Indian J Hematol Blood Transfus (Apr-June 2014) 30(2):120–125
DOI 10.1007/s12288-012-0224-1

ORIGINAL ARTICLE

A Randomised Controlled Trial to Compare Intravenous Iron Sucrose and Oral Iron in Treatment of Iron Deficiency Anemia in Pregnancy

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Received: 21 March 2012 / Accepted: 12 December 2012 / Published online: 10 January 2013

Abstract The aim of this study was to compare the efficacy and safety of intravenous iron sucrose with oral iron therapy in pregnant patients with anemia. The primary outcome of the study was increase in haemoglobin on day 7, 14 & 28 and rise of serum ferritin over 28 days. The study population consisted of 100 patients with singleton pregnancy between 24 and 34 weeks, hemoglobin levels between 7.0–9.0 gm/dL and serum ferritin levels less than 15 ng/mL. The participants in the oral group were given daily 180 mg elemental iron in three divided oral doses for 4 weeks. Total calculated dose of iron sucrose with a target hemoglobin of 11 gm %, was given in 200 mg dose on alternate days. Mean haemoglobin rise was 0.58 gm/dL in the IV group as compared to 0.23 gm/dL in the oral group on day 14 and 1.9 gm/dL in the IV group & 1.3 gm/dL in the oral group on day 28, ($p < 0.05$). In the IV group, 76% of the subjects achieved haemoglobin levels of $\geq$11 gm% at the time of delivery, as compared to only 54% of the subjects in the oral group who achieved these levels. Serum ferritin value was significantly higher in the IV group, 37.45 ± 5.73 ng/mL as compared to 13.96 ± 1.88 ng/mL in the oral group at 4th week ($p < 0.001$). There was no major side effect in the IV group. 36% subjects in the oral group developed gastrointestinal side effects & 10% of the subjects were non compliant. The rate of hemoglobin rise is faster with intravenous iron sucrose therapy as compared to oral iron therapy which can be beneficial in pregnant women presenting with anemia at a later period of gestation. Intravenous iron sucrose is very well tolerated during pregnancy.

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Keywords Iron deficiency · Pregnancy · Hemoglobin rise · Iron sucrose · Cord blood hemoglobin

Introduction

Anemia is the most common medical disorder in pregnancy and has a varied incidence, etiology and degree of severity in different populations, being more common in the developing countries [1]. In India, more than 90 % of anemia cases are estimated to be due to iron deficiency, because of largely vegetarian dietary patterns [2]. Diet alone can't fulfil the increased demand of iron during latter stages of pregnancy. Moreover, most women begin their pregnancy with little or no iron reserve, which is further compounded by repeated & closely spaced pregnancies and prolonged periods of lactation.

Oral iron is the treatment of choice for anemia because it uses body's normal mechanism. However, it takes 4–6 weeks for oral iron to raise the hemoglobin & takes another 2–3 months to build up the stores [3]. Therefore, many patients fail to comply with such prolonged oral iron replacement therapy. Parenteral iron is recommended under following situations : inability to tolerate the side effects of orally administered iron, peptic ulcer & non compliance with oral regimens [4]. It is generally accepted that parenteral iron therapy induces a similar erythropoietic response than oral iron replacement. However, parenteral iron therapy ensures that patient gets complete dose of iron as required, replenish iron stores and overcomes the problem of compliance. Pain on injection, staining of the skin, unpredictable delivery & absorption make the intramuscular route undesirable. The use of older iron preparations, like iron dextran is associated with allergic reactions & fatal anaphylaxis. Since its introduction in the

European market in 1950, iron sucrose has compiled a consistent safety record [5].

Iron Sucrose is rapidly distributed to the bone marrow for erythropoiesis and the reticuloendothelial system of liver & spleen for storage of iron. The biggest advantage of Iron Sucrose is that, unlike the iron dextrans, it is not necessary to administer a test dose during first time administration [5].

The aim of this study was to compare the efficacy and safety of intravenous iron sucrose with oral iron therapy in pregnant patients with anemia.

