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Original Research Article

A comparative study of intravenous ferricarboxymaltose and double dose oral iron therapy in treatment of anemia in pregnancy

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ABSTRACT

Background: During pregnancy, iron deficiency is due to an imbalance between demand and supply, this worsens as pregnancy advances, according to CDC (centres for disease control and prevention) anemia is defined as Hb concentration lesser than 11 gm/dl in the first and third trimesters, and/or lesser than 10.5 gm/dl in the second trimester.
Methods: The prospective comparative study was planned with the objective to assess the effectiveness of intravenous ferricarboxymaltose and oral double dose iron in treating anaemia in pregnant women. This study was conducted from January 2019 to June 2020 among 100 (50 in each group) pregnant anemic women attending a rural tertiary care centre.
Results: This comparative study between double dose oral iron and i.v. iron treatment showed, hemoglobin levels improved at comparable rate across both treatments, however significantly more women achieved anemia correction with ferric carboxymaltose than oral iron More women achieved significant improvement in Hb with single dose of ferric carboxymaltose, whereas with oral iron additional dose of iron supplementation was required. Treatment related adverse reactions were seen more which oral iron treatment than with FCM. With markedly higher rates of gastrointestinal disorders.
Conclusions: FCM is comparable more effective and better tolerated than oral iron treatment in pregnant women. Rapid correction of anemia was seen with i.v. FCM, thus in late stage pregnancy, when time to delivery is a limiting step, administration of FCM may be a more appropriate option than oral iron for rapid and effective anemia correction.

Keywords: Double dose oral iron treatment outcome, Iron deficiency anemia, I.V. ferricarboxymaltose treatment outcome

INTRODUCTION

Anemia is defined as a hemoglobin (Hb) value lesser than the lower limit of normal and it is not explained by state of hydration.[1] It defines the amount of Hb per unit volume of blood which determines the oxygen-carrying capacity of blood. The normal value of Hb for an adult female is 14.0±2.0 gm/dl.[1]

In pregnancy, there is greater increase in plasma volume than the red cell mass (i.e., hemodilution of pregnancy), according to CDC, anemia is defined as Hb concentration lesser than 11 gm/dl in the first and third trimesters, and/or lesser than 10.5 gm/dl in the second trimester.[2]

30% of women of reproductive age are anemic according to worldwide estimation and half of these cases are due to iron deficiency.[3-5] The incidence of anemia is 14-52% without iron supplementation and 25% with supplementation, depending on iron dosage.[5] The incidence of anemia was found to be significantly higher

in black women than in white women, that is 24% and 3%, respectively.[6]

Iron deficiency anemia is the most common cause of nutritional deficiency anemia (McLean et al, 2009; WHO, 2017).[5] During pregnancy, iron deficiency is due to an imbalance between demand and supply, this worsens as pregnancy advances. The prevalence of anemia for low- and middle-income countries is 50% it is due to nutritional deficiency, infections etc. (Balarajan et al, 2011).

If hemoglobin concentration reduces by more than 2% then it is associated with mortality and morbidity.[7]

As there is increased demand for iron this puts the mother and fetus at risk of developing iron-deficiency anemia (IDA). IDA in pregnancy disposes the mother and fetus with an increased risk of preterm birth, low birthweight, fetal growth restriction, and increased perinatal and maternal mortality. They are also predisposed to postpartum IDA, peripartum blood transfusion, infections, and precipitate heart failure.[8] IDA is treated with oral iron supplement, but because of gastrointestinal side effects such as nausea, vomiting, and constipation, there is poor compliance and hence might lead to discontinuation.[7,8] Hence, intravenous iron administration are recommended for women who are non-compliant with oral iron, with severe IDA, also who require rapid intervention.[2,9] Hence iron deficiency anemia should be treated whether they are symptomatic or not.[10]

The present study aimed to compare the efficacies of intravenous ferric carboxymaltose and oral double dose iron in pregnant women diagnosed with IDA.

METHODS

The prospective comparative study was planned with the objective to assess the effectiveness of intravenous ferricarboxymaltose and oral double dose iron in treating anaemia in pregnant women. This study was conducted from January 2019 to June 2020 for a period of 18 months among 100 (50 in each group) pregnant anemic women attending a rural tertiary care centre (PES Medical College, Kuppam, Andhra Pradesh).

Inclusion criteria

All pregnant women with 14 to 34 weeks of gestation with iron deficiency anemia with haemoglobin between 6.5 gm% to 9 gm%.

Exclusion criteria

Haemo-dynamically unstable patient, non-complaint to oral therapy (but not denied of treatment); associated with other complications: multiple pregnancy, cardiac disorders, infections, other forms of anemia; thyroid disorder.

Tools to be used in the study were proforma for data collection, investigations: hemoglobin, peripheral smear, serum ferritin, i.v. injection ferricarboxymaltose 1 gm in 100 ml NS, tablet oral iron (ferrous form of iron contains 100 mg of elemental iron).

