

Is it safe to use intravenous iron sucrose during pregnancy? A randomized controlled trial

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ABSTRACT

Background: To compare the efficacy and safety of intravenous iron sucrose to oral iron in the treatment of iron deficiency anemia in pregnancy.

Methods: In this randomized trial 200 pregnant women with hemoglobin between 7g/dl and 9g/dl and serum ferritin <15 ng/ml received either iron sucrose or oral iron sulphate. The iron sucrose dose was calculated from the following formula: weight (kg) x (110 g/l – actual hemoglobin (g/l) x 0.24 + 500mg. Treatment efficacy was assessed by clinical and laboratory response on 2nd week, 4th week of therapy, after that 4th weekly till delivery. Statistical analysis was done with paired and independent samples “t” test applied. Hemoglobin measurements were analyzed by repeated- measures of analysis of variance with Huynh and Feldt corrections. Serum ferritin measurement across the time within each group was analyzed by two sample test with equal variance .Adverse drug reactions, fetal weight, blood transfusions were also recorded.

Results: The significant rise in hemoglobin from 8.0 ± 0.79 gm/dl to 10.80 ± 0.61 gm/dl in intravenous group as compared to oral iron group from 8.19 ± 0.60 gm/dl to 9.86 ± 0.61 gm/dl was seen at 4th week of treatment ($P = 0.000$). After 2 week of treatment rise in serum ferritin values were higher in intravenous group from 6.25 ± 1.05 ng/ml; to 155.33 ± 57.4 ng/ml and in oral group from 5.71 ± 1.71 ng/ml to 20.8 ± 9.5 ng/ml ($p=.000$). No serious adverse drug reactions were observed in intravenous group.

Conclusion: Iron sucrose is safe to use during pregnancy. It raises hemoglobin and restores iron stores faster than oral iron.

Keywords: Anemia, Iron deficiency anemia, Intravenous iron therapy, Iron sucrose, Serum ferritin

INTRODUCTION

Iron deficiency anemia is the most common nutritional disorder in the world, affecting approximately 25% of the world's population.¹ The prevalence of iron deficiency anemia in pregnant women is estimated to be 35%-75% (average 56%) in developing countries where as in industrialized countries the average prevalence is 18%.^{2,3} Anemia during pregnancy has been shown to be associated with two fold risk of preterm delivery⁴ and three-fold risk for low birth-weight as well as maternal

mortality.⁵ The World Health Organization (WHO) estimates that anemia contributed to approximately 20% of the 515,000 maternal deaths worldwide in 1995.⁶

According to recent studies, the prevalence of iron deficiency anemia in first trimester ranges from 3.5% - 7.4% and increases to 15.6%-55 % in third trimester.⁷ With adequate iron stores, daily iron requirement increases from an average of 2mg-3 mg /day in early trimester to 6mg-8mg /day in the last trimester which is explained by hemodilution phenomenon.⁸

Oral iron is the treatment of choice because of its effectiveness, safety and low cost. Parenteral iron is reserved for those in whom oral treatment fails due side effects, noncompliance, decreased absorption like ulcerative colitis and last trimester of pregnancy when rapid correction of anemia is needed.

As compared with oral iron, IM iron dextran injections are painful with risk of skin staining. However, intravenous iron dextran induces similar or slightly more rapid erythropoietic response than oral iron.⁹ The advantage of IM iron dextran is that, it can be administered in primary care after test dose, although facilities for resuscitation should be available as there is a small risk of allergic and anaphylaxis reaction.

Iron sucrose is a complex of polynuclear iron III – hydroxide in sucrose for intravenous use. The polynuclear iron III – hydroxide cores are superficially surrounded by a large number of noncovalently bound sucrose molecules resulting in a complex with a molecular weight of approximately 60000 Daltons. The Iron in the polynuclear cores is bound in a similar structure to that of physiological condition. Its i.v. route makes availability of elemental iron for incorporation at the pro-erythroblast stage and hence it can provide quick rise in Hb within 5 to 7 days. The short half life of 5-6 hrs is responsible for rapid erythropoiesis as compared to iron dextran; which has serum half life of 3-4 days.¹⁰ Rate of iron delivery is a major factor in the regulation of marrow proliferation¹¹ so it produces a more rapid increase in hemoglobin concentration than oral iron and iron dextran.¹² It is administered without a test dose¹³ and have lower incidence of allergic reactions. Death from anaphylactic reactions has not been reported till date with its use.¹⁴

Iron III carboxymaltose and Iron III isomaltose are new intravenous iron preparations which have advantage of giving large amount in single dose but data's are not available regarding their use in pregnancy.

