

Ferric Carboxymaltose Injection in Postpartum Iron Deficiency Anemia: Results from the prescription-event monitoring study

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Abstract

Introduction: Ferric Carboxymaltose (FCM), a dextran free iron formulation can be administered in large doses without the risk of severe anaphylactic reactions in postpartum anemia (PPA). Evidence suggest that FCM is highly effective in correcting anemia and restoring iron stores faster.

Aims & Objective: To gather real-world clinical practice events on safety and efficacy of FCM injection in Indian patients with PPA.

Materials and Methods: This was a prospective, observational, non-comparative, non-interventional, prescription event monitoring study. Data were collected from 535 postpartum iron deficiency anemia patients treated with FCM injection. Safety was assessed from adverse events reported within 1 week post FCM administration. Treatment efficacy was assessed by change in Hb from baseline, at 1 week after treatment.

Results: There were no serious adverse events (AE) reported. Only 4 patients (<1%) reported AE (mild nausea, n=1; shivering, n=1; palpitation, n=1; pruritus and breathlessness, n=1). Mean change in Hb evaluated in 498 patients showed significant increase from baseline of 8.5 ± 1.2 gm/dl to 10.5 ± 1.0 gm/dl (difference = 2 ± 1.03 gm/dl; $p < 0.001$) at 1 week post-treatment. Increase in Hb was maximum (2.95 ± 1.08 gm/dl) in severely anemic patients with baseline Hb ≤ 7 gm/dl (n = 87). Safety and efficacy of FCM was rated by physicians as 'very good and good' in 99% patients.

Conclusion: Intravenous FCM was safe with AE profile similar to earlier reports. Clinical utility of FCM in the treatment of PPA was demonstrated with significant improvement in Hb in 1 week.

Keywords: Ferric Carboxymaltose, Postpartum anemia

Introduction

The postpartum period, defined as the period beginning just after childbirth throughout the subsequent 6 weeks, serves as a time to restore iron lost during pregnancy and delivery. The prevalence of iron deficiency anemia (IDA) in the postpartum period is reported to be 10-30% in studies conducted in high-income countries and about 50-80% in developing countries.^(1,2)

World Health Organization (WHO) has defined postpartum anemia (PPA) as hemoglobin (Hb) of <10 gm% during the postpartum period.⁽³⁾ The major causes of PPA are prepartum iron deficiency and anemia in combination with acute blood losses at delivery.⁽²⁾ Postpartum anemia is associated with an increased prevalence of tiredness, breathlessness, palpitations and may predispose to puerperal sepsis.^(2,4) There is a strong negative correlation between iron status and depression, stress, cognitive function in mothers during the postpartum period all of which can complicate mother-child interactions.⁽⁵⁾ Severe anemia in postpartum period can increase maternal morbidity, increase the length of hospital stay, cause difficulty in breastfeeding and sometimes also result in severe cardiovascular problems.⁽⁶⁾ Hence, postpartum IDA requires prompt intervention and high-quality care.

Oral iron therapy is the preferred treatment modality for correction of iron deficiency anemia because of its low cost and ease of use but it is associated with frequent gastrointestinal side effects, thus leading to poor compliance and may also take longer time to replenish

iron stores. Parenteral iron helps in restoring iron stores faster and more effectively than oral iron without gastrointestinal side effects.⁽⁷⁾ Use of first generation intravenous (IV) iron preparation iron dextran has been restricted owing to the risk of life-threatening anaphylactic reactions. Second generation IV iron preparations like ferric gluconate and iron sucrose has made iron therapy simpler and safer but multiple doses and prolonged infusion times are typically required.⁽⁸⁾ Ferric Carboxymaltose (FCM) is a novel non-dextran IV iron agent having a very low immunogenic potential and therefore not predisposed to high risk of anaphylactic reactions. Its properties permit the administration of large doses (maximum of 1000 mg/infusion) in a single and rapid session (15-minute infusion) without the requirement of a test dose. Evidences suggest that FCM is highly effective in correcting anemia and restoring iron stores faster than oral iron and iron in patients with PPA.^(8,9,10,11) Thus, to further strengthen the data suggesting good efficacy and safety of FCM in PPA and to gather real-world clinical practice events on safety and efficacy of FCM injection in Indian patients with PPA, this study was planned.

