ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Randomized clinical trial of IV iron sucrose and IV ferric carboxymaltose in the treatment of moderate iron deficiency anaemia in pregnancy

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Article History:

Received on: 08 Apr 2020
Revised on: 10 May 2020
Accepted on: 12 May 2020

Keywords:

Iron Sucrose,
Ferric Carboxymaltose,
Iron Deficiency,
Anaemia,
Pregnancy

ABSTRACT

In India, the national nutritional anaemia control programme (NNACP) was started in 1970 and is being implemented through primary health centers and sub centers. It recommended pregnant women to take one iron tablet per day for at least 100 days (each tablet containing 100 mg of natural iron and 500 mcg of folic acid) after first trimester of pregnancy; a similar dose applies to lactating women. Study Design: Randomized clinical trial. 160 pregnant ladies going to antenatal clinic at 14-36 weeks of gestation with Hb 7- 9.9g%. Who met the inclusion criteria were arbitrarily distributed into two groups. One with odd registration number was given iron sucrose and one with even was given FCM. Hematological profile includes Haemoglobin, Reticulocyte count, Blood indices (MCH, MCHC, MCV) Fringe smear, Serum iron and Serum TIBC. 52% cases from FCM group observed in the age gathering of 21-24 years and 39% cases from Iron Sucrose group were observed in the age gathering of 25-28 years. 54% cases from FCM and 46% cases from Iron sucrose were observed in the gestational Age of 29 to 36 weeks. 43% cases from FCM and 46% cases from Iron sucrose were primigravida. Patients from FCM group and 4 patients from Iron sucrose group did not follow up. 2 pts. From FCM group and 1 pt. from Iron sucrose group refused treatment. The rise in mean Hb level after 1 week and 4 weeks of treatment with FCM is more than Iron sucrose. The rise in mean Sr. Iron level after 1 week and after 4 weeks of treatment with FCM is more than Iron sucrose. The reduction in mean Sr. TIBC level after 4 weeks of treatment with Iron sucrose is more than FCM. The rise in mean MCH, MCHC and MCV levels after 1 week and 4 weeks of treatment with FCM is more than Iron sucrose. There was no serious adverse effect noted in both groups.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i3.2796

Production and Hosted by

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INTRODUCTION

Anaemia is most common haematological abnormality diagnosed during pregnancy. As per WHO, anaemia during pregnancy is characterized as haemoglobin concentration of less than 11gm% and hematocrit less than 33%. Anaemia is one of major contributing factors in maternal mortality and morbidity in third world countries and according to the WHO, contributes to 20% maternal deaths (Kharde *et al.*, 2012). Anaemia is widely prevalent in developing countries like India. Most

common affected group is women of child bearing age particularly pregnant women. The main cause of iron deficiency in pregnancy is found to be iron deficiency (Dhanani *et al.*, 2012). Studies have shown that low Hb during pregnancy is related with expanded danger of low birth weight and preterm birth and the incidence of which increases as severity of anaemia increases (Gopalan, 1989; Goonewardene *et al.*, 2012).

In India, the national nutritional anaemia control programme (NNACP) was started in 1970 and is being implemented through primary health centres and sub centres. It recommended pregnant women to take one iron tablet per day for at least 100 days (each tablet containing 100 mg of natural iron and 500 mcg of folic acid) after first trimester of pregnancy; a similar dose applies to lactating women. Despite the vigorous efforts of NNACP, iron deficiency anaemia (IDA) is still widely prevalent in pregnant women (Kumar, 1999).

The different elements required for erythropoiesis are proteins (erythropoietin), minerals (iron), follow components (counting zinc, cobalt and copper), nutrients (especially folic corrosive, nutrient B12 [cyanocobalamin], nutrient C, pyridoxine; and riboflavin), and hormones (androgens and thyroxine). Notwithstanding the regular lacks of iron and folate, there is a developing assemblage of proof to ensnare nutrient A (significant for cell development and separation support of epithelial honesty and typical insusceptible capacity) and Zn (significant in protein amalgamation and nucleic corrosive digestion) in wholesome anemias (Sharma *et al.*, 2003; Ross and Gardner, 1994).

