Original Research Paper

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FERRIC CARBOXY MALTOSE IN ANAEMIA IN PREGNANCY

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ABSTRACT

BACKGROUND: Iron deficiency is the common nutritional deficiency amongst women of child bearing age. Peripartum iron deficiency anaemia is associated with significant maternal, fetal and infant morbidity. Current options include oral iron supplementation, which can be ineffective and poorly tolerated, parenteral iron preparations and red blood cell transfusions, which carry an inherent risk and should be avoided. Ferric carboxy maltose is a new treatment option that may be better tolerated. The study was designed to assess the safety, efficacy and tolerability of intravenous ferric carboxymaltose for correction of iron deficiency anaemia in antenatal or postnatal period.

METHOD: Prospective cohort study, 50 iron deficiency anaemic antenatal or postnatal women received ferric carboxy maltose. Anaemia was diagnosed based on Hb levels and iron deficiency was diagnosed based on serum ferritin levels(<30µg/l). Administration of FCM (15 mg/kg, maximum of 1000 mg) over 15 minutes was well tolerated. Treatment effectiveness was assessed by follow up hemoglobin levels after 3 weeks. Safety and tolerability was assessed by analysis of adverse drug reactions and fetal heart rate monitoring in antenatal patients during the infusion.

RESULTS: Most of the women were in the age group of 22-30 years and had moderate anaemia as per WHO guidelines. Intravenous ferric carboxy maltose infusion significantly increased mean Hb values above baseline levels in almost all women. Increased Hb values were observed at 3-8 weeks post infusion. No serious adverse effects were found.

CONCLUSIONS: Intravenous ferric carboxymaltose was safe and effective in antenatal and postnatal patients with iron deficiency anaemia. It elevates Hb level and restores iron stores faster than other IV iron injectables and oral iron.

KEYWORDS : Ferric carboxy maltose, intravenous iron, iron deficiency anemia, safety.

INTRODUCTION

According to NFHS-4 2015-16, prevalence of iron deficiency anaemia in India, in pregnant women age 15-49years is 50.3%, in urban states it is 45.7% and in rural it is 52.1%. India contributes to about 80 percent of maternal mortality due to anaemia[1]. IDA is associated with significant maternal, fetal and infant morbidity. Poor outcomes for the fetus and infant include: preterm birth, fetal growth restriction, intrauterine fetal death, low Apgar scores and infection[2]. Women with iron deficiency are also at risk of adverse effects requiring medical interventions such as red blood transfusion[3], cardiovascular problems, reduced physical and cognitive performance, reduced immune function, tiredness and increased depressive episodes[4]. Peri-partum maternal iron deficiency has also been associated with childhood developmental problems[5] and negative mother-infant interactions such as an increase in negative statements and decreased responsiveness[6]. Progression from iron deficiency to iron deficiency anaemia (IDA) in pregnancy is common, due to the increased demand for iron during pregnancy, required to support maternal haemoglobin mass expansion, as well as the growing fetus and placenta. During pregnancy, the need for absorbed iron increases from 0.8mg/day in the first trimester to 7.5mg/day in the third trimester. WHO has classified anaemia into mild(9-11gm%), moderate (7-9gm%) and severe(<7gm%) categories[7]. This is further aggravated by blood loss associated with delivery. Deliveries by both caesarean section and vaginal deliveries that require instrumentation/intervention represent an even greater risk[4] increasing a woman's vulnerability for peri-partum blood transfusion[3], chronic iron deficiency anaemia and iron store depletion, all compromising maternal well-being[8]

