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Original Research Article

Comparative study of efficacy and safety of parenteral iron sucrose versus ferric carboxymaltose in treatment of postpartum iron deficiency anaemia

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ABSTRACT

Background: Postpartum anaemia often leads to multiple clinical complications in mother as well as infant and iron supplementation with parenteral iron is the preferred treatment modality. The present study was planned to compare the efficacy and tolerability of IV iron sucrose and IV ferric carboxymaltose in treatment of postpartum iron deficiency anaemia.
Methods: This randomized, parallel, open label, prospective 4-weeks study was conducted from June 2019 to December 2020 in women with postpartum anaemia admitted to obstetrics and gynaecology inpatient department of a tertiary care hospital. Women with postpartum iron deficiency anaemia (N=60) were randomly divided into two groups; receiving Injection iron sucrose (N=30, maximum dose 500 mg) or Injection ferric carboxymaltose (N=30, maximum dose 500 mg). Change in haemoglobin and serum ferritin levels from baseline to the end of 2 and 4 weeks of treatment were evaluated.
Results: The results showed early, sustained and significant increase in the haemoglobin levels in both the groups. However, the difference was not significant between groups ($p=0.2$). Evaluation of replenishment of iron stores (serum ferritin) showed improvement in both the groups, however in FCM group the rise was found to be significant ($p<0.05$).
Conclusions: FCM in a lower dose of 500mg was found to be safe and effective in significantly improving haemoglobin concentration as well as in replenishing iron stores in patients with postpartum anaemia.

Keywords: Ferric carboxymaltose, Iron sucrose, Postpartum iron deficiency anaemia

INTRODUCTION

Globally, iron deficiency is considered to be one of the most common single-nutrient deficiencies. Incidence of iron deficiency anaemia (IDA) is predominantly high in many developing countries like India and is the most commonly encountered health problem during pregnancy and postpartum period.[1] Postpartum anaemia (PPA) has been defined by WHO as haemoglobin of less than 10 gm% during the postpartum period.[2] The prevalence of PPA ranges from 4 to 27% in western population.[3] In India, the prevalence of postpartum iron deficiency anaemia was found to be higher i.e., 65%,[4] ranging from 26.5% in a rural Karnataka to 94.6% in rural area of Rajasthan.[5,6] This high prevalence of postpartum anaemia makes it a major public health problem.

Chronic iron deficiency due to inadequate intake/lack of iron supplementation during pregnancy, repeated pregnancies and postpartum haemorrhage are important

causes of postpartum anaemia. Patients with postpartum anaemia have a longer average length of hospital stay, are more likely to receive blood transfusion, and incur higher hospitalization cost.[7] Effects of iron deficiency during pregnancy and post-partum period include fatigue, cardio-respiratory problems, increased chances of infection, reduced immunity, lactation failure, increased post-partum depressive episode, and post-partum haemorrhage.[8] It is also associated with anxiety, depression and imposes a substantial disease burden during the critical period of maternal-infant interaction and may give rise to lasting developmental deficits in infant of affected mothers.[9]

Prophylactic iron supplementation reduces the risk of maternal anaemia by 70% and iron treated women had a greater probability of higher haemoglobin concentrations at term and in the postpartum period.[10] The first choice in the treatment of iron deficiency anaemia for the majority of patients is the oral iron replacement therapy. However, oral iron is notorious for its gastrointestinal side effects like diarrhoea, nausea, epigastric pain and constipation which may limit the compliance of oral iron seen in almost 20% of patients.[11] Alternatively, parenteral iron therapy could provide advantages such as faster and higher increase of haemoglobin (Hb) levels and body iron stores in several clinical situations.

