STUDY OF INTRAVENOUS FERRIC CARBOXY MALTOSE IN IRON DEFICIENCY ANEMIA DURING PREGNANCY AND POST-PARTUM PERIOD- SAFETY AND EFFICACY

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ABSTRACT

Background and objectives: *Iron deficiency is common among women of childbearing age in both the developed and developing countries. Intravenous Ferric carboxy maltose (FCM) is a novel molecule which can be safely administered in a single dose as large as 1000mg in as little as 15 minutes with no significant adverse effects.*

Methods: *A hospital based prospective study included 39 antenatal women >20-36 weeks gestation and 119 postpartum women with documented iron deficiency anemia. Intravenous Ferric carboxy maltose (FCM) was administered and improvement in hemoglobin and iron stores was assessed after 3 weeks. Safety of intravenous FCM was also assessed during the study.*

Results: *There was a significant improvement in hemoglobin over a period of 3 weeks from mean Hb 8.97±1.05 gm/dL to 11.34±0.90 gm/dL with p value <0.001 which was statistically significant. There was also a significant improvement in serum ferritin levels with p value <0.001. No serious adverse effects of FCM were noted in this study.*

Conclusions: *Intravenous FCM is effective in treatment of iron deficiency anemia without significant adverse effects in pregnancy after first trimester and during post-partum period. FCM should be offered to all women with IDA to minimize maternal morbidity & mortality.*

Key words: *Iron deficiency anaemia, Postpartum anaemia, Intravenous iron, Ferric carboxy maltose*

INTRODUCTION

Iron deficiency is recognized as a common nutritional deficiency amongst women of childbearing age in both the developed and developing world [1]. Effects of iron deficiency during pregnancy and post-partum period include - fatigue, cardio-respiratory problems, increased chances of infection, reduced immunity, lactation failure, increased post-partum depressive episodes, post-partum hemorrhage and requirement of packed cell transfusion as well as mortality[2].

WHO has defined anemia as hemoglobin less than 11 gm% during pregnancy and post-partum period. Lack of iron intake, increased iron demand, faulty dietary habits, parasitic infections & malaria are common causes of iron deficiency during antenatal and post-partum period. WHO estimates that, of the 529000 maternal deaths occurring every year, 136000 or 25.7% take place in India, where two-thirds of maternal deaths occur after delivery, post-partum hemorrhage being the most commonly reported complication and the leading cause of death (29.6%) [3].

There are various iron preparations available for the treatment of iron deficiency anemia. Oral iron is the preferred route of administration for mild anemia. Treatment with oral iron preparations is used routinely in pregnant women, if iron deficiency with or without anemia develops. However, oral iron supplementation often leads to adverse effects, such as constipation, diarrhea & abdominal pain. If these unwanted gastrointestinal effects arise, adherence to iron treatment decreases. Packed cell transfusion is reserved for cases with severe anemia but carries significant risk of transmissible diseases as well as risk of anaphylactic and allergic reactions. Intravenous iron preparations like iron dextran, iron – sucrose and ferric carboxy maltose (FCM) have been considered as an alternative to oral iron. Iron dextran may cause allergic reaction and iron sucrose requires repeated doses infusion. Ferric carboxymaltose is a novel molecule composed of a polynuclear iron (III) hydroxide complexes to carboxymaltose. The ability to safely inject a single dose as large as 1000mg in as little as 15 minutes and thereby reducing the need for multiple IV iron infusions and very less adverse reaction render this novel agent a potentially ideal candidate for the treatment of iron deficiency anemia. FCM is cost effective with other positive benefits of fewer hospital visits and improved patient compliance [4].

To date, there are few clinical studies using ferric carboxymaltose in pregnant women. The primary aim of this study was to assess the use of intravenous ferric carboxymaltose in the correction of iron deficiency anemia in pregnant women after first trimester and postpartum patients. The secondary aims were to determine the extent and severity of adverse effects of ferric carboxymaltose, and to evaluate the perceived quality of life of women in the post-partum period.

MATERIALS AND METHOD

This is a prospective study conducted over a period of 11 months from December 2013 to October 2014 including 158 patients attending the Obstetric department of Institute of Kidney Disease and Research Center, Ahmedabad. Approval of ethical committee was taken.

