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Original Research Article

Intravenous ferric carboxymaltose versus iron sucrose in iron deficiency anemia of pregnancy

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ABSTRACT

Introduction: Iron deficiency is the most common nutritional deficiency worldwide. Anemia, defined by the World Health Organization as hemoglobin < 11 g/dl, is frequently seen in the antenatal period and affects 4-48% of women who give birth and severe anemia, with hemoglobin levels <9 g/dl .This study is to evaluate the efficacy and safety of intravenous Ferric Carboxymaltose. (FCM) in comparison with intravenous Iron sucrose complex (ISC) for treatment of iron deficiency anemia in pregnancy.

Materials and Methods: A comparative, interventional, prospective study was carried out in 100 antenatal patients with Anemia (hemoglobin level between 5 to 9.5 gm/dl) in the department of obstetrics and gynecology, Government Medical College, Baroda, Gujarat, India from September 2017 to August 2018. The subjects were randomized in two groups. First group receiving 1000 mg of intravenous iron sucrose divided in five doses on alternate days (200 mg each) and Second group receiving 1000 mg of intravenous ferric carboxymaltose.

Results: Maximum number of patients in our study were belonged to low socioeconomic group, significantly higher number of women achieved rise of hemoglobin >2gm/dl in FCM group, which was highly significant (p value <0.001). Mean rise of hemoglobin was 1.9 g/dl for FCM group and 1.66gm/dl for iron sucrose group, which was also significant. Serum ferritin level in ferric carboxymaltose group was rises more as compared to iron sucrose group. Unpaired‘t’ test was used to test the significance of rise and compare the rise between two groups.

Conclusions: Ferric carboxymaltose is an efficient and better alternative to Iron Sucrose in treating iron deficiency anemia of pregnancy. It has an added advantage of single dose regime with lower side effects.

1. Introduction

Iron deficiency is the most common nutritional deficiency worldwide; it affects 1.6 billion people (nearly a quarter of the world’s population) (World Health Organization, 2008).[1] Iron deficiency (ID) and iron deficiency anemia (IDA) are often encountered in the general population, particularly among children and women with abnormal uterine bleeding (AUB) (Morrison J et al., 2008)[2] and during pregnancy as well as postpartum period (Van Wyck DB et al., 2007).[3]

Since iron is the functional component of hemoglobin and is also an essential constituent in a large number of enzymes important for all major metabolic pathways[4] reduced iron levels limit energy production. Common symptoms that may result from ID are fatigue[5] exhaustion[6] susceptibility to stress and underperformance.[6–8]

ID is also associated with decreased mental and cognitive performance, lack of concentration, and increased susceptibility to infections.[8]

In order to make a parenteral iron formulation bioavailable, it has to contain iron (III) oxyhydroxide

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complexed with another protein or carbohydrate molecule. This prevents release of free iron from the molecule that can cause oxidative damage to body tissues. This iron complex can act like ferritin, the physiological carrier for iron in our body which also contains iron (III) hydroxide at the core of Apo ferritin molecule. Such iron complexes can deliver iron to physiological transport system at neutral pH (Qunibi WY, 2010).[9]

As a Type I complex, FCM delivers iron gradually and mainly to the RES of the liver. This targeted and slow release accounts for the low toxicity of FCM and the large safety margin between normal and lethal dosing (66 times the maximum weekly dose recommended for clinical use artd 5 times greater than the lethal dose for iron sucrose).

Because of these factors and because of the neutral pH and physiological osmolarity of the FCM formulation, high doses can be administered with good local tolerance.

Providing the iron dose is calculated according to the needs of each patient, toxicity is very unlikely to occur during clinical use of FCM.

As FCM does not contain dextran or its derivative unlike iron dextran, ferumoxytol and iron isomaltoside 1000, it is not likely to cause dextran-induced anaphylactic reactions.

Together with its very low potential for immunogenicity, results in an excellent safety profile and convenience for both patients and medical professionals. The ability to give large doses in a single session will also enhance the cost-effectiveness of iron replacement therapy.

2. Materials and Methods

The study was a prospective comparative interventional analytical study. Study period was 1 year and carried out in the department of obstetrics and Gynecology at SSG Hospital, Baroda from September 2017 to August 2018.

