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Research Article

FERRIC CARBOXYMALTOSE: A BETTER OPTION FOR TREATMENT OF POSTPARTUM IRON DEFICIENCY ANEMIA

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ABSTRACT
Iron deficiency anemia is the most common cause of maternal morbidity and mortality especially in developing countries, which is both preventable and treatable by therapeutic intervention during postpartum period. A randomized study was conducted in 70 patients of postpartum iron deficiency anaemia with Haemoglobin 6-8 gm% and S. Ferritin <15µg/L. They were divided into two groups of 35 each. Group A received oral iron sulphate 200mg thrice a day for 4 weeks and Group B received IV ferric carboxymaltose 1000 mg as infusion. Haemoglobin, haematocrit, RBC indices, reticulocyte count and serum ferritin was estimated before treatment and after 4 weeks of treatment. A significant rise of haemoglobin, hematocrit and serum ferritin in group B patients (p value 0.001) was seen. No major adverse reactions occurred in both groups. Group A patients had more gastrointestinal side effects not seen in group B. IV carboxymaltose is an effective and safe therapeutic intervention for treating postpartum anemia. In developing countries with poverty, inadequate or in accessible health facilities, Inj ferric carboxymaltose will help all postpartum anemic patients to build up iron stores before next pregnancy and improved quality of life.

Keywords: *Ferric Carboxymaltose, Post Partum Iron Deficiency Anemia, Oral Ferrous Sulphate, Type I Parenteral Iron*

INTRODUCTION
Anemia as defined by WHO, hemoglobin less than 11gm% is the commonest cause of maternal morbidity and mortality especially in the developing countries. Iron deficiency is the most common cause of postpartum anemia, with rates as high as 50.0% reported in 1st postpartum week (Asma *et al.*, 2014). In developing countries higher prevalence, 50-80% has been reported (Milman *et al.*, 2011). In India prevalence of postpartum anemia at 6 weeks has been quoted as 70% (Somdatta *et al.*, 2009).
Postpartum anemia is associated with postpartum depression (Goshtasebi *et al.*, 2013), emotional instabilities, cognitive impairment (Jauregni *et al.*, 2014), impaired quality of life, longer hospital stay and higher hospitalization costs.
It is also associated with increased weakness, tiredness, fatigue, breathlessness, poor work performance, increased susceptibility to infection (Sherman *et al.*, 2013), sepsis and lactation failure. Poor mother-child interaction also affects infant development in anemic mothers. Severe anemia can cause palpitation, breathlessness, increased risk of cardiac failure. Thus, intervention is required to treat postpartum anemia in order to minimize the above postpartum morbidities.
The modalities of postpartum anemia treatment are oral iron therapy, parenteral iron and blood transfusion. Although oral iron is widely used for treatment of iron deficiency anemia (IDA), not all patients respond adequately to oral iron, due to its side effects, predominantly gastrointestinal discomfort leading to poor compliance and lack of efficacy.
The use of parenteral iron preparations i.e. iron dextran has been sometimes associated with serious side effects (Rodolfo *et al.*, 2011), therefore, was underutilized. Iron sucrose complex, developed later offers better compliance and tolerance with a better safety profile but multi-dosing still remains an issue (Agarwal *et al.*, 2013).

Keeping in mind the various drawbacks of oral and parenteral iron therapy; a newer iron preparation i.e. ferric carboxymaltose (FCM), a macromolecular ferric hydroxide carbohydrate complex is being studied.

MATERIALS AND METHODS

This randomized case control study was conducted in the Department of Obstetrics and Gynecology, Hindu Rao Hospital and associated NDMC Medical College, New Delhi from June 2014 to May 2015. Approval from institutional ethical committee was obtained. After written informed consent 70 women in postpartum period with diagnosis of iron deficiency anemia with hemoglobin of 6-8 gm/dl and serum ferritin less than 15mcg/L were enrolled for the study.

Women with known hypersensitivity reaction to oral or intravenous iron, anemia other than iron deficiency, history of chronic bleeding, active infection, acute illness, women requiring blood transfusion, women with co-morbid hepatic or renal diseases, cardiopulmonary or any systemic diseases were excluded from the study.