RESULTS

Baseline demographics

Age distribution: mean age- oral versus i.v.

Age: Total participants in this study were 100 (50 in each group). Maximum participants were found between the age 21-30 years. This association of age with double dose oral iron and intravenous FCM was found to be statistically non- significant (p=0.762).

Table 1: Association of age with double dose oral iron and intravenous FCM treatment.

Age in years	No. of patients	Percentage
<20	16	16
21-30	77	77
>30	7	7
Age in years	**Iron supplementation**	
	Oral	**I.V.**
Mean	24.8	24.34
SD	4.14	4.1

Unpaired t test; p value- 0.762, non-significant

Body mass index: mean BMI- oral versus i.v.

Body mass index: Total participants in this study were 100 (50 in each group). Maximum participants BMI was between 20-25 kg/m^2. This association of body mass index with double dose oral iron and intravenous FCM was found to be statistically non- significant (p=0.962).

Table 2: Association of body mass index with double dose oral iron and intravenous FCM treatment.

Body mass index	No. of patients	Percentage
<20	16	16
20-25	71	71
>25	13	13
Body mass index	**Iron supplementation**	
	Oral	**I.V.**
Mean	22.59	22.59
SD	2.68	2.65

Chi square test; p value- 0.962, non-significant

Parity: oral versus i.v.

Parity: Total participants in this study was 100 (50 in each group). Of which 48% were primis, 37% were G_2, 13% were G_3 and 2% were G_4. This association of parity with double dose oral iron and intravenous FCM was found to be statistically non-significant (p=0.320).

Table 3: Association of parity with double dose oral iron and intravenous FCM treatment.

Parity	No. of patients	Percentage
Primi	48	48
G_2	37	37
G_3	13	13
G_4	2	2
Parity	**Iron supplementation**	
	Oral	**I.V.**
Primi	20	28
G_1	20	17
G_2	9	4
G_3	1	1

Kruskal Wallis test; p value- 0.320, non-significant

Gestational age: gestational age- oral versus i.v.

Gestational age: Total participants in this study were 100 (50 in each group). Of which 2% were less than 16 weeks of gestation 63% between 16-28 weeks and 35% more than 28 weeks of gestation. This association of gestational age with double dose oral iron and intravenous FCM was found to be statistically non- significant (p=0.359).

Table 4: Association of gestational age with double dose oral iron and intravenous FCM treatment.

Gestational age	No. of patients	Percentage
<16 weeks	2	2
16-28 weeks	63	63
>28 weeks	35	35
Gestational age	**Iron supplementation**	
	Oral	**I.V.**
<16 weeks	2	0
16-28 weeks	31	32
>28 weeks	17	18

Kruskal Wallis test; p value- 0.359, non-significant

Safety and efficacy

Treatment group

Oral iron treatment: 50 participants in this study were given oral double dose iron. The mean rise in Hb after treatment was 10.56 gm. This treatment with oral double dose iron was found to be statistically significant (p=0.001).

Table 5: Efficacy of oral iron treatment.

Treatment group	No. of patients	Percentage
Oral iron	50	50
Iv iron	50	50
Oral iron	**Mean**	**SD**
Before	8.67	0.64
After	10.56	1.31

Paired t test; p value- 0.001, significant

I.V. iron treatment

Intravenous FCM treatment: 50 participants in this study were given intravenous FCM The mean rise in Hb after treatment was 11.12 gm. This treatment with intravenous FCM was found to be statistically significant (p=0.001).

Table 6: Efficacy of i.v. FCM treatment.

I.V. iron	Mean	SD
Mean	8.33	0.69
SD	11.12	1.41

Paired t test; p value- 0.001, significant

Hemoglobin before treatment

Hb before treatment: Total participants in this study were 100 (50 in each group). mean Hb before treatment with oral iron was 8.67 gm and mean Hb before treatment with i.v. FCM was 8.33 gm. This association of Hb before treatment with double dose oral iron and intravenous FCM was found to be statistically non- significant (p=0.104).

Table 7: Association of hemoglobin value before treatment with double dose oral iron and intravenous FCM treatment.

Hb- before treatment	Oral	I.V.
Mean	8.67	8.33
SD	0.64	0.69

Unpaired t test; p value - 0.104, non-significant

Hb after treatment: Total participants in this study were 100 (50 in each group). mean Hb after treatment with oral iron was 10.56 gm and mean Hb before treatment with i.v. FCM was 11.12 gm. This association of Hb after treatment with double dose oral iron and intravenous FCM was found to be statistically non- significant (p=0.092).

Table 8: Association of hemoglobin value after treatment with double dose oral iron and intravenous FCM treatment.

