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Original Research Article

Study of Safety and Efficacy of Ferric Carboxy Maltose in Treatment of Anaemia in Pregnancy

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Abstract:

Introduction: Iron deficiency anaemia is the most common cause of anaemia in developing countries. Oral iron preparations have limitations in their use. Treatment of iron deficiency is essential to prevent complications. Parenteral iron preparations overcome these limitations and can be used in treatment of anaemia.

Objective: To study the effectiveness and safety of ferric carboxymaltose in treatment of anaemia in pregnancy.

Method: Pregnant women between 28 to 36 weeks of gestation, with moderate anaemia (Hb 7.1 – 10g/dl) were included in the study. Iron deficiency anaemia was confirmed by complete haemogram, serum iron indices and peripheral smear. Women who were intolerant, non-compliant or not responding to oral iron therapy were included in the study. Women with history of previous parenteral iron infusion, blood transfusion, adverse reactions to iron preparations, anaemia due to other causes except iron deficiency anaemia, chronic infections and chronic medical diseases were excluded from the study. 1000mg of FCM infusion was given under supervision to all women. Blood indices were rechecked at 2 week and 4 weeks interval after FCM administration. Results were tabulated.

Results: Total 64 women completed the study. Mean Hb before FCM administration was 8.2g/dl and mean ferritin level was 40.2 ng/ml. Mean Hb observed after 2 and 4 week of administration of FCM was 9.6gm/dl and 11.2gm/dl respectively ($p<0.001$) and mean increase in Hb observed 2 and 4 weeks was 1.1gm/dl and 2.9gm/dl respectively ($p<0.001$). 20% had mild adverse effects; most of them were self-limiting and managed conservatively.

Conclusion: Ferric carboxymaltose was found to be safe and effective in treatment of iron deficiency anaemia in pregnancy with moderate anaemia.

Keywords: Anaemia, Pregnancy, Iron Deficiency, Intravenous.

Introduction

Iron deficiency anaemia (IDA) is a leading cause of anaemia, which leads to maternal morbidity and mortality in India. The World Health Organization (WHO) aims to achieve a worldwide target of reducing anaemia in women in the reproductive age group by 50% by 2025 [1]. Patients with IDA have intrapartum complications, longer hospital stay, risk of PPH, infections, delayed wound healing and need for blood transfusions. Hence it should be diagnosed and treated as early as possible. The most common parameter to diagnose IDA is serum haemoglobin (Hb%), blood indices, peripheral smear andiron studies. The common drawback of oral iron therapy is gastrointestinal intolerance and non- compliance. Blood transfusion is reserved for severe and life threatening cases. To overcome these problems parenteral iron preparations are used. [2,4]

Ferric carboxymaltose, an iron replacement product. It is an iron carbohydrate complex with the chemical name of polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-Dglucopyranosyl)-oxy-2(R),3(R),5(R),6-tetrahydroxy-hexanoate. It has a molecular weight of approximately 150,000 Da. It corresponding to the following empirical formula:

$[FeOx(OH)y(H2O)z]n[\{(C6H10O5)m\ (C6H12O7)\}l]k$, where $n \approx 103$, $m \approx 8$, $l \approx 11$, and $k \approx 4$(l represents the mean branching degree of the ligand).

Ferric carboxymaltose (FCM) is a third generationparenteral iron formulation. FCM is a novel

non-dextran IV iron agent and it has very low immunogenic potential. Ferric carboxymaltose is a

novel parentral iron preparation that over comes the limitation of existing iron preparations. It is effective in improving Hb% and replenishes iron stores. Single large dose can be given and associated with minimal adverse effects. [3,7]

Materials and Methods

This is a single centre, prospective, observational study conducted at the Basaveshwara medical college and hospital, Chitradurga, Karnataka from June 2022 to December 2023 after obtaining ethical clearance from institutional ethical committee.