Demographic details, history and examination findings were recorded.

Women were assigned to two groups of Group A (n=35) and Group B (n=35).

Baseline investigations i.e. complete blood count, peripheral smear for type of anemia, RBC indices (MCV, MCH, MCHC) serum ferritin and reticulocyte count were done on day 2 or 3 of postpartum in both the groups.

Group A received 200 mg of ferrous sulphate tablets containing 60 mg of elemental iron, thrice daily empty stomach or 1 hour before meals from day 2-3 of delivery, for 4 weeks. Group B women received single dose of 1000 mg of injection ferric carboxymaltose (FCM), diluted in 250 ml of 0.9% isotonic sodium chloride infused over 15 minutes. No test dose was given. They were monitored for vitals, any sensitivity reactions like rashes, chills, anaphylactic reaction or hypotension etc. during the period of infusion.

All women were followed up at 4 weeks postpartum. Any adverse effects observed during this period in both the groups were recorded. All the investigations were repeated and results were analyzed statistically using SPSS 20.0 software.

RESULTS AND DISCUSSION

Post partum anemia (IDA) treatment is an important issue that needs aggressive treatment. 'Better Blood Transfusion' guidelines require hospitals to provide alternatives to allogenic blood transfusion where possible and the use of intravenous iron may be an effective way to achieve this.

In search for an effective and safe therapy to treat post partum anemia, the present study was undertaken. We have evaluated the efficacy and safety profile of Injection Ferric Carboxymaltose by comparing with the commonly used oral Ferrous Sulphate.

Our aim of the study was to compare the efficacy and safety of intravenous ferric carboxymaltose and oral ferrous sulphate in women with postpartum iron deficiency anemia. In our study majority of women were found to be unbooked (67.1%) or received antenatal care quite late in pregnancy (41.4%); illiterate (15.7%) or educated only up to primary school (37.1%). All the patients were multipara (100%). Most of them belonged to Hindu community (88.6%). Women belonging to lower socio-economic status were 81.4%. All these observations reinforce the facts that poor access to health services unawareness about importance of antenatal care and family planning services, multiparity, poor socio economic status hence, lack of adequate diet deficient in essential nutrients, poor and unhygienic living conditions, contribute to the post partum anemia (Table I).

No statistical difference in the demographic parameters was observed between the 2 groups. No statistical difference was observed between the baseline haematological parameters in the two groups in our study (p value > .05).

It was seen that all the haematological parameters i.e. haemoglobin, hematocrit, serum ferritin, MCV, MCH, MCHC and reticulocyte count were increased in both the groups after 4 weeks from the baseline levels (p value =.001). When comparing the increase of hematological parameters at 4 weeks between the

two groups it was observed that the RBC indices i.e. MCV, MCH, MCHC and reticulocyte count increase was not significant in FCM group compared to the oral group. However, rise of haemoglobin, hematocrit and serum ferritin at 4 weeks was significantly more in the FCM group compared to oral group.

Table I: Demographic Details

S. No	Demographic Details	Oral Iron Group n=35	FCM Group n=35	Total
1.	Age Mean (years)	24.40	24.43	
2.	Unbooked at our Hosp.	22	25	47 (67.1%)
	Booked 3or>3 Visits	4	3	7 (10.0%)
	Registered <3 Visits	9	7	16 (22.9%)
3.	Parity Primipara	Nil	Nil	Nil
	Multiparity			
	P1	14	8	22 (31.4%)
	P2	14	19	33 (47.1%)
	≥P3	7	8	15 (21.4%)
4.	Literacy			
	Illiterate	5	6	11 (15.7%)
	Upto Primary School	14	12	26 (37.1%)
	≥ Middle School	16	17	33 (47.1%)
5.	Community Hindus	29	33	62 (88.6%)
	Muslims	6	2	8 (11.4%)
6.	ANC Care – Proper Care	4	3	7 (10.0%)
	Improper Care	9	6	15 (21.4%)
	Received Late	14	15	29 (41.4%)
	Not Received	8	11	19 (27.1%)
7.	Socio-Economic Status			
	Upper	Nil	Nil	Nil
	Middle	8	5	13 (18.6%)
	Lower	27	30	57 (81.4%)