Hb- after treatment	Oral	I.V.
Mean	10.56	11.12
SD	1.31	1.41

Unpaired t test; p value- 0.092, non-significant

Table 9: Association of extra dose requirement with oral double dose iron and i.v. FCM treatment.

Extra dose required	Iron supplementation	
	Oral	**I.V.**
Yes	9	2
No	41	48

Chi square test; p value- 0.001, significant

Extra dose required: Total number of participants in this study were 100 (50 in each group) of which 11 patients

required extra dose. 18% of participants treated with oral iron required extra dose and 1% of the participants treated with i.v. FCM required extra treatment. This association with extra dose requirement with oral double iron was found statistically significant (p=0.001)

Side effects

Side effect: oral versus i.v.

Side effects: Total number of participants in this study were 100 (50 in each group) of which 9 patients experienced side effects such as constipation (2) giddiness (2) and nausea (5). 14% of participants treated with oral iron had these side effects and 1% of the participants treated with i.v. FCM had side effects. This association of side effects with oral double iron was found statistically significant (p=0.018).

Table 10: Association of side effects with treatment with oral double dose iron and i.v. FCM.

Side effect	No. of patients	Percentage
Constipation	2	2
Giddiness	2	2
Nausea	5	5
Nil	91	91
Side effect	**Iron supplementation**	
	Oral	**I.V.**
Present	7	2
Absent	43	48

Mann Whitney test; p value- 0.018, significant

Summary of results

Hemoglobin levels improved at comparable rate across both treatments, however significantly more women achieved anemia correction with ferric carboxymaltose than oral iron (the mean improvement in Hb with oral iron was to 10.36 gm% and that with ferric carboxymaltose was to 11.12 gm%).

Table 11: Study findings.

Outcomes	P values
Treatment with double dose oral iron	Significant
Treatment with i.v. FCM	Significant
Extra dose requirement	Significant
Side effects	Significant
Age	Non-significant
BMI	Non-significant
Parity	Non-significant
Gestational age	Non-significant
HB before treatment	Non-significant
HB after treatment	Non-significant

More women achieved significant improvement in Hb with single dose of ferric carboxymaltose, whereas with oral iron additional dose of iron supplementation was required (the extra dose requirement with oral iron was with 18% of cases whereas with FCM it was with 1% of cases which showed a p value of 0.001 which was significant).

Treatment related adverse reactions were seen more which oral iron treatment than with FCM. With markedly higher rates of gastrointestinal disorders (14% of cases with oral iron therapy experienced adverse reactions whereas with FCM 1% of cases experienced adverse reaction which showed a p value of 0.018 which was significant).

However, the difference with Age, BMI, parity, gestational age, Hb before treatment did not significantly affect the treatments with oral iron or FCM.

DISCUSSION

Our study was a prospective comparative study, and has analysed the effectiveness of intravenous ferricarboxymaltose and oral double dose iron in treating anaemia in pregnant women.

Significant rise in Hb level was found in group treated with IV FCM. The mean improvement in Hb level was to 11.12 gm%,

According to study by Van Wyck et al it was a randomized control study which compared i.v. FCM and oral ferrous ascorbate for treatment of common disorder, postpartum IDA significant rise in Hb was observed in subjects treated with FCM, the mean Hb rise was greater than or equal to 3gm/dl.[11]

According to study by Sied et al a randomised control study to assess the efficacy and safety of i.v. FCM in postpartum IDA it showed a single dose of i.v. FCM showed significant rise of Hb within 1 week of administration.[12]

According to Mishra et al study of intravenous ferric carboxy maltose in iron deficiency anaemia during pregnancy and postpartum period safety and efficacy showed there was a significant improvement in haemoglobin over a period of 3 weeks from mean Hb 8.97gm/dl to 11.34 gm/dl.[13]

According to Breymann et al study a randomised control trial to compare the efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy showed that the group receiving i.v. FCM treatment showed significant rise in Hb within 3 weeks of treatment the mean rise in Hb in this study was 1.23 gm/dl.[15]

According to Shim et al study a randomised controlled study for efficacy and safety of ferric carboxymaltose

versus ferrous sulfate for iron deficiency anemia during pregnancy: subgroup analysis of Korean women showed significant improvement in Hb from baseline to 3 weeks with i.v. FCM group the mean improvement in Hb with FCM was 1.23±0.89 gm/dl.[14]

The rise in Hb was seen in both groups in our study, the mean rise of Hb with i.v. FCM (11.12 gm%) was more than with oral iron group (10.36 gm%) however in our study the rise in Hb level after treatment with both groups was statistically not significant.

This finding was in accordance with study by Shim et al a randomised controlled study for efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy: subgroup analysis of Korean women Hb level increases were comparable between the two treatment groups in Korean women at week 3 (FCM 1.23±0.89 gm/dl versus FS 1.14±1.72 gm/dl) but not statistically significant.

