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Original Research Article

Ferric carboxymaltose in the management of anemia due to non-obstetric conditions in women: a sub-group analysis of a large multi-center real-world study/PROMISE from India

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ABSTRACT

Background: Real-world data on the efficacy and safety of intravenous ferric carboxymaltose (FCM) for treating iron deficiency anemia (IDA) in Indian women is limited.
Methods: This was a sub-group analysis of the real-world PROMISE study, which analyzed data of women who received FCM for the management of IDA due to non-obstetric causes. Hematological parameters were retrieved from the charts at baseline and at 4±1 week and analyzed for the whole sub-group and by the severity of anemia.
Results: In 442 women with anemia, Hb and serum ferritin improved by 2.77 gm/dl and 62.07 µg/l, respectively ($p<0.001$ for both) at 4 weeks. There was a significant increase in red blood cell (RBC) count, hematocrit, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) ($p<0.001$ for all). In 192 subjects with severe anemia, there was a significant increase in Hb by 3.19 gm/dl, serum ferritin by 61.67 µg/l, RBC count, hematocrit, and MCV ($p<0.001$ for all); and MCH ($p=0.002$). In 226 subjects with moderate anemia, there was a significant increase in Hb by 2.41 gm/dl, serum ferritin by 62.75 µg/l, and MCV ($p<0.001$ for all); and MCH ($p=0.003$). No subject had mild anemia. No new safety signals or serious adverse events were reported. Physicians rated the efficacy and safety of FCM as very good to good in 94.1 and 94.2% of subjects, respectively.
Conclusions: In Indian women, FCM effectively and safely corrects IDA due to non-obstetric causes, in a short span of 4 weeks.

Keywords: Anemia, Efficacy, Females, Ferric carboxymaltose, India, Iron deficiency, Safety, Women

INTRODUCTION

Anemia in women is a global public health concern. According to the World Health Organization's (WHO's) anemia estimates (2021 edition), 29.9% of the of the women aged 15-49 years across the globe had anemia in 2019.[1] Anemia in women is a bigger health concern in India as the 2019-2020 National Family Health Survey showed that 57% of all Indian women in the age group of 15-49 years had anemia.[2] According to the recent WHO estimates, >40% of women aged 15-49 years in India have severe anemia.[3]

The high prevalence of anemia in women in childbearing age (15-49 years) points towards causes peculiar to this age

group. Pregnancy and postpartum hemorrhage are the commonest causes of anemia in women in child-bearing age. However, anemia can occur in these women due to gynecological causes that result in heavy menstrual bleeding (HMB) or abnormal uterine bleeding (AUB) (hypermenorrhea, menorrhagia, polymenorrhea or metrorrhagia) such as adenomyosis, uterine fibroids, or endometrial hyperplasia.[4]

Iron deficiency anemia (IDA) is the most common cause of anemia in Indian women.[5] In India, IDA is usually treated with oral iron preparations.[5-8] However, moderate to severe anemia, as is prevalent in Indian women, needs aggressive and quick improvement in hematological parameters, which cannot be achieved through oral iron preparations.[5,6] Indian women have poor compliance with oral iron therapy due to several causes, such as gastrointestinal side effects and not considering anemia serious enough to warrant continued therapy.[8,9] Also, given that Indian women often present with severe anemia, their iron requirement is too high to be replenished and sustained orally.[6]

Moderate to severe anemia can be treated by blood transfusions. However, blood transfusions are usually reserved for acute blood loss of >30% of blood volume and severely symptomatic anemia, as they have the risk of serious infectious and non-infectious complications.[10] The other option to treat moderate to severe anemia is to use parenteral iron preparations. The goal of parenteral iron therapy is to quickly and safely improve anemia, replenish iron stores, overcome the shortcomings of oral therapy, and avoid the need for blood transfusion in moderate to severe anemia.[11]

The ideal parenteral iron therapy should be effective as a single dose, have low immunogenic potential and reduced risk of anaphylactic reactions, and administered in clinic settings. Ferric carboxymaltose (FCM) is a third-generation parenteral iron formulation with very low immunogenic potential and reduced risk of anaphylactic reactions.[5] FCM can be administered quickly (15-minute) in large doses (maximum of 1000 mg/infusion) in a single infusion without the need of a test dose.[5,12,13] It is seen that in women with IDA, FCM corrects anemia and replenishes iron stores faster than other commonly used parenteral iron preparations but with minimal side effects.[14-17]

