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Role of ferric carboxymaltose in the treatment of postpartum anemia in a rural tertiary care hospital in India

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Abstract
Introduction: Postpartum iron deficiency anemia is common in India as a consequence of post partum hemorrhage. Recent studies have evaluated the use of parenteral iron as a better tolerated treatment modality. Compared with oral iron supplements, parenteral iron is associated with a rapid rise in serum ferritin and hemoglobin and improved maternal fatigue scores in the postpartum period. Parenteral iron may be considered for the treatment of postpartum anemia.
Objective: The objective of the study was to evaluate the efficacy, safety, and tolerability of intravenous ferric carboxymaltose, in women with postpartum anemia.
Study Design: A clinical observational study was undertaken in a tertiary care hospital, 50 women within six weeks of delivery with Hb≥6g/dl and ≤10 g /dl received 1000 mg of ferrium, over 15 minutes or less, repeated weekly to a calculated replacement dose (maximum 2500 mg) . Hemoglobin and serum ferritin levels were recorded prior to treatment and on day 21after completion of treatment.
Results: Ferric carboxymaltose-treated subjects achieved a hemoglobin rise of ≥ 3 g/dL quickly, and attained higher serum ferritin levels in a short time period (21 days). It was also associated with good patient compliance, and shorter treatment period. Drug-related adverse events occurred less frequently with ferric carboxymaltose. The only noted disadvantage was that it was more expensive when compared to other iron preparations.
Conclusion: Intravenous ferric carboxymaltose is safe and well tolerated with good efficacy and good patient compliance in the treatment of postpartum iron deficiency anemia.

Keywords: ferric Carboxymaltose, post partum anemia, parenteral iron, hemoglobin, serum ferritin

Introduction

In modern times, the maternal health has improved rapidly due to advances in knowledge and technology. However in developing countries like India the progress in reducing the maternal mortality is limited. Most maternal deaths have resulted as a consequence of the poor health and nutritional status of the mother coupled with inadequate care before, during, and after delivery. Unfortunately the problem continues as it is accepted as inevitable in many societies, because it is so common, and it is widely thought that improvements in newborn & maternal health require sophisticated and expensive technologies and highly specialized staff. What is actually needed is essential care during pregnancy, the assistance of a skilled birth attendant during childbirth and the immediate postpartum period, and a few critical interventions for the newborn & mother.

Iron deficiency anemia, is defined by the World Health Organization as hemoglobin (Hb) less than 12 g/dL. It is the most common cause of anemia in the postpartum period, with rates as high as 37% reported in the first postpartum week [1, 2]. The prevalence of post partum anemia varies from 4% to 27% [3]. In a survey from a north Indian village, about 70% women in the postpartum period were found to be anemic [4]. Postpartum anemia is caused primarily by inadequate iron intake prior to and during pregnancy and by peripartum blood loss [5, 6]. Each ml of blood loss results in loss of 0.5 mg iron. About 20% of maternal deaths worldwide can be attributed to anemia [7]. In India, about 36% of the total maternal deaths are attributable to postpartum hemorrhage or anemia [8]. In healthy women after normal delivery, the prevalence of anemia one week postpartum is 14% in iron-supplemented women and 24% in no supplemented women [9].

Patients with postpartum anemia have a longer average length of hospital stay, and are more likely to receive a blood transfusion, and incur higher hospitalization costs. Postpartum anemia has been associated with postpartum [10] depression, stress, anxiety, cognitive impairment, [2, 11] poor mother-infant interactions, and delayed infant development [12]. Infants of mothers with iron deficiency anemia have lower developmental test scores at 10 weeks, and these developmental deficits in infants of iron deficient mothers have been shown to persist at nine months of age, even after correction of maternal iron status [12].

Currently, the Center for Disease Control and Prevention (CDC; Atlanta, Georgia) recommends selective anemia screening at four to six weeks postpartum for women who have had "anemia continued through the third trimester," "excessive blood loss

during delivery" and "multiple births [13]." For a diagnosis of iron deficiency anemia, it must also be shown that the patient is iron deficient. Serum ferritin has been regarded as the gold standard in establishing iron deficiency [14]. The generally accepted cut-off level for serum ferritin, below which iron stores are considered to be depleted is, < 15 ng/mL and ferritin level < 12 ng/mL is associated with iron deficiency anemia [15].

Despite a paucity of definite evidence for substantial benefit to either mother or child, the overwhelming consensus appears to be that iron deficiency anemia in the post partum period should be treated quite vigorously. The standard approach to treatment in the majority of UK institutions is oral iron supplementation, with blood transfusion reserved for more severe or symptomatic cases. However, the transfusion trigger is clinician dependant and a number of studies and audits have shown that the transfusion level varies widely between medical teams and institutions, with a significant proportion of transfusions given inappropriately [16]. Oral iron supplementation is more commonly used than blood transfusion for postpartum IDA. However, it is unreliable in the treatment of severe anaemia due to its limited absorption and gastrointestinal adverse effects that affect compliance [17, 18].

