Safety and Efficacy of Ferric Carboxymaltose in Comparison with Iron Sucrose for the Management of Iron Deficiency Anaemia in Pregnant Patients Presenting at a Tertiary Care Hospital in Lahore

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Abstract

Objective: To compare the safety profile and determine the efficacy of ferric carboxymaltose with iron sucrose in pregnant patients with iron deficiency anemia

Material and Methods: This comparative study was conducted at Central Park Teaching Hospital from 1st January 2023 to 30th June 2023. A hundred women from 16 to 36 weeks of gestation presenting with iron deficiency anemia who fulfilled the inclusion criteria were enrolled and randomized into groups. They were infused with Iron sucrose (IS) or ferric carboxymaltose (FCM) as per the calculated dose. Adverse effects were noted, hemoglobin was measured after 3 weeks, and data was analyzed statistically.

Results: The mean pre-treatment haemoglobin in IS group was 8.71

Conclusion: This study concludes that ferric carboxymaltose is a drug with more efficacy and safer than intravenous iron sucrose for the treatment of iron deficiency anemia in pregnant women.

Keywords: Ferric carboxymaltose, Iron sucrose, Iron deficiency Anemia, Intravenous iron therapy

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Introduction

Anemia is amongst the key causes of maternal morbidity and mortality directly or indirectly all around the world, affecting around two-thirds of pregnant women in low-income countries.[1] It is also associated with increased perinatal morbidity and mortality as iron is essential for all physiological functions in body from oxygen transport to muscle contraction.[2] Iron deficiency is the cause of about 90% of cases of anemia either due to dietary insufficiency, absorption issues or chronic blood loss.[3] Most of the studies show that in low-resource countries approximately 25% of babies with low birth weight, 44% of preterm births, and around 21% of perinatal mortality are due to anemia in pregnant women.[4] More risks were associated with moderate and severe anemia.[5]

During the antenatal period, oral iron is typically prescribed from the 2nd trimester to prevent iron deficiency and is suggested as the first-line therapy for iron deficiency anemia in pregnancy.[6] However, women show poor compliance due to forgetfulness or intolerable adverse events (GIT upsets). It also can't be effective due to poor absorption and isn't adequate for correcting moderate and severe anemia, mainly within the late second and the third trimesters. Treatment with parenteral iron is more effective in these women, and might prevent the need of blood transfusions during the antepartum and postpartum period.[7]

Iron sucrose and ferric carboxymaltose are parenteral iron preparations for the treatment of iron deficiency anaemia in pregnancy.[8] The most commonly used is iron sucrose complex (ISC). It has trivial side effects

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and test dose is not required. The only downside of iron sucrose is a restricted dose per sitting. The commonly used dose is 200 mg in one sitting or 600 mg per week. Because of this limited dose per sitting, a woman requires multiple visits to the hospital, which is inconvenient for the patient and her family, and the total cost can also be increased. The present inclusion in intravenous iron preparations for the treatment of iron deficiency anemia in pregnancy is Ferric Carboxymaltose (FCM). The FCM molecules contain a core of iron-hydroxide surrounded by a carbohydrate shell. Macrophages take up this complex completely, resulting in minimal levels of non-transferrin-bound iron, thus preventing iron toxicity and oxidative stress.[9] and may be given at high doses allowing rapid infusion (up to 1000 mg in a single dose infused over 15 min). Ferric carboxymaltose presents an appealing option to iron sucrose due to its risk profile, effectiveness, patient comfort, convenience, and efficient use of staff and institutional resources.

Several research papers have been released regarding the application of FCM for managing anemia after childbirth. However, literature is scarce on the administration of FCM during pregnancy. There are only a small number of prospective studies and a limited number of randomized controlled studies that compare FCM with the iron sucrose complex during pregnancy. In Pakistan, Hira Jamal et al conducted this trial.[10] The efficacy, safety, and cost-effectiveness of FCM in treating iron deficiency anemia during pregnancy were evaluated in the current study, while comparing to the iron sucrose complex.

Material and Methods

This comparative study was conducted as a randomized clinical trial at Central Park Teaching Hospital from 1st January 2023 to 30th June 2023. After Institutional Ethical Review Board granted ethical approval with IRB number CPMC/IRB-NO/1377A Dated:04-01-2023, One hundred patients from the antenatal outdoor of Central Park Teaching Hospital as well as patients admitted in the antenatal ward for any indication fulfilling the inclusion criteria were selected and randomized into two groups, Ferric carboxymaltose (FCM) group and Iron Sucrose(IS) group, using an opaque envelop technique.

All women between 16 and 36 weeks of pregnancy experiencing moderate to severe iron deficiency anemia who have intolerable side effects of oral iron, non-compliant, oral iron is ineffective or severe anaemia on first presentation. All women presenting after 32 weeks of gestation with moderate or severe iron deficiency anaemia. Twin pregnancy and pregnancy with placenta Previa with mild anaemia were also included. Anaemia due to other causes (non-iron deficiency). Previous history of allergic reactions to intravenous iron. History of asthma, raised liver enzymes (1.5 times of normal). Blood transfusion during current pregnancy.