Threat of unpredictable anaphylactic reaction by conventional parenteral iron preparations (Iron dextran and iron sorbitol citric acid) prevented their wide use. Hence, modern formulations of IV iron (IV iron sucrose(IS) and IV ferric carboxymaltose (FCM)) have emerged as a safe and effective alternative for IDA management.[12] Studies show that iron sucrose is safe, effective and economical for the management of anaemia and can be administered without a test dose at most peripheral health centres with minimum facilities but it requires multiple doses and prolonged infusion time.[13] Ferric carboxymaltose on the other hand can be administered in high single dose without the risk of severe anaphylactic reactions.[12] The therapeutic efficacy of IV FCM has been evaluated in several randomized, Phase III, open-label, controlled, multi-centre trials in a diverse range of conditions associated with absolute or functional iron deficiency with or without anaemia.[13] However, there are very few published clinical studies using ferric carboxymaltose in postpartum anaemia and there is paucity of data in Indian context. Moreover, there are very few studies comparing parenteral iron preparations in postpartum anaemia. Therefore, this study was planned to compare the efficacy and tolerability of IV iron sucrose and IV ferric carboxymaltose in treatment of postpartum iron deficiency anaemia.

METHODS

This randomized, parallel, open label, prospective 4-weeks study was conducted in tertiary care teaching hospital in Central India from June 2019 to December 2020. The trial procedure was designed in accordance with the ethical standards laid down by the Indian council of medical research (ICMR) and ethical guidelines for biomedical research on human subjects. Informed consent was obtained from all patients prior to their inclusion in the study.

Postpartum women (n=106) admitted to department of obstetrics and gynaecology were screened and sixty women with postpartum iron deficiency anaemia with haemoglobin <10 g/dl were included in the study. Patients with anaemia due to other causes such as aplastic, megaloblastic or haemolytic anaemia, acute or chronic infection, inflammation, liver or renal disease, and recent administration of parenteral iron preparation, blood transfusion and intolerance to iron derivatives were excluded from the study. Patients were randomly divided into two groups of 30 each in the ratio of 1:1 using random number table to receive either Injection iron sucrose or Injection ferric carboxymaltose. Allocation to one of the two groups was done after it had been established that the participant fulfilled all the inclusion criteria and none of the exclusion criteria by the treating obstetrician. Study drugs were procured from Vinayak agency, Gandhibag, Nagpur and were given free of cost to the patients.

After allocation to one group, clinical examination and evaluation of laboratory parameters like HB, HCT, MCV, MCH was done at baseline for all participants. All participants were dewormed. Women who had dimorphic anaemia were given folic acid and B12 tablets along with iron supplementation. Target iron deficit was calculated at baseline using the Ganzoni's formula: target iron deficit = BW in Kg (target Hb–actual Hb) x 0.24+500.[14]

Injection iron sucrose was given in a dose of 200 mg dissolved in 100 ml normal saline during the study period; first dose was given at baseline and second dose after two weeks. If needed, as suggested by the calculated iron deficit, one additional dose of 100 mg was administered. Patients in ferric carboxymaltose group received single dose of ferric carboxymaltose 500 mg dissolved in 100ml normal saline at baseline. Dose calculation was done on the basis of formula for target iron deficit. Test dose was administered to all patients prior to administration of therapeutic dose. Patients in both the groups were instructed to inform health care providers if they develop any discomfort in chest, breathlessness and itching. Clinical examination and evaluation of laboratory parameters like HB, serum ferritin was done at each follow-up; i.e. 2 and 4 weeks of treatment.

Outcome measure

Primary end point of the study was to compare the change in serum haemoglobin levels in both groups at the end of 4 weeks. Other end points included; comparison of change in ferritin levels in both groups at the end of 4

weeks, change in haemoglobin level from baseline in both groups at the end of 2 and 4 weeks of treatment, change in serum ferritin level from baseline in both groups at the end of 2 and 4 weeks of treatment and number of adverse events or treatment emergent adverse drug reactions reported or observed in both the groups. Any adverse drug reaction if experienced by the patient during infusion or after drug administration was evaluated and was noted in the appropriate case record form.

Statistical analysis

Results were expressed as mean (±SD). Intergroup comparison of baseline demographic parametric data was done by unpaired t-test. For primary efficacy parameters, repeated measures ANOVA followed by Tukey's multiple comparison post-hoc test was used for within group comparison at different follow-up visits. Unpaired t-test was used for comparison between different groups.