Mean increase of haemoglobin was 2.1 gm% in oral group and 4.2 gm% in FCM group, a significant increase in the FCM group (p value <.001). Increase of mean hematocrit % was 4.6% in oral group and 12.1% in FCM group again a significant increase in FCM group (p value <.001). Mean ferritin also increased 31.3 µg/L in oral group and 411.8 µg/L in FCM group, a highly significant increase in the FCM group (p value <.001) (Table II, III) (Figure 1, 2).

Table II: Haematological Parameters in Both the Groups

	A Oral Iron Group Baseline	B Oral Iron Group After 4 Weeks	C FCM Group Baseline	D FCM Group After 4 Weeks	p Value A/B	p Value C/D	p Value B/D
Hb (gm%)	7.33±0.662	9. 40±0.784	6.81±.600	11.03±0.788	.001	.001	.001
#Hct %	24.40±3.093	29.03±2.197	21.97±3.021	34.03±2.577	.001	.001	.001
Serum ferritin	8.56	39.78	9.27	421.41	.001	.001	.001
MCV	77.94±8.089	84.60±6.659	76.84±7.075	87.77±7.140	.001	.001	.528
MCH	24.01±3.375	28.25±2.623	23.49±2.371	28.34±2.070	.001	.001	.705
MCHC	29.71±2.515	32.69±1.769	30.53±1.515	32.20±1.635	.001	.001	.680
##Retic %	.99±.783	1.71±.441	.89±.566	1.60±.520	.001	.001	.280

Hemoglobin, ## Reticulocyte count

Table III: Serum Ferritin in Oral and FCM Group at 4 Weeks

Serum Ferritin	Oral group 4 Weeks	FCM Group 4 Weeks	P Value
Mean	39.78	421.41	
Median	28.9	353.61	.001
Inter Quartile Range	25.61-38.15	238.76-666.08	