Materials and methods

This prospective randomised controlled trial was carried out from October 2009–December 2010 in department of Obstetrics & Gynaecology, Maulana Azad Medical College & Lok Nayak hospital, a tertiary care teaching hospital. The study population consisted of 100 patients fulfilling the inclusion criteria of singleton pregnancy between 24 and 34 weeks, haemoglobin concentration between 7.0 and 9.0 gm/dL and serum ferritin levels less than 15 ng/mL. Exclusion criteria were known hypersensitivity to iron, thalassemia, clinical evidence of inflammation or auto immune disease. The study protocol was approved by the instituitional ethics committee. Written informed consent was obtained from each subject.

The primary outcome of the study was increase in haemoglobin & ferritin levels over 4 weeks. Secondary outcomes included reticulocyte count rise, mean haemoglobin at the time of delivery, side effects & perinatal outcome in each group.

All the women in the study were screened for thalassemia. Each woman was given a course of antihelminthic treatment with 100 mg mebendazole twice daily for 3 days due to high prevalence of worm infestation reported in the same institution [6]. At enrolment, around 5 mL venous blood was taken from each of the patients and divided into 2 aliquots. 3 mL of blood was transferred to an evacuated tube containing EDTA solution for the estimation of hemoglobin & reticulocyte count. The other part of the sample (2 mL) was used for the estimation of serum ferritin value. It was centrifuged at 2000 rpm for 10 min in a refrigerated centrifuge. The separated serum was then transferred to microcentrifuge tubes, and the aliquots were stored at −80 °C for later measurement of serum ferritin. Hemoglobin was obtained by automated counters & serum Ferritin was measured by using enzyme linked immunosorbent assays with pathozyme ferritin kits.

The subjects were assigned to two groups of 50 each by randomization table. Sample size was calculated as 35 subjects in each group from α risk of 5 %, with a power of 90.0 % on the basis of published data [7]. We included 50 subjects in each group in the oral group (group A) & in the intravenous group (group B). The opaque envelope, numbered using randomization table was opened to allocate the patient to either group. Blinding could not be possible due to different technique of drug administration.

Group A

The participants in the oral group were given daily oral doses of 180 mg elemental iron in divided dose. Each 200 mg of ferrous sulphate tablet available in our hospital supply contained 60 mg elemental iron & was given thrice a day on an outpatient basis for 4 weeks. The compliance to medication was checked by asking the women to bring back the empty blister packs and asking them about the colour of their stools at each antenatal visit.

Group B

The women in the intravenous group received total dose of Iron Sucrose calculated as:-

$$\text{Body weight} \times (\text{Target Hb} - \text{Actual Hb in gm/dL}) \times 2.4 + 500\,\text{mg (In Kg)}\ (7, 8, 9,)$$

Target hemoglobin was taken as 11 gm % & 500 mg is for the restoration of iron stores. The total dose was rounded off to the multiples of 100 mg. Patients received divided doses of 200 mg each on alternate days with maximum of 600 mg per week as recommended by French Drug Agency [5]. Patient was advised a short hospital admission for the administration of the drug. Dose of 200 mg was diluted in 200 mL of normal saline & administered as intravenous infusion. When iron sucrose was given for the first time, the first 10–15 mL was given over 15 min (50 mL/hr). If no adverse reaction was seen, the rate of administration was slowly increased to 100 mL/hr or approximately 14 mg/min, not exceeding 20 mg/min. The patient was monitored for any evidence of reaction. Appropriate precautions were taken in the eventuality of any anaphylactic reaction. All the major or minor side effects were noted in both the groups.

All the women were followed up routinely in the antenatal clinic till delivery. Rate of improvement in both the groups was measured by comparing the changes with the baseline values. The early response to the treatment was assessed by measuring the reticulocyte count in both the groups on day 7 & 14. Hemoglobin was repeated on day 7, 14, 28 & at the time of delivery. Serum ferritin was measured on day 28. At the time of delivery, 2 mL of maternal blood sample was withdrawn to measure hemoglobin.