Few studies¹⁵⁻¹⁹ have compared efficacy and safety of intravenous iron sucrose with oral iron during pregnancy. A recent Cochrane review²⁰ on treatments for iron deficiency in anemia highlighted the need for good quality randomized controlled trials in this setting, in particular to assess clinical outcomes and adverse events. This study was conducted due to lack of quality trials regarding its safety and efficacy.

METHODS

This study was carried out in the Department of Obstetrics and Hematology, Postgraduate Institute of Medical Education and Research Chandigarh during year 2006 to 2008 after clearance from ethical committee. All pregnant women attending antenatal clinic were screened for anemia between 20-34 weeks of gestation. Screening was done in laboratory attached to the clinic. Iron deficiency anemia was diagnosed on the basis of

automated red cell counts, peripheral blood smear, serum ferritin level and serum iron parameters. Hb electrophoresis and HbA₂ quantitation was done when it was indicated, to exclude beta thalassemia trait. Two hundred women were included in the study who fulfill the inclusion criteria. Eligible criteria included were: hemoglobin level between 7-9g/dl, singleton live pregnancy, gestation age 20-34 weeks, microcytic hypochromic anemia, serum ferritin level < 15ng/ml.

Exclusion criteria included anemia other than iron deficiency, history of hematological disease, blood transfusion during current pregnancy, medical disorders, chronic blood loss, placenta previa. All eligible women were invited to gave informed consent were consecutively enrolled. A detailed history, physical and obstetric examination was done. All eligible women were randomly assigned to either intravenous or oral iron treatment. Opaque envelopes were consecutively numbered by means of a computer - generated randomization table. As each patient gave consent for the study, the next envelope was opened to assign the patients to either of the 2 groups.

Group A: Intravenous therapy.

Group B: Oral iron therapy.

Group A received intravenous iron sucrose. Dose was calculated by the following formula.

$$W \times (\text{target hemoglobin} - \text{Actual hemoglobin}) \times 0.24 + 500 \text{ mg}$$

Total dose rounded up to the nearest multiple of 100 mg.

W = Weight taken was pre-pregnancy weight or at the time of first visit.

Target hemoglobin-11g/L. Actual hemoglobin was the patient hemoglobin at the time of inclusion in the study.

Maximum dose administered in each infusion was 200 mg on alternate day. Women were kept in day care ward during and few hours after transfusion. Ten ml iron sucrose was diluted in 100 ml of 0.9% sodium chloride, immediately prior to infusion and infused over 30-45 minutes. Test dose was not given.

Blood pressure was monitored before, during and after each infusion. All adverse events after each infusion were identified by physical examination and direct enquiry of each patient using standard forms encoded for adverse effects. Day 1 was the first day of intravenous therapy. Treatment was completed after administration of calculated dose. No further additional oral iron therapy was given in this group.

Group B received 100 mg elemental iron three times a day throughout pregnancy. Patients were advised to take

on an empty stomach, 2 hours before or after their meals and to record any side effects.

Both groups received 0.5mg folic acid per day.

In case of any adverse effects or intolerance in either of the groups, further treatment was given as per discretion of concerned physician.

Monitoring and Follow-up

Follow up was done according to our hospital protocol. Laboratory evaluation was performed at the time of inclusion in the study, Day 14 and Day 28 and then 4 weekly till delivery. Initial evaluation included; automated complete blood cell count including MCV, MCH, MCHC, and reticulocyte count, peripheral blood smear, iron studies. Subsequently complete blood count, reticulocyte count, iron studies were done at follow up visits. Two ml of blood sample was taken in EDTA for complete hemogram. For iron studies overnight fasting blood samples were collected. Five to 6 ml blood in iron free tube was taken and serum was separated and stored for iron studies

Complete blood counts were measured by AutoAnalyzer; serum iron- binding capacity and serum ferritin were measured by chromogen assay, ferritin levels were determined by immunochemiluminescence.

Primary outcome was hemoglobin on day 14 and 28 after delivery, increase in reticulocyte count, increase in serum ferritin and sides effects and complications. Secondary outcome were percentage of patients who achieved desired hemoglobin (11g/dl) throughout pregnancy, pregnancy outcome, birth weight of baby and need of blood transfusion.

