Abstract

Objective: (1) To determine an alternative iron supplementation with better efficacy, compliance & safety in treatment of iron deficiency anemia during pregnancy, (2) to reduce blood transfusion during pregnancy, labor and puerperium.

Material and Method: A prospective comparative study. A total number of 60 pregnant women with the gestational age of 12 - 34 weeks were included in the study who were suffering from iron deficiency anemia. They were divided in 3 groups (A, B and C). Group A (n=15) received intravenous iron sucrose according to recommended dose containing 500 mg of iron sucrose for storage, in group B (n=20) iron sucrose was administered according to deficit calculated as per formula but 200 mg of iron was given for storage instead of 500 mg, to reduce cost. While group C received intra muscular iron Sorbitol in the dose used as practice.

Results: Mean hemoglobin in group A and B was 8.0 ± 1.1 g/dl and 8.9 ± 0.7 respectively, in group C, it was 8.8 ± 0.9 g/dl. In group A & B initial hemoglobin was assessed 3 weeks post therapy which showed an average rise of 2.8 g/dl (group A) and 1.9 g/dl (group B) and second assessment of Hemoglobin was done prior to delivery (aye: 6.6 weeks) showed a total rise of 3.8 g/dl (group A) and 2.4 g/dl (group B). Pre delivery mean Hemoglobin in group A and B was 11.8 g/dl and 11.3 g/dl respectively. In group C, the Hemoglobin was assessed only prior to delivery (average: 8.4 weeks from the start of therapy), and a rise of 1.4 g/dl was observed with pre delivery mean Hemoglobin of 10.2 g/dl. Target hemoglobin levels i.e. lig/di was achieved by 80% in Group A, 70% in Group B and 28% in Group C by the time of delivery. Blood transfusion was not required in any group. In group A and B one patient had moderate abdominal pain, 2 had weakness and shivering and 3 had phlebitis at the site where intravenous canula was retained. None of patient discontinued the therapy due to any adverse effect. In group C majority complained of pain at injection site while 5 patients dropped out from the study due to intolerance.

Conclusion: Intravenous iron therapy is safe, convenient and more effective then intramuscular iron therapy in treatment of iron deficiency anemia during pregnancy. The intravenous iron therapy can replace blood transfusion in antenatal period (JPMA 52:392, 2002).

Introduction

Iron serves as oxygen and electron carrier and acts as catalyst for oxygenation, hydroxylation and other metabolic processes, hence is required by every cell of the body. Iron deficiency is the most common deficiency disease worldwide. In the first stage of iron deficiency, stores are depleted without decline in iron containing compounds (hemoglobin, myoglobins, heme and non-heme enzymes). In the second stage erythropoiesis does take place but metabolism at cellular level is affected, hence adverse effects on nervous system, physical performance,
intellectual capacity and immune system are evident clinically with or without microcytic hypochromic anemia. About 11-20% of non-pregnant women in Western world are in this stage. In the final stage of iron deficiency, the classical picture of hypochromic and microcytic anemia appears affecting 1-3% of non-pregnant women in western communities. Hence during pregnancy, majority will become iron deficient in the absence of iron supplementation. However, the magnitude of problem is large in developing countries, where more than 50% of women in reproductive age are anemic due to nutritional deficiency, malabsorption, menstrual loss and high parity. Other important causes of iron deficiency are worm infestation, malaria, vitamin A deficiency and inhibitors of iron absorption in food. Oral iron is often prescribed with food and antacids to alleviate side effects, these contain phytates, tannates, calcium and phosphates that inhibit iron absorption. During pregnancy about 700 to 1400 mg of extra iron is required for the fetoplacental unit, red cell expansion, hemorrhage at parturition and lactation. The problem becomes more severe in iron deficient women. Moreover, nausea, vomiting, reflux oesophagitis and motility disorders adversely affect the iron intake and absorption from the gut, although iron absorption is increased during pregnancy.

The adverse effects of anemia on pregnancy are well-known, namely pre-eclampsia, pyelonephritis, puerperal sepsis, peripartal-bleeding complications, delayed involution, wound healing. The anemic failure-contributes directly in 8 to 16% and largely indirectly to maternal mortality especially in the developing countries. Fetal effects are less pronounced but studies have shown high risk of abortion and placental insufficiency leading to intrauterine growth restriction and death. A recent metaanalysis has shown relation of anemia in early pregnancy to increase in preterm birth. There is risk of neonatal behavioral and developmental delays (that can be reversed by iron therapy) and infantile iron deficiency anemia, though cord blood at birth shows normal Hemoglobin and iron levels. In iron deficient mothers with babies born with low birth weight and increased ratio of placental weight/birth weight there is higher incidence of adult hypertension.