About 1000 mg of iron is required during pregnancy (Milman *et al.*, 1999). 500-600 mg for RBC extension. 300 mg for baby and placenta and the rest for the developing uterus. Because of amenorrhea there is a sparing of around 150 mg of iron and consequently, around 850 mg of additional iron is required during pregnancy. Diet alone can't give the additional iron and stores which have around 500 mg of iron get drained.

In any case, if iron stores are as of now inadequate, iron lack paleness shows. Iron insufficiency sickliness (IDA) is the commonest kind of anaemia in pregnancy (Centers for Disease Control, 1989). The equalization of iron digestion in solid people overwhelmingly reflects three factors: healthful admission, iron misfortune, and current interest. The nourishing iron admission identifies with the measure of processed iron in nourishment and the capacity to assimilate iron from the stomach related tract (Zimmermann and Hurrell, 2007).

The proportion of iron expended depends, all things considered, upon the proximity or nonattendance of pathology of the gastrointestinal tract or a comorbidity, (for instance, relentless provocative diseases) that may realize verbalization of the iron managerial proteins and a peptide called hepcidin, which in the long run squares iron maintenance (Valore and Ganz, 2008; Meyron-Holtz *et al.*, 2011; Galy *et al.*, 2010).

The step by step essential of external iron remains as small as between 1 to 8mg step by step. Be that as it may, progressively outside iron is required to adjust expanded interest for iron particularly with physiological necessities during development, pregnancy, and lactation (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 2001; Trumbo *et al.*, 2001). This critical expanded interest for iron is required to build up the baby and placenta notwithstanding bolster mother's blood volume. Furthermore, pregnant women are subject to iron loss during and after delivery (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 2001; Russell *et al.*, 2001).

MATERIALS AND METHODS

Study Design - Randomized clinical trial

Sample size - 160 pregnant ladies going to antenatal clinic at 14-36 weeks of gestation with Hb 7- 9.9g%. 160 patients who met the inclusion criteria were arbitrarily distributed into two groups. One with odd registration number was given iron sucrose and one with even was given FCM.

Inclusion criteria

Pregnant women with gestational age between 14 weeks to 36 weeks.

1. Heamoglobin level between 7 g%- 9.9 g% with iron deficiency anaemia. Patient intolerant to oral iron.
2. Patient not responding to oral iron(i.e. No rise in Hbi.e>2gm% in 4 weeks) Patients not compliant to oral iron.

Exclusion criteria

1. Pregnant women who received Blood transfusion.
2. Anaemia not caused by iron deficiency.
3. Known hypersensitivity to FCM or other IV iron preparations.
4. Patients with Mild and severe anaemia

Table 1: Age wise distribution of cases in

Age in years	FCM (n=80) No. (%)	Iron Sucrose (n=80) No. (%)
<20	9(11.25%)	8(10%)
21-24	42(52.5%)	30(37.5%)
25-29	22(27.5%)	31(3875%)
29-32	5(6.25%)	9(11.25%)
>32	2(2.5%)	2(2.5%)
Total	80(100%)	80(100%)
Mean ± SD	23.85years ±9.36	24.75years ± 8.97

The above Table 1 52% cases from FCM group observed in the age gathering of 21-24 years and 39% cases from Iron Sucrose group were observed in the age gathering of 25-28 years.

Table 2: Gestational age wise distribution of cases

Gestational Age (in weeks)	FCM (n=80) No. (%)	Iron Sucrose (n=80) No. (%)
14-21	9	11
22-28	28	32
29-36	43	37
Total	80	80
Mean ± SD	28.19 ± 8.67	27.43 ± 8.54

Table 2 found that 43% cases from FCM and 37% cases from Iron sucrose were observed in the gestational Age of 29 to 36 weeks.

