ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A comparative study of ferric carboxymaltose and iron sucrose as a parenteral iron treatment in iron deficiency anemia during pregnancy in a tertiary care hospital

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Submission: 02-12-2023 Revision: 26-02-2024 Publication: 01-04-2024

ABSTRACT

Background: Anemia from the Greek word (anhaima) meaning "without blood" is the deficiency of red blood cell and/or hemoglobin which result in reduced oxygen-carrying capacity of blood causing tissue hypoxia. **Aims and Objectives:** To study the efficacy and safety of intravenous ferric carboxymaltose (FCM) versus iron sucrose in the management of iron deficiency anemia in pregnancy. **Materials and Methods:** A prospective, single-center, comparative interventional randomized study was carried among 180 antenatal mother admitted to antenatal ward in the Department of Obstetrics and Gynaecology of Burdwan Medical College and Hospital, from July 1st, 2020, to December 30th, 2021. **Results:** A total of 180 patients, 90 patients in each FCM and iron sucrose group, were included in the study. There was significant (P = 0.001) mean change in hemoglobin (Hb) level in both the groups from pre-treatment to 3 and 6-week post-treatment. There was also a significant (P = 0.001) mean change in ferritin level in both the groups from pre-treatment to 3 and 6-week post-treatment. The mean change in Hb level and ferritin level was higher among patients of FCM compared to iron sucrose. The adverse reactions were lower among patients of FCM than iron sucrose. **Conclusions:** This study found that FCM is safer than iron sucrose. Treatment with FCM resulted in rapid replenishment of iron stores in pregnant women with significantly high rise of Hb and ferritin levels over a 6-week period with lesser adverse effects.

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i4.59941

E-ISSN: 2091-0576

P-ISSN: 2467-9100

Key words: Ferric carboxymaltose; Iron sucrose; Anemia; Iron deficiency anemia

INTRODUCTION

Anemia from the Greek word (anhaima) meaning "without blood" is the deficiency of red blood cell and/or hemoglobin (Hb) which result in a reduced oxygen-carrying capacity of blood causing tissue hypoxia. Iron deficiency anemia is the most common and major hematological, nutritional deficiency but manageable health problem encountered among the pregnant women globally but more common in developing countries, especially in tropics like India, especially in under privileged population. Iron deficiency anemia is the most common anemia with significant effect over health status.[1] According to the World Health Organization (WHO), prevalence of anemia in developed and developing countries in pregnant women is 14% and 51%, respectively. About half of the global maternal mortality due to anemia occurs in South Asian countries and India contributes to 80% of it.[2] The WHO defined anemia in pregnancy as Hb level <11g/dL and hematocrit <33%. Anemia affects all age groups starting from puberty and adolescence to peri-menopausal age. High incidence of anemia in India is because of low dietary intake of iron, poor bio-availability of iron, faulty food habits, phytate-rich Indian diet, chronic blood loss during menses, and high prevalence of infections such as malaria and hookworm infestations.[3] In a typical singleton gestation,