Pregnant women in third trimester, between 28 weeks to 36 weeks of gestation with moderate anaemia (Hb 7.1 to 10 gm/dl) were included in the study. Pregnant women with anaemia who were not responding to oral iron or intolerable to oral iron therapy or oral iron therapy was inappropriate based on clinical judgement of investigator were part of this study.

Complete blood counts with peripheral smear and iron studies of all patients were done and iron deficiency was confirmed in all cases. Routine antenatal investigations were done according to the standard departmental protocol.

Women who were pretreated with other parentral preparations, blood transfusion, megaloblastic, dimorphic anaemia or anaemia due to other cause, women with any chronic infections like hepatitis and HIV, serum transaminases >1.5 times the upper limit of normal, serum creatinine level >2.0 mg/dl or history of allergic reaction to intravenous iron infusion were excluded from study after investigation. Total 67 cases were enrolled in the study.

FCM was used as per the institutional protocol and locally approved prescribing information. After obtaining consent, patients were transfused with Inj. FCM 1000mg in 250ml Normal saline infusion over 15-20 minutes. Pre and post transfusion vitals were monitored and women were watched for any adverse effects during the procedure. The drug was administered under direct supervision and infusion was stopped immediately in case of adverse effects and treated accordingly. Women treated with Inj. FCM were followed and reassessed with investigations at the end of 2 weeks and 4 weeks after the administration.

Statistical analysis: The collected data was compiled in EXCEL sheet and Master sheet was prepared. SPSS (Statistical Software for social Sciences) software version 24 was used for analysis of this data.

Results:

Total 67 pregnant women matching inclusion and exclusion criteria and provided written consent entered the study. Out of them, 64 patients completed the study (3 lost for follow up). All pregnant women received single IV infusion of FCM 1000 mg over 15 minutes. The mean age in this study was 26.37 years (range 18 to 34 years). Majority of them, 36(56%) were multigravida and 28 (44%) were primigravida. Majority 39(61%) of them were between 28-32 weeks gestation, 20(31%) were between 32 to 36 weeks of gestation and 5 (8%) of them were >36weeks of gestation. (Table 1 and Figure 1)

Table 1: Associated risk factors among the study subjects

Risk factors	Frequency (%)
Hypothyroidism	9 (14.1%)
Preeclampsia	8 (12.5%)
RH negative pregnancy	2 (3.1%)
Previous LSCS	21 (32.8%)
GDM	1 (1.6%)
Nil	23 (35.9%)
Total	**64 (100%)**

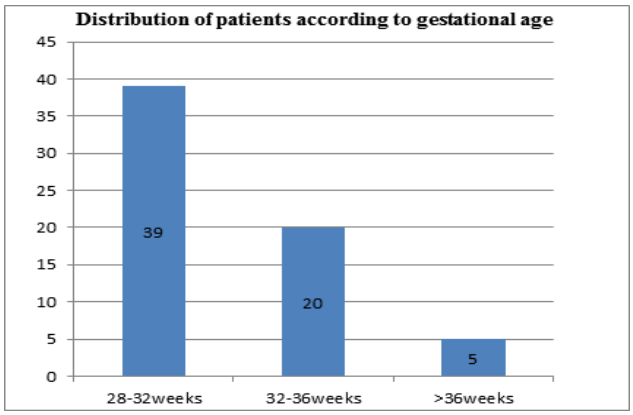

Figure 1: Gestational age at the time of FCM infusion

Mean haemoglobin before administration of FCM was 8.2gm/dl (7.5gm/dl-9.4gm/dl). The average haemoglobin of primigravida on admission was 9.8gm/dl, and the situation worsened with increase in parity with average haemoglobin of 7.8gm/dl in multigravida. Mean serum ferritin before FCM administration was 40.2 ng/ml. Number of patients with Hb 7-8gm/dl, 8-9gm/dl and 9-10gm/dl were 34,17and 13 respectively. (Figure 2)

