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Original Research Article

Randomized comparative study between ferric carboxymaltose and iron sucrose for correction of anemia in antenatal women

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ABSTRACT

Background: Anemia during pregnancy is a significant global health concern. This study aims to evaluate the efficacy and safety of Ferric Carboxymaltose (FCM) compared to Iron Sucrose (ISC) in treating mild to moderate iron deficiency anemia (IDA) in pregnant women.

Materials and Methods: A randomized prospective control study was conducted with antenatal women suffering from mild to moderate anemia at Sri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital from December 2018 to November 2019. Participants were randomly assigned to either Group A (FCM) or Group B (ISC).

Results: A total of 128 women were randomized, with 64 in each group. The mean increase in hemoglobin was significantly higher in the FCM group (1.34 g/dl) compared to the ISC group (0.98 g/dl) ($p < 0.001$). FCM required fewer administrations, improving patient compliance. Both treatments were well-tolerated, with minor local reactions observed.

Conclusion: FCM offers a more effective, convenient, and well-tolerated treatment option for IDA in pregnancy compared to ISC.

1. Introduction

Anemia during pregnancy is a global issue, directly causing 5-25% of maternal deaths and indirectly contributing to 20-40% of such deaths. According to World Health Organization (WHO) estimates, iron deficiency anemia leads to roughly 591,000 perinatal deaths and 115,000 maternal deaths globally.[1] The prevalence of anemia is notably high in South Asia, with India accounting for approximately 80% of maternal deaths due to anemia in the region.[2] Anemia affects women across different age groups, from puberty and adolescence to perimenopausal age.[3] In India, factors contributing to the high prevalence of anemia include low dietary iron intake, poor iron bioavailability, diets high in phytates, poor dietary habits, chronic menstrual blood loss, and high infection rates such as malaria and hookworm infestation. The condition worsens during pregnancy due to the increased iron requirements of the developing fetus.[4]

WHO guidelines recommend that all pregnant women in developing countries receive 60 mg of iron and 400 μg of folic acid daily.[5] In India, the government advises 100 mg of elemental iron plus 500 μg of folic acid during the second half of pregnancy for 100 days and 200 mg to treat iron deficiency anemia. Prophylactic oral iron supplementation is recommended to meet the increased demands during pregnancy. However, compliance with oral iron therapy is often hindered by gastrointestinal side effects such as bloating, diarrhea, heartburn, nausea, constipation, and dark

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stools.[6] Furthermore, oral therapy is insufficient to treat moderate to severe anemia, especially in the late second and third trimesters. Parenteral iron therapy offers a better response in these cases and may reduce the need for blood transfusions during the pre- and postpartum periods.[7]

Iron Sucrose Complex (ISC) is the most used parenteral iron preparation for treating anemia in pregnancy. It is safe and does not require a test dose; however, its use is limited by the maximum allowable dose of 300 mg per session, necessitating multiple visits and increasing the overall cost of therapy.[8] Ferric Carboxymaltose (FCM), a newer addition to intravenous iron supplements, is a dextran-free type I iron complex. Numerous studies have examined the use of FCM for treating postpartum anemia and other anemia-related conditions. Despite this, there is limited literature on FCM use during pregnancy, with few prospective studies and even fewer randomized controlled trials comparing FCM to ISC in this context.[9] This study aims to evaluate the efficacy and safety of FCM compared to ISC in treating mild to moderate iron deficiency anemia in pregnant women.

Recent evidence suggests that FCM may significantly increase hemoglobin levels more rapidly than ISC.[10] Additionally, FCM has been associated with fewer side effects and improved patient compliance. Given the high prevalence of anemia in pregnancy and the potential advantages of FCM, this study seeks to provide further evidence on its efficacy and safety in comparison to ISC.[11] The practical benefits of FCM, such as fewer required administrations and enhanced patient satisfaction, make it a promising alternative to ISC. This study is designed to fill the gap in the literature by providing robust data from a randomized controlled trial comparing FCM and ISC for treating iron deficiency anemia in pregnancy.[12]

2. Materials and Methods

This randomized prospective control study was conducted at Sri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Department of Obstetrics and Gynecology, from December 2018 to November 2019.

2.1. Inclusion criteria

Antenatal women with mild to moderate anemia between 16 and 36 weeks of gestation.

2.2. Exclusion criteria

Recent blood transfusion, non-iron deficiency anemia, known hypersensitivity to FCM or other IV iron supplements, non-consent to the study.