Table 3: Gravida wise distribution of cases

	FCM(n=80) No. (%)	Iron Sucrose(n=80) No. (%)
Gravida 1	34	37
Gravida 2	29	28
Gravida 3	14	11
Gravida>3	3	4
Total	80	80

Table 3 shows the majority v43% cases from FCM and 46% cases from Iron sucrose were primigravida

Table 4: Non-compliance of patients in both the groups

	FCM No. (%)	Iron Sucrose No. (%)
Lost follow up	3	4
Refused treatment	2	1

3 patients from FCM group and 4 patients from Iron sucrose group did not follow up. 2 pts. from FCM group and 1 pt. from Iron sucrose group refused treatment.

Table 5: Comparison of mean values of Hb from before treatment, after 1 week treatment and after 4 weeks treatment

Groups	Before treatment	After 1 week treatment	After 4 weeks treatment	Mean difference after 1 week	Mean difference after 4 weeks
			Mean ± SD		
FCM	7.80±0.58	8.86+±0.61	10.15±0.61	1.06±0.21	2.35±0.35
Iron Sucrose	7.89±0.55	8.84±0.59	9.88±0.44	0.95±0.41	1.99±0.32

The above Table 5 shows that the rise in mean Hb level after 1 wk and 4 wks of treatment with FCM is more than Iron sucrose. The rise in mean Sr. Iron level after 1 wk and after 4 wks of treatment with FCM is more than Iron sucrose.

Hematological profile includes Haemoglobin, Reticulocyte count, Blood indices(MCH, MCHC,MCV) Fringe smear, Serum iron and Serum TIBC. Test dose after calculating iron requirement was given. Calculation of the iron dose (in mg) = body weight in kg x (target Hb- actual Hb g/dl)x 2.4+500. where 500 is to replenish iron stores. 25 One group was given IV ferric carboxymaltose 1000 mg in 200 ml of normal saline over 15 minutes. The other group was given IV iron sucrose 200mg in 200 ml of normal saline over 15 minutes in multiple doses on alternate day. Side effects like pain, uritcaria and anaphylactoid reaction were looked for during and after the procedure. All emergency drugs (adrenaline, hydrocortisone) were to manage the adverse effects kept ready during the procedure. Outcome was assessed by repeating the hematological profile after 1 and after 4 weeks of treatment and a comparison of the safety and efficacy between the two gatherings was made.

RESULTS

By applying Student's Paired 't' test there is a significant increase in mean Hb level from Before treatment to After 1 week treatment and Before treatment to After 4 weeks treatment in both the groups ($p<0.01$).

Also, by applying Student's Unpaired 't' test there is a significant difference in mean Hb level at after 4 weeks treatment in both the groups($p<0.01$). It is concluded that in both the groups there is a significant increase in Hb level, but FCM group showed more increase as contrasted with Iron Sucrose group. And there is a significant difference between mean values of HB level in both the groups ($p<0.01$).

In both the groups there is a significant increase in MCH, but FCM group showed more increase as contrasted with Iron Sucrose group,MCHC, but FCM group showed more increase as contrasted with Iron Sucrose group, MCV, but FCM group showed more increase as contrasted with Iron Sucrose group, significant change in Reticulocyte count (%), but FCM group showed more change as contrasted with Iron Sucrose group, significant increase in Sr. Iron, but FCM group showed more increase as contrasted with Iron Sucrose group. And there is a significant difference between mean values of Sr. Iron in both the groups ($p<0.01$

It is concluded that in both the groups there is a significant decrease in Sr. TIBC, but Iron Sucrose group showed more decrease as compared to FCM group. And there is significant difference between mean values of Sr. TIBC in both the groups ($p<0.01$

It is concluded that in both the groups there is a profoundly noteworthy distinction in cost. Iron Sucrose group showed less cost as compared to group FCM. ($p<0.001$

DISCUSSION

Nutritional iron deficiency in pregnancy is a public health problem especially in developing countries and commonest is Iron deficiency anaemia. Iron deficiency in pregnancy is significantly associated with both fetal and maternal morbidity. Rapid improvement in Hb and iron stores in pregnancy will improve general health status of the patient and decrease complications. There are various iron preparations available for administration but differ in their efficacy and safety profile. In Our study we have compared two newer parenteral iron preparation ferric carboxymaltose and iron sucrose for treatment of moderate iron deficiency anaemia in pregnancy. Both these compounds are similarly protected and viable in rapidly improving Hb levels and iron stores.

