

Iron Deficiency Anemia with Menorrhagia: Ferric Carboxymaltose a Safer Alternative to Blood Transfusion

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ABSTRACT

Background: Menstrual disorder accounts for 5%–10% of the women presenting with iron deficiency anemia (IDA) in the perimenopausal age group. Heavy menstrual bleeding in this age group leads to severe anemia and frequently requires blood transfusion which has its own adverse effects. We today have ferric carboxymaltose (FCM) as a safer alternative to blood transfusion.

Objective: The objective of the study is to evaluate the safety and efficacy of FCM in treating anemia in patients of menorrhagia. Thus avoiding blood transfusion.

Materials and Methods: It was an open, single arm observational study including 90 women of age more than 30 years with definitive diagnosis of menorrhagia with IDA and hemoglobin (Hb) levels between 4 gm% and 11 gm%. Intravenous FCM (500–1500 mg) was administered, and the improvement in blood indices was assessed after 3 weeks of total dose infusion. Menorrhagia was controlled by medical treatment till Hb improvement was achieved and definitive surgical intervention was done.

Result: Most of the women were in the age group of 40–50 years. Blood indices measured pre-FCM and 3 weeks post-FCM showed a mean increase in Hb from 8.33 ± 1.10 to 10.89 ± 1.02 with a statistically significant $P < 0.01$. There was a statistically significant rise of packed cell volume, serum ferritin, and serum iron in the post-FCM blood levels after 3 weeks. No serious life-threatening adverse events were observed after FCM administration.

Conclusion: Intravenous FCM is an effective and a safe treatment option for IDA with a single administration of high dose without serious adverse effects obviating the need for blood transfusion before surgery.

KEYWORDS: Ferric carboxymaltose, hemoglobin, iron deficiency anemia, menorrhagia

INTRODUCTION

Perimenopausal women presenting with anemia, the most common cause reported is heavy menstrual blood loss. Menstrual disorder accounts for 5%–10% of the women presenting with iron deficiency anemia (IDA) in the perimenopausal age group.^[1] In developing countries like India where the nutritional Iron deficiency is very much prevalent in the perimenopausal age group women, menorrhagia acts as an aggravating factor leading to severe anemia. Anemia contributes to increase morbidity and mortality in this age group. Cases where active surgical intervention is needed preoperative anemia leads to an increased risk of blood transfusion, per-operative complication, and delayed postoperative

recovery. Hence, anemia needs to be treated promptly in these patients preoperatively. Oral iron is usually is not advisable in these patients as rapid correction of anemia is required before the next bout of bleeding. Hence, blood transfusion or parenteral iron preparation is the treatment of choice in these patients. However, Blood transfusion has its own adverse effects and is best avoided. The liberal use of the iron preparations

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that are available in the market such as iron sucrose and iron dextran is again limited by its life-threatening adverse effect profile and need for multiple doses. Ferric carboxymaltose (FCM) a novel iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell, allows for controlled delivery of iron to target tissues, delivering a replenishment dose of up to 1000 mg of iron during a minimum administration time of ≤ 15 min.^[2] The aim of this study was to evaluate the safety and efficacy of this molecule in patients of menorrhagia with anemia and thus provide a safer alternative for blood transfusion.

MATERIALS AND METHODS

This was an open single arm observational study including women with definitive diagnosis of menorrhagia with IDA and hemoglobin (Hb) levels between 4 gm% and 11 gm%. A total of 90 women with menorrhagia and IDA attending the gynecology outpatient department at our institute were included in the study.

Study outcome

The primary aim of the study was to evaluate the safety and efficacy of FCM in treating IDA due to blood loss in patients with menorrhagia and thus avoid the need for blood transfusion in these patients before surgical intervention.

Study design

This was observational study.

Study period

The duration of the study period was December 2013–August 2017.

Ethical clearance

Institute of Kidney Diseases and Research Centre – ITS Ethical Committee clearance was obtained before the start of the study. Approval letter No. 01/04/2017.