Iron sucrose is typically administered as a slow push injection or a 15- to 30-minute infusion in doses of 100- 200 mg, requiring multiple outpatient visits and repeated intravenous access for patients to receive the standard therapeutic course of 1,000 mg elemental iron. Iron dextran can be administered as a single dose, but this requires administration over a period of four to six hours. In addition, iron dextran complexes can cause fatal dextran-induced anaphylactic reactions [19, 20]. Anaphylactic reaction is rare, with estimates for iron dextran products of 0.6% incidence [21]. Ferric carboxymaltose is a novel non-dextran-containing complex of iron that allows for administration of a large replenishment dose (≤1,000 mg of iron) over a short infusion period (15-30 minutes), typically to the amount required for iron repletion. Ferric carboxymaltose is effective in improving hemoglobin concentration in non-dialysis-dependent patients with CKD [22]. It may be of significant benefit for use in the outpatient department or in a community setting as a result of its rapid and high-dose replacement of depleted iron stores in patients with CKD, as well as in various other adult populations with iron deficiency anaemia [22]. Our study was designed to test the hypothesis that ferric carboxymaltose is an effective drug for correction of postpartum iron deficiency anemia.

Materials & Methods

This study was conducted in a tertiary care hospital (PESIMSR) in a rural setting between 1st November 2014 to 31st August 2015. An institutional review board approved the study protocol for the study prior to initiation. All subjects gave written informed consent before enrollment. Healthy women 6 weeks or less after delivery with postpartum anemia (local laboratory Hb≥6g/dl and ≤10 g /dl and Serum ferritin less than 15 μg/L) requiring iron supplementation and willing to participate in the study were enrolled (Figure 1). Subjects were counselled about the advantages and adverse effects of ferric carboxymaltose and advised to take the study medication. After they consented for participation in the study a detailed history was teaken and clinical examination done. Demographic and standard laboratory data was collected on admission. Exclusion criteria included significant vaginal bleeding (estimated blood loss greater than 1000 cc) in the 24 hours prior to enrollment, a history of anemia other than iron deficiency anemia or blood loss due to delivery, current treatment with myelosuppressive therapy or asthma therapy, recent blood transfusions, or erythropoietin within three months prior to screening, bleeding disorders & hemoglobinopathies.

Subjects were withdrawn from the study if they required an intervention (ie, erythropoietin, blood transfusion, intravenous or oral iron outside the study protocol). Those women whose study medication was discontinued for safety reasons remained in the study. The dosage of ferric carboxymaltose was based on patient's body weight and Hb level (Table 1).

Table 1: Dosage of ferri carboxymaltose based on patient's body weight

Hb[g/dl]	Patient body wt ≥35kg and less than 70kg	Patient body weight ≥70kg
less than 10g/dl	1500mg	2000mg
≥10g/dl	1000mg	1500mg

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Ferric carboxymaltose was given weekly until the individual's calculated cumulative dose had been reached or a maximum of 2000 mg of ferric carboxymaltose had been administered. The maximum single weekly dose of ferric carboxymaltose did not exceed 1000 mg/dose. It was administered intravenously over 15 minutes or less. The dilution of FCM injection for IV drip was done based on the prescribed format (Table 2).

Table 2: Dilution plan of FCM injection for IV drip infusion

FCM	Iron	Max amount of sterile 0.9% nacl solution
2 to 4ml	100-200mg	50ml
4 to10ml	200-500mg	100ml

[each ml contains 50mg]

Central laboratory assessment of Hb% and serum ferritin were performed on days 0 and 21 days after the last dose of parenteral iron. This observational study was designed to evaluate the efficacy, safety, and tolerability of ferric carboxymaltose in women with postpartum anemia. The procedure was explained to the subjects in their own colloquial language. Side effects such as headache, myalgia, arthralgia, nausea, vomiting, epigastric discomfort and anaphylactoid reactions were looked for during the procedure. The patients were observed for one hour after infusuion after which they were allowed to go home. Mild allergic reactions were managed by stopping the infusion and giving inj. Chlorpheniramine 10 mg i.v slowly. All emergency drugs [like adrenaline, hydrocortisone etc] were readily available to manage any adverse reactions.

Heamoglobin was analysed by sysmex and Serum ferritin was analysed by VIDAS FERRITIN.

The primary efficacy endpoint was the percentage of subjects achieving Hb greater than 12 g/dL between baseline and end of

study. Major secondary endpoints, in ranked order of testing, were: maximum increase in Hb & serum ferritin over 3 weeks; Number of doses of the study medication needed;adverse drug reactions and compliance to study medication.
To detect the increase in Hb% with 90% power at the 5% significance level, we calculated that 50 women needed to be recruited to each group. All analyses were conducted using SPSS for Windows, version 10.0 (SPSS Inc, Chicago, IL, USA). The effect of iron supplementation on maternal iron status was analysed by Student's t-test.

