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Intravenous Iron Sucrose versus Oral Iron in Treatment of Iron Deficiency Anemia in Pregnancy: A Randomized Clinical Trial

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Abstract: ***Aim: Iron deficiency is a leading cause of anemia in pregnancy. The present study aimed to compare the efficacy of oral and intravenous iron therapy in improving iron deficiency anemia in pregnancy and restoring iron stores, compare the obstetric outcome in the two groups and evaluate the safety of intravenous iron sucrose. Material and Methods: This was a prospective study, where 100 anemic antenatal women with hemoglobin 7-9 g/dL, mean corpuscular volume <85 fL and serum ferritin <15 ng/mL, were randomized into two groups. In group A (n = 50), the women 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. Primary outcome measure was treatment efficacy, assessed by measurement of hemoglobin, red blood cell indices and reticulocytes on days 7, 14, 21, and 30 and at delivery, and of ferritin on day 30 and at delivery. Any side-effects of treatment and the neonatal outcome were studied as secondary outcome measures. Results: There was a statistically significant difference in increase of hemoglobin levels (3.1 g/dL in group A vs 5.1 g/dL in group B; 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. Conclusion: Intravenous administration of iron sucrose is a safe treatment for correction of anemia in pregnancy, without serious side-effects.***

Keywords: anemia, intravenous iron sucrose, iron deficiency, oral iron sulphate, pregnancy

1. Introduction

Iron deficiency anemia is the principal cause of anemia in pregnancy, with 30% of anemic women having hemoglobin (Hb) levels below 10 g/dL, and about 10% having Hb below 8 g/dL.[1] Decreased availability and poor absorption of iron, and closely spaced pregnancies constantly decrease the iron stores of pregnant women.

Although the best way to replace iron stores is oral iron supplementation, the gastrointestinal tract has a limited capacity for iron absorption. Oral iron supplementation requires several weeks to raise hemoglobin and months to replenish iron stores. Therefore, many patients fail to comply with such prolonged oral iron replacement therapy.

In late pregnancy, when there is a need for faster rise in hemoglobin levels, parenteral iron therapy overcomes the problem of compliance and ensures that patients receive the required dose of iron.[2] Parenteral administration by intramuscular injection is painful, might cause staining of the skin and abscess formation, and has a variable efficacy. [3] Intravenous treatments with iron sucrose is associated with better efficacy, compliance, safety and a shorter hospital stay. It rapidly corrects anemia in pregnancy and restores the stores, as the total dose can be given over a shorter duration of time. [4-6]

The present study aimed to compare the efficacy of oral and intravenous iron therapy in improving iron deficiency anemia in pregnancy and restoring iron stores, compare the obstetric outcome in the two groups and evaluate the safety of intravenous iron sucrose

2. Material and Methods

This was a randomized prospective study carried out in the Department of Obstetrics and Gynaecology, Dr Ulhas Patil Medical College and Hospital, Jalgaon Kh, India, after approval by the institutional ethical committee. The study population consisted of 100 women >18 years old with a singleton pregnancy between 24-34 weeks of gestation, with moderate iron deficiency anemia (hemoglobin 7.0-9.0 g/dL), mean corpuscular volume <85 fL, ferritin level <15 ng/mL, negative naked eye single tube red cell osmotic fragility test (NESTROFT) and no associated obstetric or medical complications. Women with anemia due to any cause other than iron deficiency; those with severe anemia (Hb <7.0 g/dL), asthma, viral hepatitis, cirrhosis, cardiovascular disease, autoimmune disease, suspected acute infection, intolerance to iron derivatives; those who had received parenteral iron treatment earlier; and those not willing to participate in the study were excluded. Written consent was taken from all the subjects fulfilling the inclusion criteria.

A detailed history was taken, including socioeconomic and dietary history, and a general physical, systemic and obstetric examination was done. Investigations done on inclusion (day 0) included hemoglobin, hematocrit and peripheral smear to diagnose iron deficiency anemia, reticulocyte count, blood indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular

hemoglobin concentration (MCHC) and serum ferritin, NESTROFT test (to screen for thalassemia), urine culture and sensitivity and stool examination for occult blood.

