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COMPARATIVE STUDY OF ORAL IRON AND INTRAVENOUS IRON THERAPY FOR THE TREATMENT OF IRON DEFICIENCY ANEMIA IN PREGNANCY

Obstetrics & Gynaecology

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ABSTRACT

Aim: To compare the safety and efficacy of intravenous iron sucrose with oral iron (Ferrous Sulphate) in the treatment of iron deficiency anemia (IDA) in pregnancy. **Materials and Methods:** An institution-based observational comparative study was conducted in the Department of Obstetrics and Gynecology in a tertiary care hospital in India on 120 registered antenatal women with proven iron deficiency anemia with a singleton, uncomplicated pregnancy from 24-34 weeks of gestation with hemoglobin levels between 7-10g/dL. Out of 120 antenatal women, 60 each were selected to receive oral iron and intravenous iron by non-probability consecutive sampling technique. Primary outcomes assessed were change in hemoglobin levels at different time points and energy levels along with tolerability side effects. Secondary outcomes assessed were gestational age at delivery, mode of delivery, fetal birth weight, and postnatal infections. **Results:** A significant difference in the trend of hemoglobin was observed in both groups, being significantly more in the intravenous group from the first visit versus at 3 weeks (21% vs 8.5%), 6 weeks (26.5% vs 16.8%) and at delivery (31.3% vs 26.2%). No significant difference was observed in the change in energy levels (88.3% of the oral iron group and 85% of the intravenous group). A significant difference was observed in the tolerability of both groups (18.3% oral group women versus none in the intravenous group). **Conclusion:** The correction in hemoglobin levels was faster and more pronounced in the intravenous group, making it more effective and better tolerated, despite additional cost.

KEYWORDS

Hemoglobin, Iron deficiency anemia, pregnancy, Oral Ferrous Sulphate, Iron sucrose.

INTRODUCTION

Anemia is the decreased oxygen-carrying capacity of blood, which affects approximately 33% of women in reproductive age group globally[1]. Anemia is the primary factor in 57.9% of maternal deaths in India. [2] Haemoglobin levels below 11 g/dL are considered anemic in the first trimester of pregnancy, whereas values below 10.5 g/dL are termed anemic in the second and third trimester. [3] Iron deficiency anemia, megaloblastic anemia, and hemoglobinopathies-related anemia are the next most common types of anemia after nutritional anemia. In a patient with a mean corpuscular volume (MCV) of 95 fL or less, iron deficiency is diagnosed if their blood iron is below 60 mcg/dL, their total iron binding capacity is over 450 mcg/dL [4], and their serum ferritin is below 15 ng/dL. Pregnancy-related anemia caused by iron shortage is often caused by increased iron needs, poor nutrition, poor eating habits, previous deficiencies, and impaired absorption. The severity and tolerability of the patient's anemia, which both alter with the gestational age, are often used to guide treatment decisions for iron deficiency anemia during pregnancy. Early gestation with even severe compensated anemia can be treated with oral therapy. Late gestation with moderate anemia might have to be treated with parenteral iron. All pregnant women with decompensated anemia need blood transfusion, irrespective of gestation. Oral iron therapy is an outpatient noninvasive technique requiring compliance, tolerance and absorption, which is dependent on multiple dietary and intestinal factors. Intravenous iron therapy bypasses the absorption barrier by directly entering the bloodstream but is invasive incurring additional cost of hospitalization and risk of anaphylaxis and drug reactions. India has a >40% prevalence of iron deficiency anemia, according to the World Health Organization, [5] making it essential to create a successful strategy for iron correction.

This study evaluated the effects of intravenous iron sucrose and oral ferrous sulphate on hemoglobin levels, the severity of any adverse effects, and patients' desire to continue taking the medication to treat iron deficiency anemia during pregnancy.