Results

In Table 3 it was noted that the 50 women who were treated with the study medication were similar in their demographic profile. All the women were haemodynamically stable at the time of inclusion into the study. The median age group was 24 yrs. We did not have many subjects in extremes of age group. Most women belonged to low socio economic status - class four upper lower group according to Kuppuswamy 2012 classsification. In our study we have more number of booked cases.

Table 3: Demographic data of the treatment group

Demographic Table	Ferric Carboxymaltose
Age	24.24±3.80
Socioeconomic status	
Upper(I)	1(2%)
Upper Middle (II)	5(10%)
Lower middle (III)	6(12%)
Upper Lower (IV)	28(56%)
Lower (V)	10(20%)
Booking	
Booked	38(76%)
Un Booked	12(24%)
Parity	
Primi	36(72%)
Multi	14(28%)

The most common risk factor for post partum anemia in the study population was antenatal anemia (58%).
The other risk factors were few and insignificant. (Table 4).

Table 4: Risk factor for post partum anemia

Risk factor	Ferric Carboxymaltose
PPH	10(20%)
APH	2(4%)
Hypertension disorders	
Gestational hypertension	1(2%)
Mild preeclampsia	3(6%)
Severe preeclampsia	1(2%)
Exclusive breast feeding	49(98%)
Antenatal anemia	
Yes	29(58%)
No	21(42%)
H/O of intake of oral iron	
Yes	45(90%)
No	5(10%)
H/O bleeding PR, Malena, hematemesis	1(2%)
H/O of heavy menstrual bleeding	1(2%)

*PPH – Post partum hemorrhage
APH – Ante partum hemorrhage
H/O – history of

The most common mode of delivery was vaginal (56%) of which four cases had instrumental delivery. However the difference between vaginal & caesarean was not statistically significant (Table 5).

Table 5: Mode of delivery

Type of delivery	Ferric carboxymaltose
LSCS	22(44%)
Vaginal delivery	28(56%)

Table 6,7 and Figure 1 show the comparision of mean haemoglobin and serum ferritin levels on day 0 and day 21 of therapy. The mean baseline haemoglobin was 8.095±0.505. After three weeks of treatment with ferric carboxymaltose, rise in haemoglobin was 12.761±0.968. The haemoglobin increased by 4gm% in three weeks. The mean baseline serum ferritin was 15.5±20.5. After three weeks of treatment with ferric carboxymaltose, rise in serum ferritin was 110.3±44. The rise in serum ferritin & haemoglobin following treatment was statistically significant

Table 6: Comparision of mean haemoglobin before & after treatment

	Ferric carboxymaltose
Baseline Hb	
0 day	8.095±0.505
21 day	12.761±0.968
P-Value	0.000**
Absolute Raise	4.666±0.463
Percentage Raise	57.64%
Minimum Raise	2.7
Maximum Raise	6.4

Table 7: Comparision of serum ferritin before & after treatment

Baseline serum ferritin	
0 day	15.5±20.5
21 day	110.3±44.5
P-Value	0.000**
Absolute Raise	94.8±24
Percentage Raise	611.61%
Minimum Raise	23.63
Maximum Raise	191.5

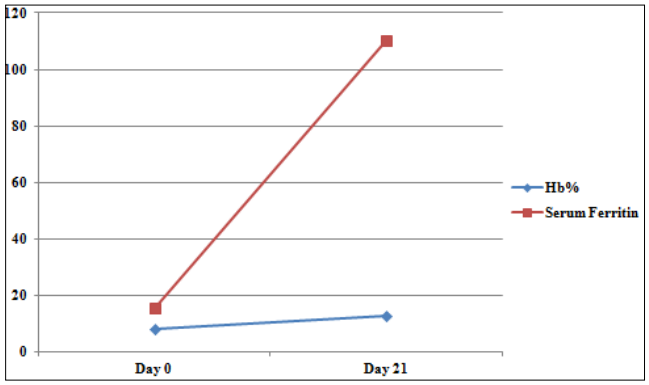

Fig 1: Comparision of Hb% & serum ferritin before & after treatment

The side effects noted were very few and insignificant. 96% of women did not have any adverse effects. There were no haemodynamic disturbances observed either during infusion or after infusion (Table 8). Most of the women (92%) required two doses of ferric carboxymaltose (Table 9).

