



A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF FERRIC CARBOXYMALTOSE VERSUS IRON SUCROSE IN TREATMENT OF POSTPARTUM ANAEMIA

Dr. Akanksha*	Third year postgraduate student, Department of Obstetrics and gynaecology, Sawai man Singh medical College, Jaipur , Rajasthan *Corresponding Author
Dr. Lata Rajoria	Senior Professor, Department of Obstetrics and gynaecology, Sawai man Singh medical College, Jaipur , Rajasthan
Dr. Suman Bala	Associate professor, Department of Obstetrics and gynaecology, Sawai man Singh medical College, Jaipur , Rajasthan
Dr. Prachi Lochab	Third year postgraduate student, Department of Obstetrics and gynaecology, Sawai man Singh medical College, Jaipur , Rajasthan

ABSTRACT **Background:** Anaemia is the most common nutritional deficiency. The incidence of postpartum anaemia is 14-24 %. It imposes a big disease burden in developing countries. Although oral iron preparations are more cost effective, injectable iron formulation replenishes iron store faster and more efficiently. Among the various intravenous preparation, Ferric carboxymaltose complex (FCM) is a non-dextran containing intravenous iron agent, having a very low immunogenic potential, designed to be administered in large doses in a short period of time. In this study we aim to compare the efficacy, tolerability and safety of intravenous Ferric carboxymaltose and intravenous Iron sucrose for treatment of anaemia among postpartum women. **Methods:** A total of 70 Postpartum women were selected with haemoglobin between 7-10 g/dl. Two groups A and B will be randomly selected with 35 postpartum anaemic patients each. Women in group A received Ferric carboxymaltose and those in group B received Iron sucrose. Complete haemogram and serum ferritin of each patient will be sent before administration of the iron compound and at 2 and 4 weeks. Adverse effects were monitored in both groups after administration of the drugs. **Results:** In FCM group the average Hb increase was about 11.28(2.75g/dl) from 8.53, whereas in iron sucrose group it increased from baseline value of 8.61g to 10.96 (2.35 g/dl) at 4 weeks. Among iron sucrose group serum ferritin increased from baseline (35.35 to 190.39 at 2 weeks; 114.37 at 4 weeks). But the improvement is greater among FCM group (32.80 to 264.69 at 2 weeks and 128.69 at 4 weeks). Adverse reactions following both groups were mild, 17.1% women in Iron sucrose group developed adverse reactions whereas only 8.5 % women in FCM group experienced mild adverse reactions. **Conclusion:** On comparing the two intravenous iron preparation, women in FCM group had better and faster improvement in haemoglobin, serum ferritin and had fewer adverse reactions. FCM seems to be clinically more efficient and safer than iron sucrose in treatment of postnatal iron deficiency anaemia.

KEYWORDS : Intravenous iron sucrose, Ferric carboxymaltose, Postpartum anaemia, Haemoglobin, Serum ferritin

INTRODUCTION

Anaemia is the most common nutritional deficiency in the world. It is defined as decreased oxygen carrying capacity of blood. About one third of the global population is anaemic. WORLD HEALTH ORGANIZATION defines postpartum anaemia as haemoglobin less than 10 g/dl¹, and has estimated that prevalence of postpartum anaemia ranges from 4- 27%⁴. Prevalence of anaemia in South Asian countries is highest in the world. WHO estimates that even among the South Asian countries, India has the highest prevalence of anaemia (65-75%) Half of the global maternal death due to anaemia occur in South Asian countries; India contributes to about 80% of the maternal deaths due to anaemia in south Asia. Menstruation and pregnancy put women at higher risk for anaemia².

Most common type is the nutritional anaemia- IRON DEFICIENCY ANAEMIA. Postpartum women from low economic status disproportionately imposes a substantial disease burden in mother child interaction which might adversely affect the development of the infant. Iron deficiency anaemia in pregnant mother is mainly due to increased demand or due to poor absorption. This unmet need during antenatal period may lead to postnatal anaemia superimposed with bloodloss during delivery and increased demand of iron during lactation. Treatment of postpartum anaemia is important as it causes decreased work capacity, fatigue, depression, reduced mother child interaction and cognitive impairment⁶.