The mode of delivery, gestation at delivery, and the birth weight of the newborn were noted in all cases. Cord

Table 1 Baseline characteristics of study population

Characteristic	IV iron group ($n = 50$)	Oral iron group ($n = 50$)	p value
Age (yr)	25.2 ± 2.33	25.2 ± 2.28	0.93 (NS)
Multiparity	41(82 %)	40 (80 %)	1.00 (NS)
Literacy less than 10th grade	46 (92 %)	47 (94 %)	1.00 (NS)
Gestational age at inclusion (wk)	30.5 ± 2.16	29.2 ± 2.42	0.07 (NS)
Hemoglobin (g/dL)	7.81 ± 0.43	7.88 ± 0.42	0.34 (NS)
Reticulocyte count (%)	1.7 ± 0.24	1.7 ± 0.22	0.86 (NS)
Serum ferritin (ng/mL)	10.7 ± 1.47	10.4 ± 1.89	0.37 (NS)

blood sample was taken at the time of delivery for estimation of hemoglobin & ferritin of the newborn.

Data was entered in the predesigned proforma. Entire data was expressed by the descriptive statistics i.e. mean and standard deviation. For quantitative data, difference between means was measured by student's unpaired t test. For qualitative data, Chi square test was applied, wherever applicable. If p value was less than 0.05, the difference was considered to be statistically significant.

Results

100 women participated in the study with 50 women in each group. None of the patients lost to follow up or excluded during the study. Both the groups were comparable in terms of sociodemographic, clinical & baseline hematological parameters, as shown in Table 1.

The mean haemoglobin values during each follow up have been shown in Table 2. On day 14, mean haemoglobin rise was 0.58 gm/dL in the IV group as compared to 0.23 gm/dL in the oral group (p 0.004).The mean rise in hemoglobin on day 28 from baseline was 1.9 gm/dL in the IV group & 1.3 gm/dL in the oral group (p value < 0.001). The mean rise in haemoglobin levels from baseline to the time of delivery was 3.53 gm/dL in the IV group & 2.43 gm/dL in the oral group (p value < 0.001).

In the IV group, 76 % of the subjects achieved haemoglobin levels of ≥11 gm % at the time of delivery, as compared to only 54 % of the subjects in the oral group achieved these levels (p value 0.003).

Mean dose of intravenous iron sucrose given was 932.4 ± 130.5 mg, ranging from 737.6 to 1095.2 mg. Mean duration required for completing IV iron dose was 8.7 ± 1.2 days, ranging from 7 to 11 days. Each woman in the oral group received 5040 mg of elemental iron over 28 days.

Reticulocyte count was compared from the baseline values with values on day 7 &14. A significant higher response was noted on both day 7 &14 in the IV group. On day 7, reticulocyte count rose from 1.71 ± 0.22 % to 0.36 ± 0.69 % in the oral group & in the IV group from 1.71 ± 0.24 % to 4.47 ± 0.38 %, the difference being very significant between the two groups (p value < 0.001). A significant difference was also noted on day 14 between the two groups, mean reticulocyte count being 4.20 ± 0.39 % in the IV group & 3.53 ± 0.71 % in the oral group (p value < 0.001).

There was no major side effect in the IV group & the incidence of minor side effects was 10 %, which were mainly related to the administration of the injection. One patient experienced pain at the site of injection during administration of the first dose & didn't complaint during subsequent dosing. Two patients developed superficial redness & swelling at the site of administration, 24 h after the administration of 2nd dose in one patient & 12 h after 3rd dose in the second patient. One patient developed low grade fever of 99 °F two hours after administration of the 1st dose which resolved on taking antipyretics & didn't occur with further doses. 36 % subjects in the oral group developed gastrointestinal side effects (Table 3). Most of the symptoms resolved with further doses & none discontinued the treatment. 10 % of the subjects in the oral group didn't adhere to the thrice daily regimen of oral iron regularly as evidenced

Table 2 Increase in hemoglobin levels in oral and I/V group

Hemoglobin (gm/dL)	Baseline (Mean ± SD)	1 week (Mean ± SD)	2 week (Mean ± SD)	4 week (Mean ± SD)	Delivery (Mean ± SD)
IV GROUP	7.81 ± 0.43	7.82 ± 0.42	8.39 ± 0.43	9.80 ± 0.46	11.50 ± 0.78
Oral group	7.88 ± 0.42	7.89 ± 0.45	8.11 ± 0.45	9.18 ± 0.55	10.84 ± 1.12
P value	0.34	0.42	0.002	<0.0001	<0.0001

Serum ferritin value was significantly higher in the IV group, 37.45 ± 5.73 ng/mL as compared to 13.96 ± 1.88 ng/mL in the oral group at 4th week ($p < 0.001$)