Statistical analysis

Using SPSS software on computer, paired and independent samples “t” test was applied Hemoglobin measurements were analyzed by repeated- measures of analysis of variance (Levene’s test) with Huynh and Feldt corrections. Serum ferritin measurement across the time within each group was analyzed by two sample test with equal variance and multivariate tests including Pillai’s trace, Wilks’lambda, Hotling’s trace and Roy’s largest root were applied. All significance tests were 2 –tailed, with an alpha level of 0.05.

A Sample size calculation: A sample size analysis was performed before initiation of the study. The proposed study is a two arm repeated measure (base-line, 2nd week, 4th week and 8th week) and therefore to see if the changes in measures from base-line to post intervention is statistically significant, the required sample size is calculated based on following formula.

$$N_t = \frac{\{2(Z_{\alpha} + Z_{\beta})^2\} \{1 + (n-1)\rho\} \sigma_d^2}{[\mu_{dc} - \mu_{dt}]^2}$$
, where ‘ α ’ the two sided level of significance is taken to be 5% and power of the study (β) is taken as 90%. It is assumed that mean (μ_{dc}) of difference between base-line and second (n) follow-up in control is 1.5 and mean (μ_{dt}) of differences between base-line and second follow-up in treated group is 2.0. The common variance (σ_d^2) of differences is assumed to be 1 and correlation (ρ) between base-line and follow-up measures is taken as 0.3. The ratio of cases to control is set to be one and accordingly the sample size in each group is worked out to 89.

RESULTS

Two hundred women were included in the study. At the end of study, we had complete data for 198 patients (100 patients in intravenous group and 98 patients in oral iron group). Two patients dropped out from oral group. One patient complained of itching after intake of oral iron sulphate and another had epigastric pain. At 8th week all patients were delivered except 7 patients from I.V group and seventeen from oral group were left for follow up. Samples of 2 patients for serum ferritin and two for complete hemogram was not available at 8th week from oral group and I.V group respectively.

All the patients in Group A received calculated total dose. The median dose was 800mg (range 600-1000 mg).

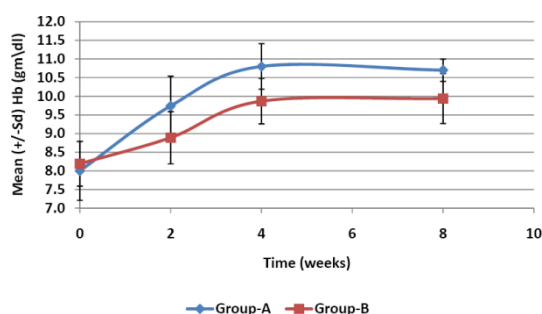
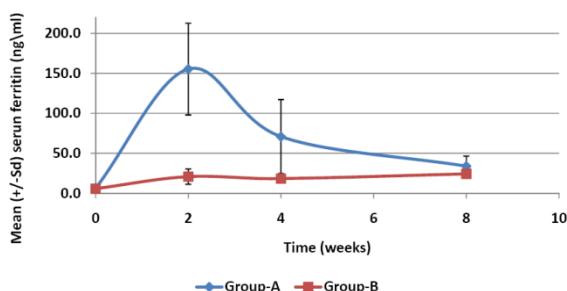
Demographic and clinical characteristics were similar in 2 groups (Table 1). Pregnancy related complications were comparable in both groups. One patient had thrombocytopenia, (2) Gestational hypertension and (2) had cholestasis of pregnancy in each group. Gestational hypertension had developed near term. One patients from oral group received platelet transfusion prior to cesarean section however one with thrombocytopenia in intravenous group had adequate platelet count to undergo vaginal delivery. None of the patients received blood transfusion in both the groups.

Notably there were significant differences in the hemoglobin levels at each measurement in both the groups shown in Fig.1. The rise in hemoglobin at subsequent week as compared to baseline was 1.7 ± 0.92 gm/dl at second week, 2.80 ± 1.03 gm/dl at 4th week and 2.46 ± 1.09 gm/dl at 8th week in intravenous group which was 0.71 ± 0.40 gm/dl at second week, 1.68 ± 0.86 gm/dl at 4th week, 1.84 ± 0.77 gm/dl at 8th week in oral group. P value was 0.000 at second and 4th week. At 8th week rise in hemoglobin was not significant (P=0.163) as it may be due to very small sample size.

The rise in serum ferritin was 155.33 ± 57.4 ng/ml compared with 20.8 ± 9.5 ng/ml at second week (p=0.000) and 70.85 ± 46.25 ng/ml compared with 18.34 ± 3.15 ng/ml at the fourth week (p=0.000) and at 8th week 33.85 ± 12.7 ng/ml compared with 24.2 ± 4.6 ng/ml (p= 0.016) in intravenous and oral groups, respectively (Figure 2).