Informed consent

Patients were explained about the requirement of FCM injection, its adverse effects, and written informed consent were obtained from all the women and attenders.

Inclusion criteria

- Women with menorrhagia and blood loss anemia
- Hb levels between 4 gm% and 11 gm%.

Exclusion criteria

- Previous allergic reactions to Iron therapy
- Anemia due to other causes (sickle cell anemia, thalassemia minor, and megaloblastic anemia)
- Women with hemodynamic instability.

Iron deficiency was diagnosed based on the World Health Organization (WHO) criteria Hb < 12 g/dL in women

serum ferritin < 30 ng/mL.^[3] Other parameters such as serum iron, packed cell volume (PCV), peripheral blood smear, and total iron binding capacity (TIBC) were also measured. Pre- and post-FCM values were studied at an interval of 3 weeks. Iron requirement was calculated based on Hb deficit and body weight using the Ganzoni formula.

Dose calculation

Cumulative iron deficit (mg) = body weight in kg \times (Target Hb – Actual Hb g/dL) \times 2.4 + Iron storage depot (mg)

The factor 2.4 is derived from blood volume, which is 7% of body weight and iron content of Hb, which is 0.34%. $0.07 \times 0.0034 \times 100 = 2.4$ (conversion from g/dL to mg).^[4]

Depot iron = 15 mg/kg in case of body weight < 35 kg and 500 mg in case of weight > 35 kg.

Ferric carboxymaltose administration

FCM was administered based on the recommendations and iron requirement of the patients. A maximum of 1500 mg of FCM (30 ml) was administered in a single sitting. FCM was administered as an infusion diluted in sterile 0.9% sodium chloride (NaCl) solution. FCM dose of 500 mg was diluted in 100 ml 0.9% NaCl and administered over 6 min. Doses between 1000 mg and 1500 mg required dilution with 250 ml 0.9% NaCl and were administered over 15 min. Drug was administered under direct supervision, and infusion was stopped in case of any adverse effect. Patients were followed up after 3 weeks to assess the improvement in Hb and iron stores based on the same parameters as mentioned before. Either hormonal or nonhormonal treatment was given to stop the abnormal uterine bleeding and avoid further blood loss.

Statistical analysis

The change in the Hb level and other parameters before and after FCM administration was studied using the IBM SPSS version 20 software, (IBM, Bangalore). The Wilcoxon signed rank test and paired *t*-test of significance was used to analyze the data.

RESULTS

A total of 90 women with menorrhagia and blood loss anemia attending our outpatient department were included in the study. Most of the women were in the age group of 40–50 years ($n = 43$, 47.78%) [Figure 1]. Dose of FCM based on Ganzoni formula was calculated. Majority of the cohort ($n = 47$, 52.22%) showed an iron requirement of 1000 mg of FCM [Figure 2]. Hb and other blood indices were measured pre-FCM and 3 weeks' post-FCM. Both values were statistically

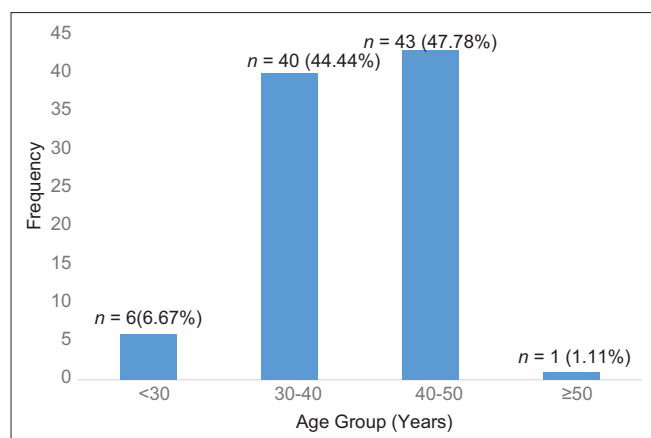


Figure 1: Age-wise distribution

Numerical data for histogram age-wise distribution

Age group	Frequency (%)
<30	6 (6.67)
30-40	40 (44.44)
40-50	43 (47.78)
≥50	1 (1.11)

analyzed which showed a mean increase in Hb from 8.33 ± 1.10 to 10.89 ± 1.02 and was statistically significant ($P < 0.01$). There was a statistically significant rise of PCV, serum ferritin, and serum iron in the post-FCM blood levels after 3 weeks with a statistically significant $P < 0.01$ [Table 1].

