Parenteral Iron therapy for anemia in pregnancy: ferric carboxy maltose versus iron sucrose

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Abstract:

Objectives: To compare the effectiveness and safety of intravenous ferric carboxy maltose (FCM) with intravenous iron sucrose (ISC) in pregnant women with Iron deficiency anemia**. Materials and methods:** Pregnant women between 16 to 36 weeks period of gestation and fulfilling the inclusion criteria were enrolled and divided to receive either FCM or iron sucrose. Baseline complete hemogram and serum ferritin was done. Patients were monitored for maternal vitals and fetal heart during infusion and side effects were noted. Women were followed up till delivery. Complete hemogram was repeated at 3 weeks, 6 weeks and 12 weeks to note the rise in hemoglobin and serum ferritin levels. Any serious adverse effects were noted during the antenatal visits and maternal and fetal outcomes were noted. **Results:** The rise in mean hemoglobin in FCM group is 3.2 g/dl and 2.2 g/dl in iron sucrose group at 12 weeks. The p value is < 0.05 in both groups. The number of doses required to achieve the target hemoglobin was signifantly less in the FCM group. No major adverse effects were noted. Minor side effects were reported in both the groups but was signifanly less in the FCM group. **Conclusions:** Ferric carboxy maltose is associated with faster rise in hemoglobin levels and significant rise in serum ferritin levels.

Keywords: Anemia in pregnancy, ferric carboxy maltose, iron sucrose.

Anemia in pregnancy is a global health concern. Anemia during pregnancy in India contributes to 20% maternal death directly and 50% of maternal mortality indirectly [1]. When hemoglobin concentrations of an individual are below two standard deviations in comparison to the mean distribution of the normal population of same age and gender and live in the same altitude, it is called Anemia[1]. It is projected that India has the utmost prevalence of anemia i.e., 57-96.2%, among the South Asian countries [2]. ICMR (Indian Council of Medical Research) has categorized anemia during pregnancy as - mild- Hb -10-10.9 gm%, moderate- Hb-7-9.9 gm%, severe- Hb-4-6.9 gm%, very severe-Hb <4gm% [1].

Anemia in pregnancy causes susceptibility towards recurrent infections, intrauterine growth restriction, preterm delivery, increased perinatal morbidity and mortality [3]. Anemic pregnant women have increased chances of postpartum hemorrhage requiring blood transfusion leading to longer hospital stay, reduced lactation, and postpartum mood disorders [4].

Several health programmes have been rolled out to prevent anemia in pregnant women. Despite prolonged and persistent efforts by the government, anemia in pregnancy continues to contribute to maternal mortality and morbidity. The reasons could be poor nutrition, oral intolerance. The main issue with oral iron therapy is

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noncompliance due to inconsistency of intake due to ignorance, associated gastrointestinal side effects like bloating, diarrhea, heartburn, nausea, constipation, and dark stools. Also, oral therapy is not sufficient for treatment of moderate to severe anemia, especially in the late second and third trimester. Parenteral therapy promises a better response in these patients and can obviate the need for blood transfusions in the antenatal and postpartum period [4]. Parenteral iron therapy is more compliant, efficacious. Parenteral iron causes rapid replenishment of iron stores and hence used in chronic blood loss, gastrointestinal disorders, and impaired iron absorption [5].

Parenteral iron therapy consists of intramuscular iron and intravenous iron preparations. Intramuscular iron preparations are rarely used now days because of the side effects associated with it.

Iron sucrose is an intravenous preparation approved by FDA in 2000 for treatment of anemia in pregnancy. The major disadvantage with iron sucrose is limited dose per sitting (200mg/day and 600mg/week) thus requiring multiple hospital visits. Ferric carboxymaltose is a dextran-free molecule which allows rapid administration of high single doses of iron (up to 1000 mg iron in 15 min) once a week and thus reducing the dosage frequency [6].

The FCM molecules consist of an iron hydroxide core chelated in a carbohydrate shell and this complex is taken up by macrophages, leaving behind very low levels of non-transferrin bound iron, thus preventing iron toxicity and oxidative stress [7]. These properties make ferric carboxymaltose an attractive alternative to iron sucrose in terms of efficacy, patient comfort and convenience, adverse reactions.

The present study is undertaken to study the efficacy and safety profile of ferric carboxy maltose in comparison to iron sucrose for treatment of anemia in pregnancy.

