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Comparative study of oral iron versus 3 doses of intravenous iron sucrose in mild to moderate anemia in 2nd and 3rd trimester of pregnancy

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Abstract
Background: Iron deficiency anemia is the most common type of nutritional anemia in pregnancy. Oral iron is the first treatment of choice because of its safety, easy availability and low cost, but compliance is a major issue due to its gastrointestinal side effects. Injectable iron sucrose can be an alternative in treatment of anemia where compliance is an issue with oral iron.
Objective: Present study was done to compare the safety and efficacy of oral iron with intravenous iron sucrose in cases of mild to moderate anemia in pregnancy.
Methodology: This was a prospective, randomised, interventional, comparative study carried out at GCS Medical College, Hospital and Research centre, Ahmedabad. The sample size was 100 with 50 patients in each group of treatment (oral iron and I.V. iron sucrose). The study was carried out from September 2015 to August 2016. Patients with haemoglobin 7 to 10 g/dl gestational age 14 to 36 weeks were considered for the study. Patients were randomly divided into 2 groups, group 1 was given oral iron in the form of ferrous fumarate containing 100 mg elemental iron twice a day for 4 weeks, while patients in group 2 were given 3 doses of I.V iron sucrose 200mg in 100 ml 0.9% normal saline on alternate days. Patients were followed up at 4 and 6 weeks of treatment.
Results: The rise in haemoglobin levels after 4 and 6 weeks of treatment was comparable in both the groups and showed no statistical significance. Whereas the rise in serum ferritin levels after 4 and 6 weeks of treatment was much higher in I.V iron sucrose group as compared to oral iron group and it was found to be statistically significant (P<0.0001). There were no significant side effects or allergic reactions in I.V iron sucrose group.
Conclusion: Oral iron and I.V iron sucrose had similar effects on rise in haemoglobin levels but iron sucrose had more effect on serum ferritin levels, hence it replenishes iron stores better and it has lesser side effects compared to oral iron.

Keywords: iron deficiency anemia, oral iron, iron sucrose, haemoglobin, serum ferritin

Introduction
In developing countries, anemia is a major contributory factor of maternal and perinatal morbidity and mortality [1]. Iron deficiency anemia is the most common nutritional deficiency anemia worldwide with highest prevalence in pregnant and postpartum women [2]. The overall global mean figure for the incidence of gestational anemia is 25% [3]. WHO defines anemia in pregnancy as Hb less than 11g/dl [4]. The Centre for Disease Control and Prevention defines anemia in pregnant women as Hb less than 11g/dl in first and third trimester and less than 10.5g/dl in second trimester [5]. WHO has estimated the prevalence of anemia in developed and developing countries in pregnant women as 14% in developed and 51% in developing countries and 65 to 75% in India [6].
Iron deficiency is thought to be the most common cause of anemia in the world, although other conditions such as folate or vitamin B12 deficiency, chronic inflammation, parasitic infections and inherited disorders can all cause anemia. In India more than 90% of anemia cases are estimated to be due to iron deficiency, because high iron requirements during pregnancy are not easily fulfilled by food, especially when iron bioavailability is poor [4]. Most women begin their pregnancy with partially or completely depleted iron reserves. Thus the severity of anemia is inversely related to the amount of iron reserves [7]. Di*et alone* cannot supply the 30-40 mg iron that is required for absorption of the 4-6 mg iron per day needed during the later stages of pregnancy and postpartum period. Anemia interferes with the normal intrauterine growth leading to fetal loss and perinatal deaths. It is associated with increased preterm labor (28%), preeclampsia (31%), and maternal sepsis [8].
The Government of India in the National Nutritional Anemia Control Programme has recommended that all pregnant women should be given one tablet of iron and folic acid containing 100mg elemental iron and

0.5 mg folic acid in the second half of pregnancy for atleast 100 days. Oral iron is the treatment of choice and almost all women can be treated effectively with oral iron preparations. However, parenteral administration of iron is necessary under certain circumstances and may be suitable under the following situations like inability to tolerate the side effects of orally administered iron, inflammatory bowel disease, peptic ulcer, non compliance with oral regimens, iron malabsorption and pregnancies near term. Severe systemic side effects associated with iron dextran and iron-sorbitol-citric acid complex limited the use of intramuscular iron. However, iron sucrose is reported to be safe and effective for the management of anemia in pregnancy.

This study was carried out to compare the efficacy and safety of oral iron and injectable iron sucrose in patients of iron deficiency anemia.

Materials and Methods

The present study was conducted as GCS Medical College, Hospital and Research Centre, Ahmedabad.

Duration of study: September 2015 to August 2016.

This was a prospective, randomised, interventional, comparative study.

The study was approved by institutional ethical committee.

Written and informed consent of the patients were taken before enrolling them in the study.