RESULTS

Women with post-partum iron deficiency anaemia (n=103) were screened and sixty patients fulfilling the study criteria were included in the study. The selected patients were randomly allocated to two treatment groups; intravenous iron sucrose (N=30) or intravenous ferric carboxymaltose (N =30). The mean (±SD) age of patients receiving iron sucrose was found to be 25.13±0.69 and those treated with ferric carboxymaltose was 24.93±0.59; having no significant difference between the groups. Mean haemoglobin levels (8.20±0.14 vs. 7.89±0.11; p=0.10) and mean serum ferritin levels (82.77±11.17 vs. 81.88±14.43; p=0.10) were also found to be comparable in both the groups. Other laboratory parameters such as HCT, MCV, MCH were also statistically similar in both treatment groups as shown in (Table 1). Other parameters such as parity and severity of anaemia were also compared between the groups and were found to be similar. The results are shown in (Table 2).

Table 1: Baseline parameters of patients with post-partum iron deficiency anaemia.

Baseline parameters	Iron sucrose (N=30)	FCM (N=30)	P value
Age	25.13± 0.69	24.93± 0.59	0.82
BMI	22.99±3.2	22.69±2.4	0.3
HB	8.20±0.14	7.89±0.11	0.10
HCT	26.86±0.46	25.76±0.47	0.10
MCV	78.95±0.76	79.68±1.27	0.62
MCH	27. 57±0.56	26.31±0.55	0.11
Sr. ferritin	82.77±11.17	81.88±14.43	0.96
Iron deficit	557.2±4.90	575.9±12.00	0.15

Values are expressed as mean±SD; unpaired t test, p<0.05 is significant.

Patients receiving iron sucrose therapy were evaluated for change in haemoglobin levels at the end of 2 and 4 weeks of treatment and the increase was found to be significant (Table 3). Similarly, significant increase in haemoglobin at both 2 weeks and 4 weeks in patients receiving ferric carboxymaltose was also observed (Table 4).

Table 2: Baseline parameters influencing disease severity in study population.

Baseline parameters	Iron sucrose (N=30)	FCM (N=30)	P value
Parity			
Primipara	12	13	0.4
Multipara	18	17	0.37
Severity of anaemia			
Mild	13 (43.4)	11 (36.7)	0.07
Moderate	17 (56.6)	19 (63.3)	0.09

Values are expressed as N (%); unpaired t test, p<0.05 is significant.

Table 3: Change in haemoglobin levels in patients receiving parenteral iron sucrose.

HB (week)	Mean difference	P value
0-2	$0.62^{\$}$	$<0.001^{\#*}$
2-4	$0.77^{\$}$	$<0.001^{\#*}$
0-4	$1.39^{\$}$	$<0.001^{\#*}$

Values expressed as mean difference, #Repeated measures ANOVA, $Tukey's multiple comparison test, *p<0.05 is significant

Table 4: Change in HB from baseline 2 weeks and 4 weeks in FCM group.

HB (week)	Mean difference	P value
0-2	$0.44^{\$}$	$<0.001^{\#*}$
2-4	$0.94^{\$}$	$<0.001^{\#*}$
0-4	$1.38^{\$}$	$<0.001^{\#*}$

Values expressed as mean difference, #Repeated measures ANOVA, $Tukey's multiple comparison test, *p<0.05 is significant, FCM=Ferric carboxymaltose

The changes in haemoglobin were also compared between the study groups and it was observed that there was no significant statistical difference in rise in haemoglobin at 4 weeks between the two groups (Table 5).

Table 5: Change in haemoglobin from baseline in study population.

Change in Hb from baseline at 4 weeks	Iron sucrose	FCM	P value
	1.23±0.10	$1.40±0.11^{\#}$	0.2

Values expressed as mean ± SD, # unpaired t test, *p<0.05 is significant.