In our unit incidence of anemia in pregnant women was more than 50% although oral and intramuscular iron were routinely prescribed. Considering the above-mentioned facts, we conducted this study to find out an alternate iron therapy with better efficacy, safety and good compliance. Our aim was also to compare the percentage of patients who achieved the target hemoglobin of 11 g/dl at the time of delivery in the study groups. We also aimed to minimize the blood transfusion in antenatal and perinatal periods by finding new alternatives.

Subjects and Method

Sixty pregnant patients with gestational age of 12-34 weeks selected from the antenatal clinic were included in the study. Iron deficiency anemia was provisionally diagnosed on Hemoglobin levels and blood indices or peripheral film. Patients with Hemoglobin levels 5 - 10 g/dl with PCV of < 30%, MCV < 80 fl, MCH < 28 pg, microcytic, hypochromic anemia were included in the study. Patients suffering from chronic disease, inflammatory conditions, asthma, folic acid deficiency, thalassemia and those showing signs and symptoms of anemic failure were excluded. Patients with Hemoglobin levels <7 g/dl (n=2) were given intravenous iron sucrose (Venofer®) as an alternative to blood transfusion and those with Hemoglobin levels between 7-10 g/dl were randomized for intravenous iron sucrose (Venofer®) or intramuscular iron sorbitol (Jectofer). The patients were divided into 3 groups.

Group A (n=15): Iron sucrose was administered intravenously as recommended according to the
following formula containing 500 mg of iron for storage.

**Formula:** total iron deficit (mg) = body wt (kg) x (target Hemoglobin - actual Hemoglobin (g/dl)) x 0.24 + 500.

**Group B (n=20):** iron sucrose administered intravenously according to deficit calculated as per formula but 200 mg of iron being given for storage instead of 500 mg of ISC, aiming at reducing cost of therapy by Rs. 1300 - 1500.

The mean iron deficit in this group was 1050 mg. A total of 750 mg of iron Sorbitol was given intramuscularly daily or alternate days. After parenteral administration oral iron therapy (Ferrous Gluconate 250 mg) was continued till the time of delivery.

**Administration**

Iron Sucrose Complex (Venofer®: Vifor Int.) - a test dose of 1 ml (20 mg) diluted in 9 ml of 0.9% NaCl was infused in 2-3 minutes, prior to first dose of therapy. If no adverse effect was observed in 15 minutes, rest of the 200 - 300 mg (2-3 ampoules) of iron sucrose in 100-150 ml of 0.9% NaCl infused in 45 - 60 minutes. In few patients, 500 mg (5 ampoules) in 300 ml of 0.9% NaCl was infused in 3.5 hours with an interval of 7 days to reduce the number and cost of visits.

No other iron preparation was prescribed during pregnancy.

Iron Sorbitol (Jectofer®) - A test dose of 0.1 ml (5 mg) was administered intramuscularly. If well tolerated, after 15 - 30 minutes, rest of the 1.4 ml (70 mg) was injected deep in gluteal muscle.

One ampoule (75 mg) was injected daily or on alternate days. Oral iron therapy was continued after the therapy as practiced.

**Monitoring:** Because of financial constraints, only Hemoglobin levels and blood indices / peripheral film was advised for monitoring. After completion of iron sucrose therapy in groups A and B initial monitoring was done after 3-4 weeks. Final monitoring was done at the time for delivery, average time interval being 6.3 weeks, in group C, since duration of treatment was long only one assessment was done when patients came for delivery, average time interval was 8.5 weeks.

**Side Effects**

In group A and B one patient had moderate abdominal pain during infusion of 500 mg (5 ampoules) in 300 ml of normal saline, 2 had shivering and feeling of weakness within few hours of infusion and 3 had phlebitis at the site where intravenous canula was retained. None of the patients discontinued therapy due to adverse effects. In group C majority complained of pain at injection site while 5 patients dropped out from the study due to intolerance.

