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Oral versus Intravenous Iron for Treatment of Anaemia in Pregnancy

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Abstract: ***Anaemia is a condition in which either the number of circulating red blood cells or their haemoglobin concentration is decreased. As a result, there is decreased transport of oxygen from the lungs to peripheral tissues.In pregnancy, the total volume of plasma is dramatically increased (50%) along with increase in red cell mass (18-25%) depending on iron status, and the haemoglobin is consequently reduced to a varying extent, occasionally, as low as 80% making anaemia the most common haematological abnormality diagnosed during pregnancy. Also contributing significantly to maternal morbidity and mortality, intrauterine growth retardation, preterm delivery and perinatal morbidity and mortality. The Centers for Disease Control and Prevention (1990) defined anaemia as haemoglobin (Hb) less than 11 gdl-1 in first and third trimester and less than 10.5 gdl-1 in second trimester. WHO defines anaemia as haemoglobin concentration less than 11 gdl-1 and a hematocrit < 0.33. Diet alone can not supply such amounts of iron in non-industrialized countries making iron supplementation a necessity in all pregnant women. Iron can be supplemented by mouth, intramuscular or intravenous injection. Alternatively, blood transfusion and recombinant erythropoietin are used. The traditional treatments i.e. oral iron therapy and blood transfusion involve significant drawbacks. Oral iron is frequently restricted by limited absorption, low tolerability, non-compliance and side effects. Therefore, intravenous iron alone or in association with recombinant human erythropoietin (rHvEPO) therapy, has been considered as an alternative in the management of iron deficiency in this setting.***

Keywords: Anaemia in Pregnancy, Oral Iron, Iron Sucrose, Ferritin

1. Introduction

Iron deficiency anaemia (IDA) is the most common nutritional disorder in the world affecting approximately 25% of the world's population.[1] The prevalence of iron deficiency anaemia in pregnant women is estimated to be 35-75% (average 56%) in non industrialized countries, whereas in industrialized countries, the average prevalence is 18%.[2] It is responsible for 40-60% of maternal deaths in non industrialized countries.[3,4]Surveys in different parts of India reveal that 87% of pregnant women suffer from anaemia and about 10% have severe anaemia (<8gdl^{-1}).[5]The Centre for Disease Control and Prevention defines anaemia as haemoglobin (Hb) concentration of <11gdl^{-1} in first and third trimester and <10.5 gdl^{-1} in second trimester. WHO defines anaemia as haemoglobin <11 gdl^{-1} and hematocrit <0.33.[6] With adequate iron stores, daily iron requirement is 4mg/day (2.5 mg/day in early pregnancy; 5.5 mg/day from 20-32 weeks and 6-8 mg/day from 32 weeks onwards).[7] In an average pregnancy, the requirements are basal iron (280 mg), expansion of red cell mass (570mg), transfer to fetus (200-350mg), for placenta (50-150 mg) and blood loss at delivery (100-250mg).[8] After deducting the iron conserved by amenorrhoea (240-480 mg), an additional 500-600 mg of iron is required in pregnancy or 4-6 mg/day of absorbed iron, which can only be achieved by mobilising iron stores in addition to maximum iron absorption from the diet.[9] As iron absorption is <10% (3-4% in low bioavailability diet) for a minimum of 4-6 mg absorption, at least 40-60 mg of iron should be available in the diet. Diet alone cannot supply such amounts of iron in non industrialized countries making iron supplementation a necessity in all pregnant women.[7] Iron deficiency in pregnancy has varied adverse consequences on both the mother and fetus. Apart from anaemia, iron deficiency is also associated with preterm labour (28.2%); pre eclampsia (31%), sepsis, hemorrhage and low birth weight delivery.[10] It is also postulated that the pregnant women with iron deficiency anaemia may give birth to infants with low iron stores, which may result in abnormal child development (physical and cognitive), if the deficiencies are not corrected early.[2] Iron supplementation is a public health strategy designed for the prevention of iron deficiency and its consecutive anaemia. Standard obstetrics practice has included screening for anaemia without requiring the determination of iron deficiency and oral supplementation as the treatment of choice due to its low cost and high effectiveness. Almost all women can be treated effectively with oral preparations. In recent years, new IV iron preparations have been introduced in the market as substitutes of iron dextran for the intravenous treatment of anaemia, which represent a low risk alternative to oral iron therapy with a very low incidence of anaphylactic reactions. The ACOG recommends routine supplementation with a daily dose of 30mg of elemental ferrous iron during the second and third trimester.[11] WHO recommends 60mg of iron per day with 400 µg of folic acid in areas where the prevalence of iron deficiency is <20%, and recommends to double this amount in areas where the prevalence is higher.[12] The iron preparations for parenteral route can be used intramuscular or intravenous. Till now, parenteral iron therapy is reserved as an alternative for only a small number of patients in whom oral treatment fails due to dose related side effect, non compliance or iron intolerance, decreased absorption like ulcerative colitis or also for those who are resistant to oral iron and for patients who present with anaemia in last trimester of pregnancy when rapid correction of anaemia is needed over a short time period. The main drawback of intramuscular injections are the pain and staining of the skin and the possibility of abscess formation at the injection site, which are major inconvenience due to the need of repeated intramuscular injections.[13]

