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Original Research Article

Safety and efficacy of ferric carboxy maltose in pregnant women- a pilot study

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ABSTRACT

Background: Iron deficiency is a common nutritional deficiency amongst women of childbearing age. It is associated with significant maternal, fetal and infant morbidity. Current options for treatment include oral iron, parenteral iron and red blood cell transfusions. Ferric carboxy maltose is a newer i.v. iron formulation which can be used at high doses with rapid administration. This study was undertaken to assess the safety and efficacy in pregnant women.

Methods: Prospective observational study was conducted in VIMS Ballari. 50 pregnant women between 28-36 weeks of gestation having moderate anemia with confirmed iron deficiency were administered with 1000 mg of ferric carboxy maltose (FCM). These women were followed after 2 weeks, 4 weeks and till delivery. Safety and efficacy were assessed.

Results: There was significant improvement in both hemoglobin and serum ferritin levels ($p < 0.01$). None of them had significant reactions.

Conclusions: Ferric carboxy maltose is well tolerated. Ability to transfuse in single high dose makes it a preferred drug for faster and higher replenishment of iron stores and correction of hemoglobin levels during pregnancy especially in third trimester.

Keywords: Iron deficiency, Ferric carboxy maltose, Parenteral iron therapy, Peripartum anemia

INTRODUCTION

Iron deficiency is a common nutritional deficiency amongst women of childbearing age. Peri-partum iron deficiency anemia (IDA) is associated with significant maternal, fetal and infant morbidity causing major public health problem in India.^{1,2} It contributes in preterm birth, fetal growth restriction, intrauterine fetal death, low Apgar scores and infection in fetus and infants.³⁻⁵ Peri-partum maternal iron deficiency has also been associated with childhood developmental problems and negative mother-infant interactions such as an increase in negative statements and decreased responsiveness.^{6,7} Progression from iron deficiency to iron deficiency anaemia (IDA) in pregnancy is common due to the increased demand for iron to support maternal haemoglobin mass expansion and for the growing fetus and placenta.⁸ 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 increasing a woman's vulnerability for peri-partum blood transfusion, chronic iron deficiency anaemia and iron store depletion, all compromising maternal well-being.^{9,10} However, this recognition has not resulted in a universal approach of iron supplementation.¹¹

For many decades the mainstay treatment of IDA has been oral iron 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.¹² Intravenous iron formulations offer an alternative

approach in the presence of moderate or severe anaemia, intolerance of or non-adherence to oral iron and malabsorption states.¹³ Ferric carboxymaltose (FCM) is an i.v. iron formulation which can be used at high doses and allows rapid administration (up to 1000 mg in a single dose infused in 15 minutes). Because it is free of dextran and its derivatives, FCM does not cross-react with dextran antibodies and never needed the administration of a test dose.^{2,3} The FCM molecules consist of an iron-hydroxide core chelated in a carbohydrate shell and this complex is taken up as a whole by macrophages, leading to very low levels of non-transferrin bound iron, avoiding iron toxicity and oxidative stress.³ FCM's clinical efficacy and safety have been proven in several large clinical studies across different indications with up to one-year follow-up in severe disease types such as chronic kidney disease and chronic heart failure.¹⁴⁻²⁴ At least four postpartum studies compared the safety and efficacy of FCM versus oral iron.²²⁻²⁵ Faster and greater Hb-responses were achieved in FCM-treated patients compared to those receiving oral iron and FCM replenished iron stores efficiently. Few studies or cases with limited numbers of FCM-treated pregnant women have been reported.²⁶⁻²⁹

This study was undertaken to evaluate safety and efficacy of FCM during pregnancy.

METHODS

This prospective observational study was conducted in VIMS, Ballari. Pregnant women in third trimester between 28 weeks to 36 weeks of gestation attending antenatal clinic with moderate anemia (Hb 8 to 10 gm/dl) were included in the study. After taking the consent complete blood counts with peripheral smear and iron studies of all patients were done and iron deficiency was confirmed. Women who were pretreated with other i.v. preparations, blood transfusion, megaloblastic, dimorphic anemia or other type of anemia were excluded after investigation. Total 50 cases were enrolled in the study.

Cases were transfused with Inj. FCM 1000mg in 100ml NS IV over 15-20 minutes. Pre and post transfusion vitals were monitored and women were watched for any reactions during the procedure.

These women were followed and reassessed with investigations and sense of wellbeing at the end of 2 weeks and 4 weeks after the transfusion. They were followed till delivery and investigations repeated 24 hours after the delivery. Maternal and fetal complications noted.

Statistical analysis

The collected data was compiled in EXCEL sheet and Master sheet was prepared. For analysis of this data SPSS (Statistical Software for social Sciences) software version 24th was used. Qualitative was represented in form values

and percentages. One sided ANOVA test was applied to check association between different parameters. P value was checked at 5% level of significance.

RESULTS

Among 50 patients, 2 had transfusion reactions which were managed conservatively and transfusion was stopped. They were advised oral haematinics and examined postnatally with CBC, PS and Iron profile. Their Hb levels and serum ferritin levels did not show much increase postnatally.