Materials and Methods

This was a prospective, observational, non-comparative, non-interventional, prescription event monitoring (PEM) study. Data were collected from 61 centres across India from the health records of 535 patients with postpartum iron deficiency anemia who

were administered IV FCM as per the treating physician's judgement and the product's (Orofer FCM, Emcure pharmaceuticals, limited, Pune) prescribing information. Following details were recorded in to the CRF: patient's age, weight, mode of delivery, history of postpartum haemorrhage (PPH), co-morbidities, history of blood transfusion (if any in preceding 1 month), details of FCM administration (total dose, method & duration of administration) along with baseline Hb values and results of other laboratory parameters (Hb, RBC count, serum ferritin, TSAT) if done. These laboratory parameters assessed after 1 week of FCM injection were also recorded in to the CRF. Patients were categorized as having mild, moderate or severe anaemia based on baseline Hb values (9.1-10, 7.1-9 and <7 gm/dl respectively). No additional investigations were done beyond the standard clinical practice for the purpose of study.

Safety was assessed from adverse events reported within 1 week post FCM administration. Treatment efficacy was assessed by change in Hb from baseline, at 1 week after treatment. Only those patients with baseline Hb <10 gm/dl were considered for efficacy analysis. Also, physician's opinion on efficacy and safety of FCM (as very good, good, fair or poor) was noted in the CRF. Other laboratory parameters such as RBC count, serum ferritin and TSAT were not analysed in this study as they were not consistently done before and after 1 week of FCM injection for all the patients.

Statistics: We performed a descriptive analysis of the data. Continuous variables are presented as mean \pm standard deviation (SD). Categorical variables are presented as proportions. Student paired T test was used for change in Hb and p value <0.05 was considered statistically significant. Missing data was not considered for calculating percentages. The statistical analysis was performed using SAS software package (version 8.1).

Results

Demographic and baseline characteristics: Total 535 adult patients with mean weight of 56.2 ± 10.23 kg and mean baseline Hb of 8.48 ± 1.19 gm/dl were treated with IV FCM. As shown in Table 1, 41.9% patients had normal vaginal delivery while 51.2% patients had undergone caesarean section and in 6.9% patients, the type of delivery was not documented. Total 14.6% patients had history of PPH while 2.4% patients were

having co-morbid conditions (hypothyroidism, gestational diabetes mellitus, pregnancy induced hypertension and coeliac disease) and were receiving disease-specific treatment. Most of the patients (54.61%) were having moderate anemia. As documented, out of 342 patients, 14 patients received blood transfusion in the preceding month.

Ferric Carboxymaltose dosing: FCM was administered only as IV infusion diluted in 0.9% normal saline; maximum single dose of 1000 mg (20 ml) per week. It was administered in dose of 500, 1000, 1500 and 2000 mg in 31%, 65%, 3% and 1% patients respectively. Mean elemental iron administered through FCM was 817.8 ± 253.74 mg.

Table 1: Baseline demographic variables of study participants

Parameters	Value
Total number of patients	535
Age (years; mean \pm S.D.)	27.8 ± 5.21
Weight (kg; mean \pm S.D.)	56.2 ± 10.23
Type of delivery (n;% Vaginal Vs Caesarean)	224 (41.9%) Vs 274 (51.2%)
History of PPH (n ;%)	78 (14.6%)
Co-morbidities (n ;%)	13 (2.4%)
Mild anemia (9.1-10 gm/dl)	139 (27.91%)
Moderate anemia (7.1-9 gm/dl)	272 (54.61%)
Severe anemia (<7 gm/dl)	87 (17.46%)