All women recruited in the study were given tablet mebendazole (100 mg twice daily for three days) for deworming and 5 mg folic acid daily along with a high protein diet. Patients were allocated to two groups of 50 each by a randomization table.

In group A (per oral group), participants were given 200 mg tablets of ferrous sulphate, each tablet containing 60 mg elemental iron three times a day on an out-patient basis for 4 weeks. Adherence to the treatment was monitored by asking the women to bring back the empty packs and carefully mark the consumption of tablets on a calendar.

In group B (iv group), women were admitted for a short duration for the treatment. The total iron sucrose (Anofer-S, Sun Pharmaceuticals Industries Ltd, India) dose to be administered was calculated as follows:
pre-pregnancy bodyweight (kg)
x Hb deficit x 0.24 + 500 mg.6

Target Hb was taken as 12 g/dL because of physiologic hemodilution during pregnancy; 0.24 was a correction factor taking into account the patient's blood volume and hemoglobin iron content and 500 mg was for the restoration of iron stores.

This total dose was rounded up to the nearest multiple of 100 mg and given in divided doses on alternate days (three doses of 200 mg each, i.e. 600 mg per week) to avoid any adverse reaction. The dose of 200 mg was diluted in 200 mL of isotonic sodium chloride solution and administered by slow intravenous infusion over a minimum period of 2 h.

The first 12.5 mL of the first injection were given very slowly over 15 min (50 mL/h) and the patient was monitored for signs of intolerance. If no adverse reaction was seen, the rate of administration was slowly increased to 100 mL/h. Throughout this time, patients were watched for any evidence of reaction or significant change in vitals. Patients were discharged after 2 h of observation. Additional oral iron supplementation was not given during the 4 weeks of study.

Treatment was stopped either on completion of the calculated dose administration or when the hemoglobin reached a target level of 12 g/dL. After the completion of treatment, women in both groups continued to receive 100 mg elemental iron and 500 mg folic acid (in accordance with the National Nutritional Anemia Control Program).

Table 1: Anthropometric and biologic data for antenatal women in groups A and B

Parameter	Group A (per oral; n =50)	Group B (iv; *n* = 50)	*P*-value
Age (years)	23 ± 3.5	24 ± 5.5	NS
Weight (kg)	51 ± 11	53 ± 12	NS
Parity (median)	2	2	NS
Gestational age on inclusion	27 ± 4	26 ± 4	NS (weeks)
Hemoglobin level (g/dL)	7.6 ± 0.8	7.7 ± 0.5	NS
Mean corpuscular volume (fL)	83.3 ± 10.5	82.8 ± 11.2	NS
Reticulocyte count (%)	0.7 ± 0.2	0.8 ± 0.3	NS
Ferritin level (ng/mL)	16.5 ± 5.9	18.1 ± 4.6	NS

NS, no statistically significant difference (according to Mann-Whitney test).

The two groups were monitored for both clinical changes and improvement in laboratory parameters. Primary outcome measure was efficacy of treatment, which was determined by studying the rate of improvement in both the groups (by comparing the changes with the baseline values of Hb, MCV, MCH, MCHC and reticulocyte count on days 7, 14, 21, and 30). On day 30, changes in peripheral smear and serum ferritin were also recorded. At the time of delivery, Hb, MCV, MCH, MCHC and serum ferritin level were recorded in the mother. Any postpartum events, especially requirement for blood transfusions or signs of anemia, were also noted.

On each visit, adverse reactions likely to be linked with the treatment (such as arterial hypotension during injections, tachycardia, hyperthermia, chest tightness, abdominal pain, vertigo, headache, digestive problems, allergic reactions and discontinuation of therapy due to adverse events) were noted. Any requirement of blood transfusion and duration of hospital stay were also recorded.

Fetal outcome was recorded in terms of fetal maturity (gestational age at delivery), birth weight and Apgar score at birth. The baby's iron status was evaluated by measurement of cord blood hemoglobin and ferritin levels. Thus, any side-effects of treatment and the neonatal outcome were studied as secondary outcome measures.