Materials and methods

This was a prospective study conducted in the department of obstetrics and gynecology at East point College of Medical Sciences and Research Centre located at Bangalore rural, Karnataka, India. The study was conducted from 20/11/2019 to 20/01/2021. Ethical clearance was obtained from institutional ethical committee. Informed consent was taken from the study participants. The study was conducted in accordance with the principles of the declaration of Helsinki. Pregnant women attending the antenatal clinic between 16 to 36 weeks period of gestation were screened for the study.

Inclusion criteria:

1. Gestational age between 16 to 36 weeks
2. Hb > 6.0 g/dL and < 10.0 g/dL with iron deficiency anemia (IDA) as evidenced by blood indices.

Exclusion criteria

1. Anemia due to causes other than IDA
2. Chronic infections like hepatitis and HIV
3. History of cardiac disease, renal impairment
4. History of allergic reaction to intravenous iron infusion

Sample size

$$N = \frac{2(a+b)^2 \sigma^2}{(\mu^1-\mu^2)^2} \qquad \frac{2(1.96+0.80)^2 (2)^2}{1}$$

a – conventional multiplier of alpha 1.96

b - conventional multiplier of power - 0.80

$\mu 1-\mu 2=1$

The sample size was determined using the above formula.100 patients fulfilling the inclusion criteria were enrolled for the study. 100 pregnant women were randomized using a computer generated block randomization table into two groups in a 1:1 ratio and were administered either FCM or ISC.

Group 1: Intravenous ferric carboxymaltose (1000 mg/week)

Group 2: Intravenous iron sucrose (200mg on alternate day, maximum - 600 mg/week).

Demographic profile and history with respect to obstetric score, previous pregnancy details, symptoms of anemia, intake of oral iron and side effects related to oral iron was obtained. On clinical examination, skin and mucosal pallor was noted and obstetric examination done. Investigations included complete blood count, blood indices and peripheral blood smear for typing of anemia.

The iron replenishment dosage was calculated by using Ganzoni's formula.

Total iron dose = ((Body weight) (kg) × (Target Hb - Actual Hb) [g/L)) × 2.4 + Iron stores (500mg if body weight is >35Kg) where, 2.4 is a correction factor that takes into account the patient's blood volume, estimated at 7% of body weight and Hb iron content, which is 0.34%.

Ferric carboxymaltose (FCM) is administered as 500mg in 100ml NS over 6 mins and 1000mg in 250 ml NS over 30 mins as intravenous infusion. Maximal dose per sitting was 1000 mg which was diluted in 200 ml 0.9% normal saline and administered as an IV infusion over 15 to 20 min. Subsequent doses (if needed) were planned on day 7 and day 14 and doses were rounded off to the nearest 100 mg. Patients in ISC group were administered IV ISC as 200 mg in 100 ml NS over 15-20 min twice weekly till dosage was completed, not to exceed 600 mg per week. Maternal blood pressure was taken every five minutes during infusion. FHR monitoring was done before and after the infusion. Women were observed for one hour post infusion, before being discharged home.

Outcome measures -

Demographic characteristics and baseline data included maternal age, gestational age, educational level, and results from peripheral blood counts. Outcome data will be collected on adverse events and pregnancy outcomes. Adverse events (AEs) in patients were defined as allergic or hypersensitivity reactions during or after the infusion of parenteral iron. Assessed pregnancy outcomes were hospital admission (before delivery, for other reasons than iron administration), intensive care unit admission, intrauterine growth restriction (IUGR), hypertension/preeclampsia, placental abruption, major adverse outcomes (maternal or fetal), minor maternal adverse outcomes, Hb at delivery (g/dL), need for red blood cell transfusion, gestational age at delivery, mode of delivery, fetal weight (g), and neonatal Apgar score.

Major maternal adverse outcomes were defined as death, stroke, neurological symptoms, severe preeclampsia, HELLP (Hemolysis, Elevated Liver Enzymes, Low platelets) syndrome, and delivery before 34 weeks of gestation. Major adverse fetal outcomes were defined as death, respiratory problems (requiring intubation), neonatal intensive care unit admission, pneumonia, and Apgar score <7. All patients were followed up till delivery. The hemoglobin was rechecked at 3 weeks, 6 weeks, 12 weeks and at delivery post infusion.