Other parameter evaluated in our study was estimating the change in serum ferritin levels in both the groups at the end of 4 weeks of treatment. There was statistically significant rise in serum ferritin levels from baseline values at 4 weeks in both iron sucrose and ferric carboxymaltose group (Table 6).

Table 6: Changes in serum ferritin level in both the groups at the end of study.

Parameters	Baseline	4 weeks	P value
Iron sucrose group	82.77±11.17	129.5±10.68$	0.003*
FCM group	81.88±14.43	162.3±13.20$	<0.001*

Values are expressed as mean±SD; $ (unpaired 't' test), p<0.05 is significant * FCM=Ferric carboxymaltose.

To test whether treatment with ferric carboxymatose was more efficacious than iron sucrose, we compared the rise in serum ferritin values in both groups after 4 weeks of treatment from baseline. The rise in serum ferritin levels at 4 weeks was found to be significantly greater in ferric carboxymaltose group as compared to iron sucrose group. (Figure 1). The adverse reactions reported in both the groups were mild and did not need any intervention; Pain at injection site was the most common side effect in both the groups; Iron sucrose group (N=3) and FCM group (N=2). Other single incidences of ADRs were headache and nausea in both the groups.

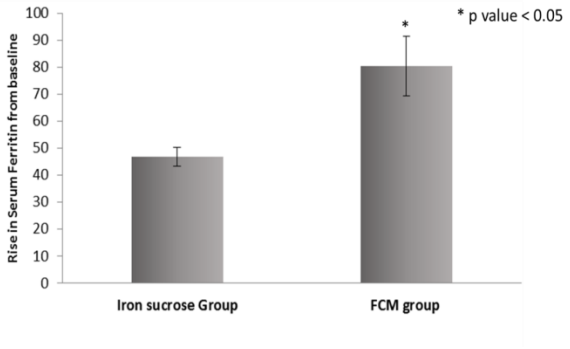

Figure 1: Rise in serum ferritin from baseline in study population. Values expressed as mean±SD, # unpaired t test, *p<0.05 is significant, FCM=Ferric carboxymaltose

DISCUSSION

Illiteracy and poverty contributes to poor nutrition and lack of awareness of nutritional and health services provided by government collectively leads to poor maternal health. The average age of study participants was less than 25 years and belonging to lower socioeconomic strata; similar patient population were included in studies by Lunagariya et al, Hol et al, Joshi et al and others.[15-17] WHO recommends postpartum prophylactic use of oral iron supplementation of 60 mg elemental iron+400 µg folic acid for 3 months.[18] In India, the ministry of health and family welfare (MoHFW) guidelines recommends 100mg elemental iron with 500 µg folic acid orally for all non-anaemic women and 200 mg elemental iron with 1000µg folic acid in mild to moderately anaemic women in postpartum period. Oral iron supplementation increases the haemoglobin levels by 2-3 g/dl within 4-12 weeks in postpartum women.[19-21] However, lower compliance due to poor tolerability and side effects such as indigestion, constipation, nausea, vomiting, and reflux esophagitis is common with oral iron supplementation.[22]

Various preparations of parenteral iron supplementation are available. However, studies demonstrated that ferric carboxymaltose was superior to all.[23] Ferric carboxymaltose is non-dextran iron complex with neutral pH and physiological osmolarity.[24] It can be administered in high single dose without the risk of severe anaphylactic reactions. The advantage of being non-dextran-containing and having a very low immunogenic potential of ferric carboxymaltose is that the risk of anaphylactic reactions is very less. Its properties permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid session (15 minute infusion) without the requirement of a test dose. Postpartum anaemia represents an urgent need for iron supplementation and hence parenteral iron supplementation are found to be better treatment strategy compared to oral iron supplementation. Our study compared two commonly used and recommended parenteral iron preparations; iron sucrose and Ferric carboxymaltose in postpartum women with baseline mean haemoglobin of 8.20±0.14 in iron sucrose group and 7.89±0.11 in FCM group. The mean Hb levels in the study population suggest presence of moderate anaemic (Hb 7-9 g%) 23 and such patients warrant parenteral iron therapy to replenish the stores so as to reduce the associated complications. In this study iron sucrose and FCM were used as per the protocol by calculating target iron deficit and both were effective in treating postpartum anaemia with very few mild adverse events. There was significant rise of Hb in both the groups from baseline. However, when compared between the groups, no significant difference was noted (mean increase in Hb of 1.23+0.10 in Iron sucrose group and 1.40+0.11 in FCM group).