MATERIALS AND METHODS

This study was conducted from January 2019 to August 2019 at the Department of Obstetrics and Gynecology at a tertiary care facility with approval from the hospital's ethical committee. Women between 24 and 32 weeks of pregnancy who visited the prenatal clinic were tested for anemia. After obtaining their consent, 120 registered women who met the criteria for iron deficiency anemia were included in the study.

Inclusion Criteria

- Singleton and uncomplicated pregnancy
- 24-34 weeks gestation
- hemoglobin levels in the 7-10 g/dL range, indicating iron deficient anemia
- Willing to enroll in program
- Willing to return for more therapy
- Compliant to oral iron therapy.

Exclusion Criteria

- Parenteral iron allergy.
- Hemoglobin of <7g/dL or ≥10g/dL.
- Antepartum hemorrhage, Gestational diabetes, and Pregnancy-induced hypertension.
- Patients with infections like malaria and dengue.
- Pregnant women with major medical disorders like cardiac disease, chronic kidney, liver disorders, bronchial asthma.
- Surgical illness in the recent past such as cardiovascular accident
- anemia due to causes than iron deficiency
- previous history of menorrhagia
- Symptomatic patients with breathlessness, signs of decompensation

The participants were randomly split into two groups of 60 by a non-probability sequential sampling method until the necessary sample size was reached. Initial testing included a complete blood count (CBC) and measures of hemoglobin and iron (serum iron and TIBC). Every woman received 500 ug of folic acid daily. A dose of 400 mg of Albendazole was used to treat worm infections. High-protein diets were recommended for the patients.

Oral Iron Group

60 antenatal study patients were treated with ferrous sulphate 200mg tablets, with 60mg elemental iron content, available as a part of government supply, given twice daily. The tablets should be taken on an empty stomach, without any calcium supplements, and neither coffee nor tea should be consumed within an hour after taking the tablets. Compliance was confirmed by checking empty blister packets.

Intravenous Iron Group

60 participants received an intravenous dose of 200 milligrams of iron sucrose in 100 milliliters of Normal saline three times each week. An

Iron Sucrose infusion test dose of 15 mL was given slowly, and then the patient was monitored for anaphylactic reactions like chills, rigors, fever, breathlessness, tachycardia, and anaphylaxis for the next 15 minutes while emergency drugs like steroids and antihistamines were kept ready. If no adverse effects occurred, the remainder of the infusion was administered. Oral iron was stopped during the study.

Ganozi formula[6] was used for the calculation of the total iron deficit. Total Iron requirement = 2.4x pre-pregnancy body weight (kg) x (target Hb – initial Hb) + 500 mg. The extra 500mg was administered to top up storage as the goal Hb level was 11 g/dL. The patients were followed up 48 hours after starting therapy, after 3 weeks, 6 weeks and at delivery in addition to routine antenatal follow-up for estimation of Hemoglobin levels and subjective parameters of change in energy levels and side effects. The primary outcomes assessed were change in hemoglobin levels and side effects. Secondary outcomes assessed were gestational age at delivery, mode of delivery, fetal birth weight, and postnatal infections.

Statistical Analysis

Data was analyzed with Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0, SPSS Inc, Chicago). Descriptive statistics were generated by computing mean and standard deviation (SD) for continuous data and frequencies and percentages for categorical variables. Statistical analysis was carried out using the Chi-Square test for categorical variables, the Wilcoxon-Mann-Whitney U Test to make group comparisons of non-normally distributed data, Fisher's exact test where the total number of cells had an expected count of less than 5 and the t-test to make group comparisons where data was normally distributed. The level of statistical significance was set at 0.05.

RESULTS

Both the intravenous and oral iron groups were found to be similar in terms of distribution (Table 1) according to Gravida status, period of gestation, duration of time between previous and current pregnancies, dietary habits, history of blood transfusion, number of transfusions received, time since last transfusion and Body Mass Index.

