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Original Research Article

Evaluation of efficacy of injection ferric carboxymaltose in pregnant women

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ABSTRACT

Background: Iron deficiency anaemia (IDA) continues to be a very common problem in developing countries leading to a spectrum of adverse events in pregnant women. The objective of this study was to determine the efficacy, side effects and tolerance of ferric carboxymaltose as compared to available iron preparations for the prophylaxis and treatment of mild to moderate iron deficiency anaemia during pregnancy.
Methods: One-year clinical study (from June 2017 to May 2018). A total 100 patients were enrolled after matching inclusion and exclusion criteria. The efficacy assessment was performed during 4, 8, and 12 weeks of starting therapy. If the patient is not responding to therapy in either arm as documented by no rise or fall in haemoglobin levels patients may be removed from study for other therapy. Treatment duration up to 12 weeks. Safety and efficacy follow-up visit at 4, 8 and 12 weeks. Institutional ethics committee permission was taken.
Results: On intra-group comparisons there was significant increase in haemoglobin levels at 8 and 12 weeks in oral iron group as compared to day 1 haemoglobin levels while there was significant increase in haemoglobin levels at 4, 8 and 12 weeks in IV iron group as compared to day 1 haemoglobin levels. On intergroup comparisons between oral and IV iron group, there was significant increase in haemoglobin levels at 4, 8 and 12 weeks in IV iron group as compared oral iron group haemoglobin levels.
Conclusions: Intravenous iron therapy with ferric carboxymaltose causes significant improvement in haemoglobin more quickly and more effective in correcting iron deficiency anaemia in pregnancy compared to oral treatment in terms of increase in haemoglobin levels at 4, 8 and 12 weeks. Intravenous ferric carboxymaltose is safe and effective option for pregnant women with iron deficiency anaemia.

Keywords: Injection ferric carboxymaltose, Iron deficiency anaemia

INTRODUCTION

Iron deficiency anaemia (IDA) continues to be a very common problem in developing countries leading to a spectrum of adverse events in pregnant women. Iron deficiency anaemia continues to be the leading single nutrient deficiency in the world, affecting the lives of more than 2 billion people, despite considerable efforts to decrease its prevalence for the past three decades.

Treatment with IV iron in some clinical situations could present some advantages over oral iron, such as faster and higher increases of haemoglobin (Hb) levels and body iron stores.[1-4] For these reasons, modern formulations of IV iron have emerged as a safe and effective alternative for IDA management.[5-8]

FCM is a parenteral iron dextran-free drug and the first of the new agents approved to replenish depleted iron stores rapidly and at high doses. FCM is an iron complex composed of a core of ferric hydroxide stabilized by a shell of carbohydrates. The architecture of the carbohydrate complex of macromolecular ferric hydroxide allows regulated iron delivery to the

reticuloendothelial system cells and subsequent delivery to the iron-binding proteins, ferritin and transferrin with limited risk of release into the serum of significant quantities of ionic iron.[9]

FCM is a stable complex with the advantage that it is non-dextran containing and has very low immunogenic potential and thus not predisposed to a high risk of anaphylactic reactions. Its properties allow large doses (15 mg/kg; maximum 1000 mg/infusion) to be administered in a single, rapid session (15-minute infusion) without the need for a test dose.[10-13]

Intravenous route is generally preferred for administration of parenteral iron. Keeping in mind the above-mentioned facts, it was decided to undertake a study to compare the effects of the two modes of iron administration i.e. oral and intravenous for treatment of anaemia in pregnancy in terms of the effect on the haemoglobin level as well as side effects of the therapy and perinatal outcome.

The objective of this study was to determine the efficacy, side effects and tolerance of ferric carboxymaltose as compared to available iron preparations for the prophylaxis and treatment of mild to moderate iron deficiency anaemia during pregnancy.

METHODS

One-year prospective case control study (from June 2017 to May 2018). This was conducted on total 100 patients who were enrolled after matching inclusion and exclusion criteria. Subjects with anaemia from cause other than iron deficiency, history of hematological disease, history of previous blood transfusions in this pregnancy. Multiple pregnancies were excluded. Institutional ethics committee permission and informed consent was taken. Oral iron-50 pregnant women with gestational age between 28-36 weeks with iron deficiency anaemia (haemoglobin levels between 7 to 11 gm%) who received available oral iron preparations through national programme in hospital. IV iron-50 pregnant with gestational age between 28-36 weeks with iron deficiency anaemia (haemoglobin levels between 7 to 11 gm%) who received inj. ferric carboxymaltose 1000 mg single dose infusion in 250 ml normal saline over 15 mins. The efficacy assessment was performed during 4, 8, and 12 weeks of starting therapy. If the patient is not responding to therapy in either arm as documented by no rise or fall in haemoglobin levels patient may be removed from study for other therapy. Treatment duration up to 12 weeks. Safety and efficacy follow-up visit 4, 8 and 12 weeks.

