ORIGINAL ARTICLE

Effectiveness of Single-dose Ferric Carboxymaltose in Enhancing Hemoglobin Levels in Pregnant Women with Moderate-to-Severe Iron-deficiency Anemia

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Abstract

Background: Anemia contributes to increased pregnancy-associated morbidity and mortality; hence warranting rapid correction. Parenteral ferric carboxymaltose (FCM) has FDA and DCGI approval for use in pregnancy-linked iron-deficiency anemia, with minimal and nonserious side effects. Ferric carboxymaltose is given as a single-dose administration, requiring lesser hospital visits and costs. FCM has been accepted for clinical use in the Indian population. However, there is limited evidence about its use for moderate or severe anemia among antenatal women. This study aims to analyze the efficacy and safety of single-dose intravenous ferric carboxy maltose among anemic pregnant females.

Methods: Prospective observational study comprising 150 iron-deficiency anemic pregnant women between 16 and 32 weeks of gestation with hemoglobin between 5 and 9 gm/dL. Single dose of FCM (dose calculated by Ganzoni's formula) was administered and treatment effectiveness was assessed by serial hemoglobin measurement at 2 weeks and 6 weeks after administration of FCM and then at the time of delivery. Safety was determined by analysis of adverse drug reactions and biochemical tests at the aforesaid time intervals.

Results: The mean rise in hemoglobin at 2 weeks was 1.35 gm/dL, at 6 weeks was 3.08 gm/dL and at delivery was 4.80 gm/dL ($p < 0.001$). No serious adverse effects were found.

Conclusions: The present study bolsters clinical use of intravenous FCM in anemic pregnant females in view of its efficacy and safety. Low-risk single dose dispensation and subsequent upsurge in hemoglobin levels should place FCM as a preferred alternative in moderate-to-severe anemia management during pregnancy.

Keywords: Anemia, Ferric carboxymaltose, FCM, Hemoglobin, Iron deficiency, Pregnancy.

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Introduction

WHO defines anemia in pregnancy as hemoglobin levels below 11 gm/dL and a hematocrit of less than 33%.[1] As per 2015–2016 report by National Family and Health Survey, 50.3% of pregnant women in India were anemic.[2] Iron-deficiency anemia (IDA) is reportedly linked with significant maternal–fetal morbidity as well as mortality. Anemia in pregnancy period has negative physiological, psychological, and immunological impact on both the mother and fetus well-being. It also severely disturbs the feto-maternal circulation. Severe iron-deficiency anemia (hemoglobin <7 gm/dL) during antenatal period increases the risk of postnatal maternal demise by more than two folds.[3,4]

At present, the treatment options for iron-deficiency anemia are varied. Oral iron supplementation is prophylactically recommended in pregnancy but is inadequate for moderate-to-severe anemia treatment, especially in advanced trimesters. Oral iron supplementation is often poorly tolerated due to associated constipation, bloating, gastritis, nausea, and vomiting.[5] Thus, parenteral iron comes into the picture which offers a better response and can also eliminate the need for blood transfusions.[6] The iron sucrose complex (ISC) is the commonest parenteral iron for anemia in pregnancy with minimal safety problems. However, iron sucrose has decreased compliance due to its multiple dosing required to achieve the target hemoglobin. Other intravenous iron preparations like iron dextran carry a risk of anaphylactic reactions.[7] Lastly, red blood cell transfusions, however quick they may be, are fraught with the inherent risk of hemolytic and allergic reactions.

Ferric carboxymaltose (FCM) is an intravenous iron agent incorporating a complex of ferric hydroxide and attached carbohydrate, offering sustained iron delivery to reticuloendothelial cells system.[8] FCM is recommended as single-shot intravenous infusion. Steady mean hemoglobin rise was seen over weeks after FCM dispensation is significantly more than oral iron use.[6] Also due to its low immunogenic potential, it has decreased the risk of anaphylactic reactions. As stated by Gupte et al. FCM is

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well-tolerated with only 4.06% of patients reporting adverse effects mainly as mild itching over the injection site.[9]

In India, antenatal visits of pregnant females and their follow-up is of major concern. The single-sitting administration of FCM should require a lesser number of visits and therefore should be feasible both for patients and health administrators. However, there is limited evidence about its use for moderate or severe anemia among antenatal women, especially in the Indian scenario.