Patients having IDA have longer hospital stay, risk of post-partum haemorrhage and need for blood transfusion. Hence IDA requires a great attention and high quality care. The most reliable parameters to assert IDA is haemoglobin and serum ferritin. In present study sr. Ferritin could not be done due to unavailability of investigation. The customary medications, for example oral iron treatment and blood transfusion include critical disadvantages. Oral iron admission is constrained by gastrointestinal symptoms and rebelliousness. Because of danger of diseases, blood transfusions are save evere cases and particularly in life threatening situations. To overcome this problems IV iron preparations (e.g. iron sucrose, ferric carboxymaltose) are used. However iron-dextran is not used now a day because of safety issues and iron sucrose must be surrendered multiple doses to replenish the iron stores. In present study, the mean difference of rise in haemoglobin level was 2.3 for FCM and 2 for Iron sucrose. It was statistically significant. The mean difference of rise in MCV, MCHC, MCH and sr. Iron levels was more for FCM than for Iron sucrose and it was statistically significant. No serious side effects were observed in either groups. Overall incidence of side effects was found lower in FCM group than Iron sucrose group.

(Joshi *et al.*, 2016) study showed a factually noteworthy ascent in hemoglobin and red cell indices in FCM group. This was comparable to present study. The tolerance and safety profile of ferric carboxymaltose was demonstrated in various studies for its use in iron deficiency anaemia. (Bashiri

et al., 2003; Breymann *et al.*, 2010) No safety concerns have been identified in breast feeding infants of mothers receiving FCM. Its use is approved in second and third trimester in pregnancy. The study showed that FCM was well tolerated in pregnant women and has less number of adverse effects than iron sucrose in much higher dose. The occurrence of medication related adverse effect was low. This was also comparable to present study. Iron sucrose group had higher incidence of pain at injection site while urticaria was noted the main drug related reaction with FCM group. No anaphylactic reaction was noted. None of the adverse events required further medical interventions. As opposed to more frequent small dose administrations, frequent high dose administration of intravenous iron lessen the recurrence of emergency clinic visits, consequently making less interruption patients way of life particularly if working. The general time burned through going to the medical clinic can be decreased. This is probably going health care professionals and to improve patients compliance. Such high portion organizations have been appeared to diminish holding up list, travel costs are decreased which may profit the patient and the human services economy and the insurance agency. Rehashed venupuncture are dodged which decreases the danger of disease. Patel et al62 study indicated that both FCM and Iron sucrose can be used in pregnant patients with iron lack pallor not just for remedy of shortfall in the hemoglobin yet additionally for rebuilding of iron stores. Both modalities had increase in haemoglobin level after 1st and 4 weeks of treatment but increment was more in patients treated with FCM and Iron sucrose. The occurrence of medication related unfriendly occasions was low and comparable to those described for ferric carboxymaltose and iron sucrose in other studies. Registered adverse events were all mild and quickly reversible and mostly restricted to local reactions at the infusion site. There were no treatment-related serious adverse events. No anaphylactic or anaphylactoid reaction was detected. No venous thrombosis was registered. None of the adverse events required further medical intervention. Despite higher cost, FCM has multiple advantage of single dose regime, less hospital visits, lower incidence of side effects and decreases the burden on health care resources. (Christoph *et al.*, 2012) study, the mean rise of haemoglobin level was 1.5 for FCM and 1.1 for Iron sucrose. It was statistically significant. (Dillon *et al.*, 2012) study, the mean rise of haemoglobin was 2.7 for FCM and 2.4 for Iron sucrose. It was statistically significant. The mean rise of MCV level was 7 for FCM and 5.6 for Iron sucrose. It was statistically significant. They showed that increase in haemoglobin level in patients treated with FCM was significantly greater as compared to treatment with Iron sucrose. As their examination was too little they didn't have a lot of contrasts in unfriendly impacts. (Mishra *et al.*, 2015) mean absolute iron shortage was around 1000 mg against which mean genuine basic iron managed through FCM infusion/imbuement was likewise 1000mg speaking to 100% recharging of shortfall. Treatment with FCM expanded mean Hb by 2.37 gm/d in all patients which is measurably huge. Ascend in hemoglobin was related with increment in serum iron essentially. Their outcomes approve a few randomized controlled, multicenter preliminaries in pregnancy where FCM was viewed as exceptionally powerful in the treatment of sickliness.

