Original Article

Iron Sucrose Versus Oral Iron Therapy in Pregnancy Anemia

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ABSTRACT

Background: Iron deficiency anemia (IDA) is the most common medical problem in pregnancy. Parenteral iron is a useful treatment, although iron dextran use decreased due to anaphylaxis. Iron sucrose is a newer agent that has overcome the shortcomings of iron dextran. **Objective:** The aim of this study was to compare the efficacy and tolerance of intravenous iron sucrose (IVIS) therapy with oral iron (OI) therapy in pregnant women with IDA and to study the factors influencing treatment. **Materials and Methods:** This prospective, randomized clinical trial included pregnant women between 14 and 36 weeks with established IDA who were treated with IVIS or OI (ferrous fumarate). All patients were monitored for laboratory response and adverse effects. Independent sample-*t* test, Chi square test and ANOVA were used for statistical analysis. $P < 0.05$ was considered significant. **Results:** Although hemoglobin increased in both the groups, increase in the reticulocyte count and percentage increase in hemoglobin was significantly higher in the IVIS group than in the OI group (23.62% vs. 14.11%). Serum ferritin was significantly higher in the IVIS group than in the OI group ($P = 0.000$). The IVIS group had no major side-effects. Compliance was good with OI, although 23% had gastrointestinal side-effects. Patient weight, gestation at diagnosis, initial hemoglobin and ferritin levels did not influence the response to treatment. **Conclusion:** IVIS is safe and effective in the treatment of IDA during pregnancy. Iron stores increased better with IVIS compared with OI.

Keywords: Intravenous iron sucrose, iron deficiency anemia, oral iron, pregnancy anemia, serum ferritin

Introduction

Iron deficiency anemia (IDA) is one of the most widespread of all nutritional deficiencies in pregnancy. Estimates from the World Health Organization (WHO) report that from 35% to 75% of pregnant women in developing countries are anemic.[1]

The standard treatment in majority of the institutions is oral iron (OI), with blood transfusion reserved for severe or emergency cases. However, it is unreliable in the treatment of severe anemia. Blood transfusion has its own hazards, including transfusion of wrong blood and deadly infections like HIV, CMV, hepatitis and anaphylaxis. Thus, there is a need for a safe and effective alternative to OI or blood transfusion in the treatment of anemia. Iron dextran, the first parenteral iron used, lost its popularity due to anaphylaxis. Iron sucrose was then discovered as a parenteral iron that could be safe and effective.

This study was undertaken to find out the usefulness of iron sucrose for the treatment of IDA in pregnancy.

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Materials and Methods

The objectives of the study were to compare the efficacy and tolerance of intravenous iron sucrose (IVIS) therapy with OI therapy in pregnant women with IDA and to study the factors influencing treatment.

This prospective randomized clinical trial registered under the Clinical Trial Registry, India, was carried out from July 2008 to September 2010. Ethical committee

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clearance was obtained from the hospital ethical committee. Pregnant women, from 14 to 36 weeks of gestation, with hemoglobin level 6.5–10.9 g/dL and ferritin levels less than 27 ng/dL were enrolled after taking informed consent. This cut-off of serum ferritin was chosen because the lower limit in our laboratory is 27 ng/dL. Women with severe anemia requiring blood transfusion, bronchial asthma and suspected acute infection were excluded from the study. Target hemoglobin for the study was 11 g/dL.

A sample size analysis was done at the initiation of the study. Standard deviation of hemoglobin was estimated to be approximately 1.5 g/dL. Based on a two-tailed α of 0.05, it was determined that 37 patients per group were required to detect a 1 g/dL hemoglobin difference in the outcome variable with a power variable of 80%. On the assumption of an overall rate of loss to follow-up of about 30–35%, 50 subjects per group were enrolled. Block randomization was done to assign patients to either the IVIS or the OI group.

After detailed history and examination, laboratory investigations performed were hemoglobin, packed cell volume (PCV), red cell count, red cell indices, reticulocyte count and peripheral smear. IDA was confirmed by serum iron profile consisting of serum ferritin, serum iron and total iron binding capacity. After 10 days, reticulocyte response was checked while other investigations were repeated after 1 month.

