FERRIC CARBOXYMALTOSE (FCM) COMPLEX IN THE TREATMENT OF POSTPARTUM ANAEMIA- NON-INFERIORITY OF A 500 MG VERSUS 1000 MG SINGLE-DOSE ADMINISTRATION

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ABSTRACT

BACKGROUND

The aim of the study is to determine the non-inferiority of a single dose of 500 mg Ferric Carboxymaltose (FCM) (Group 1) to a single dose of 1000 mg (Group 2) in treating women with postpartum anaemia.

MATERIALS AND METHODS

Women were recruited within 24 hours of delivery and randomised to one of the two study groups excluded were mothers with non-iron deficiency anaemia, iron intolerance and haematological disease. Haematological markers were measured at baseline and at 6 weeks after treatment.

Main Outcome Measures- The primary outcome was an Hb increase ≥20 g/L. Secondary outcomes included the proportion of patients attaining Hb ≥120 g/L and the mean Hb change.

Design- Open label, randomised, non-blinded, prospective study.

Setting- Maternity units of four hospitals in Southern India.

Population- Women ≥18 years old with haemoglobin of >60 - <100 g/L.

RESULTS

There was no difference in the proportion of women achieving an Hb increase of >20 g/L between Groups 1 and 2 (91.4% versus 96.7%). Similar proportions of women in both groups became non-anaemic achieving an Hb of >120 g/L (57% versus 45.7%). The mean Hb change was comparable between the groups and both doses were well tolerated.

CONCLUSION

A single dose of 500 mg FCM (cost INR 2000.00) is non-inferior to a 1000 mg dose (cost INR 5000.00) in the treatment of postpartum anaemia. This has major implications for the scaling up of the eradication of iron-deficiency anaemia in India, since double the number of women who would otherwise have been treated with the 1000 mg dose can be treated with half the dose at less than half the cost with similar outcomes.

Tweetable Abstract- A single dose of 500 mg FCM is a safe, efficacious and cost-effective treatment for PPA in India.

KEYWORDS

Ferric Carboxymaltose (FCM)/Anaemia/Iron Deficiency/Postpartum/Haemoglobin.

HOW TO CITE THIS ARTICLE: Divakar H, Ramarajan A, Bhandiwad A, et al. Ferric Carboxymaltose (FCM) complex in the treatment of postpartum anaemia- non-inferiority of a 500 mg versus 1000 mg single-dose administration. J. Evid. Based Med. Healthc. 2016; 3(98), 5386-5392. DOI: 10.18410/jebmh/2016/1119

BACKGROUND

Iron-Deficiency Anaemia (IDA) is a major scourge of pregnancy in low-resource parts of the world with a prevalence of 50-80% in developing countries,[1-2] but also disproportionately affecting low-income women in the developed world.[3] In India, where it is implicated in 36% of all maternal mortality,[4] it has as a prevalence of 65-75%.[5] Furthermore, India contributes almost 80% of all maternal deaths due to anaemia in South East Asia.[5] In 2011, there were 32 million pregnant women with anaemia of whom 7,50,000 had severe anaemia.[6] Across all categories including pregnant women, the high incidence of anaemia in India has been attributed to low dietary intake of iron, poor iron and folate intake, poor bioavailability of iron in the diet and chronic blood loss due to infections.[5] IDA should ideally be treated before a woman embarks upon pregnancy, but the practical reality is that most women in such settings

Financial or Other, Competing Interest: None.
Submission 15-11-2016, Peer Review 22-11-2016,
Acceptance 05-12-2016, Published 08-12-2016.
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DOI: 10.18410/jebmh/2016/1119

receive no effective pre-pregnancy care and a variety of programs to eradicate IDA in pregnancy, such as the IFA in India, have failed spectacularly. Thus, the problem of IDA often presents as postpartum anaemia defined as a haemoglobin concentration of less than 100 g/L during the postpartum period.[7,8] Pre-partum IDA is the strongest predictor of postpartum anaemia,[9] but other causes include acute blood loss during delivery.[10]

Postpartum anaemia can impair maternal functioning and health affecting physical performance, mood, cognition and the immune response.[10,11-13] These symptoms may in turn interfere with the mother-child interactions including emotional bonding and may negatively affect infant development and behaviour.[12,14] Indeed, research has shown that maternal postpartum anaemia can lead to irreversible developmental delays in the first 10 weeks of life.[12]