Dataset was checked for normality using Anderson Darling test employing Microsoft Excel 2010 (with QI Macros software). Mann-Whitney and Wilcoxon tests were used for comparison of non-paired and paired dataset, respectively for non-Gaussian population. A *P*-value of <0.05 was considered to be statistically significant.

3. Results

On inclusion, the two groups were comparable in terms of demographic, biologic and hematologic parameters (Table 1). Most patients (73%) had nutritional deficiency anemia. Two patients were excluded during the study because one patient in group A (per oral group) failed to follow up and another patient in group B (iv group) had a premature delivery three days after inclusion.

The difference in increase of Hb in the two groups was statistically significant from the third week of treatment. On day 30, there was a statistically significant difference in increase of hemoglobin levels (mean Hb increased by 3.1 g/dL in group A and 5.1 g/dL in group B; $P = 0.002$) and in the increase in ferritin levels between the two groups (mean ferritin increased by 61.1 ng/mL in group A and 85.9 ng/ mL in group B; $P = 0.005$). In group B, the mean values of hemoglobin and serum ferritin levels were 8.8 g/dL and 36.[5] ng/ dL, respectively, seven days after the initiation of treatment and 12.8 g/dL and 104 ng/mL, respectively, 30 days later. Compared to this, in group A, the rise in hemoglobin and ferritin levels was significantly lower (Table 2). MCV, MCH, MCHC and reticulocyte counts also increased in both groups, but the difference was not statistically significant (NS). Only THREE patients in group B attained the target hemoglobin before administration of the calculated dose of iron. Further intravenous treatment was not administered in these cases. None of the patients in group A achieved the target hemoglobin earlier than 30 days after initiation of treatment.

Adverse effects of the iron treatment were mild but more prominent in group A; mostly nausea and constipation (Table 3). Despite this, all patients in the oral group were compliant, except one who had to interrupt the treatment because of diarrhea. No patients reported pain on intravenous injection.

Table 2: Mean values of blood results before and after iron treatment

Parameter	Time interval	Group A (oral)	Group B (iv)	*P*-value
Hemoglobin (g/dL)	Pre-treatment	7.6 ± 0.8	7.7 ± 0.5	NS
	Day 7	8.4 ± 0.8	8.8 ± 0.6	NS
	Day 14	8.9 ± 0.6	9.7 ± 0.8	NS
	Day 21	9.6 ± 0.9	10.9 ± 0.8	0.009
	Day 30	10.7 ± 0.7	12.8 ± 1.1	0.002
	At delivery	11.2 ± 0.9	13.4 ± 0.9	0.002
MCV (fL)	Pre-treatment	83.3	82.8	NS
	Day 7	84.2	84.6	NS
	Day 14	85.1	86.1	NS
	Day 21	86.8	87.2	NS
	Day 30	88.5	88.8	NS
	At delivery	89.8	90.1	NS
MCH (pg/cell)	Pre-treatment	24.6	25.4	NS
	Day 7	24.7	26.1	NS
	Day 14	25.7	26.4	NS
	Day 21	26.6	28.3	NS
	Day 30	28.1	28.5	NS
	At delivery	29.2	29.9	NS
MCHC (g/dL)	Pre-treatment	28.9	29.1	NS
	Day 7	29.2	29.2	NS
	Day 14	30.4	30.7	NS
	Day 21	31.5	31.6	NS
	Day 30	32.2	32.6	NS
	At delivery	33	33.8	NS
Reticulocyte count (%)	Pre-treatment	0.7	0.7	NS
	Day 7	0.9	1.1	NS
	Day 14	1.2	1.5	NS
	Day 21	1.2	1.6	NS
	Day 30	1.8	2.1	NS
Ferritin (ng/mL)	Pre-treatment	16.5 ± 5.9	18.1 ± 4.6	NS
	Day 7	22.8 ± 9.8	36.5 ± 8.7	NS
	Day 30	77.6 ± 13.7	104 ± 13.4	0.005
	At delivery	94.6 ± 14.2	128.8 ± 15.8	0.001

MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

Table 3: Adverse effects of iron treatment and neonatal outcome

Adverse effect	Group A (per oral)	Group B (iv)	*P*-value
Headache	1	0	NS
Nausea	3	0	NS
Heartburn	2	1	NS
Hiccup	0	0	NS
Constipation	4	2	NS
Diarrhea	2	0	NS
Neonatal outcome			
Gestational age (weeks)	37 ± 2	38 ± 1	NS
Weight (g)	2695 ± 765	2870 ± 680	NS
Hemoglobin (g/dL)	15.9 ± 2.2	16.3 ± 2.1	NS
Ferritin (ng/mL)	138 ± 98	141 ± 101	NS
Apgar score	7, 9, 9	7, 9, 9	NS

Overall, 77 patients had a normal vaginal delivery and 21 had a cesarean section. Mode of delivery was not significantly different in the two groups. All cesarean sections and normal deliveries were performed by senior registrars. The estimated blood loss was between 500-800 mL for the cesarean sections and within normal limits in all normal deliveries. One patient in group A was transfused two units of packed red blood cells in the immediate post-delivery period because of atonic postpartum hemorrhage. However, in group B, one patient was not transfused blood even after atonic postpartum hemorrhage, though the hemo-globin level was 8.1 g/dL at delivery, because she was hemodynamically stable and her iron stores were con-sidered to be sufficient to cope with such anemia.

Neonatal outcome was comparable in the two groups. There was no statistically significant difference in birthweight between babies born to mothers in the two groups, although babies in group B had a mean birthweight of 175 g more than those born in group A (Table 3). However, the sample size of our study was not sufficient to draw definitive conclusions regarding obstetric and neonatal outcome.

4. Discussion

Iron deficiency is a leading cause of anemia, affecting over 500 million people worldwide. According to the National Family Health Survey III (2005-2006), the prevalence of anemia in India is 57.9%.[7] A Federation of Obstetric and Gynaecological Societies of India/World Health Organization (FOGSI-WHO) study (1997) on maternal mortality revealed that 64.4% of women who died had a hemoglobin of 8 g/dL.[8]

During pregnancy the needs for iron are increased by about 1000 mg. [9] Iron deficiency during pregnancy and postpartum could be due to poor intake, insufficient absorption and increased needs. Anemia increases the risk of requiring blood transfusion in women in the peripartum period, as they are unable to cope with blood losses of delivery. Severe anemia is associated with poor outcome, which may be fatal.

We recruited pregnant women with moderate anemia in mid pregnancy because treatment of anemia at this time ensures that antenatal women do not present with severe anemia at term, and avoids the need of blood transfusions later at term.

Oral iron supplementation (which uses the body's normal mechanisms) is the ideal way to replace iron stores. However, frequent problems associated with oral iron, including gastrointestinal discomfort, nausea, bloating, diarrhea and constipation, make it undesirable for many patients. Second, the gastrointestinal tract has a finite capacity for iron absorption. Most orally consumed iron is not absorbed in the gut and even when 100 mg of elemental iron is consumed orally, only 2-3 mg is absorbed. [10] Thus, replenishment of iron stores with oral iron takes a very long time, especially with ongoing blood loss. Such prolonged medical regimens lead to compliance failure in many patients, eventually leading to therapeutic failures. For such patients intravenous iron therapy may be the preferred treatment.

Intravenous iron treatment is indicated for antepartum iron deficiency anemia in patients with poor com pliance to oral supplementation, non-responsive (or intolerant) to oral iron replacement (in cases with poor iron absorption such as bowel operations or diseases), anemia in a high-risk setting requiring quick replacement of iron stores (placenta previa/accreta or Jehovah's Witness or other decliners of blood transfusions), severe anemia from obstetric hemorrhage (antepartum or postpartum) and post-autologous donation with need for rapid replenishment.[1, 11]

Response to therapy with parenteral iron is similar to that with oral iron. The hemoglobin rises at a similar rate, although stores will be replenished more efficiently with parenteral iron. [12]The main advantage of parenteral therapy is the certainty of its administration to correct anemia and build up the stores.

