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# Comparison of Intravenous Iron Sucrose and Ferric Carboxymaltose Therapy in Iron Deficiency Anemia during Pregnancy and Postpartum Period

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**ABSTRACT:**

Objective of presented study was to compare intravenous iron sucrose and ferric carboxymaltose therapy in iron deficiency anemia during pregnancy and postpartum period. Methods: A clinical observational study was undertaken at tertiary care teaching hospital over a period of 4 months in 30 pregnant women and 30 post partum women. The baseline hemoglobin and serum ferritin levels were recorded prior to treatment. After completion of the treatment the women were followed up for changes in hemoglobin and serum ferritin levels on day 8 and day 15. The mean rise of hemoglobin value was 5.2 for ferric carboxymaltose and 4.1 g/L for iron sucrose in pregnant women. For postpartum women mean rise of hemoglobin was 4.9 on the 15$^{th}$ day of treatment. Side effects were reported in 40% among patients treated with iron sucrose as compared to 16.67% in case of ferric carboxymaltose. Ferric carboxymaltose administration in pregnant women is safe and well tolerated by pregnant as well as post partum women. Ferric carboxymaltose is associated with fewer side effects as compared to iron sucrose in present study. It also offers the advantage of a much higher iron dosage at a time reducing the need for repeated applications and increasing patients' comfort.

**KEY WORDS:** Anemia; ferric carboxymaltose; hemoglobin; intravenous iron therapy; iron deficiency; iron sucrose; pregnancy

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## INTRODUCTION:

Anemia is one of major contributing factors in maternal mortality and morbidity in third world countries and according to the WHO, contributes to 20% maternal deaths.[1]Anemia is widely prevalent in developing countries like India and the most common affected group is women of child bearing age particularly pregnant women with an estimate of nearly two-thirds of all pregnant women. The main cause of anemia in pregnancy is found to be iron deficiency, i.e. about 95%.[2]

In pregnancy, iron deficiency is exaggerated because of the ability of foetus to extract its requirement in obligatory direction; from a mother whose body iron levels are already depleted. Iron absorption may be adequate in healthy, iron-replete women. However, it is far below the iron requirement of an iron depleted or deficient pregnant women. [3, 4] Therefore, more amount of iron, exceeding the daily requirement, is to be supplemented. This is aggravated by gastrointestinal effects of pregnancy like nausea and vomiting, motility disorder with reflux esophagitis, indigestion, constipation, and a tendency to develop hemorrhoids. These factors increase the severity of anemia. [5]

Postpartum anemia is observed in up to 27%of women. Postpartum anemia is associated with longer hospital stays, depression, anxiety, and delayed infant development. At the present time, there is no consensus on the management of postpartum anemia, and clinical practice varies from one clinic to another. The standard approach to treatment in the majority of institutions is oral supplementation, with blood transfusion reserved for more severe or symptomatic cases, [6] but there are a number of hazards of blood transfusion including transfusion of wrong blood, anaphylaxis and risk of transmission of infections, any of which would be devastating for the young mother. Therefore, parenteral iron treatment is expected to be advantageous in cases in which treatment with oral iron is notpossible due to gastrointestinal (GI) side effects, in patients with poor compliance, or in patients with severe anemia.[7]

Iron dextran and iron sorbitol citric acid are widely used parenteral iron preparations since long time. However, threat of unpredictable anaphylactic reactions by these conventional parenteral iron preparations prevented their wider use.[2]Iron sucrose has been used for years for intravenous treatment of iron deficiency in second and third trimester of pregnancy and post partum period.[1] However, its use is limited to low dose due to local and systemic side effects in higher doses. Recently, ferric carboxymaltose has been introduced. This preparation can be used intravenously in high doses with up to 1000 mg infused in l5 min with low risk of side effects. However its use in pregnancy is approved for second and third trimester only. [8]

The aim of our study is, therefore, to compare intravenous ferric carboxymaltose with iron sucrose during pregnancy and post partum period regarding the efficacy and safety profile.

## MATERIAL AND METHODS

**Study design, study setting and study period:** Hospital based, Prospective, Comparative trial was carried out in the obstetric ward of S.B.K.S. Medical College & Research Institute, Piparia, Vadodara, Gujarat in the study period of 4 month (October 2013-January 2014).