2. Aims and Objectives

To determine the efficacy and side-effects if any, of injectable iron sucrose and compare it with oral ferrous sulphate therapy in the treatment of iron deficiency anaemia of pregnancy.

3. Material and Methods

The present study was carried out at the Antenatal clinic of Department of Obstetrics and Gynaecology in collaboration with the Department of Biochemistry, Pt B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak on 200 antenatal women suffering from iron deficiency anaemia (IDA).

Two hundred women were divided into groups:
Group I (n=100) : Women who were given oral iron therapy
Group II (n=100) : Age and gestation matched women were treated intravenously with iron sucrose

Inclusion Criteria
1) Women with haemoglobin between 7-11 gdl^{-1}
2) Women at 26 to 34 weeks of gestation.

Exclusion Criteria
1) Anaemia not linked to iron deficiency
2) Intolerance to iron derivatives
3) Women with systemic and chronic diseases
4) Multiple pregnancy
5) Antepartum haemorrhage
6) Premature rupture of membranes
7) Hypertensive disorders of pregnancy

Methodology
An informed consent was taken from all subjects who were subjected to detailed history and clinical examination as per proforma. Before starting therapy, all women were dewormed with Tablet Mebendazole (100mg twice daily for 3 days). Infective causes were ruled out. Women were instructed to take a diet rich in iron and proteins. The baseline investigations (haemoglobin and reticulocyte counts, serum ferritin level) were carried out in all patients following inclusion in the study.

Women in group I were given oral ferrous sulphate (100mg elemental iron) (supplied by the Government of India) during pregnancy in twice daily doses for women with haemoglobin between 9-11 gdl^{-1} and thrice daily doses for women with haemoglobin between 7-9 gdl^{-1} for the rest of pregnancy. Patients were instructed to take the tablets two hours after meals.

Women in group II were administered intravenous iron sucrose the dosage of which was calculated from the following formula:[17]

Weight (kg) × (12- actual Hb)gdl^{-1} × 0.24 + 500mg.
Rounded up to the nearest multiple of 100.

The patients were admitted a day before the therapy. In each infusion, 200mg iron sucrose in 100ml of 0.9% NaCl was infused over 20-30 minutes. Repeated doses were given on consecutive days until the administration of calculated doses was completed before delivery. No additional oral iron was administered during the study. These following investigations were carried out in these patients:
1) Hb at 0 day, 2 weeks, 4 weeks and at delivery
2) Urine complete examination
3) Urine culture sensitivity
4) Stool for ova or cyst on days 1,2,3
5) Reticulocyte count at 0 day and 1 week
6) Serum protein with A:G ratio
7) Serum ferritin at 0 day and 4 weeks

Statistical Methods
The values of various parameters in different groups have been described by expressing each attribute in terms of mean and standard deviation.

$$\text{Mean} = x = \Sigma x \backslash n$$

Where sum of values of x is Σx and n is the number of values. Standard deviation i.e S.D. The difference between two means was calculated by Z test when the sample size was large. Student 't' test was used for smaller number of values. Also, regression analysis was carried out.