Table 1: Socio-demographic profile of the study subjects (n=50).

Variable	Frequency	Percent
Age group		
18-20 years	12	24
21-25 years	23	46
26-30 years	15	30
Mean±SD	23.32±3.53	
Socio-economic status		
Lower	17	34
Lower middle	18	36
Middle	12	24
Upper middle	3	6

Table 2: Associated risk factors among the study subjects (n=50).

Risk factors	Frequency	Percent
Hypothyroidism	1	2
Previous 1 ectopic	1	2
Previous 1 LSCS and 2 VBAC	1	2
Previous 2 LSCS	1	2
Previous LSCS	11	22
Rh negative status	2	4
Nil	33	66
Total	50	100

CBC and Iron profile were repeated at 2 weeks and 4 weeks post transfusion for all patients. 11 patients had first follow up at 2 weeks post transfusion, which showed modest elevation in Hb and serum ferritin. But they delivered before second follow up at 4 weeks. Postnatal investigations showed modest elevation which was statistically significant.

2 patients delivered within 2 weeks of transfusion hence first follow up was done post-natal period and there was statistically significant elevation in the markers.

For the other 35 patients, CBC and Iron profile were repeated at 2 weeks and 4 weeks post transfusion and also post-partum and these were compared. Majority 23 (46%) were in the age group of 21-25 years. 44% were primigravidae. Most of them 18 (36%) belonged to lower

middle class followed by lower class, 17 (34%). 33 (66%) did not have any associated risk factors, 34 (68%) had not taken tablets regularly. 31 (62%) were clinically pale.

Table 3: Obstetric profile of the study subjects (n=50).

Parameter	Frequency	Percent
Gravida		
Gravida 1	22	44
Gravida 2	17	34
Gravida 3	5	10
Gravida 4	1	2
Gravida 5	5	10
Parity		
Para 0	6	12
Para 1	13	26
Para 2	7	14
Para 3	1	2
Para 4	1	2
NA	22	44
Living		
Living 0	6	12
Living 1	13	26
Living 2	8	16
Living 3	1	2
NA	22	44
Abortion		
Abortion 0	16	32
Abortion 1	8	16
Abortion 2	4	8
NA	22	44

Table 4: Compliance with prophylactic IFA tablets (n=50).

Treatment regularity	Frequency	Percent
Regularly taken	34	68
Irregularly taken	14	28
Not taken	02	4

Table 6: Comparison of hematological parameters at different intervals of time before and after transfusion of ferric carboxy maltose.

Variable	Pre-transfusion (n=50)		2 weeks post-transfusion (n=46)		4 weeks post-transfusion (n=35)		Postnatal (n=47)		P value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Hb	8.78	0.58	9.98	0.54	10.14	0.36	9.62	0.64	<0.001
RBC	3.50	0.51	3.26	0.65	4.03	0.57	3.91	0.83	<0.001
MCV	62.72	1.91	74.80	7.31	75.20	4.12	74.36	4.22	<0.001
MCH	23.84	1.65	23.96	2.11	24.43	1.80	23.17	2.23	0.036
MCHC	22.18	1.47	24.37	2.48	24.71	1.30	24.21	1.82	<0.001
PI	2.90	0.74	3.20	0.50	3.43	0.78	2.77	0.73	<0.001
SI	85.72	2.51	91.87	3.92	90.34	6.86	92.83	19.15	0.006
SF	32.02	2.09	37.39	4.46	37.51	6.27	48.36	18.49	<0.001
TIBC	560.00	104.59	492.83	86.50	507.14	67.33	520.85	51.32	0.001
TS	14.74	2.15	17.22	1.32	17.74	1.54	17.74	2.22	<0.001

*One sided ANOVA test is applied

Table 5: Clinical appearance of the patient.

Pallor	Frequency	Percent
Present	31	62
Absent	19	38

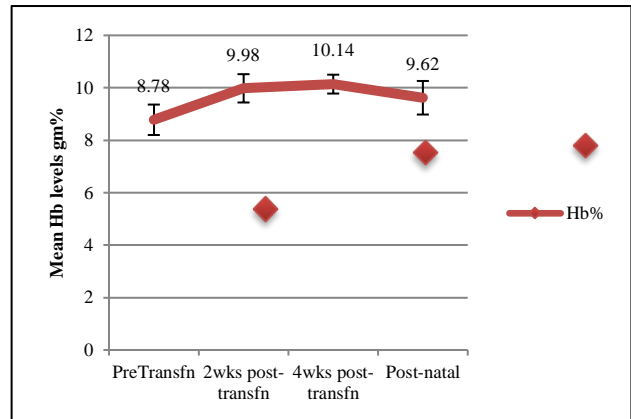


Figure 1: Comparison of Hb levels at different intervals of time.