**Results**

A total number of 60 patients with iron deficiency anemia of pregnancy were studied. Patients were divided into three groups. Group A (15 patients) mean age was 25 ± 5.6 years with the gestational age of 29 ± 4.3 weeks and the mean weight was 69 ± 18.7 kg. In Group B (20 patients) the mean age was 26 ± 4.4 years with the mean gestational age of 29 ± 5.3 weeks and the mean weight was 64 ± 8.5 kg. In group C (25 patients) the mean age was 27 ± 4.2 years, mean gestational age was 27 ± 5.6 weeks and the mean weight was 63 ± 12.1 kg. Mean number of Venofer® ampoules, duration of treatment and mean doses are shown in Table 1.
As evident from the results shown in Table 2, both the Venofer® groups (A + B) acquired better results than the Jectofer group (C). First monitoring done 3 - 4 weeks post therapy, showed rise of Hemoglobin from 8.0 ± 1.1 g/dl to 10.6 ± 0.8 g/dl in group A and from 8.9 ± 0.7 g/dl to 10.8 ± 0.7 g/dl in group B. That is, greater initial response was seen in group A vs. group B (2.7 ± 1.1 vs. 1.9 ± 0.8 g/dl). In group A, 80% of patients achieved the target Hemoglobin (11 g/dl) at the time of delivery whereas 70% achieved the target Hemoglobin in group B. Total rise of Hemoglobin was greater in group A (3.8 g/dl) in a mean duration of 6.3 ± 4.1 weeks compared to group B (2.4 g/dl) in a duration of 6.6 ±5.5 weeks. But the rise in Hemoglobin was statistically significant in both groups (P<0.001). In group C (Jectofer group with continuing oral iron therapy till delivery), 28% patients achieved the target Hemoglobin with a mean total rise of 1.4 ± 1.4 g/dl achieved in about 8.5 ± 4.2 weeks (P not significant).

**Discussion**

Our study clearly illustrates the efficacy, compliance and safety of iron sucrose. The reason being that iron sucrose consists of polynuclear iron complex analogous to ferritin with apoferritin component replaced by sucrose that is well tolerated and least antigenic and being a large molecule, less than 5% excreted by the kidneys. It is available for erythropoiesis within 5 minutes of infusion and has a 68-97% utilization rate after 2 - 4 weeks since it is stored in reticuloendothelial (RE) cells and not in the parenchymal cells of the body\(^{19,20}\). The total iron required is calculated and administered in hospital setting in 3-5 visits, hence full dose.
administration is confirmed and is convenient to the patient because of limited number of visits. Besides, the goal of iron therapy i.e. to supply sufficient iron to correct hemoglobin deficit as well as to replenish stores is achieved without the need for further iron therapy throughout pregnancy and probably after.

Comparing it with iron sorbitol, which is painful and causes staining, the absorption is unreliable and more than 30% is excreted from the kidneys in 4 hours. Within this time only a small amount is stored in liver and RE cells while a relatively high fraction of iron complex deposits in parenchymal cells of liver, kidney and heart etc. Due to this reason a dose of 1.5 mg/kg cannot be exceeded (compared to 7 mg/kg for iron sucrose). Iron overload can be toxic to cells and can be carcinogenic by inhibiting host defense and providing nutrition to unrestricted tumor cells\textsuperscript{21-24}. As evident from the study, the practice of prescribing iron sorbitol in a dose of 10 ampoules (75 mg/ampoule) with continuing oral iron therapy throughout pregnancy does not fulfill the goal of iron therapy. It is impractical to check the compliance in these patients and the therapy is cumbersome and prolonged. This correlates with the observation that prevalence of anemia has not changed in the past decade in the developing world mainly due to difficulties in prophylaxis\textsuperscript{10}. Another advantage of iron sucrose (Venofer\textsuperscript{®}) is its quick response that would indicate its usage in severe anemia as an alternate to blood transfusion.

The advantage of iron sorbitol over iron sucrose is the low cost of therapy. In an attempt to reduce the cost of iron sucrose by Rs. 1300 1500, its dose for storage was reduced from the recommended 500 mg to 200 mg in this study. It was found that the percentage of patients achieving target hemoglobin of 11 g/dl was 80% in Group A (storage iron 500 mg) and 70% in Group B (storage iron 200 mg). The percentage was significantly higher in both groups than that of group C (Iron sorbitol) where only 28% of patients achieved the target hemoglobin. The cut off value of anemia in pregnancy is 10.5-11 g/dl.

**Conclusion**

Intravenous iron sucrose is safe, more effective and user friendly in the treatment of iron deficiency. It is cost effective when its effectiveness is compared with that of alternate iron therapies and by eliminating the need for blood transfusion especially in severe iron deficiency anemia in pregnancy. By achieving hemoglobin level >10 g/dL at the time of delivery, need for blood transfusion in peripartal period (due to hemorrhage) will also automatically decline\textsuperscript{25}.

**References**