2.1. Study population

Purposively study participants were classified in 2 groups using Epi info software. Each group was of 50 pregnant woman with gestational age between 28-32 weeks diagnosed with iron deficiency anemia with hemoglobin between 5-9.5 g%.

2.2. Sample size

The study comprised of 100 cases which are to be randomly distributed into two groups consisting of 50 cases each.

Group - A: 50 cases in this group receive intravenous iron sucrose therapy.

Group - B: 50 cases in this group receive intravenous iron carboxymaltose therapy

Eligibility criteria

2.3. Inclusion criteria

100 pregnant women of 28-32 weeks gestation with hemoglobin 5-9.5 gm% with iron deficiency anemia of pregnancy.

2.4. Exclusion criteria

Anemia not caused by iron deficiency
Known hypersensitivity to FCM or IRON SUCROSE
Sickle cell disease
Not consenting

1. Calculation of total iron requirement Iron deficit was
2. Calculated by the formula:
3. Total iron dose required (mg) = 2.4 × Body weight (kg)
4. (Target hemoglobin- Actual hemoglobin in g/dl) + 500 mg.
5. Group A: Intravenous injections (iron sucrose complex) Iron sucrose complex was given as 200 mg elemental Iron (2 ampules of 5 ml) in 100 ml of 0.9% normal saline and infused over 30 min. every alternate days up to 5dose.
6. Group B: Intravenous injections (Iron carboxymaltose complex)

On enrollment, a detailed clinical history (menstrual, obstetric), previous treatment history including iron therapy, compliance with oral iron and chronic medical illness was taken. Detailed examination including anthropometry, general physical examination and obstetric examination was done. Routine antenatal investigations were done according to the standard departmental protocol. Investigations specific to anemia included hemogram, reticulocyte count and peripheral blood smear, red cell indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), hemoglobin electrophoresis, serum ferritin levels, serum iron, total iron binding capacity (TIBC) and transferrin saturation were done. After calculating total iron deficit, patients in the FCM group were administered i.v. FCM (Inj Orofer FCM, Emcure Pharmaceuticals Ltd., Pune, India). Maximal dose per sitting was 1000 mg which was diluted in 200 ml 0.9% normal saline and administered as an IV infusion over 30 min (Due to the limited availability of safety data for its use in pregnancy, a longer infusion protocol (30 min) than recommended by the manufacturer (15 min) was used). Patients in ISC group were administered IV ISC as 200 mg (Inj Orofer S, Emcure Pharmaceuticals Ltd., Pune, India) in 200 ml NS over 15-20 min twice weekly till dosage was completed, not to exceed 600 mg per week. The general condition of the patient, blood pressure and pulse rate were noted before infusion and every five minutes during infusion and fetal heart rate monitoring was done before and after

infusion.

All women were given 5 mg Folic acid once daily. Any minor or major adverse effects were noted. All patients were followed up after 4weeks and 90 days of initiation of treatment. Hemoglobin, RBC indices and serum iron studies were done after 90 days. Patients reported minor or major adverse events at follow-up visits. Primary outcome was change in hemoglobin level from baseline after 90 days. Secondary outcomes were change in ferritin levels, improvement in serum iron studies and RBC indices, safety and side effects of treatment and perinatal outcome.

From an earlier study by Christophe et al. (2012) where the final Hb after administering iron sucrose hemoglobin increased from 95.6 g/L to 110.4 g/L with a standard deviation of 11.9, taking non-inferiority limit difference in mean of hemoglobin between the two groups as 10 g/L, and the expected mean difference as zero, and standard deviation as 11.9, alpha error 5% and power of the study as 90%, the estimated sample size was 24 per group. Considering 10% loss to follow up, a mini- mum of 27 iron-deficient pregnant anemic women needed to be included in each group in the study; hence 50 patients were included in each group.

Data were presented as number (%) or mean ± SD/median (min-max) as appropriate. Baseline categorical variables were compared between the groups using Chi-square/Fisher's exact test and continuous variables were compared using Student's t-test.

The p value less than 0.05 was considered statistically significant.