Due to poor compliance to oral iron and gastrointestinal side effects and because of inherent risks following blood transfusion, parenteral iron has gained more importance to treat iron deficiency anaemia in clinical practice. Parenteral iron helps in restoring of iron stores more efficiently and at a faster rate in comparison to oral formulation⁵. Iron formulation like iron dextran, iron sorbitol, iron sucrose, ferric carboxymaltose are available for parenteral use⁶. The formulation with dextran cause pain, skin staining, myalgia etc. Among these second generation intravenous iron sucrose is most commonly used. Upcoming is third generation injection Ferric carboxymaltose. Ferric carboxymaltose in contrast to iron sucrose is dextran free, has neutral

PH, has a physiological osmolarity which allows administration of higher single dose over shorter duration of time (single dose of 1000mg over 15 minutes), and there is lesser risk of anaphylaxis and does not require a test dose⁷. In the study we have compared the efficacy and safety of ferric carboxymaltose and ferric sucrose in postpartum anaemia. The purpose of this study was to recommend treatment of moderate iron deficiency anaemia in postpartum women, so that development of severe anaemia can be prevented and its complications can be avoided.

METHODS:

This randomized comparative hospital based longitudinal study was conducted in the department of obstetrics and gynaecology, S.M.S Medical College and Attached Group of Hospitals, Jaipur from Feb 2021 to July 2022. When the desired sample size was reached and then two months were taken for data analysis and compilation.

Institutional review board and ethical committee approval was taken prior to the study. The study universe comprised of all the postpartum women attending the department of obstetrics and gynaecology, SMS Medical college and attached group of hospitals, Jaipur. Sample size was calculated at 80% study power and alpha error of 0.05 assumed. Standard deviation of 0.69 gram % The cases in the study were selected randomly from postpartum women attending the Department of Obstetrics and Gynaecology, SMS Medical college, Jaipur. The inclusion criteria was postpartum women with moderate anaemia who had haemoglobin between 7- 10 %.

INCLUSION CRITERIA

1. Women who were anaemic during the third trimester of pregnancy.
2. Women who had normal haemoglobin during pregnancy but became anaemic in postpartum period.

EXCLUSION CRITERIA

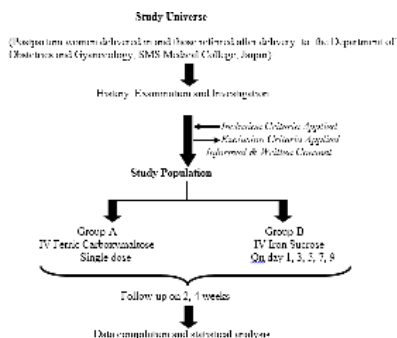
1. Women with known inherited haemoglobinopathies like thalassemia or anaemia other than iron deficiency anemia like G6PD, B 12 Deficiency anaemia,

- Anaemia due to acute blood loss .
- Women with history of blood transfusions and those with known allergy to iron formulations were excluded from the study.

After applying inclusion and exclusion criteria , the women selected for the study were allocated in one of the two groups and explained about the study , the type of drug given to them , its benefits and side effects.A written informed consent was taken from all women who were participating in the study.

Group allocation was done by coin tossing method to allocate first woman to group-A .After that , they were allocated alternatively in both groups. The study comprised of 2 groups each comprising 35 women . In group-A women received intravenous ferric carboxymaltose supplementation and in group-B women received intravenous iron sucrose supplementation. A detailed history was recorded which included information of the patient ,religion ,residential address , occupation ,literacy and socio-economic status. Past history of any medical illness, chronic diarrhea , chronic infection , parasitic infestation, jaundice ,any surgical procedure or blood transfusion.History of malabsorption or bleeding tendencies were also taken.Family history of thalassemia , sickle cell anaemia or any other hereditary anaemia was recorded . Drug use or allergy history was also noted.General physical and systemic examination done . All routine investigations i.e. haemoglobin (Hb) , bleeding time ,clotting time ,ABO-Rh blood group , fasting blood sugar, venereal disease laboratory test, hepatitis B surface antigen test , Human immunodeficiency virus test and urine complete and microscopy were done.

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STATISTICAL ANALYSIS

Continuous variables were summarized as mean and were analyzed by using unpaired t test. Nominal / categorical variables were summarized as proportions and were analyzed by using chi-square/ Fischer exact test. p-value <0.05 was taken as significant.