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the maternal need for iron averages nearly 1000 mg. Multifetal gestational requirements are considerably higher. A large French study showed depleted iron stores (serum ferritin-15 μg/L) in one out of five women (22.7%) of childbearing age.[4] During pregnancy, the physiological need for absorbed iron increases from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester. Dietary iron intake does not compensate for this strongly increased iron demand. The modest fall in Hb levels and hematocrit values during pregnancy is caused by a relatively greater expansion of plasma volume compared with the increase in red cell volume. The disproportion between the rates at which plasma and erythrocytes are added to the maternal circulation is greatest during the second trimester. The condition gets aggravated in pregnancy due to the increase demand of the growing fetus.[5] Iron deficiency anemia has been shown to be associated with an increased risk of premature birth, low birth weight baby, pre-eclampsia, placental abruption, and increased peripartum blood loss as well as cardiac failure and related death.[6,7] In pregnant women, oral iron is often used for prophylaxis of iron deficiency and is recommended as first-line treatment for pregnant women with iron deficiency anemia.[8] However, oral iron substitution has shown to be insufficient for the treatment of moderate-to-severe iron deficiency anemia in the second and third trimesters and is often associated with non-compliance due to gastrointestinal side effects such as nausea, diarrhea, heartburn, bloating, constipation, and dark stools. Therefore, guidelines recommend that physicians consider intravenous (iv) iron administration in pregnant women in case of severe iron deficiency anemia (Hb - 9.0 g/dL), intolerability to oral iron, insufficient Hb increase after oral iron treatment or if there is a need for rapid Hb reconstitution.[9,10] Parenteral therapy promises a better response in anemic patients and can obviate the need for blood transfusions in the antenatal and postpartum period.[11] The most commonly used intravenous (iv) iron preparation is iron sucrose. It does not require test dose and safe. The only disadvantage is limited dose can be given at 1 time. The maximum permissible dose is 200 mg/day or 600 mg/week and requires multiple hospital visits and puts a heavy burden on hospital resources. Ferric carboxymaltose (FCM) is the latest iv iron formulation which can be used at high doses and allows rapid administration (up to 1000 mg in a single dose infused in 15 min). Because it is free of dextran and its derivatives, FCM does not cross-react with dextran antibodies and never needs the administration of a test dose.[12,13] The present study was a comparative study of iv iron sucrose versus iv FCM as parenteral iron therapy in the management of iron deficiency anemia in pregnancy.

Aims and objectives

The aims and objectives are to study the efficacy and safety of intravenous ferric carboxymaltose (FCM) versus iron sucrose in the management of iron deficiency anemia in pregnancy.

MATERIALS AND METHODS

A prospective, single-center, comparative interventional randomized study was carried among antenatal mother admitted to antenatal ward in the Department of Obstetrics and Gynaecology of Burdwan Medical College and Hospital, from July 01st, 2020, to December 30th, 2021.

Sample size and sampling technique

After judging the inclusion and exclusion criteria, previous study (Alpesh R. P)[14] and based on the Randomized Control Trial formula for sample size calculation,

$n=(Z1-\alpha/2+Z1-\beta)\ 2\times[\{P1\ (1-P1\ )+P2\ (1-P2)\}/((P1-P2)\ 2]$ where, n=Sample size; zα=Level of confidence interval at 95% Level of Significance; Z=1.96: it is Standard deviation score for 95% set interval; Zβ= 0.84 at 80% of power; p1=Expected proportion for Group I is 33% (95% CI) is 0.33 ; P2=Expected proportion for Group II is 20% (95% CI) is 0.2 (Control Group); q=1-p(1-0.57)=0.43) (Intervention Group).

So, $n = (1.96+0.84)[\{(0.33\times0.67)+(0.2\times0.8)\}/(0.33-0.2)\ 2]$ = 176 180. Thus the final sample size became 180, i.e., 90 in each group.

Hence, Group–A (FCM): 90patients and Group–B (Iron sucrose): 90 patients.

Inclusion criteria

Pregnant women aged 18 years and above admitted in the antenatal ward with iron deficiency anemia having Hb values between 7 and 10 g%, gestational age 16–34 weeks, and having single viable fetus with no anomalies were included in the study.

Exclusion criteria

Pregnant women who had anemia due to causes other than iron deficiency, history of blood transfusion and erythropoietin treatment in present pregnancy, other medical disorders complicating pregnancy, or history of hematological diseases and have specific allergy to iron derivatives were excluded.

Study procedure

All the consequences and benefits of the therapy were explained to patient. Written and informed consent was taken after counseling. After inclusion in study, a detailed history of each patient including age, medical history, obstetric history, and family history was taken. Baseline information was collected through interview using pre-designed interview

schedule. Clinical examination was done in details and relevant documents of laboratory investigation, e.g., Hb%, ferritin level, and peripheral blood smear were reviewed.