Assessment of efficacy: Change in Hb as evaluated in 498 patients, increased significantly from 8.5 ± 1.2 gm/dl at baseline to 10.5 ± 1.0 gm/dl (difference of 2 ± 1.03 gm/dl; $p < 0.001$) at 1 week post-treatment (Fig. 1). In patients with severe anemia with Hb <7 gm/dl (n= 87), the rise in Hb was maximum and statistically significant (2.95 ± 1.08 gm/dl; $p < 0.001$ vs baseline). Efficacy of FCM stratified by severity of anemia is shown in Table 2.

Safety assessment: FCM was well tolerated in majority of patients. Only 4 patients (0.7%) reported adverse events [mild nausea, n=1; shivering, n=1; palpitation, n=1; pruritus and breathlessness, n=1 (Fig. 2)]. There were no serious adverse events reported.

Table 2: Assessment of efficacy of FCM as per severity of anemia

Patient Categories	N	Baseline Hb (gm/dl)	Hb after FCM treatment (gm/dl)	Mean change in Hb from baseline (gm/dl)	'P' value Vs baseline
Mild anemia (9.1-10 gm/dl)	139	9.55 ± 0.28	11.0 ± 0.73	1.45 ± 0.75	<0.001
Moderate anemia (7.1-9 gm/dl)	272	8.25 ± 0.57	10.36 ± 0.86	2.11 ± 0.88	<0.001
Severe anemia (< 7 gm/dl)	87	6.61 ± 0.49	9.56 ± 1.02	2.95 ± 1.08	<0.001

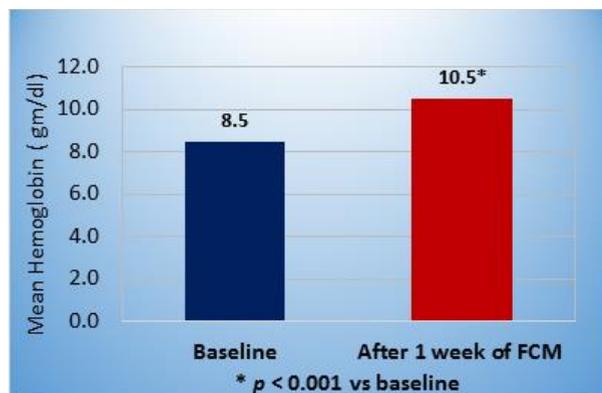


Figure. 1: Mean Change in Hb (n = 498)

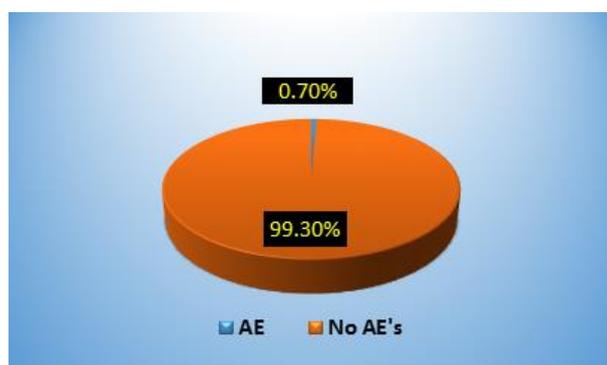


Figure. 2: Safety Assessment (n=535)
AE – Adverse Event

Physician's opinion on safety and efficacy: Efficacy of FCM as opined by the treating physicians was 'very good' and 'good' in 61.5% and 37.6% patients, respectively. Similarly, Safety of FCM as opined by the treating physicians was 'very good' and 'good' in 63.7% and 35.4% patients, respectively.