Significance Level
The significance analysis has been performed in conjunction with tables. The term significant has been used in accordance with following convention.

If an observed difference between two means is of such magnitude, that the probability (p) of obtaining a difference of at least as great as the observed value is greater than 0.05 (where the null hypothesis is assumed to hold), then that observed difference is said to be non significant.

If 'p' is 0.01-0.05 probably significant
0.001-0.1 significant
<0.001 highly significant.

4. Observations

In the present study, 200 antenatal women suffering from iron deficiency anaemia (IDA) attending the Antenatal Clinic of Obstetric and Gynaecology department of Pt. B.D. Sharma PGIMS, Rohtak were studied.

These women were divided into the following two groups each consisting of 100 subjects.

Group I (n=100): women were given oral iron therapy
Group II (n=100): women were treated intravenously with iron sucrose

Table 1: Age Wise Distribution Of Subjects

Age group (years)	Group I	Group II
<20	4	3
20-24	57	56
25-29	29	31
30-34	7	9
≥35	3	1

Age of group I ranged from 18-40 years and mean was 24.44±3.99 year. The maximum number of subjects were between 20-24 years (57%). Age of group II ranged from 19-35 years and mean was 24.22±3.50 years (Table-I). The maximum number of subjects were between 20-24 years (56%). The proportion of age in different categories among different groups was not statistically significant (p>0.05).

Table 2: Baseline Haemoglobin (gdl^{-1}), Reticulocyte (%), Ferritin ($ngml^{-1}$)

	Group I			Group II		
	Haemoglobin (gdl-1)	Reticulocyte (%)	Ferritin (mg/ml)	Haemoglobin (gdl-1)	Reticulocyte (%)	Ferritin (mg/ml)
Mean±SD	8.42±0.84	0.78±0.30	32.02±12.23	8.37±0.86	0.75±0.37	30.34±15.32
Range	7-10	0.1-0.7	4-62	7-10.2	0.1-1.9	4-99

The mean haemoglobin on day 0 in subjects in group I was 8.42±0.84 gdl^{-1} (range 7-10). The mean haemoglobin on day 0 of subjects in group II was 8.37±0.75 gdl^{-1} (range 7-10.2). The mean reticulocyte count on day 0 of subjects in group I was 0.78±0.30% (range 0.1 to 1.7). The mean reticulocyte count on day 0 of subjects in group II was 0.75±0.37% (range 0.1 to 0.9). The mean ferritin levels on day 0 of subjects in group I was 32.02±12.23 $ngml^{-1}$ (range 4-62). The mean ferritin levels on day 0 of subjects in group II was 30.34±15.326 $ngml^{-1}$ (range 4-99). The mean haemoglobin, reticulocyte count and ferritin values at day 0 were compared in the two groups the difference was not found to be statistically significant in any of the three values.

Table 3: Types of Reactions and Complications Developed during and after Therapy

	Group I	Group II
Fever	-	1
Headache	-	5
Pruritis	-	7
Dyspepsia	7	-
Emesis	3	-
Diarrhoea	4	-
Constipation	1	-
Metallic taste	1	-

Sixteen subjects in group I developed side effects – mostly gastrointestinal in the form of dyspepsia (7); emesis (3); diarrhoea (4); constipation (1) and metallic taste (1). Thirteen subjects in group II developed side effects in the form of pruritis (7); headache (5) and fever (1). None of the reactions/side effects were serious enough to be requiring cessation of therapy. None of the patients required blood transfusion for correction of anaemia. No serious life threatening anaphylactic reactions were observed

Table 4 (A): Haemoglobin Level after Oral Therapy (gdl^{-1})

Group I	0 day	2 week	4 week	Delivery
Mean ±SD	8.42±0.84	8.97±0.86**	9.65±0.91***	9.14±0.90***
Range	7-10	7.5 to 11	7.5 to 12	7 to 11

The mean haemoglobin at 2 week, 4 week and delivery in group I after starting therapy was 8.97±0.86 gdl^{-1} (range 7.5-11); 9.66±0.91 gdl^{-1} (range 7.5 to 12) and 9.14±0.90 gdl^{-1} (range 7 to 11) respectively. The rise in haemoglobin was found to be highly significant at 2 week (p<0.01) and very highly significant at 4 weeks and delivery in group I .