The dose for IVIS was calculated from the following formula:[2]

Dose (mg) = [250 × (target Hb (11 g/dL) − present Hb) +500 mg (for iron stores)]

The calculated dose was rounded up to the nearest multiple of 100 mg. Target hemoglobin in g/dL was set at 11 g/dL based on the WHO definition for anemia in pregnancy. A maximum of 200 mg of iron in 100 mL of IVIS was diluted in 200 mL of isotonic saline solution and administered as slow IV infusion. The remaining doses were given on alternate days. Infusions were given as outpatient basis in labor room with facilities for acute emergency care. Routine OI supplementation was withheld during IVIS treatment, but was restarted after 1 week.

Ferrous fumarate 300 mg with 100 mg of elemental iron was used for oral therapy. Patients were enquired about adverse effects at each visit.

Statistical package for social science (SPPS- 16) was used for statistical compilation and analysis. For statistical analysis of difference between groups, independent sample-*t* test, Chi square test or analysis of covariance were applied when appropriate. Statistical significance was accepted at $P < 0.05$.

Results

Among the 100 enrolled patients, there were six dropouts in the OI group and five dropouts in the IVIS group. Flowchart 1 gives the patient distribution in each group and result of treatment with their side-effects and change in therapy in each group. [Figure 1: Flowchart]

The baseline demographic and clinical characteristics were similar in the two groups, with no significant difference [Table 1]. Only one patient in the OI group had severe anemia (Hb 6.8 g/dl), while the others had moderate anemia in both the groups.

The IVIS group had lower hemoglobin values, red cell indices and lower serum iron profile despite randomization. To overcome this confounding factor of difference in pre-treatment values, percentage increase in these variables was calculated from repeat lab parameters thus taking care of values before giving two different types of treatment [Table 2].

Reticulocyte response was better in the IVIS group as compared with the OI group. Hemoglobin improved in both groups. However, the percentage increase in hemoglobin, PCV and red cell indices after treatment was significantly higher in the IVIS group. The increase in serum ferritin and rate of increase was much higher in the IVIS group as compared with the OI group [Table 3].

Target hemoglobin of 11 g/dL was attained by 66% of the patients in the IVIS group after 1 month of treatment as compared with 61% of patients in the OI group, which was not statistically significant. Highest hemoglobin attained in the IVIS group was 13 g/dL, while in the OI group was 12.2 g/dL after treatment.

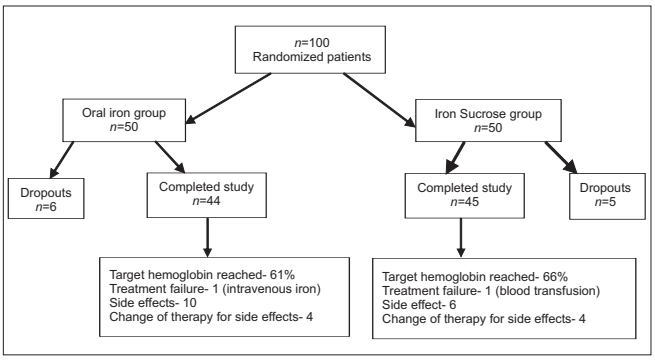

Figure 1: Flowchart showing patient distribution

Table 1: Comparison of demographic characteristics in the two groups

	Oral iron group (*n* = 44)	Intravenous iron group (*n* = 45)	*P*-value*
Age (years)[a]	27 (±2.99) (22–34)	27 (±4.09) (20–35)	0.427[1]
BMI (kg/sq m)[a]	20.5 ± 3.81 (14.9–34.1)	21.6 ± 3.69 (15.2–29.5)	0.148[1]
Mixed diet[b]	41 (93%)	38 (84%)	0.315[2]
Primigravida[b]	30 (68%)	28 (62%)	0.658[2]
Multigravida[b]	14 (32%)	17 (38%)	
Single gestation[b]	43 (98%)	43 (95%)	1.000[2]
Gestational age at inclusion (weeks)[a]	23 ± 6.09 (14–34)	22 ± 6.98 (14–36)	0.852[1]
Second trimester[b]	31	33	0.301[2]
Third trimester[b]	13	12	

*P value <0.05 significant, [1]Independent t-test, [2]Chi square test Values are given as [a]mean (± 2-standard deviation), [b]range or percentage

Table 2: Percentage increase in various parameters after treatment in the two groups