Efficacy of FCM was also analyzed based on the dosage of FCM that was given. Maximum increment in the Hb by 3 g/dl was seen with 1500 mg of FCM and was statistically significant ($P = 0.01$). However, a dosage of 1000 mg of FCM and 500 mg of FCM had an increase in Hb by 2.5 g/dl and 2.2 g/dl, respectively [Tables 2-4]. Adverse reaction was noted in 5.5% of the total cohort [Table 5]. Local reactions in the form of redness and pain at the injection site were seen in two patients after the infusion was complete. The reaction was self-limiting, and these patients had no systemic symptoms. Systemic reaction in the form of nausea and chills following the infusion after 10 min was seen in three patients. However, no life-threatening reaction was seen. The sense of wellbeing improved in all women on follow-up. The treatment was well accepted among all patients as no compliance was needed and blood transfusion could be avoided. These women were then posted for surgical intervention for definitive treatment of menorrhagia.

DISCUSSION

According to the WHO, anemia is defined as Hb levels <12.0 g/dl in women.^[5]

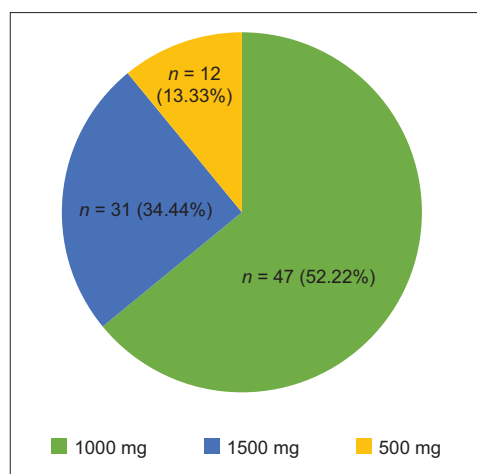


Figure 2: Distribution according to dose of ferric carboxymaltose

Numerical data for pie graph distribution according to dose of ferric carboxymaltose

Dose	Frequency (%)
1500	31 (34.44)
1000	47 (52.22)
500	12 (13.33)

Table 1: Laboratory parameters before and after ferric carboxymaltose administration

Parameters	Pre-FCM	Post-FCM	P
Hb	8.33 ± 1.10	10.89 ± 1.02	$<0.01^*$
PCV	29.85 ± 26.45	35.34 ± 2.44	$<0.01^*$
Serum ferritin	18.52 ± 18.56	118.45 ± 78.13	$<0.01^*$
Serum TIBC	379.87 ± 126.53	257.72 ± 55.27	$<0.01^*$
Serum iron	38.70 ± 21.47	82.59 ± 34.78	$<0.01^*$

*Statistical significant observation. Hb: Hemoglobin, PCV: Packed cell volume, TIBC: Total Iron Binding capacity; FCM: Ferric carboxymaltose

Table 2: Laboratory parameters before and after ferric carboxymaltose administration with 1500 mg ferric carboxymaltose

Parameters	Pre-FCM	Post-FCM	P
Hb	7.72 ± 1.00	10.52 ± 0.94	$<0.01^*$
PCV	25.60 ± 3.74	35.45 ± 1.50	$<0.01^*$
Serum ferritin	18.62 ± 16.51	95.10 ± 29.39	$<0.01^*$
Serum TIBC	365.23 ± 97.65	252.63 ± 49.38	0.04^*
Serum iron	35.45 ± 19.71	80.90 ± 34.96	$<0.01^*$

*Statistical significant observation. Hb: Hemoglobin, PCV: Packed cell volume, TIBC: Total iron binding capacity, FCM: Ferric carboxymaltose