The immediate postpartum period represents a potential window of opportunity to treat women found to be anaemic. Oral and intravenous iron therapies are frequently used,[15] but there are limitations and challenges associated with the use of both. Although, oral iron is inexpensive and often efficacious, gastrointestinal side effects[16-17] often hinder patient compliance,[18-19] which has been reported as high as 30%.[18] While intravenous iron rapidly increases blood haemoglobin levels,[20] the older formulations, which contained iron dextran ran the risk of provoking severe and life-threatening anaphylaxis.[21-23] While the newer iron sucrose or ferric gluconate-based formulations require multiple low-dose injections[24-25] again raising the spectre of incomplete dosage as women who might receive the first dose immediately postpartum tend not to return for subsequent doses once they leave the maternity ward. While blood transfusions and erythropoietin therapy can be used to treat postpartum anaemia, their use, especially in low-income countries is limited by cost and safety concerns.[26]

Ferric Carboxymaltose (FCM) complex is a novel iron dextran-free intravenous iron preparation that addresses the limitations of current intravenous iron therapies. It can be administered in doses of up to 1000 mg of iron given over a time period of 15-20 minutes.[19,27-28] Unlike iron dextran, anaphylaxis is virtually unknown in association with its use.[29-30] Thus, FCM is a promising intravenous iron preparation that is highly suited to low-resource settings. However, cost remains an issue and in this study, we sought to evaluate the non-inferiority of a 500 mg dose versus the usual 1000 mg- if 500 mg could be shown to be as efficacious as 1000 mg, two women can effectively be treated in place of one.

MATERIALS AND METHODS

Design

This was an open label, randomised, prospective, comparative, multicenter study conducted with institutional review board approval over a period of 6 months from June 2015 to November 2015. Participating centres included the Obstetric Department of Divakars Speciality Hospital, Bangalore; CSI Hospital, Bangalore; Al-Ameen Medical College, Bijapur and JSS Medical College, Mysore.

Sample Size Calculation

Based on the numerous studies that have now been published documenting the efficacy of FCM in treating IDA and using alpha 0.05 and power 80, we calculated that a total sample size of 42 (21 per group) would suffice. However, our prior experience of research involving pregnant women in India is that follow up is poor with high dropout rates especially in studies of postpartum women. As four centres agreed to participate in the trial, we determined to recruit a minimum 25 women per center to allow for a minimum loss to follow up of up to 50%.

Dose of FCM

The standard approach as recommended by manufacturers is that the total dose of ferric carboxymaltose is calculated on the basis of haemoglobin deficit and body weight using the 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 <35 kg and 500 mg in case of weight more than 35 kg. In practice, the prevalence and severity of pregnancy-related IDA in India is such that a majority of women will require at least 1000 mg, which is the recommended maximum safe dose that can be administered at one sitting. We took the pragmatic decision based on extensive practices in India to administer a single fixed dose either 500 mg or 1000 mg without applying the Ganzoni formula, since this is what actually happens on the ground.

Study Subjects

Twenty-four hours following childbirth, women were screened for anaemia using a HemoCue (HemoCue AB Kuvettgatan 1 SE-262 71 Angelholm Sweden). Women were invited to participate in the trial if they had an Hb of >60 - <100 g/L. The anaemia being attributable to iron deficiency; had either a vaginal birth (normal or instrumental) or caesarean section and were aged 18 years and above. Women were excluded if their anaemia was due to conditions other than iron deficiency, had previously received a blood transfusion, had a history of iron intolerance or had haematologic disease. Details of the study including a description of the drug, its effects and possible side effects were explained to each participant and written informed consent was obtained. Baseline laboratory measurements of haemoglobin, serum ferritin and C-Reactive Protein (CRP) were undertaken for all participants.

Intervention

A total of 177 women consented to participate in the study and were randomly assigned to one of two groups using computer generated random numbers. Group 1 received a single infusion of 500 mg FCM, while Group 2 received 1000 mg of FCM. All dilutions were made in the appropriate amount of sterile 0.9% sodium chloride solution (Health Line Pharmaceuticals Private Limited, Miraj), and were

administered over 15 minutes. The drug was administered under direct supervision and infusion was immediately stopped in the event of any side effects. Pulse and blood pressure were monitored at 15-minute intervals and patients were observed for half an hour after infusion. The patients were followed up at 6 weeks when laboratory measurements of haemoglobin, serum ferritin and C-Reactive Protein (CRP) were again undertaken.