Table 1: Demographic Distribution Of The Study Population

		Oral iron	Intravenous iron	p-value
Gravida status	G1	17	17	
	G2	21	21	1
	>G3	22	22	
Period of gestation	24-28 weeks	25	28	
	28-32 weeks	29	24	0.629
	32-34 weeks	6	8	
Gap between previous and current pregnancy (n=86)	<1year	17	16	
	1-2 years	2	23	0.726
	>2years	6	4	
Dietary habits	Vegetarian	13	13	
	Eggetarian	7	9	0.86
	mixed diet	40	38	
History of blood transfusion present		6	7	
Mean number of transfusions received		1.17	1.14	0.769
Time since last transfusion	<1year	4	3	
	1-2 years	2	3	1
	>2years	0	1	
Body Mass Index (BMI)	<18.5	1	1	
	18.5-22.9	6	11	
	23-24.9	8	12	0.086
	25-29.9	40	36	
	30-34.9	5	0	

As seen in Table 2, there was no significant difference between the groups in terms of serum Iron and TIBC at the first visit.

Table 2 Comparison Of The 2 Groups In Terms Of Serum Iron And Tibc (first Visit)

		Oral Iron group	Parenteral iron group	Test	p value
Serum Iron (mcg/dL) (First Visit)	Mean (SD)	43.55 (7.79)	38.98 (11.18)	t test =2.596	0.11
	Median (IQR)	44.5 (38-50)	40 (30-48.25)		
	Range	24 - 58	13 - 58		
TIBC mcg/dL (First Visit)	Mean (SD)	663.40 (123.71)	709.98 (152.46)	Wilcoxon -Mann-Whitney U Test W=1509	0.127
	Median (IQR)	624.5 (579.5-718.5)	716.5 (561.25-830.25)		
	Range	496 - 986	475 – 989		

HEMOGLOBIN RISE

The two groups differed significantly in terms of hemoglobin (g/dL) at the following time-points: 3 Weeks, 6 Weeks, Delivery. (Table 3)

Table 3: Comparison Of The Two Groups In Terms Of Change In Hemoglobin (g/dL) Over Time (n = 120)

	Oral iron group mean hemoglobin in g/dL (%increase in Hb levels)	Parenteral iron group mean hemoglobin in g/dL (%increase in Hb levels)	P value of the two groups at each time-point
First visit	8.94	8.85	0.576
48 hours	9.04 (1.2%)	8.98 (1.6%)	0.781
3 weeks	9.69 (8.5%)	10.70 (21%)	<0.001
6 weeks	10.43 (16.8%)	11.16 (26.5%)	<0.001
delivery	11.27 (26%)	11.59 (31.3%)	0.041
P value for change within each group	<0.001	<0.001	

As seen in Table 3, in Oral iron group, the mean hemoglobin (g/dL) increased from a minimum of 8.94 at the first visit to a maximum of 11.27 at the delivery. This change was statistically significant (Friedman Test: $\chi2 = 231.0$, $p = <0.001$). In the group receiving parenteral iron, the mean hemoglobin (g/dL) rose from a low of 8.85 at the first visit to a high of 11.59 at delivery. This change was statistically significant (Friedman Test: $\chi2 = 229.3$, $p = <0.001$). The continuous hemoglobin (g/dL) trend was significantly different between groups ($p =< 0.001$). When comparing the increase in hemoglobin levels from the first visit to the subsequent time points, the intravenous iron group showed a significantly greater increase than the oral iron group: 3 weeks, 6 weeks and delivery.

Change In Energy Levels

The majority of the study participants, 88.3% of those receiving oral iron treatment and 85% of those receiving parenteral iron therapy felt more energetic after starting iron therapy. (Table 4) The distribution of the percentage increase or decrease in energy levels did not differ significantly across the groups ($\chi2 = 0.288$, $p = 0.591$).