Table 1: Baseline parameters.

Parameter	Group A (A = 100)	Group B (n=98)	P
Age (yrs)	25.53 ± 2.99	25.23 ± 3.42	0.518
Weight (kg)	53.66 ± 5.86	52.29 ± 5.42	0.083
Nulliparity	65%	73.4%	0.196
Gestation at inclusion (weeks)	29.68 ± 1.25	29.19 ± 1.56	0.017
Baseline Hb (g/dl)	8.0 ± 0.79	8.19 ± 0.66	0.068
Reticulocytes (%)	1.84 ± 0.84	1.61 ± 0.83	0.074
S. Iron (µg /ml)	44.91 ± 27.5	45.38 ± 14.9	0.881
TIBC (µg /ml)	616.95 ± 53.2	604.9 ± 38.59	0.064
Transferrin saturation (%)	8.75 ± 6.6	8.84 ± 3.71	0.90
Serum ferritin (ng/ml)	6.25 ± 2.60	5.71 ± 1.71	0.130

**Figure 1: Comparison of Hb level at different time points in two groups of patients.****Figure 2: Comparison of serum ferritin level at different time points in two groups of patients.**

At 4th week 62% of patients in group A achieved target hemoglobin (≥ 11 g/dl) whereas only 5.0% achieved in group B ($p = 0.00$).

Only 6% of patients from Group A had adverse events. Tachycardia (2), vomiting (2), change in taste (1), giddiness (1) and one developed thrombophlebitis. First

patient had extreme pain due to thrombophlebitis. We had changed this practice of using I.V. cannula which has higher chances for displacement within the vein due to its long length. After that it was infused by scalp vein cannula with no complication of thrombophlebitis. All other symptoms were seen in those patients who accidentally received fast infusion. It has seen that slower the infusion lesser will be the side effects.

Two patients from oral group dropped out due to side effects. Out of 98 patients 18 (18.4%) patients had some side effects. Eight suffered from constipation, 5 complained of epigastric pain, 3 suffered from diarrhea and two experienced nausea. Most of these side effects seen during initial phase of treatment. Incidence of gastrointestinal related side effects were significantly higher in oral therapy ($p = 0.001$). There no significant difference in mode of delivery ($p = 0.055$) and birth weight of baby ($p = 0.100$).

DISCUSSION

The rapid rise in hemoglobin and iron stores is due to different pharmacokinetics of iron sucrose. In case of oral iron therapy, iron absorption is far below the iron requirement of an iron deficient pregnant woman. This is aggravated by the adverse effect of pregnancy on the gastrointestinal tract, which further reduces the bioavailability of iron and slow rise in hemoglobin.

Al- momen et al¹⁵ compared 52 pregnant patients treated with intravenous iron sucrose with 59 received 300 mg of oral iron sulphate 300mg (60mg elemental iron)three times a day and found that intravenous treatment resulted in higher hemoglobin levels 128.5 ± 6.6 versus

111.4 ± 12.4 g/l in the oral iron group ($P < 0.001$) in a shorter period 6.9 ± 1.8 versus 14.9 ± 3.1 weeks in control group ($P \leq 0.001$). In oral group 31.1% patients develop gastrointestinal symptoms and thirty percent had poor compliance. This study deviates from our study as baseline hemoglobin was less and target hemoglobin was 13g/dl. The factor they used in the calculation was 0.3, whereas we used 0.24, in accord with the published data. In their study up to 30% patients developed gastrointestinal trouble whereas compliance with oral treatment was good in our study. Patient's information at inclusion regarding importance of oral iron and need of intravenous iron or blood transfusion as alternative certainly helps for the good compliance.

A trial by Bayoumeu et al¹⁶ involving 50 women observed rise in hemoglobin in i.v. group from 9.6 ± 0.79 to 11.11 ± 1.3 g/dl on day 30 from 9.7 ± 0.5 to 11 ± 1.25 g/dl on day 30 in the oral group which was not significant. Ferritin levels were higher in intravenous group, on day 30 ($P < 0.0001$) and at delivery ($P = 0.01$) which was significant but less than our study. Patient compliance in the oral group was reported excellent. In general we have used the similar method to that used by Bayoumeu et al. However there are differences between our study and those carried out by Bayoumeu et al that explain the different results. The baseline hemoglobin was higher, sample size was small and iron sucrose was given over 21 day in their study.