To determine socioeconomic status of those patients, the modified Kuppuswamy's scale was used. Those who were not able to read and write had been considered illiterate and rest as literate. Detailed physical examination was carried out along with investigations such as Hb, serum ferritin, and peripheral smear. They were randomly divided into two equal groups using a computer-generated table. Group A received 1 g of iv. FCM (as single dose) diluted in 200 mL 0.9% normal saline over 30 min. Group B was treated with total dose of 1 g of iron sucrose which was divided into four equal doses on day l, day 3, day 5, and day 7 (i.e., 250 mg each) diluted in 100 mL of 0.9% normal saline given slow iv over 30 min on indoor basis. During and 1 h after infusion, each patient was monitored in the ward for any adverse reactions. After completion of the regimen patients were discharged from ward and each patient was followed up for rise of Hb, serum ferritin, and peripheral smear change at 3rd week and 6th week after completion of therapy. The results were noted in preformed proforma for each patient. Any adverse drug reactions during infusion and in follow-up period were recorded.

Ethical clearance

The study was done after obtaining the ethical approval from the Institutional Ethics Committee The study was done strictly according to the ethical principles which were adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964. From every patient, informed consent was received and their identities were concealed.

Statistical analysis

The results are presented in frequencies, percentages, and mean±standard deviation. The Chi-square test was used to compare categorical variables between the groups. The unpaired t-test was used to compare continuous variables between the groups. The paired t-test was used to compare mean change in continuous variables. The P<0.05 was considered significant. All the analysis was carried out on the SPSS 22.0 version (Chicago Inc., USA).

RESULTS

The present study was conducted among total of 180 patients, 90 patients in each FCM and iron sucrose group. About one-third of patients of FCM (33.3%) and 30% of iron sucrose were 20–25 years of age. The mean age of patients of FCM and iron sucrose was 27.31±4.89 and 27.23±5.37 years, respectively. More than one-third of patients of both FCM (40%) and iron sucrose (40%) had gestational age 26–30 weeks. The mean gestational age of patients of FCM and iron sucrose was 24.86±4.48 and 23.92±4.65 weeks, respectively. About 77.8% in FCM group and 67.8% patient in iron sucrose group had previous history of childbirth. Hence, in either group, anemia is more common in multiparous women. About 58.9% of patients in FCM group and 55.6% of patients in iron sucrose group had previous history of abortion which suggest that blood loss due to abortion made the mother vulnerable to anemia. More than one-third of patients of iron sucrose (46.9%) and of FCM (40.8%) group had 1 year of interpregnancy interval and 39.5% of iron sucrose and 46.1% of FCM had 2-year interpregnancy interval. More than half of the patients of FCM (58.9%) and iron sucrose (55.6%) groups were illiterate. Lack of education is a contributory factor for anemia. Majority of patients of both FCM (74.4%) and iron sucrose (73.3%) were homemakers. Only 7.8% of patients in FCM group and 1.1% of patients in iron sucrose group belonged to upper class. More than half (56.6%) of the patients in FCM group and approximately three-fourths (74.5%) of the patients in iron sucrose group belonged to low socioeconomic status which clearly indicate that anemia is prevalent in low socioeconomic status. More than half (52.2%) of patients of both FCM and iron sucrose (65.6%) belonged to rural area (Table 1). Intake of iron supplement (weekly) was insignificantly (P>0.05) higher among patients of FCM (8.78±5.07) than iron sucrose (8.71±4.96) (Table 2a). There was no significant (P>0.05) difference in anthropometric parameters between the groups. There was also no significant (P>0.05) difference in hemodynamic parameters between the groups except diastolic blood pressure. There was also significant (P=0.001) difference in Hb level between the groups at post-treatment 3 and 6 weeks (Table 2b). There was a significant (P=0.001) mean change in Hb level in both the groups from pre-treatment to 3 and 6-week post-treatment. The mean change in Hb level was higher among patients of FCM compared to iron sucrose. Significant (P=0.001) difference was found in ferritin level between the groups at post-treatment 3 and 6 weeks. Significant (P=0.001) mean change in ferritin level was also found in both the groups from pre-treatment to 3 and 6-week post-treatment. The mean change in ferritin level was higher among patients of FCM compared to iron sucrose. There was no significant (P>0.05) difference in peripheral blood smear at all the time periods between the groups (Table 3). The adverse reactions were lower among patients of FCM than iron sucrose (Table 4).