3. Results

The mean hemoglobin of the patients in Ferric carboxymaltose group was 10.68± 0.76 gm%. The mean hemoglobin of the patients in Iron sucrose group was 9.83± 0.74 g % there was statistically significant difference in the distribution of hemoglobin between two groups was seen in the study. (P<0.05) (Table 2)

The mean serum ferritin of the patients in Ferric carboxymaltose group was 97.27 ±22.06 (mg/L). The mean serum ferritin of the patients in Iron sucrose group was 22.65 ±3.71 (mg/L)There was statistically significant difference in the distribution of serum ferritin between two groups was seen in the study. (P<0.05)(Table 3)

4. Discussion

Present study showed that iron sucrose complex as well as ferric carboxymaltose can be used in the pregnant patients with iron deficiency anemia of pregnancy not only for correction of deficit in the hemoglobin but also for restitution of iron stores. Both modalities had increase in the hemoglobin level after 4 weeks and after 90 days which is homologous with previous studies.[10–14] But increment in the hemoglobin was slightly more in the patients treated

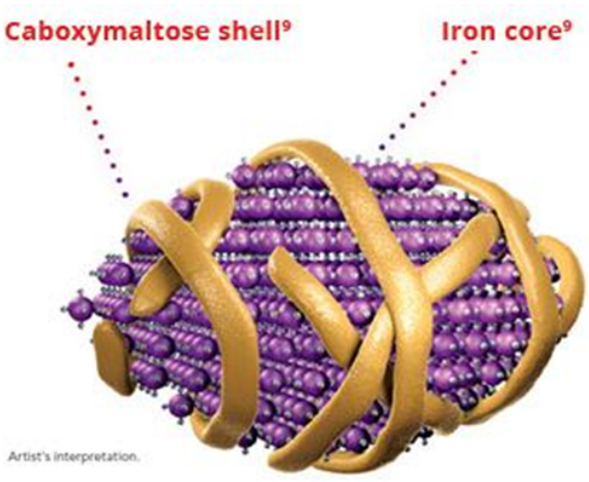

Fig. 1: Ferric carboxymaltose (FCM) showing the iron oxyhydroxide core contained in the carbohydrate shell (Source: Geisser P, 2009)

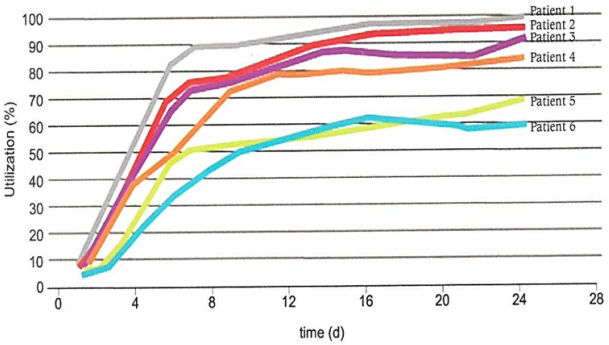

Fig. 2: Red cell utilization of 52Fe/59 Fe labeled ferric carboxymaltose following a single IV administration in patients with iron deficiency, renal anemia or functional iron deficiency (Source: Geisser P, 2009).

with FCM as compared to iron sucrose. Serum ferritin level was also increased in both treatment modalities but was more in patient treated with FCM. Registered adverse events were all mild and quickly reversible and mostly restricted to local reaction at the infusion site. There were no treatment related serious adverse events. No anaphylactic reaction was detected. No venous thrombosis was registered. None of the adverse events required further medical intervention.

In addition to hematological effectiveness, a number of additional benefits of FCM over Iron sucrose were demonstrated in my study.

FCM had a dramatically reduced burden of treatment: comparable improvements in Hemoglobin levels were achieved with a 12-fold lower total dose and a 12-fold lower duration of exposure to FCM compared with Iron sucrose.