After taking informed consent, the patient selected the envelope by lottery method, and the intravenous iron group written on the slip present in the envelope was allotted to the patient. Patients were admitted for a short stay of one to two hours in the antenatal ward where facilities for resuscitation were available in case of an anaphylactic reaction. After enrollment in study, a thorough clinical history, prior medical care involving iron treatment, adherence to oral iron medication, and chronic health conditions were all discussed. A comprehensive assessment was conducted, and the amount of iron needed was determined using Canzoni's formula.

Iron requirement (mg of I/V iron) = Total iron deficit (target Hb –actual HB) ×2.14× weight in Kg+ storage iron (500mg if weight is >35kg)

The maximum dose for the FCM group per session was 1000 mg, diluted with 200 ml of 0.9% saline and given as an IV infusion lasting 15 to 30 minutes. Additional doses, if necessary, were scheduled for day 7 and day 14, and the doses were rounded to the nearest 100 mg. Patients in the ISC group received IV ISC as 200 mg in 100 ml of Normal Saline over 15-20 minutes three times a week until the prescribed dosage was completed, not exceeding 600 mg per week. In both groups the target Hb was 11 g/dl. The patient's overall health, blood pressure, and pulse rate were observed before, during, and following the infusion. The fetal heart rate was assessed before and after the infusion. Each woman received treatment with the mebendazole 100 mg tablet twice a day for three days and 5 mg of Folic acid once a day, and any adverse effects were recorded. All patients were re-assessed after 3 weeks or just before delivery of baby whichever was earlier after initiation of treatment, and CBC was done to see the efficacy of treatment.

Iron deficiency Anaemia is defined as haemoglobin less than 11gm/dl and serum ferritin <30 µg/l Severity of anemia will be categorized as per WHO definition.[11]

Mild (hemoglobin 10–10.9 gm/dl), Moderate (hemoglobin 7–9.9 gm/dl) and Severe (hemoglobin < 7 gm/dl) Fetal bradycardia = FHR <110/minute on CTG. Fetal tachycardia = FHR>160/minute on CTG. Maternal hypotension = BP<100/60 mmHg. Maternal pain- was assessed using a verbal pain intensity scale, which includes categories such as no pain, mild, moderate, severe, very severe, and worst possible pain.

Data was analyzed using SPSS 26. Quantitative variables were measured by means and standard deviation. The frequencies and percentages were used to measure qualitative variables. The comparison of qualitative variables was done using the chi-square test while a comparison of quantitative variables between two study groups was performed using an independent samples t-test.

Results

The average age of the participants in the study was 28 years, spanning from 21 to 36 years. In terms of childbirth experience, 23 patients had not given birth before, whereas 77 patients had one or more previous pregnancies. A significant majority, 90% of the patients came from middle-class families, and 93% of them exhibited moderate anemia. The mean initial hemoglobin level before treatment was 8.7 gm%, which increased to 11 gm% after carboxymaltose infusion. On average there was a rise of 2.30gm% in hemoglobin level.

Table 1: *Mean Distribution of underline population*

Variables	Mean (SD)
Age of patients	28.58 ± 3.41
Duration of pregnancy before treatment	31.63 ± 2.60
Pre-treatment Hemoglobin	8.70 ± 0.62
Post – treatment Hemoglobin	11.00 ± 0.42
Rise in hemoglobin	2.30 ± 0.55

Table 2: *Group-wise Distribution of patients*

Variables	Group	Mean (SD)
Age of patients	FCM	28. 38 ± 0.51
	IS	28.78 ± 0.45
Gestational age (DOP)	FCM	32 ± 0.40
	IS	31.26 ± 0.33
Pre-treatment HB	FCM	8.70 ± 0.84
	IS	8.71 ± 0.09
Post-treatment HB	FCM	11.08 ± 0.07
	IS	10.92 ± 0.05
No of visits required for I/V iron	FCM	1.06 ± 0.03
	IS	4.58 ± 0.12

Table 3.1: *Pair-wise comparison of Pre and Post-treatment of hemoglobin*

Group	Pre-treatment	Post-treatment	P-value
FCM	8.70 ± 0.84	11.08 ± 0.07	0.04*
IS	8.71 ± 0.09	10.92 ± 0.05	0.84

*P-value < 0.05 Statistically Significant

When assessing the treatment effectiveness in both the FCM and IS groups, the average post-treatment values were consistently higher than the pre-treatment values. The FCM group demonstrated notably more significant outcomes compared to the IS group, indicating that FCM is superior in effectiveness to IS (Table 3).