DISCUSSION

The aim of this study was to compare the safety and efficacy of injection FCM with injection iron sucrose in antenatal

Table 1: Distribution of sociodemographic and obstetric characteristics between the groups

Age (Years)	FCM (n=90)		Iron sucrose (n=90)	
	No.	%	No.	%
<20	4	4.4	7	7.8
20–25	30	33.3	27	30.0
26–30	27	30.0	29	32.2
31–35	24	26.7	21	23.3
>35	5	5.6	6	6.7
Mean±SD	27.31±4.89	27.23±5.37	Mean±SD	27.31±4.89
Education				
Illiterate	53	58.9	50	55.6
Literate	37	41.1	40	44.4
Occupation				
Government service	13	14.4	12	13.3
Private job	10	11.1	12	13.3
Homemaker	67	74.4	66	73.3
SES*				
Class I	7	7.8	1	1.1
Class II	32	35.6	22	24.4
Class III	22	24.4	32	35.6
Class IV	27	30.0	29	32.2
Class V	2	2.2	6	6.7
Place of residence				
Rural	47	52.2	59	65.6
Urban	43	47.8	31	34.4
Gestational age in weeks				
<20	14	15.6	25	27.8
20–25	32	35.6	24	26.7
26–30	36	40.0	36	40.0
>30	8	8.9	5	5.6
Mean±SD	24.86±4.48		23.92±4.65	
Parity				
Nil	20	22.2	29	32.2
One	45	50.0	19	21.1
Two	16	17.8	32	35.6
≥Three	9	10.0	10	11.1
No. of abortions				
Nil	37	41.1	40	44.4
One	21	23.3	30	33.3
Two	21	23.3	16	17.8
Three	11	12.2	4	4.4
Inter pregnancy interval (years)	**FCM (n=76)**		**Iron sucrose (n=81)**	
	No.	**%**	**No.**	**%**
One	31	40.8	38	46.9
Two	35	46.1	32	39.5
≥Three	10	13.2	11	13.6

*Modified Kuppuswamy's scale (2021), FCM: Ferric carboxymaltose, SD: Standard deviation

Table 2a: Comparison of intake of iron supplement (weekly) between the groups

Groups	Intake of iron supplement (weekly) (Mean±standard deviation)
Ferric carboxymaltose	8.78±5.07
Iron sucrose	8.71±4.96
P-value[1]	0.92

[1]Unpaired t-test

women with IDA. A total of 180 patients, 90 patients in each FCM and iron sucrose group, were included in the study. In the present study, 33.3% of patients in FCM group and 30% of patients in iron sucrose group were 20–25 years of age. The mean age of patients with FCM and iron sucrose was 27.31±4.89 and 27.23±5.37 years, respectively (Table 1). In the study by Jose et al.,[15] the mean age of patients of FCM and iron sucrose was 27.5±3.9 and 26.2±3.6 years which was similar to this study. Where other studies[16-18] found that most of the patients (56%) belonged to age group of (20–24) years which were comparatively younger than the present study. In the present study, more than one-third of patients in both FCM (40%) and iron sucrose (40%) groups were in gestational age 26–30 weeks at the time of diagnosis (Table 1) but the mean gestational age of patients of FCM and iron sucrose was 24.86±4.48 and 23.92±4.65 weeks, respectively. In the study by Shruti

Table 2b: Comparison of anthropometric and hemodynamic parameters between the groups