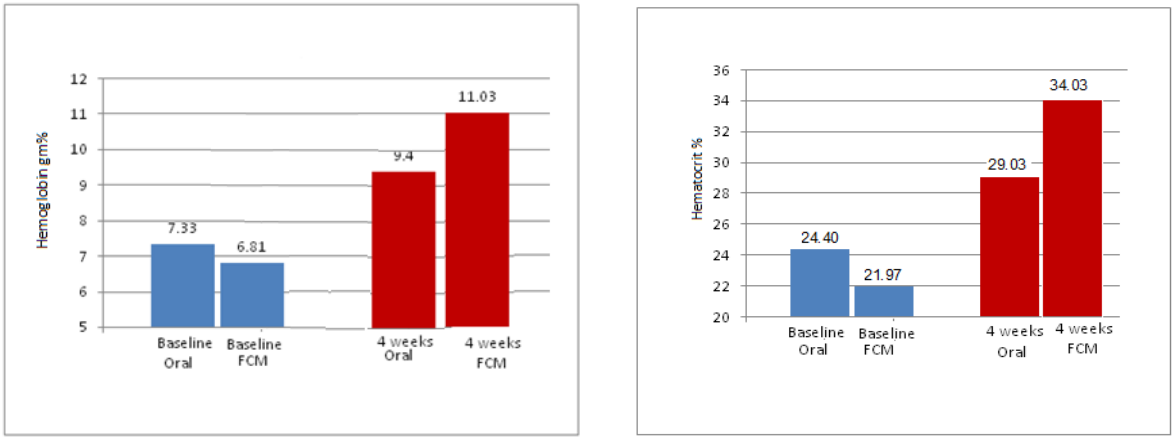

Figure 1: Hemoglobin and Hematocrit Rise at 4 Weeks from Baseline in Both Groups

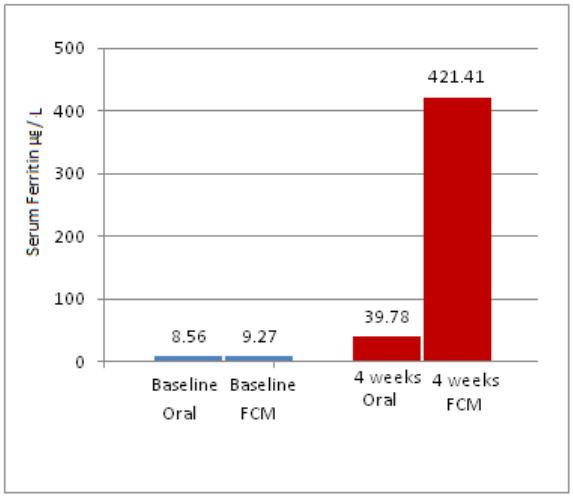

Figure 2: Serum Ferritin Rise at 4 Weeks from Baseline in Both Groups

This signifies higher efficacy of ferric carboxymaltose compared to oral ferrous sulphate. This is in corroboration with studies by Baille GR 2010, Froessler *et al.*, 2014, Rathod *et al.*, 2015 and L Williamson *et al.*, 2009 has reported a rapid and sustained increase in hemoglobin levels with FCM.

Rise of haemoglobin, hematocrit ensures a better quality of life and neonatal interaction. The significant increased ferritin, observed in our study will ensure these purpurae to have better iron reserves. No major side effects (Table IV) were observed in either group. Oral group had more gastrointestinal side effects. The few mild allergic reactions seen with FCM subsided with medication or at its own. These observations are in corroboration with other studies by Baille, (2010); Froessler *et al.*, (2014); Rathod *et al.*, 2015; L-Williamson *et al.*, 2009.

The higher efficacy of ferric coarboxymaltose can be understood by knowing the pharmacokinetics of iron complexes given parentrally.

Table IV: Adverse Effects

Side Effects	Oral FeSO4 Group	FCM Group
GI Side Effects	55.1%(n=19)	Nil
1. Nausea/ Vomiting	8.7%(n=3)	
2. Abdominal Pain	5.6%(n=2)	
3. Constipation	20% (n=7)	
4. Diarrhoea	2.9% (n=1)	
5. Metalic Taste	17.4% (n=6)	
Allergic Reactions	Nil	11.4% (n=4)
1. Pruritis, Rash		5.7%(n=2)
2. Infusion Site Burning		5.7%(n=2)
Headache	2.9% (n=1)	5.7% (n=2)
Dizziness	Nil	Nil
Anaphylactic Reactions	Nil	Nil
Total Women Having Side Effects	58% (n=20)	17.4% (n=6)

Iron is administered intravenously in the form of iron carbohydrate complexes consisting of a mineral core, composed of polynuclear iron (III)-hydroxide surrounded by the carbohydrate ligand. The main function of the ligand is to stabilize the complex and to protect it against further polynuclearization. Molecular weight of iron carbohydrate complex affects two biologic characteristics of IV iron complexes that are directly relevant to therapeutic use in patients: rate of release of iron from the ferric hydroxide core and rate of clearance of agent from the plasma after IV administration. Accordingly, these complexes can be classified as labile or robust and weak or strong.

The robust and strong complexes, have high molecular weight. They are less prone to release significant amounts of labile iron or react directly with transferrin. After intravenous injection they are taken up by macrophages of the reticuloendothelial system (RES) by endocytosis and thus iron complex is removed from the circulating plasma. The endocytes combine with lysosomes of macrophage cell to form endolysosome and iron is released from the iron-carbohydrate compound into its cytoplasm. This iron is either stored as ferritin intracellularly within the macrophage or is released from the cell extracellularly in a regulated way, to be transported by transferrin. Transferrin delivers iron to transferrin receptors on the surface of erythroid precursors for hemoglobin synthesis and maturation of the red cells. These iron complexes can be given in high doses with minimal risk of inducing oxidative stress due to release of free ionic iron (Funk *et al.,* 2010).