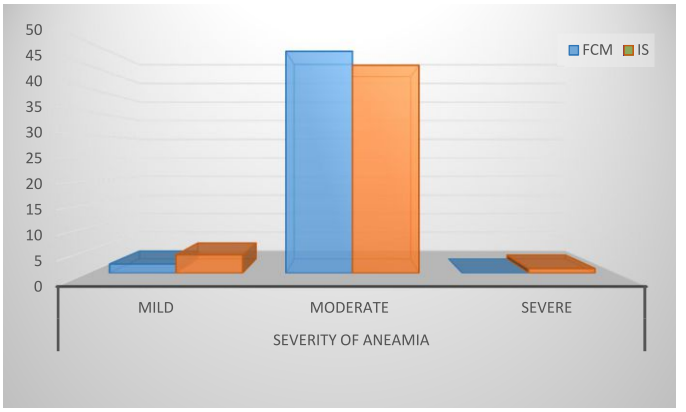

Figure 1: *Comparison of FCM and IS Groups with Severity of Anaemia*

Regarding adverse effects, as is evident from table 4,

Table 3.2: *Administration site reactions*

Group	Pain	Extravasation	Itching	no local side effect	p-value
FCM	2	0	0	48	0.011
IS	4	1	8	37	

Table 4: *Systematic side effects*

Group	Gastrointestinal disorders	no systemic adverse effect	p-value
FCM	1	49	0.753
IS	1	49	

Table 5: *Adverse effects*

Group	Yes	No	p-value
FCM	3	47	0.003
IS	14	36	

5 and 6, these were more in IS group as compared to FCM group, 28% versus 6%. No life threatening adverse effects occurred in either group. Gastrointestinal side effects (nausea) occurred in one patient of each group, while most of the local adverse effects (administration site reactions) occurred in IS group.

Discussion

Iron deficiency is the most prevalent cause of anemia during pregnancy, if effectively treated, can lead to reduced maternal and perinatal morbidity and mortality. For selecting safe and efficacious intravenous drug therapy, we compared new agent "ferric carboxymaltose" with previously commonly used "iron sucrose'' in present study.

The mean age of patients participating in our trial is 28 years, ranging from 21 to 36 years in both groups, as found in a similar study conducted by Saniya Sattar et al, in which the mean age of participants was around 26 years[12]. The Mean hemoglobin before start of treatment was almost the same in both groups. It was 8.7± 0.59 g/dl in FCM group and 8.7±0.66 g/dl in IS group. This is also reflected by study conducted by Saniya Sattar et al which showed pretreatment Hb 8.6±0.9 in FCM and 8.7±0.9 g/dl in IS group[12]. In our study, there was a significant rise (p value <0.05) in post-treatment Hb of FCM group; 11.09 ± 0.47 in FCM group versus 10.92 ± 0.35 g/dl in IS group, 3 weeks after treatment which is similar to study carried by G Jain et al13. The mean rise in Hb in study population was 2.30 ±0.55. According to most studies, the increase in hemoglobin was greater in the FCM group compared to the IS group. The study conducted by Alpesh R et al, showed mean rise in hemoglobin of 2.6g/dl in FCM group and 1.8g/dl in IS group[14]. The other study shows a mean rise of 2.92gm/dl with FCM and 1.08 with iron sucrose[15]. The results of these studies are similar to our study, in which the mean rise in Hb% in FCM group is 3.70 ± 0.49 while mean rise in Hb% with IS group is 3.30±0.60. Regarding adverse effects, these were more in IS group as compared to FCM group, 28% versus 6%. No life threatening adverse effects occurred in either group. Gastrointestinal side effects (nausea) occurred in one patient of each group, while most of the local adverse effects (administration site reactions) occurred in IS group, which is similar to the findings observed in meta-analysis.[16] Regarding the number of hospital visits required for completion of intravenous iron dose, these were much more in IS group versus FCM group. In FCM group, 94% of patients required only one hospital visit, while in the IS group there were five or more in 76% of patients. It was also observed in the study that by increasing the dose of intravenous iron up to a certain limit, the mean hemoglobin rise can be accelerated. For example, by using the Ganzoni formula, increasing the target value by 15 (normal upper limit of hemoglobin in females), the mean rise in hemoglobin can be increased.

Conclusion

After analyzing data in this study, we can conclude that ferric carboxymaltose is a drug that has more efficacy and it is safer than iron sucrose to treat iron deficiency anemia during pregnancy. Large doses can be administered all at once, which is another benefit, thus reducing the cost and increasing patient compliance. Therefore, ferric carboxymaltose is suitable for 1st line parenteral iron treatment for iron deficiency anemia, particularly in the second and third trimesters of pregnancy.

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Authors Contribution

RN, TM: Conceptualization of Project
TZ, SM: Data Collection
RN: Literature Search
RB: Statistical Analysis
RB, SM: Drafting, Revision
RN: Writing of Manuscript