We included females of more than 18 years ago with gestation age >20 weeks-36 weeks and post-partum patients irrespective of the mode of delivery. All patients had definitive diagnosis of iron deficiency anemia and hemoglobin between 6 to 11 gm. %. Iron deficiencies was diagnosed on parameters like complete blood count, peripheral smear, packed cell volume, serum ferritin, serum total iron binding capacity, serum iron. History of previous allergic reaction to iron was elicited. Patients were explained about drug, its effect and possible side effects. Informed and written consent was obtained. Patient with anemia of other causes and hemodynamic instability were excluded.

Total dose of ferric carboxy maltose was calculated on the basis of hemoglobin deficit and body weight using Ganzoni formula:

Total iron deficit (milligram)= body weight (kg) x [target Hb - actual Hb (gm %)] x 0.24 + depot iron (mg)

Depot iron= 15 mg/kg in case body weight <35kg and 500 mg in case of weight more than 35 kg

A single dose of Ferric Carboxymaltose Injection should not exceed 1000 mg of iron (20 ml) per day or 15 mg of iron (0.3 ml) per kg body weight. Not more than 1000 mg of iron (20 ml) was administered in one week. It is to be diluted only in sterile 0.9% sodium chloride solution & should be administered over 10-15 minutes.

The drug was administered under direct supervision and infusion was immediately stopped in case of any side effects. Pulse, Blood pressure and in case of pregnancy fetal heart rate were monitored at 5 minutes interval. Patients were observed for half an hour after transfusion. The patients were followed up after 3 weeks of total dose infusion to assess the status of iron stores and increase in hemoglobin levels using same parameters as previously mentioned.

RESULTS

A total of 158 women were included in study in which 39 females were antenatal with gestational age more than 20 weeks to 36 weeks and 119 were post-partum. Mean age was 28 years in this study.

Table 1-: Distribution of patients

Parameter	Value
Total no of patients	158
Antenatal patients	39 (24.6%)
Postpartum patients	119 (75.4%)
Normal delivery	34
Caserean delivery	85

Mean hemoglobin before FCM therapy was 8.97±1.05 gm/dL& mean serum ferritin was 18.30±16.39 ng/ml.

FCM was administered on basis of Iron deficit. Iron requirement in this study varied from 500 mg to 1500mg per patient with average requirement 1000 mg elemental iron per patient.

In our study all subjects were classified according to WHO guidelines of degree of anemia [3] [Table 2].

Table 2-: WHO classification of anemia

Degree of anemia	No of patients
Mild (8 to 11gm/dl)	130 (87%)
Moderate(6 to 7.9 gm/dl)	28 (13%)
Severe(<6 gm/dl)	00 (0%)

Table 3 shows safety points of drug that there was no serious life threatening adverse events reported. In 4 subjects were reported local adverse reactions like itching and irritation at local site and 5 subjects had systemic reactions in form of giddiness, headache and nausea.

Table 3-: Adverse reaction noted during FCM administration

Local reactions	4 (2.5%)
Systemic reactions	5 (3.16%)
Total adverse reactions	9 (5.66%)

Table 4 shows efficacy of the drug in IDA anemia patients in our study population. There was a significant improvement in Hemoglobin over a period of 3 weeks from mean Hb 8.97±1.05 gm/dL to 11.34±0.90 gm/dL with p value <0.001 which was statistically significant. There was also a significant improvement in IDA parameters with p value <0.001.These values indicate reasonable replenishment of iron stores along with a sense of well-being in all patients on subsequent follow up.

Table 4-: improvement in hematological parameters after FCM therapy

Parameters	Booking value	Post values	p-value
Hemoglobin (gm/dL)	8.97±1.05	11.34±0.90	<0.001
PCV	29.78±21.20	36.41±3.01	<0.001
S.TIBC (µg/dL)	402.57±97.28	275.59±47.24	<0.001
S.Ferritin (ng/ml)	18.30±16.39	104.10±32.46	<0.001
S.Iron (µg/dL)	47.23±18.87	92.89±26.93	<0.001

DISCUSSION

Iron deficiency anemia is a frequent cause of increased morbidity and mortality during pregnancy and postpartum period imposing substantial disease burden and can be very debilitating. Patients having IDA have longer hospital stay, risk of post-partum hemorrhage and need for blood transfusion. Hence IDA requires a great attention and high quality care. The most reliable parameters to assert IDA is hemoglobin and serum ferritin. The traditional treatments, i.e. oral iron therapy and blood transfusion involve significant drawbacks. Oral iron intake is limited by gastrointestinal side effects and non- compliance. Due to risk of infections, blood transfusions are reserved for most severe cases and particularly in life threatening situations. In addition, an inflammatory reaction can occur, particularly following surgically assisted deliveries and caesarean sections, leading to iron sequestration in the macrophages and decrease of intestinal absorption, so that administrated iron is not available for hematopoiesis.