Percentage increase (value%)	Oral iron group (*n* = 44)	Intravenous iron group (*n* = 45)	*P* value*
ΔHb%	14.11 (±10.66)	23.62 (±14.95)	0.001
ΔPCV%	13.36 (±12.56)	20.94 (±13.55)	0.008
ΔMCV%	5.47 (±6.49)	10.21 (±9.60)	0.008
ΔMCH%	7.18 (±9.68)	13.46 (±12.32)	0.009
ΔFerritin%	180.69 (±308.39)	2032.54 (±1974.43)	0.000

*P value <0.05 significant, Independent t-test, Values are given as mean (± 2 standard deviation), (range) Hb: Hemoglobin, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, Ferritin: Serum ferritin

One patient in the OI group with failed response was treated effectively with IVIS. Failure in another patient detected to have hypothyroidism improved only after thyroxin replacement.

There was no influence of body weight, initial hemoglobin and serum ferritin levels on percentage increase in hemoglobin in both groups. Side-effects encountered in the OI group were dyspepsia, constipation and nausea. Four of these with intolerance responded well to IVIS. One patient shifted to OI from IVIS because of giddiness after the first injection. Four patients in the IVIS group required blood transfusion for mild adverse reactions like vomiting, rashes and failure of therapy. IVIS was well tolerated by majority of the patients, with no severe anaphylactic reaction.

Hemoglobin done just prior to delivery showed no statistically significant difference (OI group 11.65 ± 0.91 g/dL vs. IVIS group 11.76 ± 0.80 g/dL). There was no significant difference in placenta weight, birth weight, preterm labor, pre-eclampsia or gestational hypertension between the two groups (P value = 0.121–1.000).

Cost of treatment was significantly higher in the IVIS group as compared with the OI group. Cost of iron sucrose injection is Rs. 490 per 200 mg ampoule and ferrous fumarate is Rs. 1.69 per tablet. The treatment duration was significantly higher in the OI group (mean 12 weeks) as compared with the IVIS group (mean 2 weeks), with a P value of 0.000.

Table 3: Laboratory parameters before and after treatment in the two groups

Parameters	Before treatment			After treatment		
	Oral iron (*n* = 44)	Intravenous iron (*n* = 45)	*P* value	Oral iron (*n* = 44)	Intravenous iron (*n* = 45)	*P* value
Hb (g/dL)	9.75 (±0.83) (6.8–10.9)	9.18 (±0.94) (7–10.5)	0.002	11.06 (±0.63) (9.2–12.2)	11.24 (±0.70) (8.9–13.0)	0.206
PCV (%)	29.38 (±2.46) (20.4–33.4)	28.21 (±2.41) (22–31.5)	0.015	33.07 (±1.86) (28.10–36.00)	33.87 (±2.28) (26.80–38.90)	0.073
MCV (fl)	82.26 (±8.63) (60.4–99.7)	76.02 (±8.79) (60–92.8)	0.001	86.35 (±6.22) (66.70–98.90)	83.08 (±5.21) (72.10–91.80)	0.009
MCH (pg)	27.21 (±3.69) (15.1–33.6)	24.79 (±3.69) (17.9–33.0)	0.003	28.90 (±2.72) (20.90–34.30)	27.76 (±2.29) (22.70–33.60)	0.035
MCHC (g/dL)	32.99 (±1.67) (25–34.8)	32.40 (±1.19) (28.2–34.3)	0.060	33.41 (±1.08) (30.00–35.50)	33.36 (±0.80) (31.30–34.60)	0.800
RBC count (cells/cu mm)	3.61 (±0.37) (2.76–4.42)	3.76 (±0.37) (3.02–4.55)	0.062	3.85 (±0.31) (3.09–4.67)	4.10 (±0.41) (3.35–5.10)	0.002
Retic (%)	2.23 (±0.69) (1.01–3.98)	2.00 (±0.76) (0.99–4.60)	0.148	2.59 (±0.78) (1.2–4.51)	3.06 (±1.01) (1.44–6.10)	0.018
Ferritin (ng/dL)	14.74 (±7.55) (2.1–26.20)	8.60 (±5.17) (2.2–23.0)	0.000	27.33 (±14.96) (14.4–111)	139.93 (±122.13) (20.9–687)	0.000

*P value <0.05 significant, Independent t-test, Values are given as mean (± 2 standard deviation), (range) Hb: Hemoglobin, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, Retic: Reticulocyte count, Ferritin: Serum ferritin