In the case of less stable preparations, release of significant amounts of labile iron from the complex can lead to saturation of transferrin and, thus, to significant amounts of non-transferrin bound iron (NTBI), particularly if high doses are administered. This weakly bound Fe is readily taken up in an unregulated way by cells of the endocrine system, heart and liver, where it can induce oxidative stress by catalyzing lipid peroxidation and reactive oxygen species formation.

Type I iron complexes like iron dextran, carboxymaltose are robust and strong. Iron dextran can be given as total dose infusion but serious adverse effects i.e. dextran induced anaphylactic reactions reported have limited its use. Injection FCM can be given in dosage of 1000 mg in a single infusion over 15 minutes and anaphylaxis has not been reported with its use. It does not show any cross –reactivity with anti-dextran antibodies (Funk *et al.,* 2010).

Type II complexes like iron sucrose complexes are semi-robust and moderately strong, have a lower molecular weight (Geisser *et al.*, 2011). They release larger amounts of weakly bound iron in the blood. Thus maximal safe single dose (200 mg for iron sucrose) is significantly lower and the administration time longer (Agarwal *et al*., 2013).

Type III complexes like Iron Gluconate, Iron Sorbitol, Iron Citrate least stable (Geisser *et al.*, 2011) and release large amounts of ionic iron into the circulation. Iron toxicity may result and therefore only low dose upto 125 mg can be given safely.

Type IV complexes-Are heterogenous mixtures of low molecular weight iron complexes Example: Iron dextrin/sorbitol/ citric acid complex, Iron sucrose/gluconic acid complex. They display properties of the constituents, including their side effects.

Toxicity profile reflects the most reactive form present in the mixed complex. In general, intravenous use of preparations containing large amounts of complexes with a molecular weight below 18,000 Daltons should only be undertaken with care (Geisser *et al.*, 2011).

Ferric Carboxymaltose is a stable complex which allows iron to be released slowly, avoiding toxicity and oxidative stress. It has a neutral pH and physiological osmolarity which allows it to be administered in higher doses (upto 1000 mg) by rapid infusion (15 min). These properties make FCM an attractive alternative to other iron therapies in terms of risk profile, efficacy, patient comfort and resource utilization.

Oral ferrous sulfate, the cheapest and most commonly prescribed oral iron supplement—shows a rapid rise in both serum iron concentration and non trasferrin bound iron(NTBI) as it saturates transferrin rapidly and hence, the greatest frequency of adverse events (Geisser *et al.*, 2011).

Oral iron is a less than ideal treatment mainly because of gastrointestinal adverse effects; lack of adherence to therapy or insufficient length of therapy for the degree of iron deficiency; poor duodenal absorption due to concomitant intake of tea, coffee, fiber rich diet especially in vegetarians, antacids, proton pump inhibitors, gastrointestinal pathologies (inflammatory bowel disease or any other cause of chronic inflammation, malignancy) and the long course of treatment needed to resolve anemia (1-2 months) and replenish body iron stores (another 3-6 months). Even in compliant patients, poor intestinal absorption, many a times fails to compensate for the iron needs (Agarwal *et al.*, 2013).

Ferric carboxymaltose, is effective, safe method for treatment of postpartum anemia compared to oral ferrous sulphate. There are no anaphylactic reactions. It should be routinely recommended in postpartum IDA before discharging the woman from hospital or health care facility after delivery, especially in a developing country.

Conclusion

Intravenous iron carboxymaltose is effective, convenient, safe for treatment of postpartum anemia. It ensures 100% compliance. The hospital stay of postpartum women thus, can be effectively utilized by giving intravenous carboxymaltose in dose of 1gm in a single infusion.

Multiple dosing is not required thereby reducing hospitalization, less time away from home, reduced injections, few side effects, reduced visits, improved out-patient management, improved cost-effectiveness are important factors for consideration for routine recommendation in postpartum IDA before discharging the woman from hospital or health care facility after delivery, especially in the developing countries.

The need for allogenic blood transfusion is reduced or avoided. In developing countries with poverty, inadequate and inaccessible health facilities, injection FCM will help these postpartum anemic patients to improve quality of life and also to build up iron stores before next pregnancy starts; thus, reducing overall maternal morbidity and mortality.

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