RESULTS

Demographic profile of both the groups were comparable with no significant difference. In age and parity the incidence of iron deficiency anaemia in both groups were comparable and is more among young age group (15-25) . In this study 59 % women had parity of 2 or 3 .

The average haemoglobin increase is about 10.96 (2.35g/dl) at 4 weeks in iron sucrose group from baseline value of 8.61g where as in FCM group Hb increase is about 11.28(2.75g/dl) from 8.53. The overall change in Hemoglobin (g/dL) over time was compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of Hemoglobin (g/dL) over time between the two groups (p = <0.001). (Table 1)

Table 1. Change in haemoglobin in group A and B over time

Hemoglobin (g/dL)	Group		P value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	A	B	
	Mean (SD)	Mean (SD)	
Baseline	8.53 (0.45)	8.61 (0.39)	0.373
2 Weeks	10.52 (0.47)	10.21 (0.53)	0.031
4 Weeks	11.28 (0.60)	10.96 (0.61)	0.105

P Value for change in Hemoglobin (g/dL) over time within each group (Friedman Test)	<0.001	<0.001
Overall P Value for comparison of change in Hemoglobin (g/dL) over time between the two groups (Generalized Estimating Equations)	<0.001	

Following bar graph showing Change in haemoglobin in group A and B over time

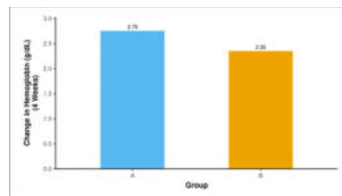
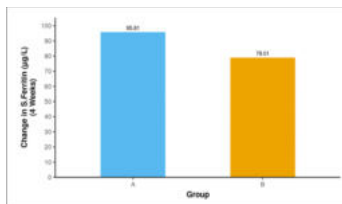


Table 2- change in ferritin in group A and B over time

Change in S.Ferritin (µg/L) (4 Weeks)	Group		t-test	
	A	B	t	p value
Mean (SD)	95.81 (20.17)	79.01 (17.81)	3.694	<0.001
Median (IQR)	98 (85.22-108.4)	81.3 (67.62-94.3)		
Min - Max	59.8 - 135	30.03 - 111.3		

The two groups differed significantly in terms of S.Ferritin (µg/L) at the following timepoints: 2 Weeks, 4 Weeks. In FCM group, the mean S.Ferritin (µg/L) increased from a minimum of 32.80 at the Baseline timepoint to a maximum of 264.69 at the 2 Weeks timepoint, and then decreased to 128.62 at the 4 Weeks timepoint. This change was statistically significant (Friedman Test: $\chi^2 = 70.0, p = <0.001$) whereas the mean S.Ferritin (µg/L) increased from a minimum of 35.35 at the Baseline timepoint to a maximum of 190.39 at the 2 Weeks timepoint, and then decreased to 114.37 at the 4 Weeks timepoint. This change was statistically significant (Friedman Test: $\chi^2 = 70.0, p = <0.001$). (table-2)

Following bar graph showing Change in ferritin in group A and B over time

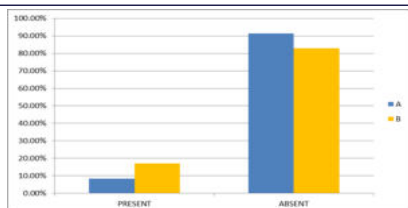


On comparing the adverse reaction in both the groups it was found that only 8.5% of the participants in the FCM group had mild adverse Events. 91.4% of the participants in the FCM group had no adverse Events. 17.1% of the participants in the Iron sucrose group had adverse Events. (Table 3)

Table 3: Adverse reactions in group A and B

Adverse Events	Group			Fisher's Exact Test	
	A	B	Total	χ^2	P Value
Present	3(8.5%)	6 (17.1%)	9 (12.9%)	0.128	1.000
Absent	32 (91.42%)	29(82.8%)	61 (87.1%)		
Total	35 (100.0%)	35 (100.0%)	70 (100.0%)		

Bar graph showing Adverse reactions in group A and B



DISCUSSION

This study compared the efficacy of intravenous ferric carboxymaltose versus iron sucrose in the management of postnatal iron deficiency anaemia. This study showed improvement in hemoglobin, serum ferritin, and blood indices in both iron sucrose and FCM group but it was attained faster and more efficiently with ferric carboxymaltose when compared with iron sucrose. Other advantages of FCM are, complete dose can be administered at a single visit and the duration of hospitalization of the patients are reduced greater. This improves the patient compliance. FCM also lacks dextran and less immunogenic. So adverse reactions are also comparatively less likely.