Against this background, the current study was planned to document the use of FCM for moderate and severe anemia in pregnancy and measure its effectiveness and safety for wider recommendations at the national level.

Materials and Methods

The study was designed as a prospective randomized trial carried out in the Department of Obstetrics and Gynaecology, Gandhi Medical College, Bhopal, a tertiary health care center in the central part of India.

Inclusion Criteria

About 150 pregnant females in 18 and 45 years age group with gestational age between 16 and 32 weeks have moderate-to-severe iron-deficiency anemia (hemoglobin levels 5 and 9 gm/dL) and not taking any other form of iron supplementation during the current pregnancy. Patients having microcytic, hypochromic anemia, with serum ferritin levels <30 µg/L were included.

Exclusion Criteria

Women with oral or parenteral iron administration during the current pregnancy, renal or hepatic impairment, allergy to iron preparations, with RBC disorders, such as thalassemia, sickle-cell anemia, or hemolytic anemia.

Data Collection and Evaluation

The demographic details of all the patients were noted. Written and informed consent was obtained from all participants. A thorough history of each patient was taken regarding education status, family history, history of drug allergy, history of no. of children, and administration of any other formulation of iron in the past. All baseline investigations were obtained. Well-being of the patients was assessed using a linear analog scale to determine any change in the quality of life.

Procedure of FCM Administration

Single-dose intravenous FCM infusion in accordance with iron requirement was administered, along with approximately 250 mL normal saline over 15 and 20 minutes.

The total iron requirement was calculated using the Ganzoni's formula: [2.4 x (body weight in kg) x (Target - Actual hemoglobin in gm/dL)] + 500 mg. In our study, target hemoglobin was estimated as 12 gm/dL.

Side effects following FCM administration were estimated by regularly monitoring pulse rate and rhythm, systolic–diastolic blood pressure, local reaction, and peripheral oxygen saturation at 10-minute intervals after beginning FCM infusion. The above-mentioned parameters and laboratory investigations were also assessed at 2 weeks, 6 weeks after FCM administration, and at the time of delivery.

Table 1: Distribution according to the baseline characteristics

Characteristics	*Groups*	*Frequency*	*Percentage*
Age (years)	<30	34	22.67%
	31–35	92	61.33%
	36–40	21	14.00%
	>40	3	2.00%
Gravidity	Primigravida	42	28%
	Multigravida	78	52%
	Grandmulti	30	20%
Socioeconomic	Lower	73	48.67%
	Lower middle	24	16.00%
	Upper	17	11.33%
	Upper lower	26	17.33%
Occupation	Homemaker	141	94.00%
	Teacher	03	2.00%
	Field worker	06	4.00%
Education	illiterate	67	44.67%
	5th	63	42.00%
	10th	07	4.67%
	12th	02	1.33%
	Graduation	11	7.33%
Locality	Rural	123	82%
	Urban	27	18%
Gestational age	<20	10	6.67%
	20–25	50	33.33%
	25–30	56	37.33%
	>30	34	22.67%
Birth interval	<1 year	07	6.66%
	1–2 year	45	41.33%
	2–3 year	38	35.33%
	>3 year	18	16.66%
Grading of anemia	Moderate	135	90.00%
	Severe	15	10.00%

Statistical Analysis

IBM SPSS ver. 20 was used to carry out the analysis. Frequency distribution and tabulation were used for table preparation. Quantitative variables were represented with mean and standard deviation. Means were compared by ANOVA test. A *p*-value less than 0.05 was taken as a statistically significant value.