**Study participants, sample size, sampling:** Purposively study participants were classified in four groups. First group was of 15 Pregnant women with gestational age between 12 and 32 weeks, diagnosed as iron deficiency anemia with hemoglobin<9 g/dl (Group A). Second group was of 15 Pregnant women with gestational age between 12 and 32 weeks, diagnosed as iron deficiency anemia with haemoglobin <9 g/dl (Group B). Third group was of 15 Women of post partum period with haemoglobin < 10.5 g/dl (Group C). Fourth group was of 15 Women of post partum period with haemoglobin level < 10.5 g/dl (Group D).

**Exclusion criteria**: a) Anemia not linked to iron deficiency b) Intolerance to iron derivatives. c) History of asthma, thromboembolism, seizures or drug abuse. d) Women with signs of infection or evidence of renal or hepatic dysfunction.

**Methods of data collection:** The study participants were selected from the ante natal and postpartum ward after fulfilling the selection criteria. After careful history taking, clinical examination and minimal investigations other causes of anemia were ruled out. The initial iron status of the woman was assessed by the clinical and laboratory examinations (complete blood picture and serum ferritin levels). Women fulfilling above criteria were included in the study. They were randomly divided into above four groups. The amount of iron needed by an individual patient is calculated by the following formula [2]:

*Body weight (kg) × 2.3 × (15-patient's haemoglobin, g/dl) +500 or 1000 mg (for stores)*

**Group A and Group C had been treated with Iron sucrose:**

Two doses intravenous iron sucrose 200 mg on day 2 and day 4 following recruitment in study in the form of iron sucrose complex, administered as short intravenous infusion (in 100 ml of 0.9% normal saline) over half an hour.

**Group B & Group D had been treated with Ferric carboxymaltose (FCM):**

FCM was administered in single, once weekly infusions of 1000 mg or 500 mg iron over at least 15 minutes on day 1 and, if needed on the day 8. Patients with a body weight < 67 kg received a maximum of 500 mg iron per infusion.

Test dose was given before the therapy. If the patient did not show any reaction within 1 h, the remaining drug was administered. Whole therapy was monitored and each recipient was kept in observation in the hospital for at least 2 h after administration of parenteral iron for signs of intolerance such as anaphylactic reactions, skin rash, dyspnoea, facial flushing, metallic taste, urticaria, hypotension, headache, chest pain, tachycardia, breathlessness etc.

**Statistical analysis:** Data were cleaned and entered in Microsoft excel 2007. Data were analysed by EPI info 7. Continuous variables were expressed as mean ± SD. Categorical variable were expressed as percentage.

**Table 1: Baseline characteristics of study participants**

| Variables | Pregnant women | | p-value |
|---|---|---|---|
| | Participants given Iron sucrose (n=15) | Participants Ferric carboxy maltose (n=15) | |
| Age (in years) | 28.4 ± 3.7 | 29.1 ± 2.4 | NS |
| Gestational week | 26.8 ± 12.8 | 29.4 ± 14.2 | NS |
| Hemoglobin (g/dl) | 8.9 ± 2.3 | 8.7 ± 3.1 | NS |
| Serum ferritin | 10.9 ± 7.8 | 11.4 ± 6.7 | NS |
| MCH (pg) | 27 ± 3.6 | 25.8 ±4.5 | NS |
| MCV (fL) | 81.2 ± 8.1 | 81 ± 10.4 | NS |
| Occupation | | | |
| Working | 4 | 6 | - |
| Housewife | 11 | 9 | |
| Smoking habit | | | |
| Yes | 0 | 0 | - |
| No | 15 | 15 | |
| Tobacco chewing | 2 | 3 | - |
| Yes | 13 | 12 | |
| No | | | |
| Drink alcohol | | | |
| Yes | 0 | 0 | - |
| No | 15 | 15 | |
| **Variables** | **Post-partum women** | | **p-value** |
| | **Participants given Iron sucrose (n=15)** | **Participants Ferric carboxy maltose (n=15)** | |
| Age (in years) | 29.6 ± 2.6 | 28.4 ± 2.3 | NS |
| Hemoglobin (g/dl) | 7.9 ± 2.7 | 7.5 ± 3.0 | NS |
| Serum ferritin | 11.2 ± 5.1 | 10.9 ± 4.2 | NS |
| MCH (pg) | 28 ± 1.8 | 27.8 ±2.1 | NS |
| MCV (fL) | 84.2 ± 9.5 | 83.2 ± 9.1 | NS |
| Occupation | | | |
| Working | 3 | 5 | - |
| Housewife | 12 | 10 | |
| Smoking habit | | | |
| Yes | 0 | 0 | - |
| No | 15 | 15 | |
| Tobacco chewing | 2 | 1 | - |
| Yes | 13 | 14 | |
| No | | | |
| Drink alcohol | | | |
| Yes | 0 | 0 | - |
| No | 15 | 15 | |