The dose required is almost 1000mg in both the groups. For iron sucrose per sitting only 200mg can be administered. So patients in iron sucrose group needs at least five visits to receive the required dose this decreases the patient compliance and increases hospital visits. Whereas in FCM group 1000 mg can be administered as a single dose. The outcomes are compared and analysed using paired T test and by Independence T test. The investigations used are haemoglobin, serum ferritin, blood indices, and peripheral smear before and after treatment. In the study by Rathod S et al (2010), the mean increase of Hb after 2 weeks was 2.4 g/dl and 3.2g/dl in iron sucrose and FCM groups respectively. Similarly Joshi SD et al (2016) also observed rise in Hb by 3.92 g/dl in iron sucrose group compared to a much higher rise of 4.68 g/dl in FCM group after 30 days. In the comparative study by Sharma N et al (2017) independent student's t test was performed which showed FCM was superior to iron sucrose (P value 0.000 and 0.000). Study by Kumari S et al (2019) showed a significantly higher increase of 3.5 g/dl in FCM group compared to 2.2 g/dl in iron sucrose group. In present study also FCM group has greater improvement in haemoglobin over 4 weeks compared to Iron sucrose group.

The present study showed that there was a significant difference between the 2 groups in terms of Change in S.Ferritin ($\mu\text{g/L}$) (4 Weeks) ($t = 3.694, p = <0.001$), with the mean Change in S.Ferritin ($\mu\text{g/L}$) (4 Weeks) being highest in the FCM Group. Similar to the present study, Rathod S et al (2010) study recorded a mean increase in serum ferritin levels of 193.1 and 307.1 ng/dl after 2 weeks and 64 and 106.7 ng/dl at 6 weeks in iron sucrose and FCM groups respectively. The Joshi SD et al (2016) showed a much higher mean increase in ferritin of 95.39 \pm 45.84 in FCM group compared to 71.07 \pm 27.23 ng/dl in iron sucrose group. Sharma N et al (2017) study showed mean increase in ferritin by 113.8 and 125.91 ng/dl in the iron sucrose and FCM groups respectively at 2 weeks. Lunagariya M et al also showed a significantly higher rise of 83.9 ng /dl in FCM group compared to 76.06 ng/dl in iron sucrose group. Kumari S et al (2019) study recorded a mean increase in serum ferritin levels from 77.91 \pm 27.4 to 182.86 \pm 33.36 in iron sucrose and from 78.05 \pm 34.69 to 195.39 \pm 44.6 ng/dl in FCM group.

Both the groups had very few adverse events. Only 8.5% participants in FCM group experienced mild adverse reaction compared to 17.1 % participants in iron sucrose group. In Joshi et al (2010) study adverse effects were seen in 7.2 % in iron sucrose group compared to 3.3% in FCM group. Similarly in Sharma N et al study (2017) FCM was found to be safer when compared to iron sucrose for treatment of postpartum anaemia with very low rate of adverse reactions. In the study conducted by Ragvi Raman et al (2021) FCM group showed no adverse reaction whereas the Iron sucrose group showed a reaction rate of 3.3%.

LIMITATIONS OF THE STUDY

The study was performed in a single centre which is a tertiary referral centre, thus it is not reflective of the whole population. Only IV routes are compared, oral and intramuscular routes are not compared the study.

CONCLUSION

This study compared the safety and efficacy of two parenteral iron preparations i.e.; FCM and Iron sucrose for treatment of postpartum

anaemia. This study showed improvement in hemoglobin, serum ferritin, and blood indices in both iron sucrose and FCM group but it was attained faster and more efficiently with ferric carboxymaltose when compared with iron sucrose. High dose of iron can be given in ferric carboxymaltose in a single dose, this reduces the number of infusions and duration of hospitalization. It also has lesser adverse reactions. This improves patient compliance. Based on our study, we recommend intravenous ferric carboxymaltose in management of moderate iron deficiency anemia in postpartum women.

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