Original Article

# Comparison of Safety and Efficacy of Ferric Carboxymaltose with Iron Sucrose for the Treatment of Iron Deficiency Anemia in Pregnancy



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## ABSTRACT

**Objective:** To compare the safety and efficacy of administration of intravenous iron sucrose and ferric carboxymaltose in pregnant females with iron deficiency anemia.

**Study Design:** Quasi-experimental study

**Place and Duration of Study:** This study was conducted at the Department of Obs / Gynae, Islamic International Medical College/Pakistan Railway Hospital, Rawalpindi from September 2020 to March 2022.

**Materials and Methods:** 70 pregnant females diagnosed with iron deficiency anemia in their second or third trimester of pregnancy were included in the study. The pregnant females in the study arm received ferric carboxymaltose while those in the control group received iron sucrose. Patients were followed for six weeks, after which they were assessed for efficacy by assessment of rise in haemoglobin levels and successful treatment was defined as a rise in haemoglobin levels of ≥2.0 g/dL from baseline. Patients were also followed up for the development of side effects, if any, to treatment.

**Results:** There was no significant difference between the mean haemoglobin levels between ferric carboxymaltose and iron sucrose groups at the time of enrollment in study: 8.6 ± 0.9 g/dL versus 8.7 ± 0.9 g/dL, respectively, (p=0.746). However, haemoglobin levels after six weeks were significantly higher with ferric carboxymaltose: 10.8 ± 1.1 g/dL versus 10.2 ± 1.1 g/dL with iron sucrose, (p=0.008). Additionally, 94.3% of patients in the ferric carboxymaltose group reported no side effects versus 48.6% in the iron sucrose group, (p<0.001).

**Conclusion:** Ferric carboxymaltose therapy for iron deficiency anaemia in late pregnancy is associated with greater increase in haemoglobin when compared to conventional therapy with iron sucrose along with better safety and tolerability.


**Key Words:** Iron Deficiency Anemia, Iron Sucrose, Ferric Carboxymaltose, Pregnancy.

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## INTRODUCTION

Iron deficiency anaemia is estimated to afflict 36.5% of all pregnancies worldwide in 2019.[1] The deficiency is more significant in Pakistani females: approximately 76.7% of pregnant women suffer from it.[2] Causes include increase iron requirement during gestation, physiologic expansion of plasma, nutritional deficiencies and parasitic infections.[3,4]

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Generally, oral preparations are used in the first trimester, however these are linked with compliance issues due to adverse effects, particularly involving the gastrointestinal system.[5,6,7] Intravenous formulations are avoided in the first trimester because of teratogenicity uncertainty, however, they have been shown to be more effective than oral preparations in later trimesters.[6-8] Several intravenous iron formulations such as ferric carboxymaltose, iron sucrose, iron derisomaltose and sodium ferric gluconate are available, each with their own efficacy, safety profile and dosing schedules.[9,10] However, little is known about the comparative safety and effectiveness of these intravenous preparations in managing iron deficiency anemia in pregnant females.

This study was conducted to compare different parenteral iron preparations available to pregnant Pakistani patients. Problems with compliance and regular follow ups translate into the requirement for a single dose, effective and safe iron preparation that can be easily administered. While significant experience has been acquired with iron sucrose preparations,

dosing is usually multiple and over alternate days. Conversely, ferric carboxymaltose can be given as a single dose, however, data with regards to its efficacy in pregnant women needs further elucidation.

# MATERIALS AND METHODS

This study was conducted as a quasi-experimental study from Sep 2020 to Mar 2022 in Obs/gyn department, Pakistan Railway Hospital. 70 patients were selected via consecutive non-probability sampling after informed consent. Iron deficiency was defined as a serum ferritin level of <30.0 ng/mL, with a haemoglobin level of <10.5 g/dL and <11.0 g/dL during the second and third trimester, respectively.[11]

The sample size was calculated using WHO sample size calculator keeping the level of significance (α) of 5%, power of the test (1-β) of 95%, population standard deviation (σ) of 0.6695, population variance ($\sigma^2$) of 0.44823025, test value of the population mean ($\mu_o$) of 13.25 and an anticipated population mean ($\mu_a$) of 11.59.[12]

**Inclusion Criteria**: Pregnant females aged between 15 and 49 years, with pregnancies greater than 12 weeks duration, with a serum ferritin level of <30.0 ng/mL, with a haemoglobin level of <10.5 g/dL and <11.0 g/dL during the second and third trimester were included.

**Exclusion Criteria**: Patients with a history of hypersensitivity to ferric carboxymaltose or iron sucrose, those who suffered from chronic diseases such as chronic viral hepatitis, chronic kidney disease, inflammatory bowel disease, malignancies, haemoglobinopathies, vitamin B12 or folate deficiency anaemia were all excluded.