There is abundant clinical evidence supporting the efficacy and safety of FCM in rapidly replenishing iron stores and correcting anemia in Indian women with IDA due to pregnancy and postpartum hemorrhage.[14,16,18,19] However, evidence on the use of FCM for IDA due to non-obstetric causes in Indian women is largely lacking. Similarly, real-world evidence (RWE) of the efficacy and safety of FCM in Indian women is largely lacking.[20] Since RWEs involve real-life patients seen in clinics, RWEs substantiate or refute the applicability of clinical trial evidence in real-life clinics.[21]

We had earlier demonstrated the efficacy and safety of intravenous FCM in the management of IDA through the real-world PROMISE study conducted in the adolescent and adult Indian population across 269 centers.[22] The PROMISE study also showed that physicians had a favorable opinion regarding the efficacy and safety of FCM in quickly correcting anemia in a short span of 4 weeks.[22] The objective of the present sub-group analysis was to assess the effectiveness and safety of FCM in the treatment of Indian women with IDA due to non-obstetric conditions.

METHODS

This sub-group analysis of the retrospective observational PROMISE study22 included non-pregnant women aged ≥14 years from 269 centers across India who had with anemia [with hemoglobin (Hb) level between 4.0 and <12 gm/dl]. The subjects were routinely treated with FCM 500/1000 mg injection (Injection Orofer FCM 500/1K, Emcure Pharmaceuticals Ltd., Pune, India) as per standard of care in real-life clinical practice between January 01, 2021 and December 31, 2021. Data of women who received FCM for treatment of IDA due to pregnancy and postpartum anemia were excluded from this sub-group The PROMISE study details can be obtained from the article by Charmila et al published in 2022.[22]

Available data on hematological parameters at baseline and/or for the minimum of 4±1 week (reported as 4 weeks for simplicity) were anonymously captured from the subjects' medical records. This sub-group analysis is part of the PROMISE study that was approved by the Ripon Independent Ethics Committee. The study was registered with the Clinical Trial Registry of India (CTRI) with a wide registration number CTRI/2021/12/039065

Demographic and hematological parameters were analyzed using descriptive statistical methods. Data were analyzed for the sub-group population, and by the severity of anemia within the specified sub-group. Quantitative data was described as mean±standard deviation (SD). Categorical data was represented as frequencies and percentages. A paired t-test was carried out to compare the hematological parameters at baselines and 4 weeks after FCM infusion.

Hb values ≥12 gm/dl were considered as normal as per World Health Organization's (WHO's) Hb cut-off values for anemia in non-pregnant women.[23] Anemia was categorized as mild, moderate and severe based on the WHO's Hb cut-off values: severe anemia (Hb <8 gm/dl); moderate anemia (Hb 8-10.9 gm/dl); and mild anemia (Hb 11-11.9 gm/dl).[23]

Physicians' global assessment of the efficacy and safety of FCM in their subjects were graded as very good, good, average, or poor based on clinical improvement (symptomatic and hematological improvement), and

adverse events/side effects of FCM noted in the medical records, respectively.

RESULTS

Baseline characteristics

This sub-group analysis included data of 442 women with a diagnosis of anemia due to abnormal uterine bleeding, perioperative anemia and anemia due to any unspecified cause in the subjects' medical records.

The mean age of women included was 35.14 years (range 14 to 80 years); with mean Hb of 7.88 gm/dl (n=431) and mean serum ferritin at 46.41. µg/l (n=65) at the baseline. The mean cumulative FCM dose was 894.88 mg, and mean FCM infusion time was 19.16 minutes. Table 1 shows the various demographic and hematological parameters at baseline.

Table 1: Patient characteristics at baseline.

