preparation and having history of blood transfusion in last 120 days were excluded from the study. After informed consent, data collected from those participating in the study were about their education, occupation, religion, diet (Vegetarian/non-vegetarian), obstetric and menstrual history, mode of previous delivery, history of blood transfusion. All the presenting complaints of patient were noted and documentation was done. Routine investigations done were Hemoglobin (Hb), Urine–Routine/Microscopy, TLC, DLC, ESR, Stool for occult blood, Blood sugar, Blood urea, Serum bilirubin. Specific investigations of Red cell indices including MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration) and Peripheral smear was done. Iron deficiency anemia was diagnosed if hemoglobin was 6-9g/dl, MCV< 78 fl, MCH< 30pg,
serum ferritin < 15µgm/L with low serum iron and elevated total iron binding capacity (TIBC) and absence of any other cause of anemia.

Patients in the oral group received 200 mg of ferrous sulphate tablets (containing 60 mg of elemental iron) twice daily for 6 weeks empty stomach. This treatment was also supplemented with 5 mg of folic acid per day. In the intravenous group, the total iron sucrose dose to be administered as Total Dose Infusion was calculated from the following formula:

Weight (in kgs) x (Target hemoglobin-Actual hemoglobin) g/dlx2.4+500mg, rounded up to the nearest multiple of 100mg.

Target hemoglobin in grams per liter was set at 11g/dl, actual hemoglobin in gram per liter was the patient’s hemoglobin level on inclusion; 2.4 was a correction factor that take into account the patient’s blood volume estimated at 7% of body weight and hemoglobin iron content; 500 mg is the quantity of stored iron in adults. Iron sucrose injection used was Ferric hydroxide sucrose complex in water at an alkaline pH of 10.5-11.1(I/V Iron Sucrose Injection), containing 50 mg elemental iron per 2.5 ml vial. The dose calculated was given as slow intravenous infusion as Out-Patients basis (On alternate days when required). The dose of 100 mg elemental iron was diluted exclusively in a maximum of 100 ml of 0.9% isotonic sodium chloride, immediately prior to infusion. The solution was infused at a rate of 100mg of iron over a period of at least 30 minutes. A maximum of 300 mg/day of iron was administered by slow infusion with each 100 mg diluted in 100ml of an isotonic sodium chloride solution over a minimum period of 1.5–2 hrs. No test dose was given. The patient was monitored intensively for vitals, any sensitivity reaction, signs of intolerance such as an anaphylactic reaction or hypotension during the period of transfusion. 500 µg of folic acid was administered orally daily with the treatment to prevent an eventual folic acid deficiency and to eliminate the influence of such a deficiency on the result.

Baseline investigations done on the day of starting the treatment, from both the group included a Complete blood count, RBC’s indices (MCV, MCH, and MCHC), Serum ferritin, Total serum iron. Results were compared after 6 weeks from the day of completion of the treatment. The rate of improvement was measured in terms of hemoglobin, RBC’s indices, S. ferritin and S. Iron. Outcome measured were Change in hemoglobin, RBC’s indices, Serum ferritin and Total serum iron; Compliance to oral iron; and Side effects of oral iron and I/V iron sucrose.

RESULTS: The demographic profiles of both the groups were similar with no statistically significant difference, as shown in Table 1. The mean age of patients in oral group was 24.8 ± 3.9 years and of the I/V group it was 25.2±4.2 years. Iron deficiency anemia was more prevalent in women belonging to upper lower and lower middle class and those who were illiterate or educated up to primary school, though the proportion of illiterate patients was higher in the oral group, the distribution differences being not statistically significant. Prevalence of Iron deficiency anemia was similar in both Primi-gravida and Multi-gravida in both the groups, with maximum (74%) subjects in both groups with anemia between 22 to 31 weeks of pregnancy.

Following the treatment, the mean increase in Hemoglobin level was slightly higher, but not statistically significant, in IV group as compared to oral group, with Hemoglobin level increasing by 2.3 gm/dl following Iron Sucrose as compared to 2.2gm/dl with oral iron. Similarly,
there was no significant statistical difference in the increase in mean MCV, MCH and MCHC following either of the therapy. Though there was no statistical significant difference in base-line mean total serum iron between two groups (p-value=0.357), but after treatment there was a statistical significant (p-value<0.001) increase in mean total serum iron after 6 weeks of Iron Sucrose treatment, with a mean increase of Total serum iron of 10.1µg/dl following Iron sucrose and only an increase of 4.5µg/dl following oral ferrous sulphate. Similarly, there was no statistical significant difference in base-line serum ferritin between two group (p-value=0.066), but statistically highly significant (p-value<0.001) increase in serum ferritin at 6 weeks after treatment with Iron Sucrose, as shown in Table 2.

During the study it was found that in both the Oral ferrous sulphate and the Intravenous Iron sucrose group, the increase in the hemoglobin level, MCV, MCH, MCHC was highest in those with a baseline Hemoglobin of 6 -7 gm/dl, followed by those with baseline Hemoglobin of 7-8 gm/dl and then 8 -9 gm/dl; the trends for Serum Iron was different with maximum increase seen in the subgroup with baseline Hemoglobin of 7 -8 gm/dl, as has been shown in Table No. 3

Regarding the analysis of side-effects of both the therapy it was found that only 6% patients receiving Iron sucrose had side-effects of mild allergic reaction (4%) and dizziness. However, 40% of patients receiving oral ferrous sulphate complained of side-effects with 20% complaining of constipation, 12% complaining of metallic taste, 4% of nausea/vomiting, 2% of abdominal pain and 2% of diarrhoea.