The approval from the hospital's ethical review committee was taken before the initiation of study. Block randomization was done to divide all the patients into two groups with 35 patients in each group. All participants received testing for blood parameters, specifically haemoglobin levels and serum ferritin levels.

Patients in the study arm received an intravenous injection of ferric carboxymaltose (Ferinject) at a dose of 15 mg/kg body weight, diluted in 250 mL 0.9% NaCl solution over thirty minutes, in a single dose. Intravenous iron sucrose (Venofer) was given at a dose of 15 mg/kg divided into five equal doses to the patients in the control arm. Each dose was given over a time period of sixty minutes after dilution in 100 mL 0.9% NaCl. Dosing was done on alternate days till completion of calculated dose. The aforementioned blood parameters were re-tested after six weeks of the first dose.

Treatment success was defined as a rise in haemoglobin levels of ≥2.0 g/dL from baseline while drug safety was defined as the absence of unexpected adverse reactions i.e. nausea, vomiting, headache and gastrointestinal upset leading to discontinuation of the drug at any time during course of treatment.

Data was analyzed using the SPSS version 26.0. Quantitative variables such as age, duration of gestation and haemoglobin levels pre- and post-treatment will be measured using means and standard deviations. Qualitative variables specifically efficacy and safety of treatment were recorded as frequencies and percentages. Qualitative variables were compared via Chi-square test, while the independent samples *t*-test was used to compare quantitative variables between the two study groups.

# RESULTS

Total study sample consisted of 70 patients divided into two groups of 35 patients each. The mean age of all the participants was 26.5 ± 6.0 years, with a range of 17 to 38 years. The mean gestational age was 24.7 ± 7.4 weeks with a range of 12 to 33 weeks. A total of 37 (52.9%) women were reported in the second trimester of pregnancy, while the remaining 33 (47.1%) reported in the third trimester. The mean baseline haemoglobin was 8.7 ± 0.9 g/dL (7.1 to 10.4 g/dL: normal range). The baseline characteristics of all patients according to the intervention arm is displayed in Table-I.

**Table No.I: Pre-Intervention Patient Characteristics According to Group**

| Variable | Study Arm (n=35) | Control Arm (n=35) | p-value |
|---|---|---|---|
| Age (years) | 26.5 ± 5.5 | 26.5 ± 6.6 | 0.984 |
| Gestational age (weeks) | 24.5 ± 7.7 | 24.9 ± 7.3 | 0.787 |
| Time of Gestation | | | |
| Second Trimester | 19 (54.3%) | 18 (51.4%) | 0.811 |
| Third Trimester | 16 (45.7%) | 17 (48.6%) | |
| Baseline Haemoglobin Level (g/dL) | 8.6 ± 0.9 | 8.7 ± 0.9 | 0.746 |

Six weeks after initiating treatment, the mean haemoglobin level for the entire sample had increased to 10.5 ± 1.1 g/dL. Treatment was effective in 40 (57.1%) patients, who noted a haemoglobin rise of ≥2.0 g/dL, while 50 (71.4%) reported that they did not suffer from any adverse effects. Patients in the study arm had significantly higher haemoglobin levels as compared to their haemoglobin levels initially, ($p$=0.008). Additionally, frequency of having an efficacious outcome were higher and less adverse effects were seen in the study arm, ($p$=0.004 and <0.001, respectively). Data for the study results according to groups is displayed in Table 2.

**Table No.2: Patient Outcomes according to Study Arms**

| Variable | Study Arm (n=35) | Control Arm (n=35) | p-value |
|---|---|---|---|
| Post-Treatment Haemoglobin Level (g/dL) | 10.8 ± 1.1 | 10.2 ± 1.1 | 0.008 |
| Efficacy of Treatment | | | |
| Yes | 26 (74.3%) | 14 (40.0%) | 0.004 |
| No | 9 (25.7%) | 21 (60.0%) | |
| Safety of Treatment | | | |
| Yes | 33 (94.3%) | 17 (48.6%) | <0.001 |
| No | 2 (5.7%) | 18 (51.4%) | |

# DISCUSSION

Iron deficiency anaemia in pregnancy requires early recognition and adequate management to prevent sub-optimal pregnancy outcomes. Ferric carboxymaltose is comparatively cheaper than other intravenous iron preparations and has been proven to be preferred by patients with iron deficiency anaemia over oral therapy, despite its added costs when compared to oral formulations due to its efficacy and ease of administration.[13] While the effectiveness of this formulation is well established in patients with iron deficiency anemia secondary to nutritional deficiency, chronic kidney disease and ischaemic heart disease, its efficacy and tolerability in pregnancy is less well known, hence the purpose of this study.[14-16]