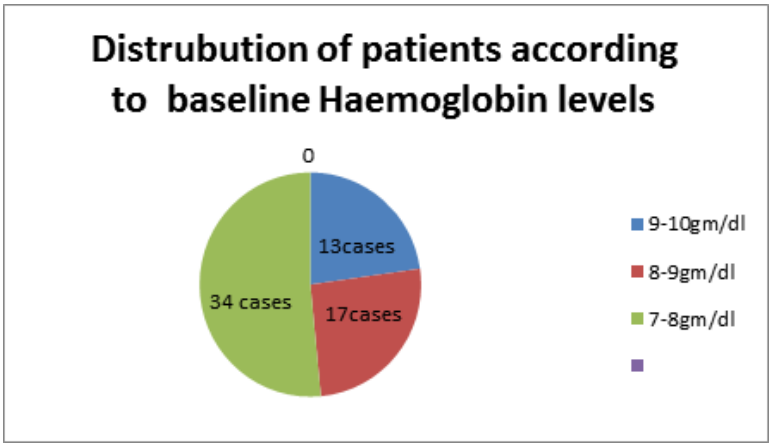

Figure 2: Haemoglobin level on admission

With respect to the serum ferritin levels on admission, 33 women fell in the range of 21-30ng/ml, and 21 in the range of 10-20ng/ml. Ten had their serum ferritin levels below 10ng/ml. (Figure 3)

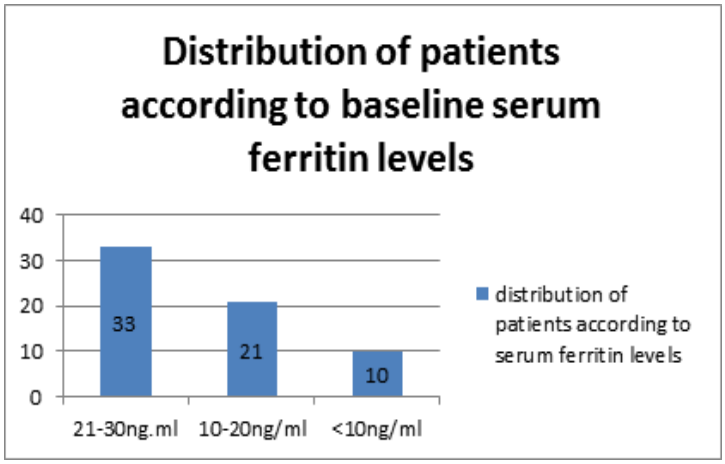

Figure 3: Serum ferritin level at admission

Mean Hb observed after 2 and 4 week of administration of FCM was 9.6gm/dl and 11.2gm/dl respectively ($p<0.001$). Mean increase in Hb observed 2 and 4 weeks after administration of FCM was 1.1gm/dl and 2.9gm/dl respectively ($p<0.001$). (Figure 4)

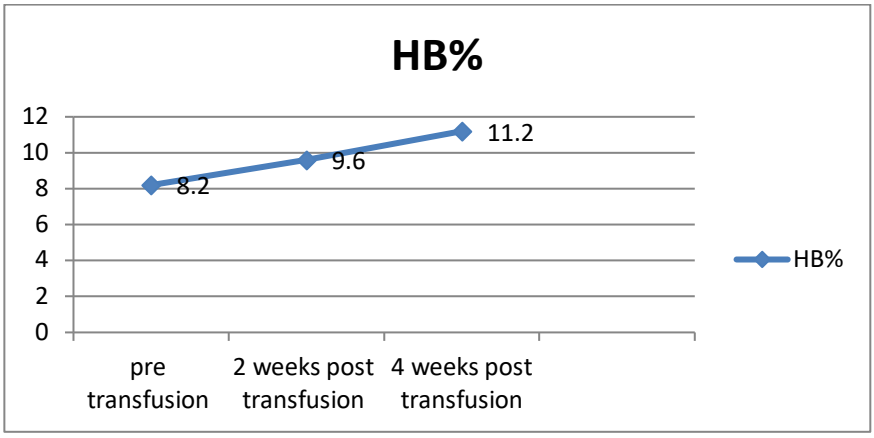

Figure 4: Comparison of mean Hb at different intervals of time

No serious life threatening adverse effects were recorded in any of the 64 women receiving infusion (Table 2). Minor side effects occurred in 7(11%) patients. Three had local reactions like slight burning at injection site. Systemic reactions like giddiness, mild headache, nausea/vomiting were seen in 1, 1 and 2 patients respectively. Most adverse events were self-limiting. Fetal heart rate monitoring did not indicate drug related adverse effect on the fetal heart pattern.