To overcome this problems IV iron preparations (e.g. iron dextran, iron sucrose, ferric carboxymaltose) are used. However iron-dextran is not used now a day because of safety issues and iron-sucrose has to be given in multiple doses to replenish the iron stores.

FCM represents a novel iron preparation that overcomes limitations of existing IV iron preparations, is effective in correction of Hb deficit and rapidly replenishes iron stores using large dose and minimum adverse reaction [5].

In this study, mean total iron deficit was around 1000 mg against which mean actual elemental iron administered through FCM injection/infusion was also 1000mg representing 100% replenishment of deficit. Treatment with FCM increased mean Hb by 2.37 gm/d in all patients which is statistically significant ($p<0.001$) after 3 weeks in all 158 patients evaluated. Rise in hemoglobin was associated with increase in serum ferritin and serum iron significantly. Our results validate several randomized, controlled, multicenter trials in pregnancy and post-partum patients where FCM was considered to be very effective in the treatment of anemia.

In a randomized trial [6] to assess safety and efficacy of intravenous FCM in the treatment of post-partum IDA, 227 women were assigned to FCM with 1000 mg maximum dose versus 117 women who received oral ferrous sulphate 100 mg twice daily. Intravenous FCM was as effective as oral ferrous sulphate with no statistically significant difference between groups at any time point despite the shorter treatment period and a lower total dose of iron (mean 1.3 gm IV iron versus 16.8 g oral iron)[6]. Similarly in our study the mean Hb rise was 2.37 g/dL with mean FCM dose of 1 gm.

In a prospective study by Froessler et al intravenous ferric carboxymaltose infusion significantly increased Hb values ($p < 0.01$) above baseline levels in all women. Increased Hb values were observed at 3 and 6 weeks post infusion and up to 8 weeks post-infusion. Ferritin values also increased significantly after the infusion. Only 4 women had repeat ferritin values post-partum which remained above baseline levels. Fetal heart rate monitoring did not indicate a drug related negative impact on the fetus. Of the 29 (44.6%) women interviewed, 19 (65.5%) women reported an improvement in their well-being and 9 (31%) felt no difference after the infusion. None of the women felt worse. No serious adverse effects were found and minor side effects occurred in 13 (20%) patients [7].Similarly, in our study no adverse effect on fetal heart rate was found.

CONCLUSION

Intravenous Ferric carboxymaltose offers rapid correction of hemoglobin and replenishment of iron storage in body without significant adverse effects in pregnancy after first trimester and during post-partum period. FCM should be offered to all women with IDA to minimize maternal morbidity & mortality.

REFERENCES

1. Jain G, Palaria U A, JhaS.k. Intravenous Iron in Postpartum Anemia. The Journal of Obstetrics and Gynecology of India. January –February 2013;63(1):45-48.
2. Beard JL, Hendricks MK, PrrezEm, Murray-Kolb LE,BergA, Tomlinson M, et al. Mother-infant interaction and infant development are altered by maternal iron deficiency anemia, J Nutr 2005;135:850-5.
3. Bodnar LM, Cogswell ME, RN PH, McDonald T. have we forgotten the significance of postpartum iron deficiency? American Journal of Obstetrics and Gynecology 2005; 195:36-44.
4. KlaireExarchou, NancyTanahill, andreaanthoney, Atif Khalil and Shahed Ahmed. Efficacy and safety profile of single dose intravenous ferric carboxymaltose in the management of renal anemia- a single center

experience. Nephrology Dialysis Transplantation May 2013; 28(1):i363-364.

5. Pfenniger A, Schuller C, Christoph P,Surbek D. Safety and efficacy of high dose intravenous iron carboxy maltose vs. iron sucrose for treatment of postpartum anemia, J perinat Med. 2012 Apr 2;40(4):397-402.
6. Breymann C, Gliga F, Bejenariu C, Strizhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Int J Gynaecol Obstet.2008 Apr;101(1):67-73.
7. Froessler et al:Intravenous ferric carboxymaltose for anemia in pregnancy. BMC Pregnancy and Childbirth 2014,14:115