Table 4 (B): Haemoglobin Level after Intravenous Therapy (gdl^{-1})

Group II	0 day	2 week	4 week	Delivery
Mean ±SD	8.37±0.86	9.00±0.83****	9.67±0.84****	10.11±0.75***
Range	7-10.2	7.5-10.7	8-12	8.5-11.5

The mean haemoglobin at 2 week, 4 week and delivery in group II after therapy was 9.00±0.83 (range 7.5 to 10.7); 9.67±0.84 (range 8-12) and 10.11±0.75 gdl^{-1} (range 8.5-11.5) respectively. The rise in haemoglobin was statistically significant at 2 week , 4 week and delivery in group II subjects. The difference of rise in haemoglobin at the time of delivery was highly significant statistically as compared to the baseline values (p<0.01). However, the rise observed after 2 week and 4 week was not significant (p>0.05).

Table 5: Ferritin ($ngml^{-1}$) Level after Therapy

	Group I		Group II	
	0 day	4 week	0 day	4 week
Mean ± SD	32.02± 12.23	69.79± 19.46***	30.34± 15.32	102.72±34.08***, +++
Range	4-62	28-104	4-99	25.4-236

The mean ferritin level on day 0 in group I was 32.02±12.23$ngml^{-1}$ (range 4 to 62). After initiation of therapy the ferritin level had risen to a mean of 69.79±19.46$ngml^{-1}$ (range 28-104) at 4 weeks. The rise in ferritin was found to be very highly significant (p<0.001) in group I at 4 week .In group II, mean ferritin level on day 0 was 30.35±15.32 $ngml^{-1}$ (range 4-99). At 4 week of therapy the mean ferritin levels were 102.72±34.08 $ngml^{-1}$ (range 25.4 to 236). The rise in ferritin was found to be very highly significant at 4 weeks of therapy in group II (p<0.001).

Table 6: Reticulocyte Count after Therapy (%)

	Group I (Oral)		Group II (Intravenous)	
	0 day	1 week	0 day	1 week
Mean ± SD	0.80±0.30	1.30±0.34***	0.75±0.37	1.28±0.35***,+
Range	0.1-1.7	0.5-2.9	0.1-1.9	0.5-2.2

In group I, the mean reticulocyte count on day 0 was 0.80±0.30 % (range 0.1-0.7). At the end of 1 week, after initiating therapy the count rose to a mean of 1.30±0.34% (range 0.5-2.9). The rise in reticulocyte count was found to be very highly significant (Table 8, $p<0.001$). In group II, the mean reticulocyte count on day 0 was 0.756±0.37% (range 0.1 to 0.9). At the end of 1 week, after receiving therapy the count had risen to a mean of 1.28±0.35 (range 0.5 to 2.2). The rise in reticulocyte count was found to be very highly significant ($p<0.001$). There was no statistically significant difference in reticulocyte count at 0 day in the two groups. There was also no statistically significant difference in the reticulocyte count in the two groups when levels at the end of 1 week were compared ($p>0.05$). The rise in ferritin was compared in the two groups at 4 weeks and the difference was found to be very highly significant ($p<0.001$)

5. Discussion

A typical Indian women of reproductive age has been reported to weight less than 50 kg before conception, having a circulating blood volume of 3-5 L (7% of body weight).[14] At the time of delivery, when blood volume would have expanded by 35% to 40%, a non-anaemic (haemoglobin concentration of 11gdl^{-1}) woman would require 1760 mg iron (Fe) within the circulating red blood cells (3.4 mg iron/g haemoglobin in a total of ~520g haemoglobin). During pregnancy, however, iron is needed not only for new RBCs, but also for the fetus and placenta (~360mg) and an additional 230mg is needed for the 0.8mg daily endogenous Fe lost over 280 days of gestation; thus a total of 590mg is needed.[15] Thus, a total of 1g is required during pregnancy (50% for obligatory loss, 300mg goes to fetus and placenta, 200mg are lost through excretion). To cover the necessities of expanded blood volume, mother uses 500mg when available and if not, anaemia develops. In such cases, addition of exogenous iron is mandatory.