Table 4: Association Between Group And Change In Energy Levels (n = 120)

Change In Energy Levels	Group			Chi-Squared Test	
	Oral Iron	Parenteral iron	Total	$\chi2$	P Value
Present	53 (88.3%)	51 (85.0%)	104 (86.7%)	0.288	0.591
Absent	07 (11.7%)	09 (15.0%)	16 (13.3%)		
Total	60 (100.0%)	60 (100.0%)	120 (100.0%)		

Tolerability

90.8% of patients in the study tolerated iron without any side effects. (Table 5) In our study, 18.3% of patients receiving oral iron had gastrointestinal adverse effects such as nausea, vomiting, stomach pain, diarrhea, or constipation, whereas no adverse effects were observed in patients receiving intravenous iron. There was a significant difference between the two groups in terms of the distribution of side effects ($\chi2 = 12.110$, $p = <0.001$).

Table 5: Association Between Groups And Side Effects (n = 120)

Side Effects	Group			Chi-Squared Test	
	Oral Iron	Parenteral iron	Total	$\chi2$	P Value
Present	11 (18.3%)	0 (0.0%)	11 (9.2%)	12.110	<0.001

Absent	49 (81.7%)	60 (100.0%)	109 (90.8%)		
Total	60 (100.0%)	60 (100.0%)	120(100.0%)		

18.3% from the oral group and 15% from the parenteral iron group had pre-term delivery. 78.3% and 83.3% respectively had term delivery while 3.3% of the oral group and 1.7% of the parenteral iron group had post-term delivery. No significant difference was found between both groups in terms of the distribution of gestation at delivery ($\chi2 = 0.626$, $p = 0.721$). In the oral group 61.7% delivered vaginally and 38.3% by LSCS while 68.3% of the parenteral group delivered vaginally and 31.7% underwent LSCS. There was no significant difference between the two groups in terms of the distribution of mode of delivery ($\chi2 = 0.586$, $p = 0.444$). The mean (SD) of fetal birth weight (Kg) in the oral iron group was 2.87 (0.38) and that in the parenteral iron group was 2.94 (0.24). There was no significant difference between the groups in terms of fetal birth weight (Kg) ($W = 1740.000$, $p = 0.752$). 3.3% in the oral iron and 5% in the parenteral iron-supplemented group had wound dehiscence. There was no significant difference between the two groups in terms of post-delivery wound dehiscence ($\chi2 = 0.209$, $p = 1.000$).

DISCUSSION

In this study,120 antenatal registered women in their mid-trimester (28-34 weeks of gestation) were compared for the efficacy of iron therapy in terms of rise in hemoglobin and its safety and tolerability in oral versus intravenous iron supplementation along with maternal and fetal outcomes.

Hemoglobin Rise

In a study by Kochhar et al., a substantial rise was seen after 4 weeks, with intravenous iron therapy producing a mean rise of 5.1 g/dL as opposed to an increase of 3.1 g/dL with oral iron therapy (p=0.002). [7] Gupta et al. found that the mean hemoglobin increased by 0.58 g/dL in the IV group after one week compared to 0.23 g/dL in the oral group, and by 1.9 g/dL after two weeks in the IV group opposed to 1.3 g/dL in the oral group ($p<0.05$). [8] In their research, Ragip et al. found that the intravenous group had a greater increase in hemoglobin from baseline than the oral group at two and four weeks (p=0.004 and p=0.031, respectively). [9] According to Tigga et al., the iron sucrose group showed significantly greater increase at 4 (p=0.01) and 8 weeks (p=0.00). [10] Bayoumeu et al. found no statistically significant difference between the IV and oral groups when comparing the increase in hemoglobin from 9.6 to 11.11 g/dL on day 30 and from 9.7 to 11 g/dL after 4 weeks.[11] Thus, most studies, except Bayoumeu et al study found the rise in hemoglobin to be faster and more effective by intravenous iron therapy as compared to oral iron therapy, which is corresponding to our study.