The increase in mean haemoglobin level after two week of therapy in Sharma et al was 2.94 in FCM group and 1.7 in iron sucrose group whereas Breymann et al reported the mean increase in Hb rise of 3.37 in FCM group and 3.29 in iron sucrose group after 12 week of therapy.[25,26] Other studies conducted by Lunagariya et al, Hol et al, Joshi et al and Sharma et al comparing the efficacy of iron sucrose and FCM, used 1000 mg of FCM and found significant rise in Hb compared to iron sucrose which was calculated according to iron deficit.[15-17,25] In our study, however, lower dose of FCM (500mg) were used as the target iron deficit was found to be low (557.2±4.90 and 575.9±12.00 in iron sucrose and FCM group respectively) and was found to be effective in early

(2 weeks), sustained (4 weeks) and significant improvement in haemoglobin levels in study population. When the replenishment of iron stores were evaluated in both the groups, the increase in serum ferritin was found to be significantly greater with FCM compared to iron sucrose (mean increase in serum ferritin of 80.39+11.06 and 46.70+3.50 respectively p=0.005). Lunagariya et al reported significant increase in serum ferritin levels FCM group than iron sucrose group (83.95±14.37 versus 76.06±16.56; p value 0.012).[15] Mean rise of serum ferritin was found to be 71.07±27.23 and 95.39±45.84 in iron sucrose and ferric carboxy maltose group in study conducted by Joshi et al.[17] These results thus support the use of parenteral iron therapy to replenish the iron stores which may help in preventing the recurrence of IDA.

Both the study groups reported very few adverse events; pain at injection site being most common (N=3 in Iron sucrose group and N=2 in FCM group). Other reactions included headache and nausea. All the reactions were mild in intensity and did not require any intervention. Our study did not find any significant difference in incidence of ADRs between the two groups. Studies referred earlier also reported similar incidences of ADRs which were mild in nature and were self-limiting.