Outcome Measures

The study was designed to establish the non-inferiority of 500 mg FCM in comparison with the standard dose of 1000 mg in reducing iron deficiency postpartum anaemia. The primary outcome measure was an Hb increase of >20 g/L at 6 weeks post FCM infusion. Secondary outcome measures included the attainment of a haemoglobin concentration of >120 g/L (correction of anaemia) and the comparative safety characteristics of the doses administered.

Statistical Analysis

All statistics were conducted using IBM SPSS Statistics version 22. For descriptive statistics, the number of patients, mean, Standard Deviation (SD), minimum, median and maximum values of Hb were calculated for continuous variables and the case number and percentage were computed for categorical values. For inferential statistics, the following statistical tests were used to determine the statistical significance of differences between groups- to compare two groups of dependent samples for normally distributed data, a paired sample t-test was applied and for non-normally distributed data, the Wilcoxon signed-rank test was performed. To compare two groups of independent samples, the t-test was applied for normally distributed data.

RESULTS

A total of 704 women were screened from whom 177 were randomised and 129 completed the study of whom 70 were in Group 1 (500 mg FCM) and 59 in the Group 2 (1000 mg FCM) (48 women were lost to follow up) (Chart 1). The baseline demographic and iron status variables of the participants who completed the study are shown in Table 1. The two groups were comparable in all key parameters (Table 1).

The primary endpoint was the proportion of women who achieved a rise in Hb of >20 g/L in the 6 weeks following iron infusion. Table 2 shows that there was no between-group difference (91.5% in Group 1 versus 96.7% in Group 2, p=0.2224). Similarly, no between-group difference was observed in the proportion of participants who achieved an Hb concentration of 120 g/L or more indicating correction of their anaemia (57.1% in Group 1 versus 45.7% in Group 2, p=0.1971). However, the proportion of women who achieved a rise in Hb of >30 g/L was significantly lower in Group 1 (48.6% versus 81.4%, p<0.0001). Similarly, there were significant differences in the median and mean Hb changes between the two groups- in Group 1, the median Hb change was 30 g/L versus 38 g/L in Group 2 (p<0.0001) with mean values of 30.7 (±9.3) and 38.7 (±10.8), respectively (Table 3).

An important variable to assess the impact of iron supplementation is serum ferritin, which reflects iron stores. However, infection and inflammation can artificially "elevate" serum ferritin levels, even in iron deficient subjects[31] and the profound involution that occurs immediately following childbirth, especially within the placental bed can be expected to be associated with inflammation. We therefore measured serum ferritin levels in our study populations both at baseline and at 6 weeks post iron infusion and took parallel measurements of CRP (C-Reactive Protein) to reflect any ongoing inflammation. Table 4 shows that in both Groups 1 and 2, the median serum ferritin concentration significantly increased from baseline (63.80 to 149.00 µg/L and 64.09 to 225.00 µg/L, respectively p<0.0001). Interestingly, however, there were no significant between-group difference in the rise in serum ferritin levels (p=0.166). CRP levels decreased significantly in both groups (48.60 to 6.50 mg/L and 27.30 to 7.10 mg/L, respectively; p<0.0001), but between-group differences were not significant (p=0.991).

The most common drug-related events in both groups were headaches and mild-to-moderate transient skin changes (rashes, urticaria and itching) and there were no differences between the two groups in the incidences of these events. Symptomatic hypotension and other adverse drug-related effects were not observed. Both doses of FCM infusions were well tolerated and the dosing schedule was not associated with any clinically relevant safety concerns. In addition, drug-related safety concerns were not identified in breastfeeding mothers who received either dose of FCM.

Baseline Characteristic	Group 1 - 500 mg FCM (n=70)	Group 2 - 1000 mg FCM (n=59)
Age (y)	25.50 (±4.62)	24.75 (±4.47)
Hg (g/L)	8.89 (±0.76)	8.08 (±0.91)
Hg category (g/L)*		
90.0-110.0 (Mild anaemia)	39 (55.7)	7 (11.9)
70.0-89.0 (Moderate anaemia)	31 (44.3)	48 (81.4)
Less than 69.0 (Severe anaemia)	0 (0.0)	4 (6.8)
Serum ferritin*	76.88 (±64.7)	117.41 (±131.67)
C-Reactive Protein (CRP)*	65.52 (±59.0)	43.10 (±44.14)

Table 1. Baseline Demographic, Haematological and Iron Status Variables in Randomly Assigned Participants who Completed the Study

Values are mean (±SD) unless indicated otherwise.

*Seven mothers from the 500 mg FCM group and 10 mothers from the 1000 mg FCM group were excluded because they experienced overt infections during the study period that would have influenced their CRP levels.