Iron deficiency is potentially both preventable and treatable. Effective management strategies that allow women to replenish iron stores, both antenatal or postnatal, restore haemoglobin values and are likely to enhance the health of the mother and infant[9]. For many decades the mainstay treatment of IDA has been oral iron, older iron injectables and red blood cell (RBC) transfusions. However, oral iron supplementation can lead to significant side effects resulting in non-compliance in many patients and the risks for RBC transfusion are well described and should be avoided whenever possible. Parenteral iron preparations is indicated when there is absolute non-compliance with, or intolerance to, oral iron therapy or proven malabsorption (RCOG, 2007). Intravenous iron is less commonly used as fear of anaphylaxis with iron dextran formulations. The development of dextran free parenteral iron formulations with an improved safety profile, and a more rapid delivery time suggests that intravenous iron should be considered as a mainstay treatment for moderate to severe IDA[10]. As free iron may lead to the production of hydroxyl radicles with potential toxicity to tissues, iron deficiency should be confirmed by ferritin levels before use of parenteral preparations. Contraindications include a history of anaphylaxis or reactions to parenteral iron therapy, first trimester of pregnancy, active acute or chronic infection and chronic liver disease[11].

The intravenous iron preparations currently available are summarized in table1[11]

	IRON DEXTRAN COMPLEX	IRON SUCROSE COMPLEX	IRON FERRICARBOXYMALTOSE
Dose of elemental iron	50 mg/ml	20 mg/ml	50 mg/ml
Test dose required	yes	First dose new patients only	No
Routes of administration	Slow Intravenous Injection, Intravenous infusion, Intramuscular injection	Slow Intravenous Injection, Intravenous infusion	Slow Intravenous Injection, Intravenous infusion
Able to administer total dose	Yes (upto 20 mg/kg bodyweight over 4-6 h)	No	Yes (up to 20 mg/kg bodyweight with maximum of 1000 mg/wk over 15 min)
Half life	5 hours	20 hours	7-12 hours
Dosage	100-200mg for IV injection upto 3 times a week. Total dose infusion upto 20 mg/kg body weight over 4-6 hours	Total IV single dose no more than 200 mg, can be repeated upto 3 times in 1 week	1000 mg by IV Injection upto 15 mg/kg per week. Total dose infusion upto 20 mg/kg body weight. Maximum weekly dose of 1000mg, which can be administered over 15 min.

Use in pregnancy	No adequate data, contraindicated in first trimester	Not in first trimester	Avoid use in first trimester
ADR	5% patients may experience minimal adverse events	0.5-1.5% of patients may experience ADR	3% of patients may experience adverse events

Ferric carboxy maltose is a newer dextran-free iron formulation with a near neutral pH, physiological osmolarity and increased bioavailability which allows for single dose, short 15minute infusion time and higher dosing (up to 1000 mg)[12]. These properties make ferric carboxy maltose an attractive alternative to iron sucrose in terms of risk profile, efficacy, patient comfort and convenience, staff and institutional resource utilization. Each 10 ml vial contains 500mg of iron as ferric carboxymaltose. Ferric carboxymaltose is administered intravenously, as a single dose of 1000mg over 15 min and it has shown superiority to oral ferrous sulphate in the treatment of iron deficiency anaemia in the postpartum period, with rapid and sustained increases in Hb[11]. Administration of FCM requires careful monitoring of patients for signs and symptoms of hypersensitivity reactions during and following each administration of ferric carboxymaltose. The patient should be observed for 30 minutes following each Ferric Carboxymaltose Injection.

There are no adequate and well controlled trials of FCM in pregnant women. A careful benefit/risk evaluation is required before use in pregnancy and FCM should not be used during pregnancy unless clearly necessary. Treatment with FCM should be confined to second & third trimester if the benefit is judged to outweigh the potential risk for both mother and fetus[13].

Most commonly reported adverse reaction is nausea followed by headache, dizziness & hypertension. Most serious ADR is anaphylactoid reaction which is rare[13].

METHODS

Women with documented IDA, defined as Hb < 10.5 g/dl in antenatal and <10g/dl in postnatal patients, who consecutively presented to receive ferric carboxy maltose infusions were recruited to this study. A total of 50 women were included. Due to the limited availability of safety data for its use in pregnancy, we adopted a longer infusion protocol (30 min) than recommended by the manufacturer (15 min). Maternal blood pressure was taken during infusion and foetal heart rate was assessed before and after infusion in antenatal patients. Blood samples were collected to measure haemoglobin, and ferritin levels. Patients with serum ferritin levels <30 µg/l prior to infusion were included in study.