Statistical analysis

All the collected data was entered in Microsoft excel sheet and then transferred to SPSS software ver. 17 for analysis. Qualitative data was presented as frequency and percentages and analysed using chi-square test. Quantitative data was presented as mean and SD and compared by t-test. p-value <0.05 was taken as level of significance.

RESULTS

The most common age group amongst study population was 21 to 25 years (52 %) followed by 26 to 39 years (35%) and less than 20 years (13%). The mean age of the study population was 23.48±3.34 years.

Most of the study population had gestational 33 to 36 weeks (47%) followed by 31 to 32 weeks (45%) and 28 to 30 weeks (8%).

Most of the study population were primigravida (63%) and multigravida were (37%).

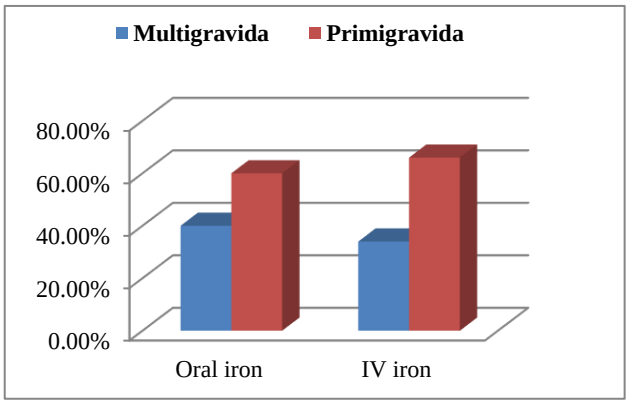

Figure 1: comparison between parity versus study groups.

In oral iron group 40% cases(n=20) were multigravida and 60% (n=30) were Primigravida while in the IV iron group, 34% cases (n=17) were multigravida and 66% (n=33) were primigravida and this difference was statistically insignificant (Figure 1).

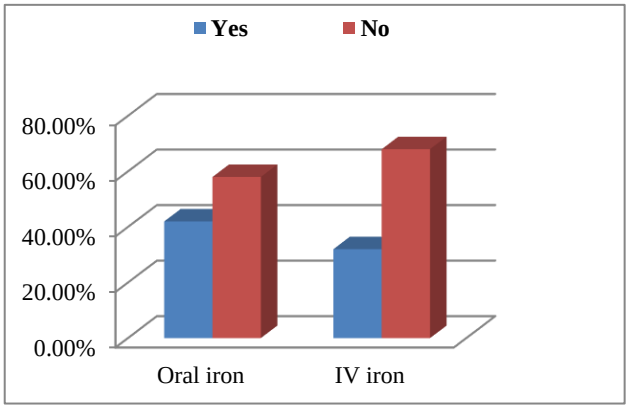

Figure 2: Comparison of previous H/O iron supplementation amongst different study population.

In oral iron group 16% cases (n=8) belonged to age group of less than 20 years, 54% cases (n=27) belonged to age

group of 21 to 25 years and 30% cases (n=15) belonged to age group of 26 to 39 years while in the IV iron group, 10% cases (n=5) belonged to age group of less than 20 years, 50% cases (n=25) belonged to age group of 21 to 25 years and 40% cases (n=20) belonged to age group of 26 to 39 years and this difference was statistically insignificant (Figure 2).

In oral iron group 42% cases (n=21) had previous H/O iron supplementation while in the IV iron group, 32% cases (n=16) had previous H/ O iron supplementation and this difference was statistically insignificant.

Side effects like nausea, vomiting, constipation, fever, dizziness and no complications was observed in 14% cases (n=7), 8% cases (n=4), 12% cases (n=6), 0% cases (n=0), 0% cases (n=0), 66% cases (n=33) respectively in oral iron group while it was observed in 0 % cases (n=0), 0% cases (n=0), 0% cases (n=0), 2% cases (n=1), 6% cases (n=3), 92% cases (n=46) respectively in IV iron group. There was statistically significant difference between side effects and different study population (p value <0.05) (Figure 3).