Table 3 Side effects in oral and I/V group

Side effects	Oral iron group ($n = 50$)	IV iron group ($n = 50$)
Nausea/vomiting	1	–
Epigastric discomfort	10	–
Constipation	9	–
Diarrhea	1	–
Metallic taste	2	–
Anaphylactic reactions	–	–
Hypotension	–	–
Fever	–	1
Itching all over body	–	1
Pain at the site of injection	–	1
Thromboplebitis	–	2

on the return of blister pack at subsequent follow up visit. Reticulocyte count also showed a subnormal response in these patients. These subjects had persistent complaints of flatulence & constipation which may be responsible for their non compliance. However, none of these patients require blood transfusion in the antenatl period. Every subject in the intravenous group was compliant with the therapy.

One patient in the IV group had atonic postpartum haemorrhage with blood loss of 700 cc. She had hemoglobin of 12.2 gm % at the time of delivery & thus didn't require blood transfusion. None of the patients in the oral iron group had postpartum haemorrhage.

Fetal consequences of anemia are an increased risk of growth retardation, prematurity & infection. Since, most of the subjects in the study were cured of anemia, 90 % of the babies born to mothers in the IV group & 88 % of the babies born to mothers in the oral group were term. In the I/V group, mean gestational age was 38.48 ± 1.36 weeks & 38.31 ± 1.47 weeks in the oral group, difference being not significant. The average birth weight was comparable in both the groups, being 2607 ± 253.28 gm in the I/V group & 2568 ± 244.19 gm in the oral group. The mean cord blood hemoglobin value were normal in both the groups at birth, being 15.8 ± 0.7 gm/dL in the I/V group & 15.6 ± 0.7 gm/dL, the difference being statistically not significant (p value = 0.106). The mean serum ferritin values of the newborns were in the normal range as compared to the reference values (25–200 ng/mL) & were comparable in both the groups, being 155.77 ± 46.34 ng/mL in the I/V group & 147.68 ± 39.05 ng/mL in the oral group, the difference being statistically not significant, two tailed p value = 0.347.

Discussion

Iron deficiency anemia during pregnancy deserves special attention because of its potential consequences.

The hemoglobin rise on day seven was comparable in both the groups. A rise in hemoglobin of 0.58 gm/dL & a rise of 1.99 gm/dL was observed on day 14 & 28 respectively, in the present study. Ragip et al. [8] observed a rise of 0.6 gm/dL on day 14 & a rise of 1.2 gm/dL on day 28 in the I/V group. The earlier response in the iron sucrose group can be explained by the fact that iron sucrose consists of polynuclear iron complex analogous to ferritin, with apoferritin component replaced by sucrose which is well tolerated & least antigenic. After the intravenous administration of iron sucrose, it is taken up mainly in the reticulo-endothelial system where it is rapidly dissociated into iron & sucrose.

Four patients in the IV group & three in the oral group presented at 32 weeks period of gestation with anemia. Mean rise of 1.9 gm/dL in the IV group over 4 weeks virtually cured anemia by the time patients achieved term gestation. Out of three patients in the oral group, two achieved a mean rise of 1.3 gm % over 4 weeks whereas one of them was non compliant & failed to achieve the target hemoglobin. Thus, earlier response achieved by Iron Sucrose can be utilised in the patients who present at a later period of gestation with anemia, when oral iron therapy may not be helpful. This can avoid the need of blood transfusion in the antenatal period.

Bayoumeu et al. [7] didn't observe any significant difference in rise in hemoglobin in the oral or I/V group at any point during treatment i.e. on day 8, 15, 21, 30 & at the time of delivery . This difference may be because they administered the total iron sucrose over 21 days as compared to a mean of 8.7 days in our study, which must have taken longer time to reach the target hemoglobin & secondly they recruited smaller number of subjects, where confounding factors such as dietary habits, absorption of iron may be represented variably.

76.5 % of the subjects achieved hemoglobin levels of ≥11 gm/dL in the IV group as compared to 54.6 % in the oral group. None of the patient in the study received blood transfusion. In the study done by Ragip et al. [8] 95.6 % reached the target hemoglobin of 11 gm/dL in the IV group & 62.2 % in the oral iron group. The higher percentage of

patients achieving target levels in the latter study can be explained by the fact that the mean hemoglobin value at the time of inclusion in the latter study was 9.9 gm/dL as compared to 7.8 gm/dL in our study.