Several intravenous iron preparations are available, of which the most widely used are iron dextran, iron sucrose and ferric gluconate. Iron dextran as well as ferric gluconate have the associated risk of causing ana phylactic reactions, which may be fatal.[13] Other non-life-threatening side-effects include facial edema, pruritus, urticaria, hypotension and dyspnea (which may be related to an allergic response).[14] It is also sug gested that excessive therapy with parenteral iron (beyond the calculated iron deficit) might lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Thus, it is essential to calculate the iron deficit and monitor the hematologic parameters and iron indices in patients receiving regular parenteral iron therapy.

Iron sucrose has been administered as intravenous push doses up to 200 mg over 2-5 min and in intravenous infusion doses up to 500 mg over 2 to 4 h. [15]It has excellent efficacy, minimum side-effects, leads to rapid rise in hemoglobin concentration and can be administered without a test dose.[13] It has not been asso ciated with any serious adverse effects or anaphylaxis, which makes it the preferred drug for parenteral iron supplementation. Occasional patients (5-10%) may have a transient metallic taste and hot flashes. This absence of side-effects is partly due to the lower allergenic effect of the sucrose complex because of the very slow release of elementary iron from the complex.[14-16]

In addition, recent evidence suggests that iron sucrose can be detected in high levels in the liver circulation and marrow within 5 min after intravenous administration. Renal metabolism is minimal (less than 5% of the total dose).[1] Thus, iron sucrose is metabolically available in only a few hours after administration, and incorporation into the bone marrow for erythropoiesis is faster than other complexes. [16]

In a study examining the optimal doses of iron sucrose, doses of 200-300 mg intravenously over 2 h were found to be well tolerated, while patients who received 400-500 mg intravenously over 2 h experienced hypotension, nausea, and backache.[17]

There have been very few studies to examine the efficacy of iron sucrose in iron deficiency anemia in pregnancy. One clinical trial, evaluating the efficacy and safety of intravenous iron sucrose compared to oral iron in treatment of anemia during pregnancy, demonstrated a significantly higher hemoglobin level with iron sucrose (12.8 ± 0.6 g/dL vs 11.4 ± 1.2 g/dL in the control group) in a shorter time period (6.9 ± 1.8 weeks vs 14.9 ± 3.1 weeks in the control group), with no major side-effects.[18]

In another similar study involving 50 patients with moderate anemia, the hemoglobin rose by 1.5 g/dL in the intravenous group and 1.3 g/dL in the oral group on day 30.6 Al *et al*. compared the effect of oral iron (300 mg elemental iron per day) with intravenous iron sucrose in 90 women with hemoglobin between 8 and 10.5 g/dL. The rise in hemoglobin was significantly higher in the intravenous group than in the oral group[19].

Our results were comparable to these previous studies. Compliance with oral iron treatment and its tolerance was good. Gastrointestinal symptoms have been reported in up to 30% of patients treated with oral iron.[18] In clinical practice, poor compliance (frequently noticed due to gastrointestinal side-effects) can lead to further deterioration of anemia. In such patients, parenteral administration of iron is indicated.[20-21]

Although newborns of anemic mothers do not have iron deficiency anemia, their iron stores are related to maternal iron stores.[22] Singla *et al*. showed that babies born to women with moderate to severe anemia had markedly lower serum ferritin levels in cord blood and thus had poor iron stores. [23] Also, adverse perinatal out-comes in the form of preterm, stillbirth, small for gestational age babies and increased mortality have been observed in the neonates of anemic mothers. [22] A recent study showed that 69.2% of 130 women with severe anemia had preterm deliveries and 24.6% babies born to such mothers had low birthweight. [24] In our study, the difference in birth weight observed between the two groups was not statistically significant. However, only six neonates in the intravenous group had a birth-weight <2500 g. In contrast, in the oral group, 13 neonates had a low birth weight, including one who had a very low birth weight of 1390 g. This is interesting to note as a number of studies have shown an association between maternal iron deficiency

and low birthweight in neonates[25-26]

Thus, intravenous administration of iron sucrose is a safe treatment for correction of pregnancy anemia or iron stores depletion, without serious side-effects. If used in time, it can help reduce the need for blood transfusion during the peripartum period.

Disclosure

There were no potential conflicts of interest, whether of a financial or other nature. No financial arrangements were made with any company. There were no commercial affiliations.

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