A study by Ragip et al¹⁷ included 90 iron deficient pregnant patients. The rise in hemoglobin at second week was 0.6gm/dl as compared to 0.2gm/dl ($p=.004$) and, 4th week 1.2gm/dl as compared to 0.6gm/dl ($p=.000$) at in intravenous and oral group respectively. The rise serum ferritin was from 11 ± 11 µg/l compared to 28 ± 26 µg/l in the intravenous group ($P < 0.001$) at the fourth week and 18.1 ± 11 µg/l, compared with 23.7 ± 13.8 µg/l ($P = 0.04$) at birth in oral and intravenous group, respectively. In our study rise in hemoglobin and serum ferritin levels was higher at 2nd and 4th week than their study.

A clinical trial by PK Kochhar et al¹⁸ on 100 anemic antenatal women. Group A(n=50) received 200 mg tablets of ferrous sulphate, each containing 60 mg elemental iron, three times a day for 4 weeks. In group B (n=50), iron sucrose was given in divided doses of 200 mg each on alternate days by slow intravenous infusion. A statistically significant difference in increase of hemoglobin levels (3.1g/dL in group A vs. 5.1 g/dL in group i.v. group; $P=0.002$) and ferritin levels between the two groups on day 30 ($P=0.005$). The adverse effects from iron treatment were mild but more prominent in group A. Neonatal outcome was comparable in the two groups. However, in our study rise in hemoglobin at 28 days was lesser than their study. This study deviates from our study due to less sample size.

Deeba Shafi, et al²⁰ conducted a randomized controlled trial on 200 patients. Oral group received 200 mg ferrous

ascorbate and intravenous group received iron sucrose. The difference in hemoglobin values from baseline in the intravenous group was 1.72 ± 0.484 at 2 weeks, 2.18 ± 0.865 at 4 weeks, 2.89 ± 0.5989 at 6 weeks compared to oral iron, which is 0.5750 ± 0.456 at 2 weeks, 1.39 ± 0.4402 at 4 weeks, and 1.9 ± 0.3020 at 6 weeks. P value was 0.000 which was clinically significant and showed that the hemoglobin levels were increased more in the intravenous group. At 2nd and 4th week rise in hemoglobin was comparable to our study. We have used similar formula to calculate dose of intravenous iron. This study deviates from our study as target hemoglobin was 12gm/dl in their study. The rise in serum ferritin in intravenous group was 48.46 ± 16.66ng/ml at 2nd week and 61.05 ± 19.66ng/ml at 4th week which was 155.33 ± 57.4ng/ml at 2nd week and 70.85 ± 46.25 ng/ml at 4th week of intravenous therapy in our study. Adverse events in the intravenous group were metallic taste in (five) patients, hot flushes (two), arthralgia (one), dizziness (one), and nausea (four). No drop out seen from oral group due to side effects. It is surprised to see as no patients developed thrombophlebitis in their study with good sample size.

Other studies have also not discussed how they have infused intravenous iron in their patients.

The review by Williams and Wheby²¹ notes that several studies considered anemia to be risk factor for low birth weight. Fetal birth weight was not different between groups in our study. No blood transfusion was required in either of the group.

New generation intravenous iron preparations are still lacking adequate trial for their use in pregnancy. Myers, B et al²² had analysed historical data of 92 pregnant patients who had received intravenous (IV) Ferric carboxymaltose and iron (III) hydroxide dextran. At four weeks, the total rise in Hb was 2.57 g/dL Ferinject, 2.34 g/dL Cosmofer. At six weeks the rise was 3.01 g/dL and 3.2 g/dL respectively. No serious adverse events were reported in either group. At 4th week rise in Hb is less than our study. So till now we can safely rely on intravenous iron sucrose for its better safety profile. Our study has a good sample size. However we have not excluded the confounding factors like intake of iron prior to inclusion in the study. Other confounding factors like dietary habits, vegetarian or non- vegetarian were not asked in the history.

CONCLUSION

However this study had showed that intravenous iron is safe to use during pregnancy. It causes significant rise in hemoglobin and iron stores within short time which helps to cope up easily with excessive bleeding during delivery. Hence, it may help to reduce the need for blood transfusion and the associated risks.

Major advantages are safety, efficacy, good compliance, simple mode of administration in an outpatient setting

and cost effectiveness because admission is not needed. It have extremely low incidence of side effects. Its use requires caution which can be reduced by giving it slowly under direct observation by the clinician.

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