Menorrhagia with severe blood loss anemia is one of the most common conditions faced by a gynecologist with patients in the perimenopausal age group. The National Family Health Survey-3 has shown that the prevalence of anemia in the age group between 15 and 49 years is

Table 3: Laboratory parameters before and after ferric carboxymaltose administration with 1000 mg ferric carboxymaltose

Parameters	Pre-FCM	Post-FCM	P
Hb	8.45±0.98	10.92±1.03	<0.01*
PCV	32.86±36.36	34.84±2.91	0.71 (NS)
Serum ferritin	18.19±20.96	137.30±101.90	<0.01*
Serum TIBC	386.51±141.64	259.89±60.05	<0.01*
Serum iron	39.72±22.85	82.55±33.76	<0.01*

*Statistical significant observation. Hb: Hemoglobin, PCV: Packed cell volume, TIBC: Total iron binding capacity, FCM: Ferric carboxymaltose, NS: Not significant

Table 4: Laboratory parameters before and after ferric carboxymaltose administration with 500 mg ferric carboxymaltose

Parameters	Pre-FCM	Post-FCM	P
Hb	9.46±0.79	11.72±0.60	<0.01*
PCV	29.03±2.07	37.00±1.60	<0.01*
Serum ferritin	19.56±14.31	104.92±18.94	<0.01*
Serum TIBC	391.67±136.73	262.33±53.57	<0.01*
Serum iron	43.08±20.73	87.08±40.72	<0.01*

*Statistical significant observation. Hb: Hemoglobin, PCV: Packed cell volume, TIBC: Total iron binding capacity, FCM: Ferric carboxymaltose

Table 5: Adverse reaction of ferric carboxymaltose

Description	Number of women (n=90), n (%)
Local reactions	2 (2.2)
Systemic reactions	3 (3.3)
Total adverse reactions	5 (5.5)

55%.^[6] The major contributor to this is nutritional iron deficiency in the Indian population. Anemia is a late indicator of iron deficiency, therefore, it is estimated that the prevalence of iron deficiency is 2.5 times that of anemia.^[6]

Abnormal uterine bleeding is one of the most common health problems concerning this age group. Women being nutritionally deficient in the iron stores are vulnerable to severe IDA due to blood loss. Conventionally, blood transfusion followed by an active surgical intervention has been the approach for treating women in the perimenopausal age group with menorrhagia and severe anemia. However, allogeneic red blood cell transfusion is associated with an increased risk of serious adverse events. Intravenous FCM is a safer alternative and has shown promising results as shown in our study. A minimum of 2 g/dl or a maximum of 3 g/dl rise in Hb was seen in 3 weeks. This was consistent with Van Wyck *et al.* who reported increase of Hb by 2 g/dL within 7 days and 3 g/dL in 2–4 weeks in patients receiving FCM.^[7] Significant increase was seen not only in the Hb level but also in the iron stores as seen from pre- and

post-FCM serum ferritin and serum TIBC levels. There was an increase in the mean ferritin level from 18.52 ng/dl to 118.45 ng/dl at 3 weeks interval which was statistically significant ($P < 0.01$). Our results were validated by Rathod S *et al.* where mean ferritin level increase from 35 ng/dL to 356 ng/dL at 2 weeks and 142 ng/dL at 6 weeks.^[4] Thus, FCM not only showed a significant rise in Hb level over 3 weeks but also helped replenish the iron stores in these patients, before the next bout of bleeding.

Dose was calculated based on the weight and iron deficit in the patients taking 12 g/dl as the target Hb. Majority of the cohort (52.22%) had a requirement of 1000 mg of FCM followed by 1500 mg in 34.44% in patients with severe anemia. However, irrespective of the iron requirement FCM dose was not exceeded above 1500 mg in a single sitting. Maximum rise in Hb was seen in patients with 1500 mg of FCM with no additional adverse effect as compared to patients receiving lower doses of FCM. However, safety of higher dose above 1000 mg still requires further research.