CONCLUSION

Our study found a significant improvement in Hb concentration as well as in early replenishment of iron stores in patients with post-partum anaemia with use of lower dose (500mg) of ferric carboxymaltose. Ferric carboxymaltose offers benefits such as large doses given in a short period of time, early improvement in haemoglobin, low immunogenicity and better tolerability profile and these advantages may help in economical use of healthcare resources as well as improving patient compliance.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Report of a WHO group of experts on nutritional anemias, technical report series 503. Available at: https://apps.who.int/iris/handle/10665/40977. Accessed on 20 September 2021.
2. Kouser S, Kouser S, Malik M, Malik A. Safety and efficacy of intravenous iron therapy in postnatal patients with iron def anaemia. J South Asian Fed Obstet Gynaecol. 2011;3:25-7.
3. Milman N. Postpartum anemia I: definition, prevalence, causesand consequences. Ann Haematol. 2011;90:1247-53.
4. National iron+initiative: guidelines for control of iron deficiency anaemia. Available at: https://www.nhm.gov.in/images/pdf/programmes/child-health/guidelines/Control-of-Iron-Deficiency-Anaemia.pdf. Accessed on 20 September 2021.
5. Bhagwan D, Kumar A, Rao CR, Kamath A. Prevalence of anaemia among postnatal mothers in coastal Karnataka. J Clin Diagnostic Res. 2016;10: LC17-20.
6. Noronha JA, Bhaduri A, Bhat VH, Kamath A. Maternal risk factors and anaemia in pregnancy: A prospective retrospective cohort study. J Obs Gynaecol. 2010;30:132-6.
7. Rathod S, Samal SK, Mahapatra PC. Ferric carboxymaltose: A revolution in the treatment of postpartum anemia in Indian women. Int J Appl Basic Med Res. 2015; 5(1):25-30.
8. Kaur K. Anaemia 'A silent killer' among women in India: Present scenario. Euro J Zool Res. 2014;3(1): 32-6.
9. 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(4):1130-3.
10. Pena-Rosas JP, De-Regil LM, Garcia-Casal MN. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015;7:Cd004736.
11. Nanjundan P. Comparison of various treatment modalities of iron deficiency anaemia in pregnancy. World J Aneamia. 2017;1(1):23-36.
12. Friedrischa JR, Cançadob RD. Intravenous ferric carboxymaltose for the treatment of iron deficiency anemia. Rev Bras Hematol Hemoter. 2015;37(6): 400-5.
13. Bailie GR. Efficacy and safety of ferric carboxymaltose in correcting iron-deficiency anemia: a review of randomized controlled trials across different indications. Arzneimittelforschung. 2010;60 (6a):386-98.
14. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. Schweizerische Medizinische Wochenschrift. 1970;3(7):301-3.
15. Lunagariya M, Kanaklatta DN, Vithal A, Patel J, Patel M. Iron sucrose vs. ferric carboxymaltose: in search of better treatment option in cases of postpartum iron deficiency anemia. Int J Contemp Med Res. 2018;5(1):12-6.
16. Hol KV, Damle H, Shekhawat GS, Hol A. Comparative study of intravenous iron sucrose versus ferric carboxymaltose for the treatment of iron deficiency anemia in postpartum patients. Int J Reprod Contracept Obstet Gynecol. 2015;4:669-73.
17. Joshi SD, Chikkagowdra S, Kumar VCM. Comparative study of efficacy and safety of intravenous ferric carboxy maltose versus iron sucrose in treatment of postpartum iron deficiency anemia. Int J Reprod Contracept Obstet Gynecol. 2016;5:2566-70.
18. Recommendations on Postnatal Care of the Mother and Newborn. Available at: https://apps.who.int/iris/handle/10665/97603. Accessed on 20 September 2021.

19. Van Wyck DB, Martens MG, Seid MH, Baker JB, Mangione A. Intravenous ferric carboxymaltose compared with oral iron in the treatmentof postpartum anemia: A randomized controlled trial. Obstet Gynecol. 2007;110:267-78.
20. Aggarwal RS, Mishra VV, Panchal NA, Patel NH, Deshchougule VV, Jasani AF. Comparison of oral iron and IV iron sucrose for treatmentofanemia in postpartum Indian women. Natl J Comm Med. 2012; 3:48-54
21. Rathod S, Samal SK, Mahapatra PC, Samal S. Ferric carboxymaltose: a revolution in the treatment of postpartum anemia in Indian women. Int J App Basic Med Res. 2015;5(1):25.
22. Longo SA, Moore RC, Canzoneri BJ, Robichaux A. Gastrointestinal conditions during pregnancy. Clin Colon Rectal Surg. 2010;23(2):80-9.
23. Management of iron deficiency anemia in pregnancy. Available at: www.fogsi.org/wp-content/uploads/ 2017/gcprrecommendtion-ida.pdf. Accessed on august 2021.
24. Drugs safety data. Available at: https://www. accessdata.fda.gov/drugsatfda_docs/label/2018/2035 65s005lbl.pdf. Accessed on 20 August 2021
25. Sharma NJ, Thiek L, Natung T, Ahanthem SS. Comparative study of efficacy and safety of ferric carboxymaltose versus iron sucrose in post-partum anaemia. J Obstet Gynecol India. 2017:67(4):253-7.
26. Breymann C. Treatment of iron deficiency anemiain pregnancy and postpartum. In: Studd J, Tan SL, Chervenak FA, eds. Current Progress in Obstetrics and Gynaecology, 1st ed. Mumbai: Tree Life Media; 2012:135-48.

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