Tolerability

Kochhar et al reported mild but more prominent adverse effects by oral iron than by intravenous iron therapy.[7] According to Gupta et al., the intravenous iron group did not exhibit any appreciable negative effects, in contrast to the oral iron group where 36% of the adverse effects were gastrointestinal. [8] Ragip et al. found that 31.1% of the oral group suffered mild gastrointestinal symptoms, 28.9% experienced upper gastrointestinal symptoms, and 8.9% had diarrhea. In the intravenous group, 13.3% had upper gastrointestinal complaints and 2.2% had other side effects. The incidence of gastrointestinal complaints increased significantly (p= 0.04) in patients who were administered oral iron. [9] Tigga et al. found that adverse events occurred only in cases receiving oral medication and that 68% of those cases had gastrointestinal adverse outcomes.[10]In the meta-analysis by Govindappagari et al ,[12] there was decreased prevalence of side effects due to intravenous iron therapy with p=0.001. Thus overall, apart from the invasive nature of therapy by the intravenous route, it appears to be safer with respect to its side effect profile and is better tolerated, as in our study.

Gestational Age And Mode Of Delivery

In our study, there was no significant difference in the number of preterm and term delivery respectively in both groups. Neogi et al in their randomized control trial, phase 3 which got discontinued midway due to futility, found equal incidence of preterm births between the group treated by oral iron vs intravenous iron. [13] Khan et al study observed a higher proportion of women from oral iron group undergoing preterm delivery as compared to women treated with intravenous iron.[14]Thus our results were similar to the observations by Neogi et al, unlike those by Khan et al.[13,14]

In our study, 61.7% of oral group delivered vaginally and 38.3% by LSCS while 68.3% of parenteral group delivered vaginally and 31.7% underwent LSCS. There was no significant difference between the oral and intravenous groups. Khan et al and Lewkowitz et al also found similar results in their study. Hence we can probably conclude that the mode of delivery does not depend primarily on the mode of iron therapy.[14,15]

Fetal Weight

In our study, the mean fetal birth weight in the oral iron group was 2.87kg and that in the parenteral iron group was 2.94kg, this difference was not significant, with a p-value of 0.752.

Kochhar et al, Ragip et al and Abhilashini et al found comparable fetal outcomes in terms of fetal birth weight in both oral and intravenous iron groups. [7,9,16] Bayoumeu et al reported a higher fetal weight by 250g in the intravenous iron group in their study, but this was not found to be statistically significant.[11] A study by Tigga et al [10] revealed that the mean neonatal birth weight was 2.67 ± 0.05kg for the oral iron group whereas it was 2.79 ± 0.89kg for the intravenous iron therapy group, thereby demonstrating the statistical significance of the difference between the two based on the neonatal outcome with p = 0.00.(60) The incidence of fetal birth weight in our study is overall similar to other related studies except a study by Tigga et al where it was significantly different between the two groups.[10]

CONCLUSION

Iron deficiency anemia in pregnancy is a common condition in pregnancy which can be easily controlled by early prophylactic supplementation, timely diagnosis and intervention. It is a major public health problem and contributes to nearly 20% of the direct maternal mortality and 20% of indirect maternal mortality. It was evident from our study that the correction of hemoglobin was faster and more pronounced in the intravenous iron therapy group and significant differences were noted after 3 weeks, 6 weeks and at delivery of starting iron therapy between 24-34 weeks of gestation. Intravenous iron sucrose was also better tolerated as compared to oral iron, which was more commonly associated with gastrointestinal complaints leading to increased chances of intolerance or non-compliance. History of blood transfusion, number of units or time lapsed since last transfusion did not contribute to a difference in the response to iron correction in current pregnancy. Change in energy levels was noted in general after commencement of iron correction, irrespective of mode of therapy.

Gestational age at delivery, mode of delivery, fetal birth weight and postnatal wound gape/fever was not significantly different between the two groups.

Thus, despite the need of hospitalization, the higher expense, and the need for numerous doses, intravenous iron sucrose treatment is more successful and more tolerated than oral iron sulphate therapy for mild iron deficiency anemia.

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