Statistical analysis: The statistical analysis was done by statistical package for social science (SPSS). Pictorial depiction, tables and graphs, percentages, mean with standard deviation was generated. The data was analyzed using student t test, using p values of ≤ 0.05 to indicate significance.

Results

Both the groups were comparable with respect to base line variables as depicted in table 1. In both groups, there was rise in hemoglobin at different periods after infusion as shown in figure 1. Ferric carboxymaltose group had early rise of hemoglobin and significant high value of hemoglobin. The rise in mean hemoglobin in FCM group is 3.2 g/dl and 2.2 g/dl in iron sucrose group at 12 weeks as demonstrated in figure 2. The p value is < 0.05 in both groups. Table 3 shows that the number of doses required to achieve the target hemoglobin was significantly less in the FCM group. No major adverse effects were noted in both the groups. Minor side effects were reported in both the groups but was significantly less in the FCM group as depicted in table 2.

Table 1: Baseline characteristics

Variables	FCM group	ISC group
Mean age	24.6	23.7
Parity		
Primi gravida	23	20
Multigravida	27	30
Gestational age (in weeks)	27	29
Baseline hemoglobin (mean±SD)	7.90±0.71 g/dl	8.01±0.64 g/dl
Serum ferritin (µg/dL)	12.56	14.83
Mode of delivery		
FTND	36	38
LSCS	14	12
Mean birth weight	2.72 kg	2.68 kg

FTND – Full term normal delivery, LSCS – Lower segment caesarian section

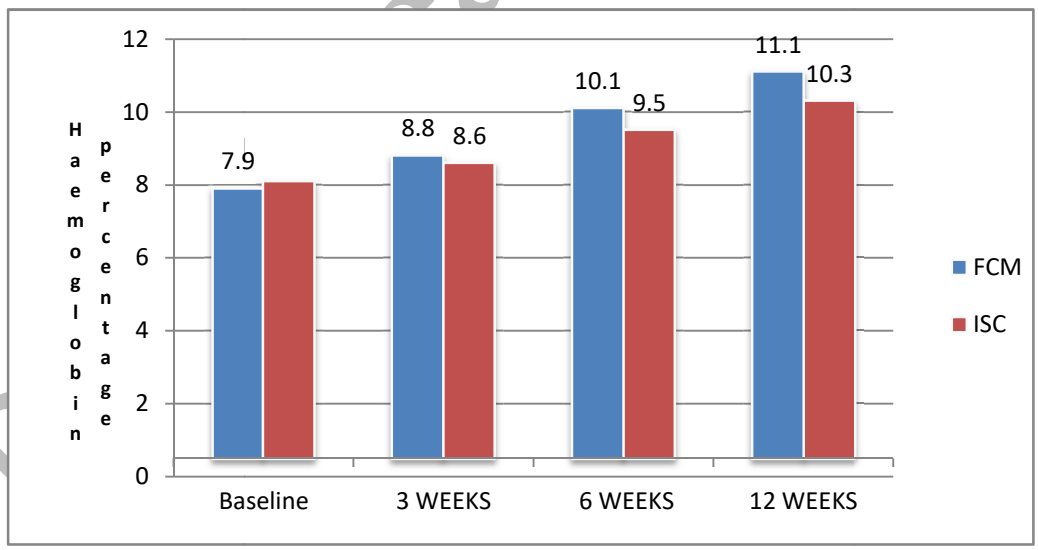

Figure 1: Comparison of rise in hemoglobin at different point of time in both groups.

The rise in mean hemoglobin in FCM group is 3.2g/d and 2.2 g/dl in Iron sucrose group at 12 weeks. The p value is < 0.05 in both groups.