Discussion

In settings where anemia is of public health concern, WHO recommends oral iron supplementation to postpartum women following delivery.⁽¹⁾ Use of oral iron is hindered by gastrointestinal side effects and poor patient compliance whereas older IV iron preparations are associated with risk of anaphylactic reactions (iron dextran) and need of multiple doses for anemia correction (iron sucrose, sodium ferric gluconate). Because of the risk of infection and immunological reactions, blood transfusions are usually reserved for most severe cases and life threatening situations.^(12,13)

The introduction of novel, dextran free, third generation parenteral iron preparations like Ferric Carboxymaltose has overcome these problems as it can be given in large single doses (1000 mg in 15 minutes) with minimal risk of hypersensitivity, which may make it a suitable treatment for iron-deficiency anaemia outside of the hospital setting. The safety and efficacy of

FCM has been well established in many randomized studies.^(8-10,14)

Commonly occurring adverse drug reactions in ferric carboxymaltose recipients include nausea, headache, dizziness, hypertension and injection-site reactions.⁽¹⁵⁾ In our study, IV FCM was well tolerated; only 4 (0.7%) patients developed adverse events namely nausea, shivering, palpitations, pruritus and breathlessness. There were no serious adverse events reported. Similarly in studies by Rathod et al. and Damineni et al., FCM was very well tolerated with reported adverse events rate of < 1%.^(10,16)

This study was carried out to gather real-world clinical practice events on safety and efficacy of FCM injection in Indian patients with PPA. In this study we found that there was significant increase in Hb levels from baseline (2 ± 1.03 gm/dl; $p < 0.001$) at 1 week post FCM administration. Results of our study are well supported by findings of several randomized, controlled studies in postpartum patients involving FCM as treatment arm. In a randomized, comparative study by Van Wyck et al., mean Hb rise with IV FCM with a mean total dose of 1.4 gm (n = 174) was compared with Hb rise with Ferrous sulphate 325mg three times a day (n = 178). Patients assigned to IV FCM achieved a significant Hb rise greater than or equal to 2.0 gm/dl earlier (7 days compared to 14 days with oral iron).⁽¹³⁾ In another Study by Damineni et al., mean increase in Hb after 1 week from the start of FCM treatment was 1.98 gm/dl ($p < 0.001$) as compared to 1.1 gm/dl with oral iron.⁽¹⁷⁾ In this study, maximum rise in Hb (2.95 ± 1.08 g/dl) was seen in severely anemic patients with baseline Hb ≤ 7 gm/dl. Similar findings have been observed in previous studies in which greater Hb response was seen in patients with severe anemia.^(8,10) IV iron replacement, particularly FCM could be most advantageous in such patients, where rapid availability of iron is important to correct anemia.

Safety and efficacy of FCM was rated as 'good to very good' by the physicians in most of their patients which is in agreement with various available evidences of better safety and efficacy of FCM in patients with PPA as compared to other IV preparations and oral iron. Thus, the total drug infusion concept with third-generation parenteral iron molecules such as IV FCM is suitable for the patient with PPA because of better patient compliance and rapid restoration of iron stores particularly in patients with severe anemia. Due to stand-out features like ultra-short duration of treatment, no hospitalization required, lesser side-effects and quicker replenishing of iron stores, IV FCM may be considered early, while treating patient with postpartum iron deficiency anemia.

Limitations of study

Various observational studies have related different levels of TSAT and serum ferritin with low Hb values, hospitalization and mortality. Also, TSAT and serum

ferritin have a significant inverse relationship with mortality and hospitalization and appears to be the better predictor. However, as data on serum ferritin and TSAT was not available for all the patients in our study, we were not able to analyse these parameters for efficacy.

Conclusion

IV FCM was safe and well tolerated without any serious adverse event. It was found to increase Hb significantly in a shorter period of time in patients with post-partum iron deficiency anemia including patients with severe anemia. The ability to deliver a high dose of iron within a short time frame may make FCM suitable for patients requiring quicker restoration of iron stores. Our study further strengthens the clinical trial findings of good safety and efficacy of IV FCM in patients with PPA in real-world clinical practice.

Funding: None

Conflict of interest: None declared.

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