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Comparative Study of Efficacy and Safety of Anaemia Correction between Iron Sucrose Vs Ferric Carboxymaltose in Pregnancy

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Abstract:
Objective: *Iron deficiency is common among women of childbearing age in both the developed and developing countries. Intravenous Ferric carboxy maltose (FCM) is a novel molecule which can be safely administered in a single dose as large as 1000mg in as little as 15 minutes with no significant adverse effects. The aim of the study was to compare the safety and efficacy of Ferric carboxy maltose (FCM) with Iron sucrose(IS) to treat iron deficiency anaemia.*
Methods: *70 women of iron deficiency anaemia were allocated into two groups. Iron sucrose group - subjects were given I.V. IS in multiple doses,200 mg/day on day,2,4,6, 8 total of 1000 mg. FCM group - subjects were given I.V. FCM 1000 mg single dose. In both groups Hb%, and serum ferritin were done on 0 and day 30 of last dose of parenteral iron. Side effects and compliance were noted.*
Results: *FCM administration in the second trimester of pregnancy is likely to be safe and effective the mean haemoglobin level achieved in the intravenous iron FCM was significantly higher than IS group. The simple FCM dosing regime was associated with greater patient compliance compared with IS.*
Conclusion: *Intravenous FCM is effective in treatment of iron deficiency anaemia without significant adverse effects in pregnancy after first trimester. FCM should be offered to all women with IDA to minimize maternal morbidity & mortality.*

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I. Introduction

Anaemia is one of the leading cause of disability & one of the most serious global public health problems. India alone contributes to 50% of global maternal death due to anaemia(1).In India 41.8% pregnant women are affected from anaemia which is the underlying cause of maternal mortality & prenatal mortality(2).Anaemia may result from inadequate dietary intake, parasite infection or malaria & may be exacerbated by the physiological effects of pregnancy & blood loss at the time of birth(3).WHO estimates that ,of the 5,29,000 maternal death occurring every year,1,36,000 or 25.7% take place in India, where 2/3rd of maternal death occur after delivery, PPH being the most commonly reported complication & leading cause of death (4).Many trials have been tried, Intravenous iron preparations like iron dextran, iron sucrose & Ferric carboxy maltose have been considered as an alternative to oral iron. Iron dextran may cause allergic reactions & iron sucrose requires repeated doses of infusion. FCM is a novel molecule composed of polynuclear iron hydroxide complexes to carboxymaltose. The ability to safely inject a single dose as large as 1000mg in as little as 15 minutes & thereby reducing the need for multiple IV iron infusion.FCM is cost effective with other positive benefits of fewer hospital visits & improved patient compliance(5).

FER-ASAP [FERic carboxymaltose-Assesment of SAfety & efficacy in Pregnancy] was the first randomised controlled trial to assess FCM.

During pregnancy, the needs of growing foetus and placenta as well as the increasing maternal blood volume and red cell mass, impose such a demand on maternal iron stores that iron supplementation of daily required dose between 18 and 100mg from 16wks of gestation onwards can't completely prevent the depletion of maternal iron stores at term.(6) In this study, we compare & evaluate the safety & efficacy of IV FCM & iron sucrose.

II. Materials & Methods

This Descriptive cross Sectional study was conducted in a private hospital in Pondicherry in a 70 antenatal women from July 2017 to June 2018. All subjects gave written informed consent before enrolment.
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Inclusion criteria-

- All antenatal with haemoglobin < 6 and > 10 g/dl
- Women with gestational age 13-28wks(second trimester).

Exclusion criteria-

- All antenatal with comorid conditions
- Iron intolerence
- Women in 1st & 3rd trimester.
- Antenatal women suffering from other chronic infections like hepatitis,HIV,serum tranaminase more than 1.5 times the upper limit of normal, serum creatinine level of more than 2.0mg/dl or history of allergic reactions to intravenous iron infusion.

A total 70 antenatal women with anaemia attending the OPD between 13-28wks of gestational age were included in our study. Cases were randomly distributed into 2 groups consisting of 35 cases each.

Total Dose Calculation for Iron Deficit: -

Total iron dose required = 2.4*body weight (kg)*(target Hb – actual Hb in gm/dl) + 500mg.