**RESULTS**

In our prospective study, 30 pregnant women with anaemia were randomized to receive IV iron sucrose (Group A) or IV ferric carboxymaltose (Group B) and 15 postpartum women with anaemia were randomized to receive IV iron sucrose (Group A) or IV ferric carboxymaltose (Group B). Before treatment, iron deficiency anaemia was confirmed with Hb levels. Table 1 is showing matching of baseline characteristics of study participants.

There was a rise in the mean level of hemoglobin in both treatment modalities. On the day 15 rise was more in ferric carboxymaltose as compared to iron sucrose in both pregnant as well as in post partum women and it was statistically significant (Table 2)

**Table 2: Comparison of hemoglobin level in both treatment modalities**

| Variables | Pregnant women | | p-value |
|---|---|---|---|
| | Participants given Iron sucrose (n=15) | Participants Ferric carboxy maltose (n=15) | |
| Hb at 0 day | 7.9 ± 2.7 | 7.5 ± 3.0 | NS |
| Hb at 8$^{nd}$ day | 9.25 ± 1.91 | 10.1 ± 1.5 | NS |
| Hb at 15$^{th}$ day | 11.6 ± 1.3 | 12.7 ± 2.4 | 0.04* |
| **Hemoglobin** | **Post-partum women** | | **p-value** |
| | **Participants given Iron sucrose (n=15)** | **Participants Ferric carboxy maltose (n=15)** | |
| Hb at 0 day | 7.9 ± 2.7 | 7.5 ± 3.0 | NS |
| Hb at 8$^{th}$ day | 9.4 ± 1.9 | 9.9 ± 2.3 | NS |
| Hb at 15$^{th}$ day | 11.2 ± 2.1 | 13.1 ± 2.3 | 0.02* |

* statistically significant

Serum ferritin also shows increment in both modalities in 8$^{th}$ and 15$^{th}$ day. But it was not statistically significant in pregnant or post partum women (table 3)

Mean rise of hemoglobin and mean rise of ferritin were high in case of intravenous ferric carboxymaltose as compared to iron sucrose but it was not statistically significant in any of the group. (table 4)

**Table 3: Comparison of serum ferritin in both treatment modalities**

| Serum Ferritin | Pregnant women | | p-value |
|---|---|---|---|
| | Participants given Iron sucrose (n=15) | Participants Ferric carboxy maltose (n=15) | |
| On 0 day | 10.9 ± 7.8 | 11.4 ± 6.7 | NS |
| On 8th day | 15.2 ± 3.5 | 16.3 ± 3.8 | NS |
| On 15th day | 20.1± 3.4 | 20.6 ±3.8 | NS |
| **Serum ferritin** | **Post-partum women** | | **p-value** |
| | **Participants given Iron sucrose (n=15)** | **Participants Ferric carboxy maltose (n=15)** | |
| On 0 day | 11.2 ± 5.1 | 10.9 ± 4.2 | NS |
| On 8th day | 16.1 ± 3.2 | 16.4 ± 3.4 | NS |
| On 15th day | 20.8 ± 2.3 | 21.0 ± 3.9 | NS |