Results

The mean maternal age of 150 pregnant subjects in this study was 32.71 ± 3.25 years. The majority of women belonged to lower socioeconomic class (48.67%) were homemakers (94%), belonged to the joint family (85.33%) and were illiterate (44.67%), and resided in rural areas (82%). Majority of the females in the present study were multigravida (52%) and most of the participants (41.33%) had birth intervals between 1 and 2 years. The general demographic details of the study participants are listed in Table 1.

Table 2 and Figure 1 show that the mean rise of hemoglobin at 2 weeks was 1.35 ± 0.93 gm/dL (*p*-value = 0.021), at 6 weeks a

Table 2: Comparing mean change in hemoglobin after FCM

Hemoglobin	*Mean*	*SD*	*Mean rise from baseline*
At time of administration of FCM	8.07	0.95	Reference
At 2 weeks	9.42	0.93	1.35
At 6 weeks	11.15	0.67	3.08
At delivery	12.87	0.96	4.80

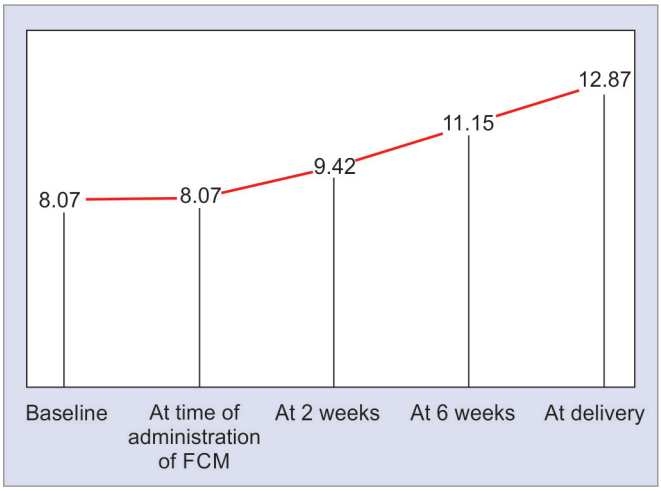

Fig. 1: Comparing mean change in hemoglobin after FCM

Table 3: Distribution of patients according to adverse events following FCM administration

Adverse effect	*Frequency*	*Percentage*
Nausea, vomiting and diarrhea	00	00
Fever	00	00
Hypotension/hypertension	00	00
Thrombophlebitis	02	1.33%
Anaphylaxis	00	00

Table 4: Comparing mean change in liver function test after FCM

LFT	*Mean*	*SD*	*Mean deviation from baseline*
At time of administration of FCM	0.60	0.14	Reference
At 2 weeks	0.58	0.15	–0.02
At 6 weeks	0.60	0.14	0
At delivery	0.62	0.14	0.02

rise of 3.08 ± 0.67 gm/dL was observed (p-value < 0.001) and at the time of delivery the mean rise in hemoglobin was 4.80 ± 0.96 gm/dL (p-value < 0.001).

Table 3 presents that two patients developed adverse reactions in the form of superficial thrombophlebitis at a local site at the time of FCM administration. No participating subject had hyper or hypotension, vomiting, diarrhea, or any other side effect till delivery. There was an improved sense of well-being among the patients following FCM administration according to the linear analog scale.

Tables 4 and 5 depicts that no significant changes were noted in the liver function test [p-value 0.688 (at the time of administration of FCM), 0.691 (at 2 weeks), 0.982 (at 6 weeks), 0.894 (at delivery) compared with baseline] or kidney function test [p-value 0.564

Table 5: Comparing mean change in kidney function test

KFT	*Mean*	*SD*	*Mean rise from baseline*
At time of administration of FCM	23.15	4.13	Reference
At 2 weeks	24.47	5.95	1.32
At 6 weeks	23.84	5.26	0.69
At delivery	23.64	4.47	0.49

(at the time of administration of FCM), 0.873 (at 2 weeks), 0.584 (at 6 weeks), 0.724 (at delivery)] compared with baseline after FCM administration.