Improvement in Haemoglobin after FCM avoided blood transfusion. Similar results were seen with Calleja *et al.* where overall fourfold reduction of transfusions was achieved using FCM preoperatively in patients with colon cancer. This was well tolerated in this group of patients and demonstrated a favorable benefit-risk profile.^[4]

Intravenous iron supplementation has been compared with oral iron in women with IDA associated with menorrhagia and heavy uterine bleeding. Intravenous iron is shown to have significantly higher increment in Hb levels compared to oral iron.^[8] However, intravenous iron preparations have its own demerits of serious adverse reactions and multiple dosing.

FCM is a novel iron molecule now available which is closest to an ideal intravenous iron preparation. FCM is a parenteral iron dextran-free product and one of its kinds approved for the first time for rapid and high-dose replenishment of depleted iron stores. The unique design of this molecule allows controlled delivery of iron to the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins, ferritin, and transferrin, thus minimizing the risk of large amounts of ionic iron being released into the serum.^[9] Intravenous administration of FCM causes rapid increase in the serum iron concentration in a dose-dependent manner. FCM is rapidly cleared from the circulation and is distributed primarily to the bone marrow (~80%) and also to the liver and spleen.^[3]

Being dextran-free FCM has a very low immunogenic potential and therefore not predisposed to high risk of

anaphylactic reactions. It is associated with low risk of oxidative stress reaction when compared to iron sucrose. In our study, local adverse reaction in the form of redness and itching at injection site was seen in only two patients. The systemic adverse reaction was noted in three patients in the form of headache and vomiting. FCM can have mild systemic reaction in the form of transient hypotension or hypertension, nausea, vomiting, and headache. The adverse effects such as vomiting was seen in more than one percent of the population involved in the clinical trials before FDA approval. Breathlessness and myalgia were also seen in the population who were involved in the clinical trial phases, but these adverse reaction were rare (<1%).^[10]

CONCLUSION

FCM is a novel iron molecule for intravenous iron administration. Patients with blood loss anemia due to abnormal uterine bleeding can be treated adequately with FCM, to rapidly improve the Hb levels and the iron stores and thus obviate the need for blood transfusion.

This robust molecule is seen to improve the well-being of these patients on follow-up, and thus these patients can be electively posted for surgical intervention of abnormal uterine bleeding with good intra- and post-operative outcome

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Todd T, Caroe T. Newly diagnosed iron deficiency anaemia in a premenopausal woman. *BMJ* 2007;334:259.
2. Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: A review of its use in iron-deficiency anaemia. *Drugs* 2009;69:739-56.
3. Calleja JL, Delgado S, del Val A, Hervás A, Larraona JL, Terán Á, *et al.* Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. *Int J Colorectal Dis* 2016;31:543-51.
4. Rathod S, Samal SK, Mahapatra PC, Samal S. Ferric carboxymaltose: A revolution in the treatment of postpartum anemia in Indian women. *Int J Appl Basic Med Res* 2015;5:25-30.
5. Cappellini MD, Motta I. Anemia in clinical practice-definition and classification: Does hemoglobin change with aging? *Semin Hematol* 2015;52:261-9.
6. Alvarez-Uria G, Naik PK, Midde M, Yalla PS, Pakam R. Prevalence and severity of anaemia stratified by age and gender in rural India. *Anemia* 2014;2014:176182.
7. Van Wyck DB, Martens MG, Seid MH, Baker JB, Mangione A. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: A randomized controlled trial. *Obstet Gynecol* 2007;110:267-78.
8. Gozzard D. When is high-dose intravenous iron repletion needed? Assessing new treatment options. *Drug Des Devel Ther* 2011;5:51-60.
9. Friedrisch JR, Caçado RD. Intravenous ferric carboxymaltose for the treatment of iron deficiency anemia. *Rev Bras Hematol Hemoter* 2015;37:400-5.
10. Thanusubramanian H, Patil N, Shenoy S, Bairy KL, Sarma Y. Adverse reactions of ferric carboxymaltose. *J Clin Diagn Res* 2014;8:HD01-2.