The mean age of the participants in our study sample was 26.5 ± 6.0 years. Adnan et al, in a study conducted in 2018, found that women presenting with pregnancy with anaemia had a mean age of 26.8 ± 3.4 years which was similar to our study, while Jose et al also reported a similar mean age at presentation of 26.2 ± 3.6 years in their study.[17,18] In contrast, Zeisler et al reported that most pregnant women with iron deficiency were in their third decade of life in their study.[19] We attribute this difference in results to earlier marriages and pregnancies in the developing world as opposed to developed countries.

Our study demonstrated that mean haemoglobin levels were significantly higher in pregnant females who were given intravenous ferric carboxymaltose than intravenous iron sucrose i.e., 10.8 ± 1.1 g/dL versus 10.2 ± 1.0 g/dL, respectively, (p=0.008) when measured after six weeks of initial therapy. Jose et al also reported a similar result with a mean haemoglobin level of 11.5 ± 4.6 g/dL with ferric carboxymaltose versus 10.9 ± 4.4 g/dL with iron sucrose after twelve weeks of initial treatment (p <0.001).[18] Rathod et al conducted a similar study and found that ferric carboymaltose produced larger increments in haemoglobin levels when compared to iron sucrose: 12.1 ± 0.8 g/dL versus 11.4 ± 1.2 g/dl, respectively, (p<0.001) after twelve weeks of follow-up.[20] Singh et al studied the difference in the efficacy of iron sucrose and ferric carboxymaltose in females at the end of gestation and found that the former raised the haemoglobin levels to 10.1 ± 0.6 g/dL while iron sucrose increased haemoglobin levels to 9.8 ± 0.6 g/dL, (p<0.001).[21] The lower increments in haemoglobin in both arms in this study compared to our results is likely attributable to the occurrence of delivery in Singh et al, where anywhere up to 500 mL of blood loss can occur depending on the mode of delivery.[22]

In our study a higher number of cases produced an increase in haemoglobin levels of more than 2g/dL from baseline with ferric carboxymaltose when compared to iron sucrose, which was considered indicative of efficacy, (74.3% versus 40.0%, respectively; p=0.004). Rathod et al also noted that efficacy was higher with ferric carboxymaltose i.e., 66.0% versus 27.0% with iron sucrose, (p<0.001).[20] Chaudhry et al, in a similar study observed an even greater difference between ferric carboxymaltose (63.3%) versus iron sucrose (0%), (p<0.001).[23] Singh et al also reported a similarly higher frequency of efficacy of 88.0% with ferric carboxymaltose versus 24.0% with iron sucrose, (p<0.001).[21] While these studies universally concluded that ferric carboxymaltose is more efficacious than iron sucrose, there was still a great degree of variability, which is likely due to the varying definitions for efficacy used by each study.

Lastly, a total of 94.3% reported that there was no incidence of adverse effects with ferric carboxymaltose versus 48.6% with iron sucrose in our study, (p<0.001). Similar results for safety were seen in comparable studies such as Singh et al (100.0% with ferric carboxymaltose versus 93.0% with iron sucrose; p=0.038) and Chaudhary et al (93.3% with ferric carboxymaltose versus 50.0% with iron sucrose; p ≤0.05).[21,23]

Our study was limited by a number of factors, lack of blinding due to the different number of injections administered in each research arm: placebo usage in the study arm was avoided considering the sensitive condition of the patients, i.e., pregnancy. Secondly, it was unclear whether there was variability present in the patient's dietary intake of iron, confounding the results. Lastly, pregnancy itself is associated with gastrointestinal complaints, nausea, vomiting and anorexia, which may have affected the results.

# CONCLUSION

Ferric carboxymaltose is a cheap, readily available iron preparation that is more effective than iron sucrose, in producing significant increases in haemoglobin levels, with lesser side effects. Moreover, the preparation is

employed as a single dose, as opposed to multiple dosing requirements with iron sucrose, which is more convenient to the patient. In view of the aforementioned, the preparation may be used as first-line therapy in pregnant patients with iron deficiency anaemia in the second and third trimester. Future research should focus establishment of safety in the first trimester of pregnancy.

**Author's Contribution:**

| | |
|---|---|
| Concept & Design of Study: | Saniya Sattar, Saadia Sultana, Wajiha Shadab |
| Drafting: | Saniya Sattar, Wajiha Shadab, Sadaf Afzal |
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| Revisiting Critically: | Saniya Sattar, Wajiha Shadab |
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**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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