	Group 1 - 500 mg FCM (n=70)		Group 2 - 1000 mg FCM (n=59)		P^b
	n	Percent	n	Percent	
10 g/L or less	0	0.0%	0	0.0%	
11 to 20 g/L	6	8.6%	2	3.4%	
21 to 30 g/L	30	42.9%	9	15.3%	
31 to 40 g/L	25	35.7%	27	45.8%	
more than 40 g/L	9	12.9%	21	35.6%	
Primary Endpoint					
Hb change ≥20 g/L	64	91.4%	57	96.7%	0.2224
Secondary Endpoints					
Hb change ≥30 g/L	34	48.6%	48	81.4%	0.0001
Hb ≥120 g/L	40	57.1%	27	45.7%	0.1971

Table 2. Numbers and Percentages Associated with Increases in Hb and Hb Concentration at 6 weeks in Both Study Groups

P^b between-group significance

Hb Statistics	Group 1 - 500 mg FCM (n=70)	Group 2 - 1000 mg FCM (n=59)	P^b
Changes in Hb			
Mean (S.D.)	3.07 (±0.93)	3.87 (±1.08)	<0.0001*
Median (95% CI)	3.00 (2.85-3.30)	3.80 (3.58-4.15)	
Z	-7.27	-6.68	
P^a	<0.0001	<0.0001	

Table 3. Descriptive and Inferential Statistics Associated with Percent Increases in Hb in the 500 mg and 1000 mg FCM Groups

P^a within-group significance.
P^b between-group significance.

Iron Status Marker	500 mg FCM			1000 mg FCM			
	Baseline	After 6 Weeks	P^a	Baseline	After 6 Weeks	P^a	P^b
Hb (g/L)	90.0 (90.0)	120.0 (11.0)	<0.0001	80.0 (14.0)	118.0 (20.0)	<0.0001	0.965
Serum Ferritin (µg/L)	63.80 (87.00)	149.00 (151.73)	<0.0001	64.09 (127.63	225 (255.70	<0.0001	0.166
CRP (mg/L)	48.60 (35.20)	6.50 (20.70)	<0.0001	27.30 (45.85)	7.10 (18.15)	<0.0001	0.991

Table 4. Median Values of Iron Status Markers at Baseline and After 6 Weeks in Participants Assigned to the 500 mg FCM and 1000 mg FCM Groups

P^a within group significance.
P^b between group significance.