Table 2: Adverse events following administration of FCM

Adverse event	Frequency (%)
Injection site irritation	3 (4.7%)
Giddiness	1 (1.6%)
Headache	1 (1.6%)
Nausea /vomiting	2 (3%)
Nil	57 (89.1%)
Total	**64 (100%)**

Discussion

This is a prospective study reporting on Inj FCM infusion in pregnancy. The key finding of our study is, in pregnant women presenting with iron deficiency anaemia(IDA), Inj FCM infusion prior to delivery significantly increased haemoglobin levels. Further, we also found that Inj FCM appears to be a safe and effective treatment modality for the correction of IDA, as no serious adverse effects and only few minor adverse effects reported.

In our study, 28 were primigravidae. 41 belonged to lower middle and lower socio-economic status showing that nutritional anaemia exists in this population. 28% of women had not taken iron and folic acid tablets regularly in spite of ANC visits. Interestingly anaemia was noted in 27% of women who had taken regular oral iron preparations. Metallic taste, nausea/vomiting, diarrhoea and wrong method of consumption might explain the lack of compliance and inadequate increase in haemoglobin levels. This shows that pregnant women taking oral iron and folic acid prophylaxis are not immune to anaemia and the need for parenteral iron preparations for correction of anaemia is required.

In our study, 11% patients had adverse reactions. Most of them were self-limiting and few managed conservatively. Transfusion was completed in all the patients. This shows that though FCM is a safeparentral iron preparation, in terms of adverse effects, warrants a thorough history of previous such reactions in all patients receiving parentral iron preparations.[4,6,7,9]

In a study by Mishra, there was a significant improvement in Hb over a period of 3 weeks from mean Hb of 8.97+/-1.05gm/dl to 11.34+/-0.90gm/dl with p value <0.001, which was statistically significant. Also no serious adverse effects of FCM were noted. The results are comparable to results of our study where mean HB% increased from 8.2gm/dl to 11.2 gm/dl over 4 weeks. Similar results were seen in few other prospective studies. [4,5,8]

In a prospective observational study by Bernard, 65 anaemic pregnant women received ferric carboxymaltose up to 15 mg/kg between 24 and 40 weeks of pregnancy. Outcome showed a significantly increased Hb values ($p < 0.01$) above baseline levels in all women. Increased Hb values were observed at 3 and 6 weeks post infusion and up to 8 weeks post-infusion. Ferritin values increased significantly after the infusion. Fetal heart rate monitoring was did not indicate a drug related adverse impact on the fetus. Of the 29 (44.6%) women interviewed, 19 (65.5%) women reported an improvement in their well-being and 9(31%) felt no different after the infusion. None of the women felt worse. No serious adverse effects were found and minor side effects occurred in 13 (20%) patients. Results were comparable to our study in which mean Hb at 2 and 4weeks post FCM infusion was 9.6 gm/dl and 11.2 gm/dl. Also adverse effects were seen in 11% of cases in our study in comparision to above study. [9]

The choice of injectable iron therapy is mainly determined by cost and convenience of administration. Though the cost effectiveness of FCM drug is less compared to iron sucrose, other parameters like multiple hospital visits and pricks, number of working days lost and travel are to be considered.

Conclusion

Ferric carboxy maltose is an effective treatment option for iron deficiency anaemia. FCM is effective in increasing haemoglobin in mild to moderate IDA in pregnancy. As incidence of anaemia is high in pregnancy, large single dose administration of FCM can help overcome the complications of anaemia if treated at right time. FCM was found to be safe for parenteral use, with no serious side effects.

Ethical approval: Ethical approval obtained from IEC.

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