2.3. Study details

1. Pregnant mothers were informed about the details of the study.
2. Informed consent was obtained before recruitment.

2.4. Sample collection

1. A complete maternal hemogram and serum ferritin samples were collected under aseptic precautions.
2. Peripheral venipuncture blood samples were collected from the pregnant subjects for determination of Hb level before and after drug administration.

2.5. Group division

2.5.1. Pregnant women were randomly divided into two groups:

1. Group A: Received a single dose of 1g Injection (Inj Ferric Carboxymaltose.
2. Group B: Received Inj Ferric Sucrose 200 mg in 5 doses on alternate days.

Both groups received Inj. B12 (2500 mcg) with folic acid (0.7 mg) to exclude B12 and folic acid deficiency as a confounding factor.

2.5.2. Hemoglobin monitoring

1. Hemoglobin levels were repeated at 3 to 4 weeks after administration of each preparation and the results were compared.
2. It takes three weeks for hemoglobin to increase after administration of IV iron supplements.

2.5.3. Hemogram and serum ferritin estimation

1. Complete hemogram was estimated by the automated cell counter method using SYSMEX KX-21 Automated Hematology Analyzer (Japan).
2. Serum ferritin was determined by the automated cell counter method using SIEMEN'S XP Analyzer.

2.6. Data analysis

All data from the different groups were tabulated and statistically tabulated using appropriate statistical tests and analyzed in SPSS software, version 26.0.

3. Results

A total of 128 women who met the inclusion criteria were randomized equally into two groups, with 64 women in each group. The average increase in hemoglobin levels was notably greater in the Ferric Carboxymaltose (FCM) group (1.34 g/dl) compared to the Iron Sucrose Complex (ISC) group (0.98 g/dl), with a p-value of less than 0.001. The FCM group required fewer doses, which improved patient

Table 1: Calculation of dose of injection FCM

Patient's weight	Hb (g/dl) <10	Hb (g/dl) 10-14	Hb (g/dl) >14
<35 kg	500 mg	500 mg	500 mg
35-70 Kg	1000-1500 mg	1000 mg	500 mg
>70Kg	2000 mg	1500 mg	500 mg

Table 2: Comparison of two groups (Iron sucrose and FCM) by Age groups

Age groups	**Iron sucrose group**	**%**	**FCM group**	**%**	**Total**	**%**
18-20yrs	15	23.44	11	17.19	26	20.31
21-30yrs	39	60.94	41	64.06	80	62.50
31-37yrs	10	15.63	12	18.75	22	17.19
Total	64	100.00	64	100.00	128	100.00
Mean	26.55		26.47		26.51	
SD	5.12		4.85		4.97	
Chi-square=0.8470 P = 0.6550						

adherence. Both treatment regimens were well-received, with only minor local reactions reported.

llustrates the age distribution of participants in the two study groups, showing their comparability. In the Iron Sucrose group, the ages of the 64 women ranged from 18 to 37 years, with a mean age of 26.55 years. The majority (60.94%) were between 21 and 30 years old (n=39), while 17.19% were aged 18-20 years (n=15), and 18.75% were aged 31-37 years (n=10). In the FerricCarboxymaltose (FCM) group, the ages of the 64 women also ranged from 18 to 37 years, with a mean age of 26.47 years. The largest percentage (64.06%) was between 21 and 30 years old (n=41), with 23.44% aged 18-20 years (n=11), and 15.63% aged 31-37 years (n=12).

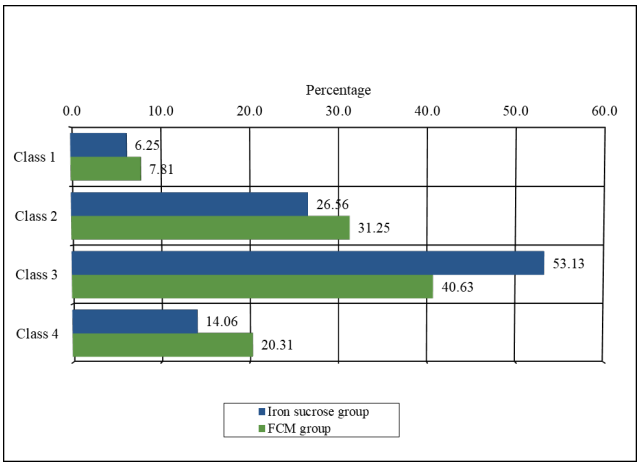

Figure 1: Comparison of two groups (Iron sucrose and FCM) by SES

Figure 1 depicts the anemic pregnant women in our study were categorized according to their socio-economic status using the modified B G Prasad classification (Figure 1). In the Iron Sucrose group, 6.25% belonged to class 1 (n=4), 26.56% to class 2 (n=17), 53.13% to class 3 (n=34), and 14.06% to class 4 (n=9). In the Ferric Carboxymaltose (FCM) group, 7.81% belonged to class 1 (n=5), 31.25% to class 2 (n=20), 40.63% to class 3 (n=26), and 20.31% to class 4 (n=13). Most anemic women in both groups were found in class 3.