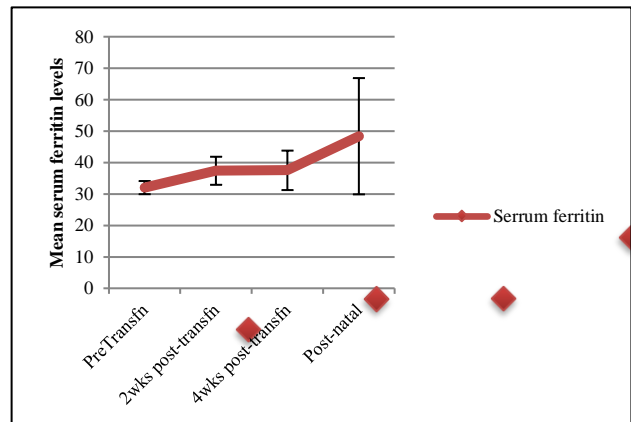


Figure 2: Comparison of serum ferritin levels at different intervals of time.

Table 6 shows the means and standard deviations of various parameters of CBC and iron profile. One sided ANOVA test was applied and was found that there is statistically significant difference between pre transfusion, post transfusion and post-natal values among the following parameters- Hb, RBC Count, MCV, MCHC, platelet count, and serum ferritin levels at different intervals of time.

DISCUSSION

Maximum number of patients (46%) were 21-25 years, 44% were primigravids, 70% (36%+34%) belonging to lower middle and lower socio-economic status indicating that nutritional anaemia exists in this population even before the first conception. Many (66%) did not have any associated risk factors implying multifactorial health issue. 68% of our women had not taken IFA tablets regularly in spite of ANC visits as a part of so many national programmes due to lack of compliance. Interestingly anaemia was noted in 28% of women who had taken regular oral iron preparations. Metallic taste, vomiting, diarrhoea and wrong method of consumption could explain the erratic absorption. This also shows that pregnant women taking IFA prophylaxis are not immune to anaemia.

Majority of the patients (62%) were clinically pale. Rest (38%) did not seem pale on clinical examination. This shows that though most moderate degree anaemia cases are apparent on clinical examination, some may be missed. 4% patients had transfusion reactions which were managed conservatively and transfusion was stopped. They were advised oral haematinics. This shows that though FCM is safer than Iron dextran in terms of anaphylactic reactions, it can rarely cause reactions, which warrants a thorough history of previous such reactions in all patients receiving i.v. iron preparations. Their Hb levels and S. Ferritin levels did not show much increase postnatally. This shows that, oral haematinics in these patients did not help much in overcoming anaemia in these patients.

For 70% of patients, CBC and iron profile were repeated at 2 weeks and 4 weeks post transfusion and also post-partum and these were compared with pre transfusion CBC and iron profile. Women also felt sense of well-being at those visits compared to pretransfusion. It was found that there was statistically significant difference between pre transfusion, post transfusion and post-natal values among the following parameters- Hb, RBC count, MCV, MCHC, platelet count, serum ferritin and transferrin saturation. This shows that i.v. FCM is beneficial in improving the above parameters.

Comparison of mean Hb levels at different intervals of time was found to increase from pre transfusion values to post transfusion values. It was maximum at 4th week post transfusion, and has a slight fall in the post-natal period, which is expected due to peripartum blood loss.

Nevertheless, these post-natal values are higher than the pre transfusion values. Comparison of mean serum ferritin levels at different intervals of time and was found to increase from pre transfusion values through post transfusion values, and was maximum at post-natal period, despite a fall in the Hb during post-natal period. This shows that, though the patient loses blood during peripartum period represented by the fall in the serum Hb, the stores of iron stay intact represented by the consistent increase in serum ferritin even in post-natal period, in patients transfused with Injection FCM. In the first study on the use of FCM for treatment of IDA in pregnancy was published by Christoph et al concluded comparable safety and tolerability of FCM to iron sucrose and that FCM offers the advantage of a much higher iron dosage at a time reducing the need for repeated applications and increasing patient's comfort. The authors documented a comparable rise in Hb levels at the end of the study.²⁶

Breymann et al compared FCM with oral iron therapy for treatment of iron deficiency anaemia in pregnancy. Hb levels improved at comparable rates in both groups. Patients in FCM group had significantly more women who achieved Hb>110 gm/l and within a shorter time frame and authors concluded to consider FCM to be first-line treatment option for correction of IDA especially in the third trimester of pregnancy.²⁴ Froessler et al have documented significantly increased ferritin levels after FCM infusion in patients with anaemia and in women with iron deficiency and no anemia.²⁸

In a recent systematic review to compare different injectable iron preparations in pregnancy, the authors failed to document the safety of any of the injectable iron therapies over others. The choice of injectable iron therapy is mainly determined by cost and convenience of administration.³⁰

Though the cost of FCM drug is more compared to iron sucrose, when other parameters like multiple hospital visits and pricks, number of working days, travel are considered may not be much difference and in India. In fact, it can be provided free of cost under JSSK (Janani Shishu Suraksha Karyakram) scheme for pregnant women by the Indian Government.³¹

CONCLUSION

Single high dose administration of FCM even during third trimester resulted in rapid replenishment of iron stores in pregnancy as well as postpartum period. No relevant safety concerns regarding mother and foetus were identified and was well tolerated. Earlier administration in storage depletion stage may still increase the efficacy and prevent anaemia related complications during antenatal period and may contribute in safe motherhood initiative. However further larger studies can be contemplated for safety and efficacy.

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