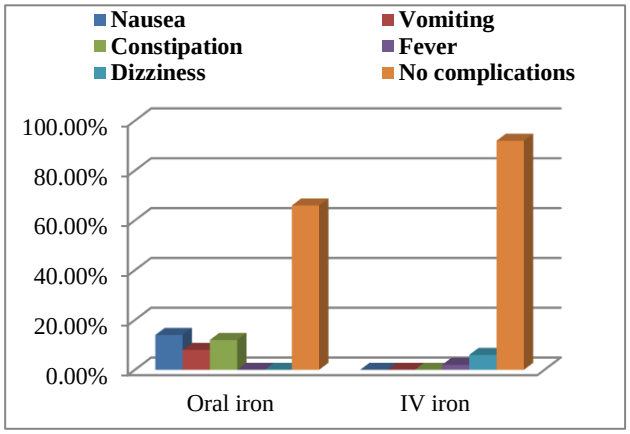

Figure 3: Comparison between side effects versus study group.

Table 1: Comparison of haemoglobin at various time interval amongst different study population.

Haemoglobin	Groups		p value
	Oral iron	IV iron	
Day 1	7.32±0.55	7.47±0.6	0.177
4 weeks	7.39±0.63	9.56±0.52	0.0001
	0.52	0.0001	
8 weeks	8.12±0.7	10.23±1.1	0.0001
	0.0001	0.0001	
12 weeks	9.42±0.9	12.13±1.1	0.0001
	0.0001	0.0001	

On intragroup comparisons there was significant increase in haemoglobin levels at 8 and 12 weeks in oral iron group as compared to day 1 haemoglobin levels while there was significant increase in haemoglobin levels at 4, 8 and 12 weeks in IV iron group as compared to day 1 haemoglobin levels (Table 1).

On intergroup comparisons between oral and IV iron group, there was significant higher increase in haemoglobin levels at 4, 8 and 12 weeks in IV iron group as compared oral iron group haemoglobin levels.

DISCUSSION

Anaemia is usually characterized according to levels of haemoglobin, which can differ most notably in age, gender and ethnicity depending on several factors. Any level below 13 g/dL is considered abnormal for males, and below 12 g/dL for females. Haemoglobin concentrations of less than 11 g/dL are considered abnormal at any time during pregnancy. When anaemia is known, authors will consider the risk of iron deficiency. Abnormalities in red blood cell indices on a complete blood count usually precede lower haemoglobin levels in development. Iron deficiency typically progresses gradually, and may not be symptomatic or clinically evident. Upon total exhaustion of iron reserves, iron accessibility to the tissues declines leading to symptomatic anaemia.

Increased postpartum haemorrhage levels in recent years, mainly due to atonic postpartum haemorrhage and elevated levels of serious postpartum haemorrhage that needs blood transfusion, hysterectomy, uterine suturing, or pelvic artery ligation / embolization.[14]

Age group

In the present study, the most common age group amongst study population was 21 to 25 years (52%) followed by 26 to 39 years (35%) and less than 20 years (13%). The mean age of the study population was 23.48±3.34 years. The mean age of the patients in the oral Iron group is 25.5 years and that in the ferric carboxymaltose group is 26.23 years. These findings are in agreement with the study conducted by Damineni et al, the mean age of the patients in the oral iron group is 27.4 years and that in the ferric carboxymaltose group was 28.044 years.

Similarly, in the study conducted by Verma S et al, in which most of the study population belongs to age group of 21 to 25 years (68%) followed by 25 to 30 years. (22.7%), more than 35 years (6%) and less than 20 years (3.3%).

Gestational age

In the present study, it was observed that most of the study population had gestational 33 to 36 weeks (47%) followed by 31 to 32 weeks (45%) and 28 to 30 weeks (8%). Haniff J et al, observed that the prevalence of anaemia increased with increasing gestational age, being

12% in the first, 32% in the second and 43% in the third trimester.[15]

Parity status

In the present study, it was observed that most of the study population were primigravida (63%) followed by and multigravida (37%). In oral iron group 44% cases (n=22) were multigravida and 56% (n=28) were primigravida while in the IV iron group, 42% cases (n=21) were multigravida and 58% (n=29) were primigravida and this difference was statistically insignificant. These findings are in agreement with the study conducted by Damineni et al, in which 57% of cases were primigravida and 43% of cases were multigravida in ferric carboxymaltose group while in 46% were primigravida and 54% of cases were multigravida in oral iron group. Similarly, in the study conducted by Choudhary K et al, observed that primiparous women comprised the maximum number of patients in both of the groups.