Dose of FCM was calculated by Ganzoni formula= 2.4* (target Hb-Actual Hb)*weight of patient+500. And FCM administered as 1000mg in 250 ml NS iv slowly over 15-30minutes. Hb% levels were repeated 3 weeks after treatment.

RESULTS

A total of 50 women with iron deficiency anaemia received a ferric carboxy maltose infusion in their antenatal or postnatal period, with pre-infusion haemoglobin data available for all 50 women. Following infusion, haemoglobin values were repeated and data were available for 80% of women i.e. 40 women(3 weeks post infusion). Depending upon the severity, moderate severity of anaemia (Hb -7 to 9) was seen most commonly in 34 patients out of total 50 women (68%).

Demographic information of women in the study

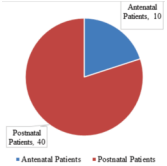

FIGURE 1. Number of antenatal and postnatal patients

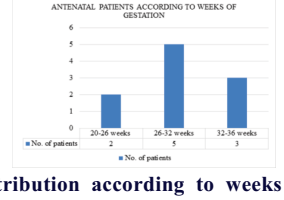

FIGURE-2 Distribution according to weeks of gestation in antenatal patients

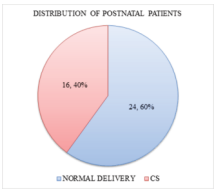

FIGURE-3 Distribution of postnatal patients

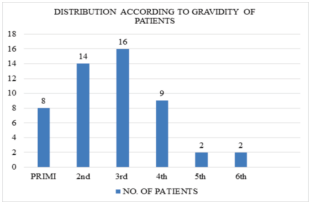

FIGURE-4 Distribution according to gravidity of patients

TABLE-2 Distribution according to degree of anaemia

Severity of Anaemia	No. Of Patients
Mild	9(18%)
Moderate	34(68%)
Severe	7(14%)

TABLE-3 Distribution according to weight of patients

Weight of patients	No. Of patients
<40 kg	2
41-49 kg	8
50-59 kg	26
60-69 kg	14

TABLE-4 Distribution according to age of patients.

AGE(YEARS)	NO. OF PATIENTS
<19 YEARS	5(10%)
20-29 YEARS	43(86%)
30-39 YEARS	2(4%)

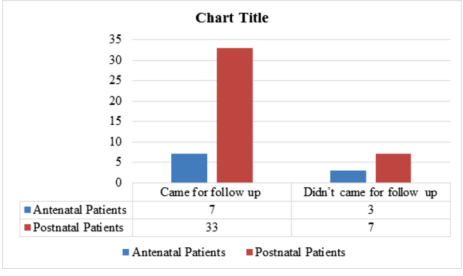

FIGURE-5 Follow up of patients.

All women responded to the treatment with increased Hb values.

The pre-infusion haemoglobin level was significantly lower than haemoglobin values measured at all subsequent visits. There was increase in haemoglobin levels from 3 to 6 weeks post-infusion (average increase 3 gm/dl). Average percentage rise in Hb in patients was 37%. When IDA severity was included in the analysis, a similar pattern of results emerged. For all three severity groups, haemoglobin levels increased post infusion at 3 weeks. No serious adverse effects were reported in any of the 50 women receiving an infusion.