Women with group A received IV iron sucrose in multiple doses 200mg/day on day 0,2,4,6,8 total of 1000mg.[Iron sucrose 200mg diluted in 100ml of 0.9%NS & given over 20-30mins]. Group B Subjects were given IV FCM 100mg single dose [FCM 1000mg diluted in 100ml of 0.9%NS given in 20-30mins]. Hb level before starting therapy was divided into 3 categories, 7-8, 8.1-9, 9.1-10 where group A and B falls under these headings which is shown in table 1.

Both groups Hb% & serum ferritin are done on day 0 & day 30 of last dose of parenteral iron. Hb level before and after therapy of mean and standard deviation in group A was 6.236±0.25 and 8.281±0.30 and group B was 5.126±0.35 and 8.321±0.32 respectively(table - 1).

The percentage of patients achieving Hb rise upto 2gm/dl after 2wks of therapy in Group A and B was 3% and 5% respectively whereas Hb rise of >2gm/dl after 2 weeks of therapy in group A and B was 10% and 20% respectively and the P value is also clinically significant(table - 2). The mean Serum Ferritin level & Haematological parameters before and after therapy in both groups are given in table 3.

Side Effects like headache, myalgia, nausea, vomiting, epigastric discomfort & anaphylactic reactions were looked for during the procedure. The drug was administered under direct supervision and infusion was immediately stopped in case of any side effects. Pulse, Blood pressure and in case of pregnancy fetal heart rate were monitored at 5 minutes interval. Patients were observed for half an hour after transfusion. The patients were followed up after 3 weeks of total dose infusion to assess the status of iron stores and increase in haemoglobin levels using same parameters as previously mentioned.

Hb level (gm/dl)	**GROUP A(n=35)**	**GROUP B(n=35)**	**P VALUE**
BEFORE STARTING THERAPY			
7-8	05(14.2%)	06(17.1%)	
8.1-9	25(71.4%)	22(62.8%)	
9.1-10	05(14.2%)	07(20%)	
Before therapy(Mean±SD)	6.236±0.25	5.126±0.35	0.02
After therapy(Mean±SD)	8.281±0.30	8.321±0.32	0.05

Table - 1. Haemoglobin level before & after 2 weeks of therapy

Hb rise after 2 weeks	**GROUP A**	**GROUP B**	**P VALUE**
Upto 2gm/dl	3%	5%	0.001
>2gm/dl	10%	20%	0.001

Table - 2. Percentage of patients achieving outcome after 2wks of therapy.

PARAMETERS	**GROUP A pre - therapy (Mean± SD)**	**GROUP B pre therapy (Mean± SD)**	**P VALUE**
SERUM FERRITIN	10.26±2.01	12.25±2.20	0.256
MCV	62.20±2.16	64.20±4.20	0.215
MCH	25.43±0.52	26.21±1.02	0.0062
MCHC	22.5±0.82	23.5±1.56	0.452
PARAMETERS	**GROUP A after 2 wks of therapy (Mean± SD)**	**GROUP B after 2 wks of therapy (Mean± SD)**	**P VALVE**
SERUM FERRITIN	60.25±10.35	70.20±12.50	0.021

MCV	65.20+-3.23	68.10+4.20	0.035
MCH	26.25+0.80	26.30+1.02	0.68
MCHC	24.5+-1.30	25.20+1.52	0.562

Table - 3. Mean Serum Ferritin level & Haematological parameters before and after therapy in both groups.

III. Results

Of the 70 patients who were treated for ante partum anaemia, 35 from iron sucrose group and 35 from ferric carboxy maltose group completed the protocol. Those who completed protocol and came for follow up were included for statistical analysis. FCM administration in the second trimester of pregnancy is likely to be safe and effective the mean haemoglobin level achieved in the intravenous iron FCM was significantly higher than IS group. The simple FCM dosing regime was associated with greater patient compliance compared with IS.

IV. Discussion

Anaemia is perhaps the most common complication of pregnancy in developing countries. Severe forms of anaemia are so common as toxaemia; they contribute to a major percentage of maternal death. Incidence of anaemia varies from 40-90% in India.

According to the WHO, anaemia contributes to 40% of maternal death in third world countries. In India , anaemia contributes to 10-15% of maternal death.