Side effects

In the present study, side effects like nausea, vomiting, constipation, fever, dizziness and no complications was observed in 12% cases (n=6), 8% cases (n=4), 10% cases (n=5), 0% cases (n=0), 0% cases (n=0), 70% cases (n=35) respectively in oral iron group while it was observed in 0% cases (n=0), 0% cases (n=0), 0% cases (n=0), 2% cases (n=1), 4% cases (n=2), 94% cases (n=47) respectively in IV iron group and this difference was statistically insignificant. This finding is in agreement with the study conducted by Damineni et al, in which no adverse reactions were seen in patients who received ferric carboxymaltose group. Seventeen patients (p-value <0.001) in oral iron group had GI complications accounting for 33.33%. Of these 3 patients reported constipation, two patients had epigastric pain and eight patients had nausea. Two patients reported both constipation and epigastric pain.

Similarly, in the study conducted by Singh K et al, in which intravenous iron is better tolerated compared to oral iron. Participants on oral iron therapy reported adverse events like gastric upset, constipation, and taste perversion. Compared with other studies there were also no reports of any adverse reactions with intravenous iron dextran, whereas there were a considerable proportion of women on oral iron therapy who reported side effects.[16]

Haemoglobin levels

In the present study, on intragroup comparisons there was significant increase in haemoglobin levels at 8 week and 12 weeks in oral iron group as compared to day 1 haemoglobin levels while there was significant increase in haemoglobin levels at 4,8 and 12 weeks in IV iron group as compared to day 1 haemoglobin levels. (7.32±0.55 to 9.42±0.9 in oral iron) versus (7.47±0.6 to 12.13±1.1 in IV iron group).

On intergroup comparisons between oral and IV iron group, there was significant higher increase in haemoglobin levels at 4, 8 and 12 weeks in IV iron group as compared oral iron group haemoglobin levels.

This result is in line with the Damineni et al. research, in which mean haemoglobin was statistically insignificant at the start of treatment in both groups. Mean haemoglobin in the oral iron group after 1 week of starting care was 10.04 g/dl while in the ferric carboxymaltose group it was 10.688 g/dl (p-value <0.001 i.e., high significance). Mean haemoglobin in the oral iron group after 6 weeks of treatment was 11.156 g/dl while in the ferric carboxymaltose group it was 11.938 g/dl (p-value <0.001).

This was in line with the study conducted by Deeba S et al, in which changes in haemoglobin were observed in each group from baseline to 6 weeks, but the increase in haemoglobin in the intravenous iron sucrose group was greater than the oral ferrous ascorbate group at each point of measurement (p=0.0001).[17] The difference in haemoglobin values from baseline in the intravenous group was 1.72±0.484 at 2 weeks, 2.18±0.865 at 4 weeks, 2.89±0.5989 at 6 weeks compared to oral iron, which is 0.57±0.45 at 2 weeks, 1.39±0.44 at 4 weeks, and 1.9±0.3020 at 6 weeks. The p value was 0.000 which was clinically important and indicated that the levels of haemoglobin in the intravenous community had risen further.

Similarly findings was observed in the study conducted by Al Momen et al, in their study intravenous iron sucrose complex group achieved significantly higher haemoglobin levels 128.5±6.6 versus 111.4±12.4 g/l in the oral iron group (p value-0.001) in a shorter period 6.9±1.8 versus 14.9±3.1 weeks in control group (p value-0.001).[18]

Goodnough LT et al, also reported that approximately 82% of the IV iron arm had increased haemoglobin ≥20 g/L compared to 62% in oral iron p<0.001. Women who achieved an increase in haemoglobin ≥30 g/L were 53% in the IV iron group compared to 36% in the oral iron group (p<0.001). In addition, more women (73%) achieved normal haemoglobin >120 g/L in the IV iron group compared to 50% in the oral iron group (p<0.001).[19] Another study shows that the change in haemoglobin from baseline was significantly higher in the intravenous group than the oral group at each measurement taken at 14th and 28th day; the changes with respect to subsequent haemoglobin were significantly higher on the 14th (p=0.004) and 28th (p=0.031) days.[20]

These observations could be explained with the fact that iron disappearance from serum depends on the need for iron in the iron stores and iron utilizing tissues of the

body. In gastric mucosa, curtain mechanism is working at cellular level which limits iron absorption from gut. Serum clearance of iron is expected to be more rapid in more iron deficient patients compared to less iron-deficient patients or healthy individuals.

CONCLUSION

Intravenous and oral treatments are effective in correcting iron deficiency anaemia of pregnancy. Side effects are seen in both groups but nothing which is major and life threatening. Intravenous iron therapy with ferric carboxymaltose causes significant improvement in haemoglobin more quickly than oral iron and is more effective in correcting iron deficiency anaemia in pregnancy compared to oral treatment in terms of increase in haemoglobin levels at 4, 8 and 12 weeks. Intravenous ferric carboxymaltose is safe and effective option for pregnant women with iron deficiency anaemia.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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