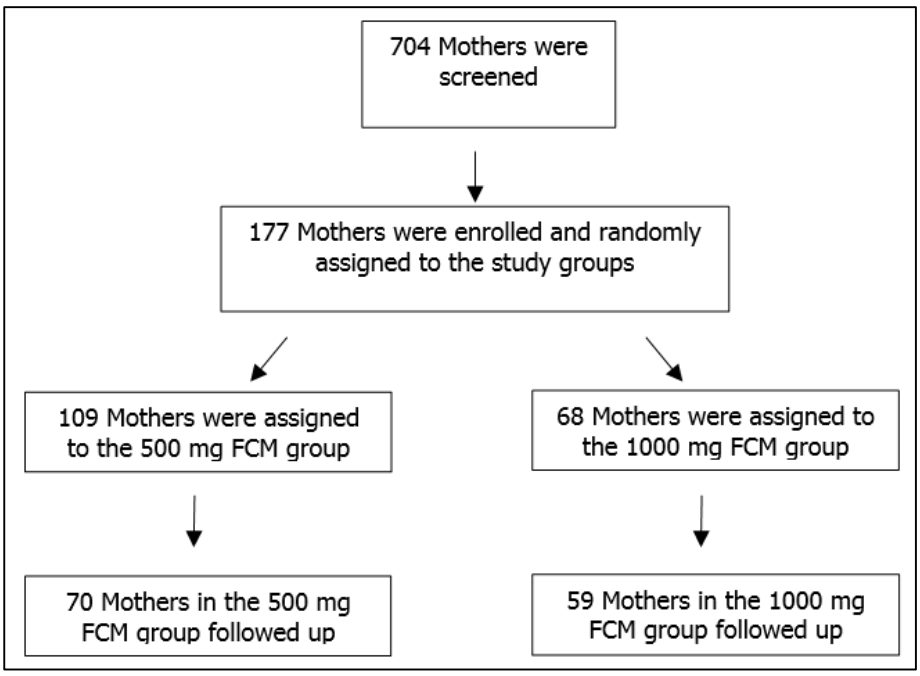

Chart 1. Flowchart of Recruitment and Participation in the Study

DISCUSSION

Numerous clinical trials involving over 2000 patients have demonstrated the unequivocal effectiveness of a 1000 mg FCM dose in raising Hb levels and replenishing iron stores[32] and this dose has been shown to be safe and well tolerated.[19,29,33] In India, the single dose of 1000 mg costs approximately INR 5000 (85 USD) while a 500 mg dose costs less than half at INR 2000 (35 USD). The demand for always seeking affordable yet effective therapy compelled us to investigate the non-inferiority of a 500 mg dose versus the 1000 mg in a postpartum population of anaemic women. A prior pilot study had suggested that the 500 mg dose could be just as efficacious as the 1000 mg and given the significantly lower cost of the 500 mg dose, it became imperative to conduct a definitive evaluation. The immediate postpartum period was the ideal time to target a vulnerable population of women with an unmet need, since they are immediately captive following delivery. Prior experience inform us that such women are difficult to follow up once they leave the maternity unit and therefore a single "total dose" infusion is ideal for such a population. Indeed, while we were able to recruit 177 in the immediate postpartum phase and administer the iron infusion at follow up. Six weeks later, we had lost 48 of our participants.

We found that a single dose of 500 mg FCM provided a clinically relevant and significant increase in Hb concentration from baseline and met the predefined criteria for non-inferiority to a single dose of 1000 mg FCM. Thus, the 500 mg dose was non-inferior with regard to the primary outcome measure of the proportion of patients with an increase in Hb of ≥20 g/L from baseline to week 6. It was non-inferior with regard to the mean change in Hb from baseline to week 6 and in the proportion of participants who achieved an Hb concentration of 120 g/L or more and therefore were rendered non-anaemic.

Dose escalation studies have previously reported a dose-dependent increase in haematological markers. Thus, Geisser et al observed a dose-dependent increase in the total serum iron and serum ferritin in mildly anaemic volunteers who received 100, 500, 800 and 1000 mg FCM given in a bolus injection over 15 minutes.[34] It therefore does not surprise that we should have found that the proportion of patients in the 500 mg FCM group with a ≥3.0 g/dL Hb increase at week 6 was significantly lower than that in the 1000 mg FCM group. However, the single dose of 500 mg FCM resulted in improved iron stores as measured by serum ferritin and CRP measures that were non-inferior to the 1000 mg FCM dose. Consistent with previous reports[28,35] both doses were well tolerated and the most common drug-related events observed such as headaches and mild-to-moderate skin changes had a similar prevalence in our two study groups.

In an effort to reduce maternal mortality the Indian government introduced two benefit programs, Janani Suraksha Yojana[36] and Janani Shishu Suraksha[37] that have increased institutional delivery among pregnant rural women and those who access public health facilities. This offers a window of opportunity to treat postpartum anaemia, but not using conventional approaches such as oral iron or IV iron sucrose since the former requires compliance and effectiveness is hampered by chronic disease and worm infestation, while the latter requires multiple visits over a course of weeks, which simply would not happen. Our study supports the concept of using a single, efficacious, cost-effective therapy such as FCM at a lower and cheaper dose allowing for the scale up of anaemia eradication programs.

We acknowledge a number of limitations associated with this study. Its open-label, non-blinded design is a potential source of bias. However, any such bias was minimised by the fact that there was no placebo arm and the measures used (Hb estimations, serum ferritin, etc.) are objective and

could not be influenced by the knowledge of the dose of FCM used. The HemoCue that was used to determine Hb concentrations has been known to overestimate Hb values.[38-40] However, since the same HemoCue was used to measure Hb levels at baseline and 6 weeks following infusion, any errors would have been minimised. Measurements of serum ferritin levels in the immediate postpartum period are subject to influence by a number of factors including the inflammatory responses that must occur with the involution of the uterus and placental bed that occurs following childbirth, but any such changes are likely to have occurred in both Groups 1 and 2 and the women were randomised.

CONCLUSION

Our study shows that a single dose of 500 mg FCM administered over a period of 15 minutes within 24 hours following delivery is as effective as the 1000 mg dose in improving haemoglobin and iron indices of women with postpartum anaemia. In a massively populated country such as India, our findings indicate that double the number of women with postpartum anaemia can be treated at a lower cost if the 500 mg dose is adopted as the treatment standard.

ACKNOWLEDGEMENTS

Prithvi Rao Administrator at Divakars Speciality Hospital and staff of all the hospitals involved in the study.

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