(Maheshwari *et al.*, 2017), 7-9 (moderate anaemia according to ICMR classification) Haemoglobin was taken as cut off and target 11% as target Hb. Intravenous injectable (iron sucrose, FCM) is superior to oral because of better compliance and no interference with absorption as it causes faster increase in haemoglobin and fastest replenishment of body iron stores. Also, it reduces the need of blood transfusions. Iron FCM has revolutionized anaemia management in pregnancy. Their study has shown that it is a highly and rapidly effective therapy without major side effects. There are also other modalities for the treatment of iron deficiency Anaemia like oral iron which have some or other drawbacks. Oral iron has poor absorption, frequent gastrointestinal side effects, metallic taste and poor compliance. Iron sucrose can cause reaction & require severe repeated dose at every alternate day. However, FCM is safe and can be repeated after a week. It is helpful and savvy (when contrasted with blood transfusion and Inj.Sucrose) in pregnant iron-inadequate ladies who can't get a satisfactory measure of iron quickly by oral course. By treatment with iron FCM it is conceivable to destroy the commonest clinical confusion of pregnancy, in this way significantly lessening maternal mortality and dismalness. Albeit iron sucrose is protected as it is a dextranfree complex. The danger of hypersensitive responses is incredibly low, it is additionally savvy as it is a choice to blood transfusion yet hospitalization time is longer when contrasted with FCM. There is quicker clinical recuperation by both infusion sucrose and Injection FCM than with oral iron treatment in iron lack pallor. Ongoing proof recommends that FCM and iron sucrose can be securely given with no antagonistic impact on liver. In this manner blood transfusion is a solid strategy with brilliant outcomes in the treatment of pallor yet is related with high hazard for

transmission of viral contaminations (HIV, Hepatitis C Virus, Hepatitis B and Cytomegalo infection) and genuine transfusion cross reactions. (Ferraris *et al.*, 2012) Therapy with iron FCM gives a decent chance to keep away from the danger of hemotransfusional diseases, contrary hemotransfusions. Through this prospective study, it has been proved that parentrally administered iron sucrose and FCM elevate haemoglobin with no serious effects. Intravenous iron sucrose and FCM administration is highly safe and effective. But FCM is more cost effective than iron sucrose as less amount of dosage given in FCM for revision of iron deficiency and coming to the objective Hb. The consequences of cost versus advantage investigation will shift in various settings, yet by and large, we recommend that the greater expense of FCM likely could be balanced by reserve funds in staff time and single mixture and with more prominent viability.

Ferric carboxy maltose complex appears to bear the cost of the adequacy of IV iron organization without the burden of numerous little portion infusions, the long imbuement times and danger of unfriendly medication impacts related with higher IV iron dosages, and the bother, antagonistic GI impacts, and danger of non adherence associated with thrice-daily oral iron therapy.

CONCLUSIONS

This study concludes that Ferric Carboxy Maltose is well tolerated in women with pregnancy in II and III trimester is highly safe, effective as compared to inj. Sucrose and oral iron.

ACKNOWLEDGEMENT

A heartfelt appreciation goes to officials of KIMSDU Karad, I would like to express our gratitude to the participants in my study I am also grateful to all who have directly and indirectly helped me in this study.

Funding Support

KIMSDU Karad.

Conflict of Interest

Nil.

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