Anaemia defined as low haemoglobin concentration resulting in a decrease in the oxygen carrying capacity of the blood. According to WHO, an Hb level less than 11g/dl is considered as anaemia during pregnancy.The centers for disease control and prevention has defined anaemia as less than 11gm/dl in the 1st & 3rd trimester and less than 10.5gm/dl in 2nd trimester. The degree of anaemia is graded according to the haemoglobin level as:

Moderate: 7-10.9g/dl, Severe: 4-6.9g/dl, Very Severe : <4g/dl

During pregnancy, the plasma volume increases by 40-45%. The red cell mass increases by 15-20%, the increases are rapid after 1st trimester of pregnancy.

The main causes of anaemia in pregnancy:Nutritional causes - a. Iron deficiency b. Folate & vitamin B12 deficiency 2) Parasitic infestation: - a. Hookworm infestation b. Malaria 3) Chronic blood loss:- a. Menorrhagia b. Haemorrhoids 4) Hemoglobinopathies:- a. Thalassemia b. Sickle cell anaemia 5) Other causes:- Aplastic anaemia

In India, nutritional causes contribute to nearly 50-55% of cases of anaemia during pregnancy. In pregnancy, iron deficiency anaemia is very common. The iron deficiency may exist prior to pregnancy, in which case pregnancy makes it worse, or it may originate during pregnancy. The various causes of iron deficiency anaemia during pregnancy are:

a. Poor intake of dietary iron
b. Poor absorption /bioavailability
c. Increased demand during pregnancy
d. Continuous loss of blood.

Studies compared, FCM and iron sucrose and found that both iron sucrose and FCM were independently more effective and safe than oral preparations. (7)

Retrospective study was conducted to assess the efficacy and safety of FCM and found effective. In a prospective trial FCM was better tolerated than iron sucrose. A retrospective study compared the safety and efficacy of intravenous (IV) high dose FCM with iron sucrose (IS) for the treatment of ante partum anaemia in

70 inpatient women in ante partum period who received superior IV high dose FCM (15 mg/kg; maximum 1000 mg) or Iron sucrose (2×200 mg), respectively. Rapid administration of IV FCM was as safe as IS in the antenatal period despite five times of higher dosage. FCM was as effective as Iron sucrose in changing Hb levels from the baseline. There was no difference in the mean daily haemoglobin increase between the groups. Women with severe anaemia showed the most effective responsiveness. The single application of FCM shows advantages of lower incidence of side effects at the injection site, a shorter treatment period, and better patient compliance. (8)

In this study, both FCM and Iron sucrose were given the same dosage but single and multiple dosages respectively. In both the group there was significant rise of Hb and Ferritin after one month of the therapy which was comparable with the other studies .Like others severe anaemia showed the most effective response in both the groups. Unlike other studies Haemoglobin rise was more than 3.5 in both the groups, this may be because of our total dose used in both the groups. In this study adverse effects occurred in 7% of women in iron sucrose group but were not severe enough to affect compliance. It has to be noted that this group of women were highly

motivated and therefore may have completed the multiple dose of the drug. Women who received FCM also expressed better-overall satisfaction to administration of treatment. (9)

To date no perspective, controlled clinical study has been performed using ferric carboxymaltose in pregnant women. A recent Cochrane review concluded that large good quality trials, assessing clinical outcome (including side effects) as well as the effects of treatment by severity of anaemia are required(10). Also use of high doses reduces the number of infusions, enabling the possibility of cost reductions compared to multiple administrations. (11-14)

V. Conclusion

To date from the prospective study is consistent with other studies that ferric carboxymaltose administration in the second trimester of pregnancy is likely to be safe and effective the mean haemoglobin level achieved in the intravenous iron ferric carboxymaltose was significantly higher than iron sucrose group the simple FCM dosing regime was associated with greater patient compliance compared with iron sucrose.

Due to properties like ultra-short duration of treatment i.e. ability to administer 1000 mg doses in a single sitting, fewer adverse reactions and better compliance makes FCM the first-line drug in the management of ante partum iron deficiency anaemia causing a faster and higher replenishment of iron stores and correction of Haemoglobin levels. Also use of high doses reduces the number of infusions, enabling the possibility of cost reductions compared to multiple administrations. (11-14)

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