Table 8: Adverse drug reactions

	Ferric carboxymaltose
No reactions	48(96%)
Breathlessness	1(2%)
Myalgia	1(2%)
Urticaria	2(4%)
Burning at Injection Site	0
Epigastric pain	0
Headache	1(2%)

Table 9: No of doses taken in ferric carboxymaltose

Number of doses	Ferric carboxymaltose
1	4(8%)
2	46(92%)

Out of the 50 women recruited for the study, we lost to follow up in four patients (8%) & two women dropped out of the study due to reactions (Figure 2). Compliance to the study medication was 88%.

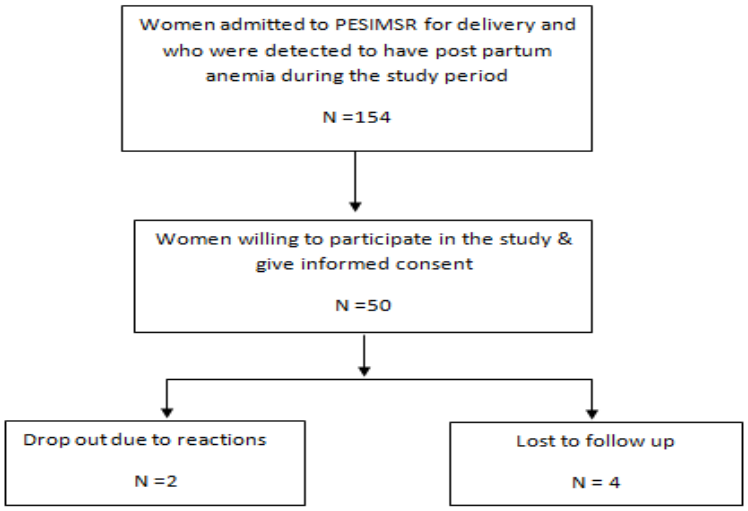

Fig 2: Study design

Discussion

Anaemia is one of the leading causes of disability and is a major global public health problem [23]. Even though the problem of iron deficiency in pregnancy is adequately emphasized, very little attention has been paid to postpartum anemia. The treatment of postpartum iron deficiency anemia with any form of iron therapy aims at raising serum Hb levels by 2.4–4.6 g/Dl [13, 24-27]. In a study by Melvin H. Seid *et al* they found that ferric carboxymaltose was superior to oral iron in improving iron stores, as measured by ferritin, and in increasing TSAT, an indicator of iron available for erythropoiesis. They found that one course of ferric carboxymaltose resulted in significantly replenished iron stores at study completion (day 42), whereas six weeks of oral iron did not [24]. In another study by Urvashi *et al*, they found that in the FCM group there was maximum increase in Hb% from the baseline Hb i.e mean rise in Hb of 3.1 g/dl after four weeks [28]. In our study we found that one course of ferric carboxymaltose increased the Hb increased by 4gm% in three weeks.

In our study, serum ferritin was used as an indicator of iron storage. Although ferritin levels are low in pregnancy due to plasma dilution, ferritin remains a reliable indicator of iron deficiency, where a cutoff level of <15 microgram/l is used [29, 30]. We found that serum ferritin increased by 94.8±24 after ferric carbxymaltose. Seid *et al*. reported that the ferritin levels were replenished at 42 day in the patients receiving FCM, but not in the oral iron group (238 ng/mL vs. 21 ng/mL; $P < 0.0001$).[24] Breymann *et al*. reported mean ferritin levels increased from 39.9 μg/L at baseline to 568.2 μg/L at week one and 161.2 μg/L at week 12. The changes from baseline were significantly higher in the iron carboxymaltose group compared with the control group for all visits, including week 12 ($P < 0.0001$) [29]. In another study by Setu Rathod *et al*, they observed that in FCM group, mean ferritin level increase from 35 ng/dL to 356 ng/dL at two weeks and 142 ng/dL at six weeks [31].

The reported incidence of adverse effects with FCM therapy is between 6.3% and 10.6% [24, 25, 27]. In the study by Setu Rathod *et al*, they had one patient who reported arthralgia and tingling sensation of feet 15 min after completing administration of the full dose of FCM [31]. In our study only 4% of women had adverse effects, all of which reduced following completion of the infusion.

Conclusion

Prevention of post partum anemia can be done by treating antenatal anemia and practising active management of third stage of labour thus reducing blood loss during delivery. Ferric carboxymaltose is a safe, effective, rapid and reliable drug for correction of postpartum anemia. The ability to administer 1000mg of ferric carboxymaltose as a single dose in a 15 minute infusion, makes it an ideal agent for outpatient use. The compliance to the medication is also improved.

The adverse effects reported are few and there is no evidence of risk to the breastfeeding infant. There are no reports on its effect on lactation, thus making it a suitable first line drug for treatment of postpartum iron deficiency anemia. The only limitation is the pharmacoeconomic consideration. More robust randomised multicentric studies are required to decide the ideal preparation of parental iron for treatment of postpartum iron deficiency anemia.

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