However according to Breymann et al study a randomised control trial to compare the efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy showed Mean changes in Hb for the FCM group were consistently superior to mean changes in Hb for FS (change in Hb at week 3: 1.23±0.95 gm/dl versus 0.96±1.38 gm/dl, respectively), although statistical significance was not reached at week 3, therefore, the primary efficacy endpoint was not met at week 3. However, a statistically significant improvement in mean change in Hb levels from baseline was achieved for FCM versus FS at week 6 (change in Hb: 1.75±1.18 gm/dl versus 1.32±1.54 gm/dl; more increase in Hb with i.v. FCM group (84% versus 70%).[15]

In our study it was observed that FCM group only 1% of the cases required extra dose of treatment whereas in oral iron group 18% of cases required extra dose of treatment which was found statistically significant this showed that significant improvement with Hb was found within 3 weeks of administration with FCM whereas with oral iron the significant improvement was seen only at the end of 6 weeks. This was consistent with studies by, Shim et al a randomised controlled study for efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy: subgroup analysis of Korean women showed (FCM 1.23±0.89 gm/dl versus FS 1.14±1.72 gm/dl).[14]

According to Breymann et al study a randomised control trial to compare the efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy showed which showed change in Hb: 1.75±1.18 gm/dl versus 1.32±1.54 gm/dl; more increase in Hb with i.v. FCM group (84% versus 70%).[15]

The most common side effects with oral iron therapy are gastrointestinal side effects. Total number of participants in this study was 100 (50 in each group) of which 9 patients experienced side effects such as constipation (2) giddiness (2) and nausea (5), in our study 14% of the cases with oral iron treatment experienced GI side effects whereas only 1% of cases treated with i.v. FCM experienced side effects the most common side effect seen with oral iron therapy was nausea and constipation whereas that with FCM was giddiness, thus showing that the main reason for non-compliance with oral iron therapy is due to gastrointestinal side effects.

According to Shim et al study a randomised controlled study for efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy: subgroup analysis of Korean women, the total incidences of treatment-emergent adverse events (TEAEs) were similar in both and were reported in 27 women (60.0%) in the FCM group and 28 women (63.6%) in the FS group. The majority of events were mild, and there were no severe AEs. Overall, common TEAEs in the Korean subgroup included headache (7.9%), dyspepsia (7.9%), and constipation (6.7%); the most common TEAEs according to system organ class were "pregnancy, puerperium and perinatal conditions" in the FCM group [20 events in 16 women (35.6%)] and "gastrointestinal disorders" in the it was observed that 33.33% subjects in the i.v. FCM group gastro intestinal (GI) complications, FS group [27 events in 14 women (31.8%)]. The most common treatment-related adverse events (TRAEs) were headache and dizziness in FCM [experienced by three women (6.7%)] and nausea and diarrhea in FS [in four women (9.1%)]. There were markedly higher rates of gastrointestinal TRAEs reported with FS (19 events) compared with FCM treatment, and two women discontinued treatment with FS because of gastrointestinal TRAEs. No hypophosphatemia TEAEs were reported during this study in pregnant Korean women.

According to Breymann et al study a randomised control trial to compare the efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy, the incidence of TEAEs was similar between the treatment arms: in the FCM group, 60 women (49%) experienced and in the FS group, 50 women (40%) the most common TEAEs with FS group were nausea (6%), headache (5%) and dyspepsia (4%), and the most common TEAEs according to system organ class were "pregnancy, puerperium and perinatal conditions" in the FCM group. Seven women discontinued treatment with FS because of gastrointestinal side effects. No hypophosphatemia TEAEs were reported during this study.[15]

However serious life-threatening events were not reported in any of these studies neither in our study. The main advantage of FCM over oral iron was the short treatment period and ensured compliance and no GI side effects. In our study, FCM showed its clinical utility in anaemia without significant safety concerns.

Though the sample size was scientifically enough for this study, further studies with larger samples can help in better comparison of treatment with oral double dose iron and IV FCM. Another limitation of this study was we did not focus on how maternal quality of life and mother and infant relations were benefitted by correcting anemia during antenatal period.

CONCLUSION

FCM is comparable more effective and better tolerated than oral iron treatment in pregnant women.The main reason for non-compliance with oral iron is gastrointestinal side effects, whereas with i.v. FCM these adverse reactions are lesser, hence FCM can be used as an alternative for pregnant women who lack a response to, are non-compliant with, or are intolerant of oral iron treatment, as well as those who have severe IDA. Rapid correction of anemia was seen with i.v. FCM, thus in late-stage pregnancy, when time to delivery is a limiting step, administration of FCM may be a more appropriate option than oral iron for rapid and effective anemia correction.

Recommendations

FCM can be used as an alternative in treatment of anemia in pregnant women who are non-compliant and require rapid correction of anemia before delivery.

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