Discussion

Anemia is an age-old crisis faced by populations across all age groups. Care of the vulnerable like pregnant women becomes a vital component as by treating anemia, we can overcome life-threatening complications both in mother and fetus. The need for rapid and efficient correction of anemia in pregnancy thus cannot be ignored. There have been multiple studies in the past documenting the greater efficacy and safety of FCM over oral ferrous sulfate[10,11] and IV ISC[12] in different subsets of population.

In the present study, the mean age of the subjects was 32.71 ± 3.25 years as compared with 24.1 years in Kant S et al.[13] study. Harsoor et al.[14] reported that 46% of participants were in 21 and 25 years age group whereas Umesh et al.[15] found the mean age to be 22.6 years. About 48.67% of participants in the present study reportedly belonged to low social and economic class whereas Harsoor et al.[14] noted 34% belonging to lower class. In the present study, 94% of the participants were homemaker. Well-educated and self-dependent women are likely to be better versed in good dietary intake and have greater influence in household food management And 85.33% of the patients in this study belonged to the joint family which was slightly higher than that stated by Umesh et al.[15] in which 81.5% of the pregnant women lived in joint families. In this study, 44.67% of the females were illiterate and 82% belonged to rural areas. Women belonging to the urban locality and good educational attainment had better awareness about healthy nutrition, consequently improving their dietary intake.

About 52% of our patients were multigravida which was analogous to that found by Umesh et al.[15] where 53.7% of the females were multigravida and Kant et al.[13] where 63.5% of females belonged to multigravida. The multigravida and grand multigravida females have higher prevalence of anemia as their body is more frequently depleted of the reserved iron stores. Anemia is more prevalent in women who get pregnant at shorter intervals of time as their body does not get enough time to replenish the iron stores. In this study, majority (41.33%) of women had a birth interval between 1 and 2 years and 16.66% had >3 years. Umesh et al.[15] found that 88% of pregnant women had a birth interval of less than or equal to 2 years.

In the present study, a change in hemoglobin levels was observed after intravenous FCM infusion at different period. The mean hemoglobin level was found to rise persistently as compared with the study by Harsoor et al.[14] where a rise in hemoglobin level was 1.2 gm/dL at 2 weeks, 1.36 gm/dL at weeks after FCM administration and 0.84 gm/dL after delivery. This slight fall in the hemoglobin value in the postnatal period was thought to be due to peripartum blood loss. According to Jose et al.,[6] the mean rise in hemoglobin at different time intervals was 2.03 gm/dL at 3 weeks,

2.91 gm/dL at 6 weeks, and 2.96 gm/dL at 12 weeks, the levels rising continuously and comparable to this study. Kant S et al.[13] reported 4.6 (3.9 and 5.0) g/dL mean increase in hemoglobin after 6 weeks of FCM injection, which was analogous to the present study.

The present study documented the safety of FCM as well. Other than minor side effects, such as thrombophlebitis at the local site which was observed in two patients, none of the patients had any other adverse reaction. No effect of FCM on liver function and kidney function was noted which indeed portrays that FCM is a safe drug. There was an improved sense of well-being among the patients following FCM administration similar to that concluded by Jose et al.[6]

Gupte SA et al.[9] reported that FCM was well-tolerated, and only approximately 4.06% patients reported adverse effects; mild local site irritation was commonest, followed by slight palpitation and temperature rise; none requiring stopping of infusion. FCM, given as a single large dose administration per setting, requires lesser dosing frequency, lesser hospital visits, and total cost compared with other intravenous preparations. The discomfort to patients was also significantly lower due to lesser needle pricks.[8] There was an improved sense of well-being among the patients over a period of time.[16,17]

Conclusion

The present study documented that administration of FCM in moderate-to-severe anemic pregnant women resulted in a rapid and sequential rise in hemoglobin. Single large dose FCM administration offers better compliance than other IV and oral preparations in moderate-to-severe anemic patients. There were no relevant safety concerns or biochemical derangements in patients following FCM administration.

The present study advocates the clinical use of low-risk single-dose intravenous FCM in anemic pregnant females in view of its efficacy and safety, as a preferred alternative in moderate-to-severe anemia management during pregnancy.

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