Anthropometric parameters	Ferric carboxymaltose (n = 90)	Iron sucrose (n = 90)	P-value[1]
Height in cm	153.23 ± 4.67	152.39 ± 3.72	0.18
Weight in kg	49.19 ± 6.36	50.12 ± 6.60	0.33
Body mass index in kg/m^2	20.94 ± 2.41	21.58 ± 2.80	0.09
Hemodynamic parameters			
Pulse	84.98 ± 6.84	85.36 ± 6.47	0.70
SBP	112.40 ± 7.19	110.42 ± 8.27	0.08
DBP	74.91 ± 4.29	73.22 ± 5.59	0.02*
Time periods			
Pre-treatment	8.36 ± 0.84	8.23 ± 0.73	0.27
Post-treatment 3 weeks	9.87 ± 0.77	9.39 ± 0.72	0.001*
Post-treatment 6 weeks	11.51 ± 0.76	10.78 ± 0.61	0.001*

[1]Unpaired t-test, *Significant, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3: Comparison of hematological changes between the groups

Time periods	Ferric carboxymaltose (n=90)	Iron sucrose (n=90)	P-value[1]
	Mean change	Mean change	
Change in hemoglobin level			
Pre-treatment to post-treatment 3 weeks	1.51±0.63	1.16±0.43	0.001*
Pre-treatment to post-treatment 6 weeks	3.15±0.79	2.55±0.52	0.001*
Change in ferritin level			
Pre-treatment to post-treatment 3 weeks	66.74±9.38	33.11±11.11	0.0001*
Pre-treatment to post-treatment 6 weeks	88.71±6.63	56.38±12.55	0.0001*
Peripheral blood smear			
Pre-treatment			
Microcytic hypochromic	84	93.3	0.20
Normocytic normochromic	6	6.7	
Post-treatment 3 weeks			
Microcytic hypochromic	63	70.0	0.11
Normocytic hypochromic	2	2.2	
Normocytic normochromic	25	27.8	
Post-treatment 6 weeks			
Microcytic hypochromic	46	51.1	0.06
Normocytic hypochromic	1	1.1	
Normocytic normochromic	43	47.8	

[1]Paired t-test, *Significant

Table 4: Comparison of adverse reactions between the groups

Adverse reactions*	Ferric carboxymaltose (n=90)		Iron sucrose (n=90)	
	No.	%	No.	%
Injection site swelling	4	4.4	7	7.8
Muscle cramp	0	0.0	3	3.3
Nausea	2	2.2	5	5.6
Nausea, vomiting	5	5.6	6	6.7
Pruritus	2	2.2	0	0.0
Redness on injection site	5	5.6	0	0.0
None	72	80.0	69	76.7

*MR

et al.,[19] most of the patients were between 31 and 34 weeks of gestation at diagnosis. This showed that iron deficiency occurs in the late 2nd trimester and 3rd trimester which may be due to hemodilution and increased iron requirement. This study found that 77.8% of patients in FCM group and 67.8% of patients in iron sucrose group had previous history of childbirth (Table 1). In either group, anemia was more common in multiparous women. Other studies[20,21] found that women with at least one previous birth or pregnancy were more likely to have anemia than women without any. In this study, 58.9% of patient in FCM group and 55.6% of patients in iron sucrose group had a previous history of abortion (Table 1). In the study of Uche-Nwachi et al.,[21] there was a positive correlation between the number of spontaneous abortions and the likelihood of developing anemia.