A total of 10 women had multifetal gestation, with 4 in the Iron Sucrose group and 6 in the FCM group. Sixteen women had gestational diabetes mellitus (12.5%), with 10 in the Iron Sucrose group and 6 in the FCM group. The time required to administer the total drug dose was 8 days for the Iron Sucrose group (5 doses on alternate days), whereas the FCM group required a single injection on day 0. The primary outcome was the increase in hemoglobin (Hb) from baseline at the end of 3-4 weeks. The mean rise in Hb at 3-4 weeks was significantly higher in the FCM group compared to the ISC group (29 g/L vs. 22 g/L; $p < 0.001$).

In this study, a total of 45 women (35.16%) were primigravida and 83 women (64.84%) were multigravida, with their distribution comparable between the two groups (Table 3). The incidence of anemia was higher in multigravida women.

In the Iron Sucrose group, the rise in hemoglobin (Hb) was 0.98 g% (11.37%), with a p-value of 0.0001. In the FCM group, the rise in Hb was 1.34 g% (15.99%), with a p-value of 0.0001. The increase in Hb was statistically significant in both the Iron Sucrose and FCM groups ($p < 0.05$).

The rise in hemoglobin (Hb) was also compared using an independent t-test. In the Iron Sucrose group, the mean pre-test Hb was 8.58 g%, and the mean post-test Hb was 9.55 g%, resulting in a rise of 0.98 g% with a standard deviation (SD) of 0.43. In the FCM group, the mean pre-test Hb was 8.38 g%, and the mean post-test Hb was 9.72 g%, resulting in a rise of 1.34 g% with an SD of 0.42. The t-value was -4.9049 with a p-value of 0.0001. We found that the difference in the rise in Hb between the FCM and

Table 3: Comparison of two groups (Iron sucrose and FCM)

	Iron sucrose group	%	FCM group	%	Total	%
Multifetal gestation	4	6.25	6	9.38	10	7.81
Primigravida	21	32.81	24	37.50	45	35.16
Multigravida	43	67.19	40	62.50	83	64.84
Hypertensive disorders	12	18.75	11	17.19	23	17.97
GDM	10	15.63	6	9.38	16	12.50
Total	64	100.00	64	100.00	128	100.00

Table 4: Comparison of pre-test and post-test transfusion Hb scores in two groups (Iron sucrose and FCM) by dependent t test

Groups	Time period	Mean	Std.Dv.	Mean Diff.	SD Diff.	% of raise	t-value	P-value
Iron sucrose group	Pretest	8.58	0.68					
	Posttest	9.55	0.82	-0.98	0.43	-11.37	-18.2564	0.0001*
FCM group	Pretest	8.38	0.68					
	Posttest	9.72	0.81	-1.34	0.44	-15.99	-24.1928	0.0001*

*p<0.05

Iron Sucrose groups was 0.36 g% ($p < 0.05$), which was statistically significant.

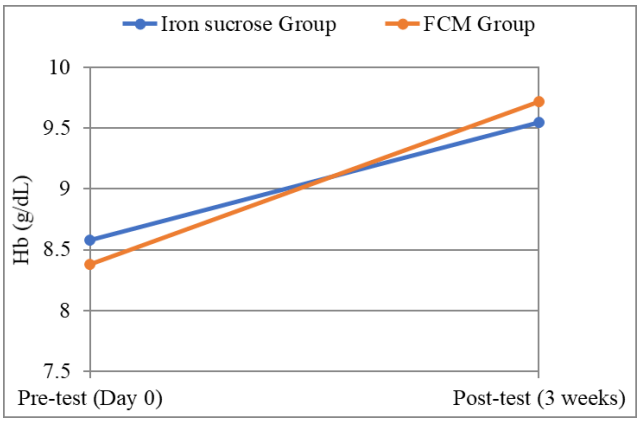

Figure 2: Rise in Hb levels in iron sucrose and FCM groups

Figure 2 shows the comparison of hemoglobin (Hb) levels between the Iron Sucrose group and the Ferric Carboxymaltose (FCM) group, measured before treatment (Day 0) and after three weeks of treatment.