	N	Mean±SD	Median (IQR)	Range (min-max)
Age	437	35.14±10.74	32 (28, 40)	14 to 80
Weight	360	58.24±9.6	58 (52, 65)	32 to 90
FCM Infusion duration (min)	362	19.16±6.63	20 (15, 20)	5 to 60
FCM dose	371	894.88±309.32	1000 (500, 1000)	500 to 3000
Hb (g/dL)	431	7.88±1.05	8 (7.2, 8.5)	4 to 10.8
Serum Ferritin (µg/L)	65	46.41±35.98	52.7 (9.45, 72)	1 to 180
RBC Count (mn/mm3)	75	3.81±1.34	3.82 (3.2, 4.2)	1.8 to 12.5
Hematocrit (%)	62	27.42±6.03	27.5 (23, 33)	16.5 to 40
MCV (fL)	72	67.41±13.62	65.5 (58, 75)	29.3 to 98
MCH (pg)	68	23.35±6.26	22.15 (19.5, 26.75)	3.6 to 37
MCHC (gm/dl)	67	30.52±3.75	30 (28.44, 32.29)	24.2 to 43.1
Types of anemia		**N (%)**		
Anemia as a broad diagnosis		423 (95.7)		
Anemia caused by abnormal uterine bleeding		16 (3.6)		
Perioperative anemia		3 (0.7)		

Abbreviations: %- percentage; µg/l- micrograms per liter; fL- femtoliters; gm/dl- grams per deciliter; Hb- Hemoglobin; IQR- Interquartile range; MCH- mean corpuscular hemoglobin; MCHC- mean corpuscular hemoglobin concentration; MCV- mean corpuscular volume; min- minutes; Min-Max- Minimum-Maximum; mn/mm^3- million per millimeter cube; N- number of participants; pg- picograms; RBC- red blood cell; SD- standard deviation; Note: 4 weeks is 4±1 week

Table 2: Comparing hematological parameters before and after administration of ferric carboxymaltose in women with anemia.

Parameter	N	At baseline (mean±SD)	At 4 weeks (mean±SD)	Mean improvement ±SD
Hemoglobin (gm/dl)	418	7.9±1.04	10.67±1.02	2.77±1.02*
Ferritin (µg/l)	49	46.33±29.76	108.4±42.77	62.07±3 3.41*
RBC (mn/mm^3)	51	3.72±1.47	4.52±0.66	0.8±1.37*
Hematocrit (%)	42	27.85±6.5	35.08±7.35	7.23±7.8*
MCV (fl)	51	70.79±13.46	82.28±8.78	11.49±10.93*
MCH (pg)	49	25.02±6.15	29.8±7.44	4.79±8.78*
MCHC (gm/dl)	48	30.77±4.05	30.86±7.3	0.09±7.22^{NS}

*P value <0.001, Statistically significant difference; NS- p value >0.05, non-significant difference.
Abbreviations: %- percentage; µg/l- micrograms per liter; fl- femtoliters; g/dl- grams per deciliter; Hb- hemoglobin; MCH- mean corpuscular hemoglobin; MCHC- mean corpuscular hemoglobin concentration; MCV- mean corpuscular volume; min- minutes; mn/mm^3- million per millimeter cube; N- number of participants; pg- pictograms; RBC- red blood cell; SD- standard deviation; Note: 4 weeks is 4 ±1 week

Efficacy outcomes

At 4 weeks after FCM infusion, Hb increased significantly by 2.77 gm/dl and serum ferritin increased significantly by 62.07 µg/l in the study population (p<0.001 for both) (Table 2). Red blood cell (RBC) count, hematocrit, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) also increased significantly (p<0.001 for all). There was non-significant improvement in mean corpuscular hemoglobin concentration (MCHC) at 4 weeks as compared to baseline (p=0.932) (Table 2).

In subjects with severe anemia (n=192), iron deficiency could be confirmed by serum ferritin levels at baseline in

16.1% of subjects (31/192). There was a significant increase in Hb by 3.19 g/dL and serum ferritin by 61.67 µg/l at 4 weeks as compared to baseline (p<0.001 for both) (Figures 1 and 2). RBC count, hematocrit and MCV (p<0.001 for all) and MCH (p=0.002) also increased significantly in severe anemia patients. MCHC improved insignificantly at 4 weeks as compared to baseline (p=0.616) (Table 3).

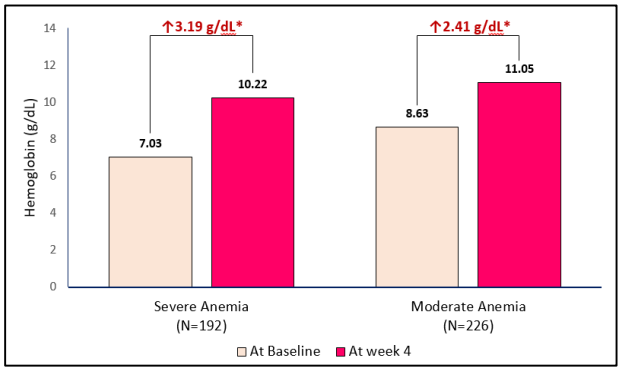

Figure 1: Change in hemoglobin after ferric carboxymaltose infusion in severe and moderate anemia.