COMMENTS: Iron-deficiency anaemia is a major health problem worldwide, but responds well to iron supplementation. The responsible constellation factors producing iron deficiency anaemia generally precedes the pregnancy, including diet poor in iron content coupled with menstrual losses and a rapid succession of pregnancies in which supplemental iron was not provided. Most women begin their pregnancy with partially or completely depleted iron reserves. Thus, the severity of the anaemia is inversely related to the amount of iron reserves. The total requirement of iron during pregnancy is approximately 1000 mg (500 mg for developing fetus and placenta and similar amount for red cell increment). Usually, this iron is mobilized from iron stores. However, women with poor iron stores become iron deficient during pregnancy. Studies have shown that Hb levels <8 g% (moderate to severe anaemia) in pregnancy are associated with higher maternal morbidity.

As compared to western women whose iron stores are sufficient and they need 30-40 mg elemental iron per day for anaemia prophylaxis in pregnancy, the stores in Indian women are deficient and they need 100 mg elemental iron per day for prophylaxis. For treatment of anaemia, dose recommended is 200 mg elemental iron per day. In the present study, 6-9 g% Hb was taken as cut-off. Intravenous iron is superior to oral iron with respect to faster increase in Hb and faster replenishment of body iron stores. Also, it reduces the need of blood transfusions, and it can be given at outpatient basis.

A random, prospective, open study conducted in France by Bayomeu et al, involving 50 patients at 6 month of gestation to compare intravenous iron sucrose versus oral route, an increase in Hb was observed, rising from 9.6± 0.79 g/dl to 11.11±1.3 g/dl on day 30 in I/V group and from 9.7±0.5g/dl to 11±1.25 g/dl on day 30 in oral group which was not statistical
significant. In the present study, an increase in mean haemoglobin was observed from 7.8±0.9 g/dl to 10.1±1.1 g/dl in I/V group, and from 7.9±0.8 g/dl to 10.1±0.8 g/dl in oral group. Though marked increase in Haemoglobin was seen in both the group, but no statistical significant difference was found in any group according to age and in groups according to period of gestation, with maximum increase was seen in the range of 6 to 7gm% in both the group. The response to iron therapy can also monitored by MCV levels as Haemoglobin levels of the patients improves, the size of RBCs also increased as depicted by increase in MCV. In the present study, in both the groups there was a significant increase in mean MCV but there was no statistical significant difference between the two group. Similar results on the increase in MCV were observed by open study conducted in France by Bayomeu et al.15 However, in a study conducted by Al Momen16 et al, I/V group obtained significantly higher level of MCV as compared to oral group (p value<0.001) in pregnant anaemic women with gestational age less than 32 weeks in a study which is comparable to our study.

In an open, randomized controlled trial, Westad et al (2008)17 analyzed the effect of IV ferrous sucrose compared with oral ferrous sulphate on hematological parameters and quality of life in women with post-partum anemia. After 4 weeks, the mean Hb values in both groups were similar (11.9 g/100ml versus 12.3 g/100 ml, p=0.89). The mean serum ferritin value after 4 weeks was significantly higher in the intervention group with 13.7 µg/L versus 4.2 µg/L in the oral control group (p<0.001).Similarly, in our current study, increase in serum ferritin level was found in both the groups. In the oral group, mean serum ferritin before treatment was 13.4±3.6 µg/L which increased to 23.3±4.1 µg/L after treatment. In I/V group mean serum ferritin was 16.8±2.0 µg/L, which increased to 31.7±10.7 µg/L after giving injectable iron. There was no statistical significant difference in base-line serum ferritin between two group (p-value=0.066), but highly significant difference (p-value < 0.000) was observed between oral and iron sucrose group with respect to serum ferritin at 6 weeks after treatment. This indicates iron sucrose not only treats but also corrects iron stores, which is not seen with oral iron. This observation is highly significant in our study thus indicating its use in anaemia during pregnancy. Similar, study by Bhandal18 et al, showed a statistical significant difference in ferritin level (p value<0.01) with ferritin levels increasing from 13 µg/L at baseline to 42.2 µg/L on day 40 in I/V group; and to 15µg/L in oral group. In our study, serum ferritin and serum iron were used as indicators of iron storage. Our study have shown that intravenous iron sucrose significantly increases Hb levels and rapidly replenish iron stores, with a mean increase in total serum iron from 30.1±6.2 µg/dl to 40.2±5.1 µg/dl. Study by Bhandal18 et al had also shown that two 200 mg doses of intravenous ferrous sucrose significantly increases Hb levels and rapidly replenish iron stores within 5 days, with a mean increase from baseline of 2.5 g/dl and only intravenous ferrous sucrose appeared to restore iron reserves, with a statistical difference throughout the treatment period.

In the present study intravenous iron sucrose tolerance seems to be excellent without only 6% having adverse effects, in accordance with literature. However, 40% patients receiving oral iron side-effects, which was in contrast to study by Bhandal et al18 and also Bayoumeu et al15 where they reported compliance with oral treatment was surprisingly good.

Overall, from our study iron sucrose appears to be a better treatment of choice with no serious side-effects, indicated in the rapid correction of anemia in pregnancy and restoring
maternal iron stores, especially because the total dose can be administered over a shorter period, particularly for pregnant mothers residing in the difficult Sub-Himalayan terrain. However, major disadvantages of intravenous treatments are cost, need for hospitalization or an outpatient setting, and the invasive nature of the procedure.

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