The Ferric Carboxymaltose (FCM) group started with a slightly lower hemoglobin (Hb) level compared to the Iron Sucrose group but demonstrated a greater increase over the three weeks of treatment. Both groups showed significant increases in Hb levels after the treatment period. Specifically, the increase in Hb was higher in the FCM group, with a mean rise of 1.34 g/dL, compared to a mean rise of 0.98 g/dL in the Iron Sucrose group. This indicates that FCM might be more effective in increasing Hb levels over the studied period.

The treatment with Ferric Carboxymaltose (FCM) was found to be more effective than Iron Sucrose in increasing hemoglobin levels over a period of three weeks, as demonstrated by mean plot analysis. The average ferritin values were 59.88 ng/ml in the Iron Sucrose group and 58.13 ng/ml in the FCM group. All patients in both groups received the full calculated dose of the drug. No serious adverse events were reported in either group. However, three women in the Iron Sucrose group experienced local reactions, such as erythema, itching, and pain at the injection site (4.69%), compared to two women in the FCM group who experienced erythema and itching (3.13%). The difference in local reactions between the groups was not statistically significant (Yates chi-square=0.0001, p-value=1.000). Additionally, there were no systemic reactions in either group during the study.

4. Discussion

This randomized prospective study investigated the routine use of intravenous Ferric Carboxymaltose (FCM) for treating iron deficiency anemia (IDA) in pregnant women from December 2018 to November 2019. The study demonstrated the efficacy of FCM in increasing maternal hemoglobin levels and highlighted that the treatment was generally safe and well-tolerated.

Several studies have reported on the safe and effective use of FCM to correct anemia during the second or third trimester, as well as in the postpartum period. Compared to intravenous Iron Sucrose, FCM has shown a similar safety profile but offers the practical advantage of delivering a higher iron dose in a single administration. This reduces the need for repeated treatments and enhances patient comfort.[5]

For instance, Patel et al. showed that the mean increase in hemoglobin levels in pregnant women on days 8 and 15 was 0.52 g/dL for FCM and 0.41 g/dL for Iron Sucrose, with adverse events occurring in 40% of patients treated with Iron Sucrose compared to 16.67% with FCM.[6]

Similarly, Christian Breymann et al. found that hemoglobin levels improved more significantly with FCM than with oral ferrous sulfate (84% vs. 70%; odds ratio: 2.06, 95% confidence interval: 1.07, 3.97; P = 0.031) and within a shorter period (median 3.4 vs. 4.3 weeks). FCM treatment also significantly improved vitality (P = 0.025) and social functioning (P = 0.049) before delivery, with treatment-related adverse events occurring in 11% of the FCM group and 15% of the ferrous sulfate group, where gastrointestinal disturbances were more common in the latter. Alpana et al. observed that in the IV Iron Sucrose group, hemoglobin levels increased from 9.69±0.49 g/dL to 11.28±0.53 g/dL over 6 weeks. In the FCM group, hemoglobin levels increased from 9.8±0.43 g/dL to 12.22±0.43 g/dL over the same period. Additionally, serum ferritin levels significantly increased in the FCM group compared to the Iron Sucrose group (p=0.049 at 2 weeks and p=0.023 at 6 weeks). A Naqash et al. reported a mean increase in hemoglobin of 2.92 g/dL with FCM and 1.08 g/dL with Iron Sucrose.[13] The mean increase in serum ferritin levels was 64.97 ng/mL with FCM and 31.64 ng/mL with Iron Sucrose. FCM was also found to be safer, with no adverse effects reported, while ferrous sucrose caused adverse effects in three pregnant women.

In our study, the Iron Sucrose group showed an increase in hemoglobin of 0.98 g% (11.37%), with a p-value of 0.0001, and the FCM group showed an increase of 1.34 g% (15.99%), with a p-value of 0.0001. This indicates that the increase in hemoglobin was statistically significant in both groups (p<0.05). The difference in the rise in hemoglobin between the FCM and Iron Sucrose groups was 0.36 g%, with a t-value of -4.9049 and a p-value of 0.0001, which is statistically significant.

No serious adverse effects were observed in either the Iron Sucrose or FCM groups. Previous studies have reported adverse effects ranging from 6.8% to 24.2%.[4] In our study, mild adverse effects such as urticaria and injection site pain were noted in 4.69% of the Iron Sucrose group and 3.13% of the FCM group.