P value <0.001, Statistically significant difference; ↑- mean improvement in hematological parameter. Abbreviations: gm/dl- grams per decilitre; N- number of participants.

In subjects with moderate IDA (n=226), iron deficiency could be confirmed by serum ferritin levels in 8% of subjects (18/226). There was a significant increase in Hb by 2.41 gm/dl (Figure 1), serum ferritin by 62.75 µg/l (Figure 2) and MCV (p<0.001 for all) and MCH (p=0.003) at 4 weeks as compared to baseline (Table 3); RBC count (p=0.373), hematocrit (p=0.324), and MCHC (p=0.569) improved insignificantly at 4 weeks as compared to baseline.

There were no subjects with mild anemia.

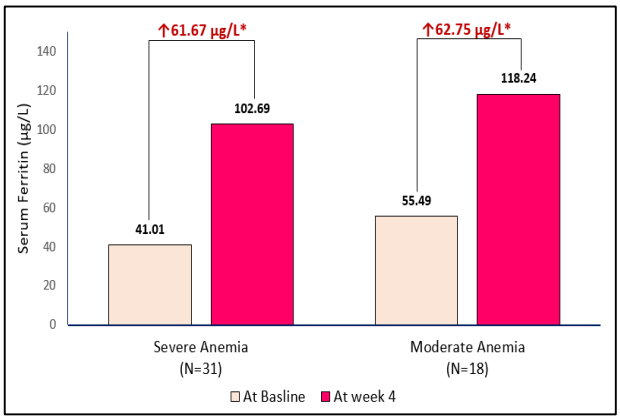

Figure 2: Change in serum ferritin after ferric carboxymaltose infusion in severe and moderate anemia.

*P value <0.001, statistically significant difference; ↑- mean improvement in hematological parameter. Abbreviations: µg/l- micrograms per liter; N- number of participants.

Table 3: Change in RBC indices after ferric carboxymaltose infusion in severe and moderate anemia.

Severity of anemia	Parameter	N	At baseline (mean±SD)	At 4 weeks (mean±SD)	Mean improvement ±SD
Severe (N=192)	RBC (mn/mm^3)	33	3.39±0.81	4.38±0.45	0.99±0.69*
	Hematocrit (%)	27	25.44±6.45	35.44±5.02	10±5.93*
	MCV (fl)	32	68.93±14.17	81.26±8.18	12.33±11.61*
	MCH (pg)	32	24.37±6.36	30.45±9.07	6.08±10.27*
	MCHC (gm/dl)	36	31.03±3.77	31.61±7.29	0.58±6.91 NS
Moderate (N=226)	RBC (mn/mm^3)	18	4.32±2.14	4.77±0.89	0.45±2.11 NS
	Hematocrit (%)	15	32.19±3.92	34.42±10.53	2.23±8.46 NS
	MCV (fl)	19	73.94±11.87	84.01±9.69	10.06±9.81*
	MCH (pg)	17	26.23±5.71	28.58±2.07	2.35±4.14 NS
	MCHC (gm/dl)	12	30.01±4.88	28.62±7.16	1.39±8.21 NS

*P value <0.001, Statistically significant difference; NS- p value >0.05, non-significant difference. Abbreviations: %- percentage; fl- femtoliters; gm/dl- grams per deciliter; MCH- mean corpuscular hemoglobin; MCHC- mean corpuscular hemoglobin concentration; MCV- mean corpuscular volume; min- minutes; mn/mm3- million per millimeter cube; N- number of participants; pg- picograms; RBC- red blood cell; SD-standard deviation; Note: 4 weeks is 4 ±1 week

Safety

Adverse effects (AEs) were seen in 5.4% of the subjects (24/442). The commonly reported AEs were: headache (3.2%), nausea (1.6%), constipation (1.6%), and allergic reaction (0.9%). No serious adverse events (SAEs) were reported in any of the subjects.

Physicians' assessment of efficacy and safety based on data available in medical records: the physicians noted very good to good efficacy and safety of FCM in 94.1% and 94.2% of subjects, respectively. Average efficacy and safety were noted in only 5.9% and 5.8% of subjects, respectively. The physicians did not report poor efficacy and safety in any of the subjects.