**Table 4: Comparison of rise in mean value of hemoglobin and serum ferritin in both treatment modalities**

| | Participants given Iron sucrose | Participants Ferric carboxy maltose | p-value |
|---|---|---|---|
| Rise of haemoglobin | 4.1 ± 1.4 | 5.2 ± 2.1 | NS |
| Pregnant women | 4.9 ± 1.7 | 5.4 ± 2.6 | NS |
| Post partum women | | | |
| Rise in ferritin | | | |
| Pregnant women | 9.4 ± 2.3 | 9.1 ± 3.2 | NS |
| Post partum women | 8.3 ± 3.5 | 9.9 ± 2.6 | 0.045 |

Adverse reactions were milder in both the cases and mostly affected to local reactions. Rate of side effect was 16.67% in case of ferric carboxymaltose as compared to 40% as in the participants treated with iron sucrose.

**DISCUSSION**

Iron deficiency anemia during pregnancy is common and deserves special attention because of its potential consequences. Oral iron is the first line of therapy in pregnancy with anemia. However, the compliance of pregnant women is much less because of its untoward effects such as

**Table 5: Comparison of adverse reactions in both treatment modalities**

| ADRs | Participants given Iron sucrose (n=30) | Participants Ferric carboxy maltose (n=30) | Total (n=60) |
|---|---|---|---|
| Pain/burning at injection site | 6 | 2 | 8 |
| Swelling at injection site | 3 | 2 | 5 |
| Blackening at injection site | 0 | 0 | 0 |
| Nausea/vomiting | 1 | 0 | 1 |
| Gastritis | 1 | 1 | 2 |
| Giddiness/hypotension | 1 | 0 | 1 |
| Other | 0 | 0 | 0 |
| Total | 12 (40%) | 5 (16.67%) | 17(28.34% |

gastritis, constipation and blackening of stool. Cumulative effects of all these warrant the use of parenteral iron. However because of cost and compliance to injectable iron, the current practice in this area is to give one fixed dose of parenteral iron then switch over to oral iron or continuations of parenteral iron according to severity of anemia. The fetus and placenta require about 500 mg of iron and a similar amount is needed for red cell increment. An average postpartum blood loss and lactation for six months each accounts for about 180 mg. From total of 1360 mg, 350 mg may be subtracted (saved as a result of amenorrhea) to give an actual extra demand for about 1000 mg. This is unlikely to be provided by dietary iron but may be mobilized from full iron stores (about 1000 mg). It is the state of stores that largely determine whether or not a pregnant woman become anemic. The smaller her stores, the earlier the anemia occurs.[9,10] Present study showed that iron sucrose complex as well as ferric carboxymaltose can be used in the pregnant patients and in post partum women with iron deficiency anemia not only for correction of deficit in the hemoglobin but also for restitution of iron stores. Both modalities had increase in the hemoglobin level on day 8 and on day 15 which is homologous with previous studies [11,12,13,14] but increment in the hemoglobin was slightly more in the patients treated with FCM as compared to Iron sucrose. (Table 2) Serum ferritin level was also increased in the both treatment modalities likewise in the previous researches but was more in the patients treated with FCM. Our study consolidates previous [15, 16] research that ferric carboxymaltose is well tolerated in pregnant women and even in post partum women

and has fewer or equal number of side effects compared to the previously used iron sucrose. The incidence of drug-related adverse events was low and comparable to those described for ferric carboxymaltose and iron sucrose in other studies. Registered adverse events were all mild and quickly reversible and mostly restricted to local reactions at the infusion site. There were no treatment-related serious adverse events. No anaphylactic or anaphylactoid reaction was detected. No venous thrombosis was registered. None of the adverse events required further medical intervention.

Limitations of our study were there was small sample size in both treatment and control group. Some confounding variables were also not taken in to consideration. Large sampled trials are required to compare the efficacy and safety of intravenous ferric carboxymaltose over iron sucrose therapy in Indian set up.

**CONCLUSION:**

Intravenous ferric carboxymaltose administration increases the hemoglobin level more rapidly as compared to iron sucrose in women with iron deficiency anemia in the pregnancy and postnatal period. It also stores iron more rapidly. Ferric carboxymaltose is well tolerated, as safe and effective alternative to blood transfusion in the treatment of iron deficiency anemia in the postpartum period.

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