A Cochrane review also found that intravenous iron treatments produce a better hematological response than oral iron & a faster replenishment of body iron stores [9]. A significantly greater increase in serum ferritin with parenteral administration of iron than with oral administration is important for correction of anemia in pregnancy, especially in patients with malnutrition & repeated pregnancies at short intervals. The adequate iron stores are also important during lactation & for future pregnancies.

Serum ferritin has been regarded as the gold standard in establishing iron deficiency, with generally accepted cut off level of <15 ng/mL, below which iron stores are considered to be depleted [10]. Both the groups displayed substantial reduction in serum ferritin concentration, indicating depletion of iron stores. Ragip et al. showed that the rise in serum ferritin at day 28 was 5 ± 2.2 to 11 ± 11 μg/L (μg/L = ng/mL) in the oral group as compared to the I/V group where serum ferritin rose from 4.1 ± 2.5 to 28 ± 26 μg/L at 4th week, p value < 0.001. Bayoumeu et al. [7] also noticed an extremely significant difference in the ferritin levels on day 30 between the two groups with iron reserves restored only in the I/V group (p value < 0.0001) & a significant difference was also observed at the time of delivery between the two groups, p value 0.01. In the study by al-Momen et al. [11], it was found that serum ferritin rose from 11.9 ± 5.0 to 95.5 ± 38.1 μg/L over 6.9 ± 1.8 weeks in the I/V sucrose group & from 12.0 ± 5.3 to 52.4 ± 3.1 μg/L over 14.9 ± 3.1 weeks in the oral group.

Reticulocyte count is a measure of response to the treatment of anemia & is the first parameter to rise after the start of treatment. The higher value on day 7 & 14 in the IV group shows that the response starts earlier with intravenous iron sucrose.

Oral iron therapy has an erratic absorption & is associated with poor compliance. Furthermore, several effects of pregnancy—nausea, vomiting, motility disorder with reflux esophagitis, indigestion, tendency to hemorrhoids disease make the tolerance to oral iron even more difficult. Most of the side effects in the oral group were gastrointestinal, which resolved with further doses. Though none discontinued the treatment, 10 % non compliance was noted in the oral group. However, Iron Sucrose was well tolerated with no major adverse effects in our study. Most of the symptoms were mild & no patient discontinued the medication.

The biggest advantage of iron sucrose is that unlike iron dextran, it doesn't require a test dose before administration. Anaphylactic reactions are virtually unknown with Iron Sucrose, the reported incidence being 0.002 % [12].

There was no significant difference in the mean birth weight, period of gestation, mean hemoglobin values & mean serum ferritin levels of the newborns in both the groups, as most of the patients were cured of anemia at the time of delivery.

One patient in the IV group who had postpartum haemorrhage had a hemoglobin of 12.2 gm % at the time of delivery. Thus, blood transfusion was not needed in the patient. This clearly implies that by achieving target hemoglobin levels at the time of delivery, need for blood transfusion in the peripartum period due to haemorrhage automatically declines.

The smaller sample size was not enough to establish the safety of intravenous administration of iron especially with regard to the infrequent serious side effects. Larger trials are needed to address other important issues like implications of oxidative stress caused by iron sucrose and its long term effects to verify an advantage of intravenous iron sucrose compared with oral treatment in the management of iron deficiency anemia in pregnancy.

Conclusion

The rate of hemoglobin rise is faster with intravenous iron sucrose therapy as compared to oral iron therapy. Iron sucrose achieves hemoglobin rise of 0.58 gm/dL as compared to a rise of 0.23 gm/dL with oral iron treatment at the end of 2 weeks. The faster rise of hemoglobin with iron sucorse can be utilized in the patients presenting with anemia at a later period of gestation, when oral iron might not help. Target level of 11 gm/dL was achieved by 76.5 % of women treated with iron sucrose in contrast to 54.6 % with oral iron therapy. This can help in reducing the risk of blood transfusions during the peripartum period. Iron sucrose is associated with minimal side effects & is very well tolerated in pregnancy. Oral iron therapy is associated with gastrointestinal side effects, which can lead to non compliance & hence worsening of anemia.

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