DISCUSSION

Moderate to severe IDA is prevalent in Indian women in childbearing age (15-49 years).[2,3] Severe anemia [hemoglobin (Hb) levels <7 gm/dl] continues to be a substantial problem in India women despite national anemia programs.[7,8,24] This is because these programs focus on oral iron supplementation and the corrective actions for severe anemia are targeted towards pregnancy and postpartum hemorrhage. For non-obstetric causes of severe anemia, the programs recommend referral to higher centers for further management. Thus, there is no clear guidance on the management of moderate to severe anemia due to non-obstetric causes.

Moderate to severe anemia is difficult to tackle in Indian women as they are not able to build up sufficient iron stores during adolescence.[8,25] This is because, Indian women are often not given the freedom to choose their diet and medical care, and usually eat poor nutritional quality food with insufficient iron as food allocations in Indian families often favor male members.[8,25,26] As a result, most Indian women have mild asymptomatic anemia which goes undetected. Additionally, Indian women consider common symptoms of anemia, such as fatigue and weakness, as attributes that define female gender.[8] Thus, Indian women become prone to moderate to severe anemia when the iron demand increases (e.g. pregnancy, lactation, HMB, AUB).[8,25]

Though pregnancy and postpartum hemorrhage are recognized as the commonest causes of moderate to severe anemia in Indian women in child-bearing age, anemia due to HMB or AUB is also a major contributor to moderate to severe anemia in Indian women.[20,27-30] Also, HMB/AUB contribute to 5%–10% of moderate to severe IDA cases in the perimeopausal age group (40-50 years).[31]

Even though IDA treatment with oral and parenteral preparations and blood transfusions are available across India, women don't take any corrective actions against anemia and ignore it until it becomes serious.[8] In such a scenario, there is often a clinical need to correct anemia quickly. Blood transfusions are not the preferred modality of correcting moderate to severe anemia (because of potential SAEs) unless there is acute blood loss.[10] A single administration of intravenous FCM is an effective and safer option for correcting moderate to severe anemia than blood transfusions.[31,32] Also, a single FCM administration is sufficient to overcome the need for blood transfusions in most cases.[31,32] There is abundant evidence supporting effective and safe use of single intravenous FCM administration in correcting anemia un Indian women.[12,14,16,18,19,31,33] Evidence through a randomized trial also shows that FCM is a better and more cost-effective method to quickly and effectively correcting anemia and replenishing iron stores than other parenteral iron preparations.[30] Also, there is abundant clinical evidence to support the effective and safe use of FCM in women with anemia associated with heavy menstrual blood loss/menorrhagia, hypermenorrhea, and preoperative menorrhagia.[6,12,31,34,35]

Though there is ample evidence from India on the effective and safe use of intravenous FCM for the management IDA due to pregnancy and postpartum hemorrhage, evidence from India on the use of FCM to treat anemia due to non-obstetric causes of moderate to severe anemia is largely lacking.[14,16,18-20] This sub-group analysis of PROMISE study also showed that FCM significantly improved Hb and ferritin levels in Indian women with HMB/AUB. The significant increase in Hb and ferritin was especially seen in moderate to severe anemia. No new safety signals were identified and there were no SAEs.

The study is limited by its retrospective design, missing data and the inability to control the number and dose of FCM given (few subjects received two FCM 500 mg infusions instead of a single 1000 mg infusion). However, to the best of our knowledge, this is the largest real-world study (N=442) demonstrating the efficacy and safety of FCM in Indian women with IDA caused by HMB/AUB. This sub-analysis is also the first study to provide physicians' assessment of efficacy and safety of FCM in Indian women with IDA caused by HMB/AUB.

CONCLUSION

IDA is very common in Indian women. This sub-analysis of data from 442 Indian women, who were a part of a large real-world PROMISE study, supports the use of intravenous FCM in clinical practice. The sub-group analysis provides real-world evidence that FCM corrects the anemia and replenishes the iron stores effectively within a short span of four weeks in women with iron deficiency anemia due to non-obstetric conditions including HMB/AUB. FCM treatment led to these improvements with a favorable tolerability. Physicians' clinical impression of efficacy and safety supports usage of FCM in daily clinical practice.

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India (CTRI) with a wide registration number CTRI/2021/12/039065

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