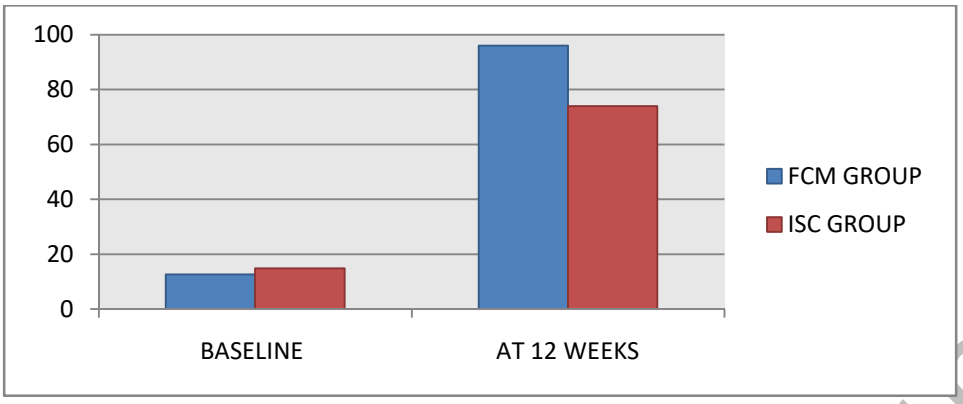

Figure 2: Shows rise of serum ferritin at 12 weeks

Table 2: Adverse effects with parenteral iron		
Adverse reaction	**FCM group**	**Iron sucrose group**
Injection site irritation	0	1
Nausea and vomiting	1	3
Hypotension	0	1
Pruritis	0	1

Table 3: Number of doses administered		
Number of vials	**FCM group (1000mg/vial)**	**Iron sucrose group (200mg/vial)**
1-3	50	14
4-6	0	35
>6	0	1

Table 4: Shows number of visits to the hospital		
Number of visits to the hospital	**FCM group**	**Iron sucrose group**
1-2	50	8
4-6	0	41
>6	0	1

The numbers of visits to the hospital were 1-2 visits in FCM group and 41 patients in the sucrose group had 4-6 visits to the hospital (table 4).

Discussion

In the developing countries anemia in pregnancy contributes significantly to maternal mortality and morbidity. Despite prophylactic iron supplementation, the prevalence of anemia in pregnancy has not come down. This is because of poor nutrition, oral intolerance and poor compliance to oral iron. This leads to anemia in second and third trimester. In these conditions, parenteral iron improves the hemoglobin significantly without the side effects of oral iron. Numerous studies have been done to document to safety and efficacy of parenteral iron in pregnancy. Ferric carboxymaltose is newer molecule with documented safety profile which has the advantage of giving large dose per sitting, thereby reducing the number of hospital visits.

In our study, anemia was more common in 20 - 25 yrs group and in multiparous women. This may be because of early marriage in the rural population and inadequate spacing between the pregnancies.

In the present study, the number of doses required to correct anemia was significantly less with ferric carboxy maltose i.e. 1-3 doses in comparison to iron sucrose thereby reducing the number of hospital visits for repeated

infusions. The rise in mean hemoglobin at 12 weeks was significantly high with ferric carboxy maltose i.e. 3.2 gm % with less frequent side effects. No side effects on the fetal heart rate were noted in both the groups. Thus, ferric carboxymaltose is found to be effective for correction of anemia in pregnancy with minimal side effects. Ambily Jose [6] conducted a randomized control study to compare ferric carboxy maltose and iron sucrose for iron deficiency anemia in pregnancy and concluded that ferric carboxy maltose is associated with faster and persistent high rise in hemoglobin over 12 weeks with least side effects.

In the study done by Amreen Naqash [9], it was found that there was a significant increase in the mean Hb from 7.76 ± 0.709 to 13.25 ± 0.606 in patients treated with FCM and 7.64 ± 0.710 to 11.59 ± 0.733 g/dL ($p < 0.001$) in patients treated with iron sucrose after four weeks of therapy which are comparable to our study.

Aakanksha Mahajan et al [10] has done a study titled 'comparative study of efficacy and safety of intravenous ferric carboxymaltose versus iron sucrose in the treatment of iron deficiency anaemia of pregnancy in a tertiary care hospital' and has concluded that ferric carboxymaltose seems superior to iron sucrose for definitive treatment of anaemia in pregnancy. The only limiting factor is its high cost but this is very well compensated when the number of visits to hospital is taken into account. Also reduced frequency of venous access reduces the risk of infection. So ferric carboxy maltose is more efficacious for parenteral iron therapy in pregnancy with least side effects and reduced number of hospital visits.

Conclusion

Ferric carboxymaltose is associated with faster rise in hemoglobin levels and significant rise in serum ferritin levels which is very crucial in second and third trimester of pregnancy thereby preventing complications of anemia. In women presenting in late second and third trimester PIFA (parenteral iron and folic acid) should be considered for faster rise in hemoglobin.

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