Discussion

In this study, the efficacy, safety and tolerability of IVIS in treating pregnancy IDA was compared with OI therapy. IVIS is safe in pregnancy. It corrects anemia at short duration and replenishes iron stores better than OI. This has been the observation in other studies too.[3-5] Comparison with other studies is difficult because of different cut-offs used for lab parameters. OI preparations used are also different. As the rate of increase in hemoglobin is faster, IVIS is suitable for treatment of IDA with lower hemoglobin in the third trimester. There was a highly significant difference in the ferritin level after treatment between the two groups, with iron reserves restored only in the IVIS group, which has also been observed by Bayoumeu *et al*.[3] Increase in ferritin is not because of direct intravenous injection of iron complex; rather, it is because the IVIS complex releases iron rapidly to endogenous iron binding proteins with no deposition in the parenchymal tissue. It has a half-life of about 6 h.[6] This is an advantage of IVIS over iron dextran or iron gluconate.

Al Momen *et al*., observed that the IVIS group achieved significantly higher hemoglobin level (P value ≤ 0.001) in a shorter period (P value ≤ 0.001).[4] In a study done by Al *et al*., hemoglobin was different for patients in the OI and IVIS groups across time in each individual group as well as at any given point of time. The hemoglobin level was significantly higher in the IVIS group.[5] In the present study, hemoglobin within an individual group was significantly higher across time, with no difference in between both groups at any point of time.

After treatment, the IVIS group maintained hemoglobin with routine supplementation of OI in the present study, unlike in Bayoumeu *et al*.'s study, where no additional oral supplementation was given. Because of the high prevalence of anemia (57.9%) in pregnant women as per the National Family Health Survey-3,[7] oral supplementation even with normal iron stores is essential in India. Unlike in the parenteral iron-treated group, once the anemia is corrected with OI, absorption slows down. This is responsible for the iron stores not being replenished with OI, unlike intravenous iron.

Many Indian studies have used the intramuscular route for parenteral iron and reported side-effects such as pain, staining at injection site and arthralgia.[8,9] IVIS cannot be given intramuscularly and does not have these side-effects.

Anemia was corrected satisfactorily in this study without the use of weight-dependent formula for calculation of iron dose. Therefore, the dose of iron sucrose used was less compared with that reported by Bayoumeu, who also used a weight-dependent formula.[3] Nevertheless, the target hemoglobin was reached. This questions whether it is really necessary to give a higher dose as calculated by weight. Parenteral iron uses calculated dose depending on the degree of deficiency, unlike OI, which has a static dose.

Various factors that influence the response to treatment of anemia were also studied. In the present study, it was seen that percentage increase in hemoglobin after 1 month of treatment was significantly related to initial hemoglobin value in both the groups. Carretti *et al*., observed that rise in hemoglobin was inversely correlated with initial hemoglobin value, and significantly larger proportions of high hemoglobin responses were observed after the 28th week of gestation as compared with the second trimester.[10] This may be due to physiological hemodilution and blunted erythropoietin response of second trimester.[10] There was no direct correlation of increase in hemoglobin with period of gestation in each individual group. But, percentage increase in hemoglobin was significantly higher in the IVIS group than in the OI group in the third trimester. Thus, lower the initial value of hemoglobin in a late trimester, it is advisable to treat with IVIS.

Gastrointestinal side-effects were about 23% in the OI group, while the reported incidence varied from negligible to 31% in other studies.[3-5] Mild adverse events noted in the IVIS group were vomiting, rashes and giddiness following first dose of iron sucrose. Other studies reported unpleasant taste and fever, which were not observed in the present study.[3,4] Because there were no serious adverse drug reactions and no episodes of anaphylaxis, we feel that it is safe for anemia in pregnancy.

Iron sucrose is costlier than OI and requires a hospital setting for administration.

The limitations of this study were that although IVIS increased serum ferritin significantly, patients were not followed-up in the post-natal period to determine whether hemoglobin 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.

We conclude that OI increases hemoglobin comparably with IVIS, but does not replenish iron stores as much as IVIS. This is significant in our country where women may become anemic again during lactation, especially when their iron stores have not been corrected. However, OI is cheaper and is easy to take.

As no major adverse effects were noted with iron sucrose,

it is a safe option with good efficacy for the treatment of IDA with a narrow side-effect profile.

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