Outside the 'compliance friendly' environment of a clinical trial, a high burden of treatment can result in low

Table 1: Distribution of anemia

Hemoglobin (gm/dl)	Degree of Anemia	IV Iron Sucrose	IV Ferric Car boxy Maltose (FCM)	Total	P value
<6	Severe	0	5(1%)	5	
6-7	Moderate	31(62%)	16(32%)	47	0.743
8-9.5	Mild	19(38%)	29(58%)	48	
Total		50	50	100	

Table 2: Comparison mean values of hemoglobin between IV ferric carboxy maltose (FCM) vs IV iron sucrose

Hemoglobin mean values (gm/dl)	IV Ferric Car boxy Maltose (FCM)	IV Iron Sucrose	P value
Before treatment	7.87	7.76	
Four weeks after treatment	9.63	9.45	0.893
90 days after treatment	10.68	9.83	<0.001

Table 3: Comparison of mean values of serum ferritin between the two groups

Ferritin (mg/l) mean values	Patient of IV Ferric Car boxy Maltose (FCM) (n=50)	Patient of IV Iron Sucrose (n=50)	P value
Before treatment	20.19	19.28	0.838
90 days after treatment	97.27	22.65	<0.001

Table 4: Adverse reaction in both treatment modalities

ADRs	Participants given iron sucrose (n=50)	Participants ferric carboxy maltose (n=50)	Total (n=100)
Pain/burning at injection site	9	4	13
Swelling at injection site	4	2	6
Blackening at injection site	0	0	0
Nausea/vomiting	4	0	4
Gastritis	1	2	3
Giddiness/hypotension	2	0	2
Other	0	0	0
Total	20 (40%)	8 (16%)	28 (28%)

compliance of patients with their medication, subsequently leading to worsening of disease and ultimately increased health care cost.

For some patients, a single dose of FCM may correct IDA with no repeated administration required, thereby providing more convenient option than Iron sucrose.

The first study on the use of FCM for treatment IDA in pregnancy was published by Christoph P et al.[15] the study concluded comparable safety and tolerability of FCM to ISC and that FCM offers the advantage of much higher iron dosage at a time reducing the need for repeated application and increasing patient's comfort. The authors documented a comparable rise in hemoglobin levels at the end of study. The current study in contrast showed significantly higher hemoglobin levels in FCM group as compared to ISC after 90 days (TABLE 2) Breymann C et al. compared FCM with oral iron therapy for treatment of IDA in pregnancy. Hb levels improved at comparable rates in both groups. Patients in FCM group had significantly more women who achieved hemoglobin>110gm/dl and within short time.[14] (Table 2)

Body iron stores are largely determined by serum ferritin levels. Froessler et al. have documented significantly increased ferritin levels after FCM infusion in patients with anemia and in women with iron deficiency and no anemia.[12] In the present study, serum ferritin levels were comparable in two groups at baseline and at the end of study after 12 weeks. It can be inferred that though FCM causes a rapid rise in iron stores, over a long term ISC is equally able to give comparable supple- mentation for replenishment of iron stores.

Limitation of our study were there was small sample size in both treatment and control group. Some confounding variables were also not taken in to consideration. Large sampled trials are required to compare safety and efficacy of intravenous ferric carboxymaltose over iron sucrose therapy in Indian set up.

5. Conclusion

Data from this prospective study is consistent with existing retrospective data that Intravenous ferric carboxymaltose

administration increases the hemoglobin level more rapidly as compared to iron sucrose in women with iron deficiency anemia in the pregnancy. It also stores iron more rapidly. No serious adverse effects were recorded. Ferric carboxymaltose is well tolerated, safe and effective alternative to iron sucrose in iron deficiency anemia of pregnancy. FCM has the advantage of a large dose administration per sitting, early rise in hemoglobin level, lesser total number of required doses (convenient dosing), hence lesser number of hospital visits and total cost involved in transportation, equipment required for infusion and the discomfort caused to the patient due to multiple needle pricks.

6. Abbreviations

FCM: Ferric carboxymaltose; IDA: Iron deficiency anemia; ISC: Iron sucrose complex; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume

7. Source of Funding

FCM and iron sucrose by Emcure Pharmaceutical, Pune, India

8. Conflict of Interest

The author declared no conflict of interest. The author has no financial conflict of interest to declare.

9. Ethical approval

All procedures followed were in accordance with the Institutional Ethics Committee for Human Research (IECHR), Medical College & SSG hospital, Baroda.

Informed consent: Informed consent was taken from all patients for being included in the study.

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