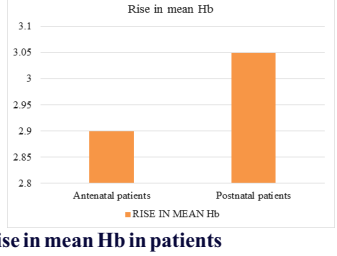

FIGURE-6 Rise in mean Hb in patients

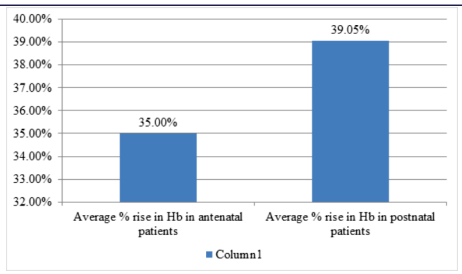

FIGURE -7 Average % rise in Hb in patients.

DISCUSSION

IDA in pregnancy is one of the important causes of maternal and neonatal morbidity. IDA is also an important indirect cause of maternal death. In majority of cases anemia can be treated effectively with oral iron preparations. Intolerance to oral iron leads to a greater percentage of failure in correction of iron deficiency anemia during pregnancy. In third trimester of pregnancy IDA can also be treated with safe blood transfusion. Inspite of all clinical tests for safe blood transfusion, still there are lots of adverse effects and should ideally be avoided. There is little number of clinical studies on using ferric carboxymaltose in pregnant women. A recent Cochrane review concluded that large, good quality trials are required to assess the efficacy and adverse effects of ferric carboxymaltose[14.] There are recent retrospective observational studies comparing ferric carboxymaltose with different intravenous iron preparations that highlighted the safety and efficacy in favor of ferric carboxymaltose[15] This observational study investigated the efficacy and safety of FCM. Most women received a single dose of 1000 mg iron. No woman in our study required more than one FCM administration. This practice of single dose administration is facilitated by the greater stability of the FCM complex compared to less stable intravenous iron compounds such as ferric gluconate and iron sucrose that require multiple administrations of lower doses[16]. Only few randomized controlled studies on the use of FCM during pregnancy are present, though its safety has been proven beyond doubt in postnatal and gynaecological women[17,18]

Important contributing factors responsible for high incidence of anaemia in our country include early marriage, teenage pregnancy, multiple pregnancies, less birth spacing, low iron and folic acid intake and high incidence of worm infections in Indian population[19]. As the number of pregnancies increase the risk of anaemia and its severity goes on increasing, if adequate spacing is not maintained due to exhaustion of already scarce iron stores. In a prospective study, intravenous FCM infusion increased haemoglobin values above baseline levels in all women. Increased haemoglobin values were observed at 3 and 6 weeks post infusion and up to 8 weeks post-infusion. Ferritin levels also increased significantly after the infusion[10]. David et al, Evstatiev et al and Iftikhar et al[20-22] proved that FCM was well tolerated and had better compliance than other iron preparations. The results of our study were consistent with the above mentioned trials.

There was an increase in mean hemoglobin levels with replenishment of iron stores and clinical improvement after FCM administration. Our study showed significant increase in haemoglobin levels from 3 to 6 weeks post-infusion (average increase 3 gm/dl). It permits a much higher single dose over a short period of time. No serious adverse effect were reported in the study (as the study group is less, chances of rare complications are also minimal). Thus rapid infusion option of a large single dose of ferric carboxymaltose offers a promising treatment modality for pregnant women with iron deficiency anaemia. This property of ferric carboxymaltose can reduce the IDA related burden of the perinatal patients' complications and improve the health care system. Thus, FCM is a safe and an effective treatment option for IDA[16].

CONCLUSION

The data from this prospective case series is consistent that ferric carboxymaltose administration in the second and third trimester of pregnancy and postpartum patients is likely to be safe and effective. In our study ferric carboxymaltose successfully corrected IDA. The intervention corrected anterpartum and post-partum anaemia. Despite moderate to severe anaemia at presentation, labour associated blood loss was tolerated well resulting in low peri-partum RBC transfusion rates. Hemoglobin levels increased upto 2.2 to 3g/dl in treated patients. No serious adverse events were recorded. Well-being also improved for the majority of women after the infusion.

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Conflict of interest: *None declared*
Ethical approval: *The study was approved by the Institutionl Ethics Committee*

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