Inclusion Criteria

1. Hemoglobin 7 to 10 g/dl
2. Gestational age 14 to 36 weeks
3. Age group 18 to 35 years
4. No other systemic illness

Exclusion Criteria

1. Unwilling subjects
2. Multifetal pregnancy
3. History of late miscarriage or still birth
4. Pre-existing systemic illness of mother
5. Patients with history of bleeding tendency, hemoglobinopathy or other red cell disorders
6. History of iron therapy or blood transfusion in last 3 months
7. Any obstetric complicating factors like pre-eclampsia, eclampsia in present pregnancy

Methodology

Patients fulfilling the above criteria were selected from antenatal clinic and were randomly assigned to either oral iron (group 1) or intravenous iron sucrose (group 2). Sample size was decided to be 100 with 50 patients in each group but more number of patients were enrolled as some patients may have loss to follow up. Thorough history and complete systemic and obstetric examination of all the patients was carried out. Period of gestation was calculated from last menstrual period (LMP) or first trimester obstetric scan, if patient was not sure of her dates.

In the oral group (group 1), the patients received two tablets of ferrous fumarate, each containing 100 mg of elemental iron daily for 4 weeks. This was supplemented with 5 mg of folic acid per day. Women were asked to bring back empty packs and asked about intake of tablets and colour of stools to know their compliance.

In the i.v. group (group 2), the patients were given 3 doses of iron sucrose as 200 mg (elemental iron) in 100 ml 0.9% sodium chloride intravenously over 20 to 30 minutes on alternate days for a total of 3 days. This treatment was supplemented with 5 mg of oral folic acid daily for 4 weeks to prevent an eventual folic acid deficiency and to eliminate the influence of such a deficiency on the results. Additional oral iron was kept on hold during the 4 weeks of study.

The 2 groups were monitored clinically and biologically. Any adverse reactions linked with or likely to be linked with the treatment were identified.

The measurements recorded at the beginning of the study were haemoglobin %, complete blood count, serum ferritin, peripheral smear for the type of anemia and urine analysis. Haemoglobin and serum ferritin levels were repeated after 4 weeks and 6 weeks of treatment to know the response to treatment.

Statistical Analysis

In present study, the statistical analysis was done using the Statistical Package for the Social Sciences (SPSS version 12.0). Data values were expressed as mean ± SD. Continuous variables were compared using Mann Whitney U test. Categorical variables were compared using the chi-square test. The quantitative variables like age, BMI, gestational age were presented by calculating mean ± SD.

Results

Total 112 patients were recruited in the study and randomised into oral iron group (group 1) and i.v. iron sucrose group (group 2). Out of 58 patients in oral iron group 8 patients dropped out due to poor compliance and loss to follow up. Hence 50 completed the study. similarly out of 54 patients in i.v. iron sucrose group, 4 patients were lost to follow up and hence 50 patients completed the study.

Participants in both the groups were matched for age, weight, BMI, gestational age and parity and there was no statistical difference ($p > 0.05$). At the beginning of the study haematological parameters like haemoglobin and ferritin were also comparable in both the study groups and did not show any statistically significant difference.

Table 1: Demographic and Biologic Data of Patients at The Beginning of The Study

Sr. No.	Parameter	Group 1 Oral iron	Group 2 I.V iron sucrose	P value
1	Mean age (years)	25.46	25.2	0.714
2	Mean BMI (kg/m2)	21.83	22.16	0.542
3	Mean GA (weeks)	25.1	24.5	0.879
4	Parity (primi/multi)	19/31	20/30	0.556
5	Mean Hb (g/dl)	8.3 ± 0.53	8.02 ± 0.58	0.051
6	Mean ferritin (ng/dl)	9.33 ± 0.93	9.12 ± 0.55	0.080

Table 2: Changes in Hemoglobin After 4 And 6 Weeks of Treatment

		Group 1 (oral iron)	Group 2 (I.V iron sucrose)	P value	Mann – Whitney U-test statistics
1	Baseline Hb	8.3 ± 0.53	8.02 ± 0.58	0.051	958
2	Hb after 4 weeks	10.6 ± 0.62	10.4 ± 0.43	0.080	998
3	Hb after 6 weeks	11.6 ± 0.61	11.8 ± 0.05	0.020	1586

Hematologic response: The increase in haemoglobin level after 4 weeks was 2.3 g/dl in group 1 and 2.38 g/dl in group 2, and that after 6 weeks was 3.3 g/dl in group 1 and 3.78 g/dl in group 2. Both were comparable and there was no statistical difference found between both the groups according to the Mann- Whitney U- test.