Serum ferritin concentration is commonly used to assess maternal iron status. However, its reliability can be affected by transient inflammatory responses, which can falsely elevate ferritin levels. Due to financial constraints, post-transfusion ferritin levels were not measured in this study.[14] The study demonstrated several advantages: it was a randomized trial, showed a significant increase in hemoglobin levels, had a good safety profile, and was conducted as a day care procedure, like the National Iron Plus Initiative.[15]

However, the study had limitations, including a small sample size, lack of long-term follow-up, and the omission of post-treatment serum ferritin measurements due to financial constraints.

5. Conclusion

This study compared the efficacy of FCM and iron sucrose in treating prenatal iron deficiency anemia. Although both groups showed improvements in hemoglobin levels, the increase was more rapid and substantial with FCM compared to iron sucrose. A significant advantage of FCM is that a higher dose can be administered in a single visit, significantly reducing the duration of hospital stay. Additionally, the quality of life was reported to be better in the FCM group. Since FCM does not contain dextran, it is less immunogenic, resulting in fewer side effects. Therefore, administering a single high dose of FCM during pregnancy could be highly effective in combating anemia in developing countries.

6. Source of Funding

None.

7. Conflict of Interest

None.

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References

1. Ezzati M, Lopez AD, Rodgers, Anthony A, Murray CJL. Comparative quantification of health risks : global and regional burden of disease attributable to selected major risk factors; 2004. Available from: https://iris.who.int/handle/10665/42770.
2. Ezzati M, Lopez AD, Rodgers A, Hoorn SV, Murray C. Selected major risk factors and global and regional burden of disease. *Lancet*. 2012;360(9343):1347–60.
3. Singh P, Toteja GS. Micronutrient profile of Indian children and women: Summary of available data for iron and vitamin A. *Indian Pediatr*. 2003;40(5):477–9.
4. Kriplani A, Mahey R, Dash BB, Kulshreshta V, Agarwal N, Bhatla N. Intravenous iron sucrose therapy for moderate to severe anaemia in pregnancy. *Indian J Med Res*. 2014;138:78–82.
5. Patel J, Patel K, Patel J, Sharma A, Date SK. Comparison of Intravenous Iron Sucrose and Ferric Carboxymaltose Therapy in Iron Deficiency Anemia during Pregnancy and Postpartum Period. *J Pharm Sci Biosci Res*. 2015;5(3):239–43.
6. Breymann C, Milman N, Mezzacasa A, Bernard R, Dudenhausen J. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international open-label randomized controlled trial (FER-ASAP). *J Perinatal Med*. 2016;45(4):443–53.
7. Singh A, Yerragudi R. Comparative study of safety and efficacy of intravenous iron sucrose and ferric carboxymaltose in the treatment of postpartum iron deficiency anaemia. *Int J Reprod Contracept Obstet Gynecol*. 2016;5:1130–3.
8. Anton M, Popa A, Ginghina C. Iron deficiency in chronic heart failure. *Rom J Cardiol*. 2017;27(3):411–7.
9. Breymann C. Iron deficiency and anaemia in pregnancy: modern aspects of diagnosis and therapy. *Blood Cells Mol Dis*. 2002;29(3):506–16.

10. Khalafallah AA, Dennis AE. Iron deficiency anaemia in pregnancy and postpartum: pathophysiology and effect of oral versus intravenous iron therapy. *J Pregnancy*. 2012;2012:630519.
11. Cantor AG, Bougatsos C, Dana T, Blazina I, Mcdonagh M. Routine iron supplementation and screening for iron deficiency anemia in pregnancy: a systematic review for the US Preventive Services Task Force. *Ann Intern Med*. 2019;162(8):566–76.
12. Jose A, Mahey R, Sharma JB, Bhatla N, Saxena R, Kalaivani M, et al. Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy- randomised controlled trial. *BMC Pregnancy Childbirth*. 2020;19:54.
13. Naqash A, Ara R, Bader GN. Effectiveness and safety of ferric carboxymaltose compared to iron sucrose in women with iron deficiency anemia: phase IV clinical trials. *BMC Womens Health*. 2018;18(1):6.
14. Nutrition and Food Safety (NFS). Iron deficiency anaemia: assessment, prevention and control. Geneva: World Health Organization; 2001. Available from: https://www.who.int/publications/m/item/iron-children-6to23--archived-iron-deficiency-anaemia-assessment-prevention-and-control.
15. Guidelines for Control of Iron Deficiency Anaemia. Ministry of Health and Family Welfare Government of India; 2013. Available from: https://www.nhm.gov.in/images/pdf/programmes/child-health/guidelines/Control-of-Iron-Deficiency-Anaemia.pdf.

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