Oral iron supplementation is standard obstetrical practice and most patients tolerate well the oral iron supplementation. Parenteral iron is indicated when oral supplementation is not possible or fails. Out of 100 subjects in group I (oral iron group), 16 developed side effects in the form of dyspepsia (7), emesis (3), diarrhoea (4), constipation (1) and metallic taste (1). Our findings are similar to those reported by Al Momen et al.[16] In the present study, no subject interrupted the oral therapy due to side effects. On the other hand, only 13 subjects in group II receiving IV iron sucrose developed side effects in the form of pruritis (7), headache (5) and fever (1). None of the subjects developed side effects serious enough to be requiring cessation of IV mode of iron therapy. Ragip et al also reported that there were no serious adverse drug reactions recorded, no episode of anaphylaxis, no hypotension, no subject withdrawals and no drug discontinuation caused by adverse drug related events.[17] Studies have also reported that local rash and itching are more common in parenteral group. Also, systemic side effects such as fever and ache, are reported more commonly in parenteral iron group. None of the subjects in the present study reported any local side effects such as rash or itching. Poor patient compliance have been reported by many workers, owing to local gastrointestinal side effects or due to non availability of free tablets from government agencies.[18] Success of oral iron therapy depends on various factors especially, patients dietary habits influence success of treatment. Absorption of iron decreases if iron is taken after meal. Iron sucrose is generally well tolerated with no side effects and anaphylaxis has not been reported as yet. Its tolerance is further improved following administration of smaller doses at frequent intervals.In group I, after starting oral therapy, haemoglobin levels at 2 weeks, 4 weeks and delivery were increased (8.42±0.84 vs. 9.66±0.91 vs. 9.14±0.90 gdl^{-1} respectively). In group II, after starting IV iron sucrose haemoglobin levels at 2 weeks, 4 weeks and delivery were significantly increased (9.00±0.83 vs. 9.67±0.84 vs. 10.11±0.75 gdl^{-1}). Our results are comparable with those reported in literature.[14,16,17] Rise in haemoglobin levels was faster and more in group II as compared to group I .In the present study, it was observed that IV iron sucrose administration led to a significantly higher haemoglobin level at delivery as compared to oral iron therapy. Iron sucrose complex has intermediate stability and strength and is quickly cleared from serum (half life 5-6 hours). Hence, it is more rapidly available for erythropoiesis.[19] Also, iron sucrose has been approved for the treatment of iron deficiency anaemia in patients undergoing chronic hemodialysis receiving supplemental erythropoietin therapy. Al-Momen et al have reported similar findings to the present study.[16]

In the present study, the serum ferritin levels were significantly higher after oral iron therapy in group I at 4 weeks (32.02±12.23 vs. 69.79±19.46 ngml^{-1}). Our findings are in agreement with those reported in literature.[16,17] Ragip et al[17] have also reported that serum ferritin levels doubled after 4 weeks.[17] The rise in serum ferritin was highly significant in subjects in both groups recruited at any period of gestation at 4 weeks after therapy. Serum ferritin levels increased two fold in group I subjects and in group II, serum ferritin levels showed three fold increase. Al-Momen et al have also reported rise in serum ferritin levels in intravenous iron sucrose complex and oral ferrous sulphate groups and the rise was more in case of iron sucrose group.[16] They observed that this rapid and profound response was directly related to high amount of iron that could be delivered directly to the hematopoietic tissues. The absorption of iron from oral supplements is influenced by dose, patient's iron stores, and time of intake in relation to meal time. Parenteral administration of iron, as an alternative for oral therapy, provides a quick and certain correction of the total iron deficit. Dede et al also observed that intravenous iron sucrose significantly increased serum ferritin levels within a short time of 28 days.[20]

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