Table 3: Changes In Serum Ferritin After 4 And 6 Weeks Of Treatment

		Group 1 Oral iron	Group 2 I.V iron sucrose	P value	Mann – Whitney U- test statistics
1	Baseline ferritin	9.33 ± 0.93	9.12 ± 0.55	0.08	869
2	After 4 weeks	31.77 ± 4.64	122.83 ± 8.4	0.000001	2480
3	After 6 weeks	47.49 ± 6.25	134.9 ± 8.13	0.000001	2500

It is observed from the data that rise in serum ferritin level is significantly higher in I.V iron group as compared to oral iron group, and it is statistically significant (P<0.0001). This suggests that I.V iron sucrose replenishes the iron stores better than oral iron.

Table 4: Adverse Effects

Sr. No.	Adverse effect	Group 1 (oral iron)	Group 2 (I.V iron sucrose)
1	Headache	-	-
2	Nausea	2 (4%)	-
3	Gastritis	5 (10%)	-
4	Diarrhoea	-	-
5	Constipation	4 (8%)	-
6	Altered taste	1 (2%)	1 (2%)
7	Thrombophlebitis	-	4 (8%)
8	Anaphylaxis	-	-

In group 1, 4% patients had nausea, 10% patients had gastritis and 8% patients had complain of constipation whereas there were no such side effects in group 2. In both the groups 1% patients had incidence of altered taste. In I.V. group 8% patients developed thrombophlebitis but no thromboembolic complications were seen. There was burning sensation, pain and swelling at the site of injection and it was relieved by applying thrombophobe ointment or ice pack or by injecting 5cc of distilled water or normal saline at the end of I.V iron sucrose infusion.

Discussion

Iron deficiency anemia is a common in pregnancy in developing countries like India. The responsible factors producing iron deficiency anemia generally precedes the pregnancy, including poor diet in iron content coupled with menstrual losses and a rapid succession of pregnancies in which supplemental iron was not provided. Oral iron is the first choice for treatment in mild anemia as it is safe, effective and low cost but compliance can be an issue due to its gastrointestinal side effects. In such cases I.V iron therapy is useful. Iron sucrose is reported to be safe and effective during pregnancy [9]. Iron dextran is a high molecular weight compound with a long half life of 3 to 4 days and relatively slow release. Adverse effects of this compound range from mild in the form of fever, arthralgia and urticaria to severe life threatening anaphylactic reactions in 0.1 to 2% of patients. It is associated with arthritis flare up and so is contraindicated in rheumatoid arthritis. On the other hand, iron sucrose is a small molecular weight compound with a short half – life of 5 to 6 hours and is quickly cleared from the serum and rapidly available for erythropoiesis. Iron sucrose has low allergenicity, hence incidence of anaphylactic reactions are rare. It is taken up mainly by the reticuloendothelial cells and it is unlikely that it will be taken up by the parenchymal cells of liver, kidney, adrenal glands or other organs, hence toxicity like myocardial, pancreatic or hepatic hemosiderosisis less likely even with iron sucrose overload.

In present study mean haemoglobin at recruitment did not show any significant difference between group 1 (oral iron) and group 2 (I.V iron sucrose). The haemoglobin levels in both the groups showed significant improvement after 4 and 6 weeks of treatment (P >0.5). There was no significant difference in terms of increase in haemoglobin level after 4 and 6 weeks of treatment between group 1 and group 2 (P<0.5). The rise in serum ferritin levels at 4 and 6 weeks of treatment was significantly higher in group 2 as compared to group 1 (P<0.0001). The results of the present study was in accordance with a study conducted by Bayoumeu *et al.* [10] in 2002 in France, where an increase in haemoglobin was observed in both oral iron and I.V iron group (not statistically significant) but the rise in serum ferritin was significantly higher in I.V group as compared to oral group (P<0.0001). Al Momen *et al.* [11] reported similar findings as in present study, that the I.V therapy resulted in higher levels of serum ferritin (P<0.05). In another study by Dede *et al.* [12] the results showed that I.V iron sucrose significantly increased serum ferritin levels within a short time with fewer side effects than oral therapy. Al Ra *et al.* (2005) found that the patients receiving I.V iron had significantly raised hemoglobin and serum ferritin values as compared to oral iron [13]. Exceptionally high levels of serum ferritin seen in the study of Breymann *et al.* [14] after 4 weeks of I.V iron sucrose therapy.

Conclusion

Intravenous iron sucrose is safe and effective in treatment of iron deficiency anemia in pregnancy. With this study it can be concluded that oral iron increase haemoglobin comparably with I.V iron sucrose, but does not replenishes iron stores as compared to I.V iron sucrose. Oral iron is cheap and easy to take, does not require medical supervision, but compliance can be an issue in view of gastrointestinal side effects. I.V iron sucrose is safe, effective and quick method to treat iron deficiency anemia with lesser side effects and good compliance. Limitations with I.V iron sucrose include the need for medical supervision and the cost of I.V iron which is higher as compared to oral iron.

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