The present study showed that 46.9% of patients in iron sucrose group and 40.8% of FCM group had 1 year of interpregnancy interval. However, 39.5% of iron sucrose and 46.1% of FCM had 2-year interpregnancy interval (Table 1). Study done by Lazovic et al.,[22] showed that the results of Hb indicating anemia were found in a greater number as pregnancy progressed in women with shorter time-interval between deliveries. The current study found that more than half of the patients of FCM (58.9%) and iron sucrose (55.6%) group were illiterate (Table 1). In different studies,[18,23,24] women who had secondary or higher education were less likely to be anemic compared to their counterparts. Educated pregnant women have better income and eat nutritious food and hence do not get nutritional anemia. This study showed that majority of the patients in both FCM (74.4%) and iron sucrose (73.3%) group were homemakers (Table 1). In the study of Mekonnen et al.,[20] by occupation, over half (58%) of the women were homemakers, which was similar to the current study. In this study, more than half (56.6%) of the patients in FCM group and approximately three-fourth (74.5%) of the patients in iron sucrose group belonged to lower socioeconomic status which clearly indicate that anemia is prevalent in low socioeconomic status (Table 1). Other studies[24-26] in which majority of anemic women were from lower socioeconomic class. This study showed that more than half of the patients in both FCM (52.2%) and iron sucrose (65.6%) group belonged to rural area (Table 1). Noronha et al.,[24] observed similar results. Majority of them belong to low socioeconomic class and this restricts the intake of iron-rich diet.

Intake of iron supplement (weekly) was insignificantly (P>0.05) higher among patients of FCM (8.78±5.07) than iron sucrose (8.71±4.96) in the present study (Table 2a). 48% of patients in the study conducted by Foressler et al.,[27] took iron supplement and 56% patients in the study conducted by Garg et al.,[26] had prior history of iron folic acid (IFA) intake. The presence of anemia even with IFA supplementation can be explained by the fact that most of such patients were irregular with IFA intake or started too late or had disturbed iron absorption. This study demonstrated that there was no significant (P>0.05) difference in anthropometric parameters between the groups (Table 2b). There was no significant (P>0.05) difference in hemodynamic parameters between the groups except diastolic blood pressure in the present study (Table 2b). Study done by Lal et al.,[28] reported that the demographic profile and the baseline parameters were comparable in both the groups. The study by Breymann et al.,[29] had a similar result where hematological parameters were comparable in both the groups. In this study, there was a significant (P=0.001) difference in Hb level between the groups at post-treatment 3 and 6 weeks. There was a significant (P=0.001) mean change in Hb level in both the groups from pre-treatment to post-treatment 3 and 6 weeks. In FCM group, the mean rise of Hb from pre-treatment to post-treatment 3 weeks was 1.51±0.63 and post-treatment 6 weeks was 3.15±0.79. In iron sucrose, it was 1.16±0.43 at post-treatment 3 weeks and 2.55±0.52 at post-treatment 6 weeks. The mean change in Hb level was higher among patients of FCM group compared to iron sucrose group (Table 3). Kumari et al.,[30] found that Hb was increased in both the groups (iron sucrose and FCM). Patients when received iron sucrose Hb increased from 8.27 g% to 10.48 g% post-therapy while who were given FCM Hb increased from 8.3 g% to 11.83 g%. Bayoumeu et al.,[31] showed the rise of Hb from 9.6±0.7 g to 11.11±1.3g/dL 4 weeks after the treatment with iron sucrose. Similar results were found in other studies[15,32-36] also. There was a significant (P=0.001) mean change in ferritin level in both the groups from pre-treatment to post-treatment 3 and 6 weeks. The mean change in ferritin level was higher among patients of FCM compared to iron sucrose (Table 3). Other studies[37,38] showed that increase in serum ferritin was significantly higher in the FCM group compared to iron sucrose group.

In this study, there was no significant (P>0.05) difference in PBS at all the time periods between the groups (Table 3). This study found that the adverse reactions were lower among patients of FCM than iron sucrose (Table 4). Other studies[39,40] reported FCM to be more effective with less side effects and better compliance compared iron sucrose group. Seid et al.,[41] in their study assessed the efficacy and safety of FCM. They reported that treatment with FCM was more effective and safer.

Limitations of the study

One of the limitations of this study was small sample size and short duration of study period.

CONCLUSION

This study found that FCM is safer than iron sucrose. Treatment with FCM resulted in rapid replenishment of iron stores in pregnant women with significantly high rise of Hb and ferritin level over a 6-week period with lesser adverse effects.

ACKNOWLEDGMENT

We are thankful to all the study participants.

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Source of Support: Nil, **Conflicts of Interest:** None declared.