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Ferric Carboxymaltose: A Boon to Indian Anaemic Pregnant Women

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Abstract
Background: *Fe deficiency is a major public health problem which can be easily diagnosed and corrected. Peri-partum Fe deficiency anaemia (IDA) is related to maternal, fetal and infant morbidity. Current alternatives encompass oral Fe supplementation, which can be ineffective and poorly tolerated, and blood transfusions, which carry an inherent danger and need to be avoided. Ferric carboxymaltose is a new remedy alternative to blood transfusion. The study is designed to assess the safety and potency of Fe deficiency anaemia (IDA) correction with intravenous FCM in pregnant women anaemia in the 2nd and 3rd trimester.*
Methods: *Prospective observational study; 50 anaemic pregnant women obtained FCM 500mg among 24-and 36 weeks of pregnancy (median 32 weeks gestational age, SD). Treatment potency assessed through repeat haemoglobin (Hb) and ferritin titers which indicate the Fe stores. Drug safety assessed by evaluation of drug reactions and fetal heart for the during and after infusion.*
Results: *Intravenous FCM infusion appreciably improved Hb values ($p<0.01$) above baseline degrees in all women. Increased Hb values were determined at 3 weeks, after delivery, 6 weeks postpartum. Ferritin values accelerated significantly after the infusion. Fetal heart rate monitoring did not show any effect on the fetus. No serious detrimental consequences have been observed and minor consequences took place in 2 (4%) patients.*
Conclusions: *Our study statistics is correlating with current observational reviews of the secure and effective use of FCM in Fe deficiency anaemia in pregnancy.*
Keywords: *Pregnancy, Fe deficiency, Peri-partum anaemia, Intravenous FCM, Red blood cell transfusion.*

Background

Fe deficiency is an alarming public health issue in pregnant ladies in India. Anaemia is answerable for 40% of maternal mortality in developing countries. It is responsible for 25% direct maternal deaths. It also causes indirect deaths from heart failure, bleeding, sepsis and pre-eclampsia. Anemia additionally increases perinatal mortality

and morbidity due to extended preterm deliveries, low birth weight infants, small for gestational babies, low Fe stores, cognitive and affective dysfunction and lower mental improvement in infants. There is increase need of Fe during child bearing age due to growth of baby and placenta. Fe deficiency is preventable and treatable. For many years the mainstay remedy of IDA has been oral Fe and red blood mobile (RBC) transfusions. However, oral Fe supplementation can result in tremendous side effects ensuing in non-compliance in lots of patients. Due to potential risk RBC transfusion should be avoided whenever possible. Intravenous Fe formulations are given in intolerance or non-adherence to oral Fe and malabsorption states.

Intravenous Fe is less commonly used in worry of allergies with Fe dextran preparations, and lengthy infusion time with Fe polymaltose, have brought about discomfort with practitioners. The development of dextran free IV Fe substitutes with an advanced protection, and a greater fast infusion time indicates that intravenous Fe should be taken into consideration as a mainstay treatment for moderate to extreme IDA.

Fe Sucrose and FCM are dextranfree intravenous Fe alternatives. When compared to oral Fe in pregnancy Fe sucrose is superior with respect to the charge of each haemoglobin growth and Fe replenishment, blended with a very good protection profile, Serious detrimental outcomes are uncommon with Fe sucrose, however minor facet effects arise in up to 18% of patients which may in component be attributed to its non-physiological physical properties (high pH and high osmolarity). FCM is a newer dextran-free Fe substitute with a close to neutral pH, physiological osmolarity and improved bioavailability which allows for single dose, quick 15 minute infusion time and higher dosing (up to 1000 mg). These qualities make FCM an appealing opportunity to Fe sucrose in terms of risk profile, efficacy, patients comfort, staff and institutional aid utilization.

To date, there are few medical research regarding the use of FCM in pregnant ladies. The primary aim of this study turned to evaluate the usage of intravenous FCM in correction of Fe deficiency anaemia in pregnant women. The secondary goals were to determine the extent and severity of unfavourable effects of FCM, and to assess patients subjective improvement.

Methods

After approval by the ethical committee, this prospective study was performed between January 2017 and may 2018 in rajah Muthiah medical college hospital. Informed consent was obtained from the patients and their relatives.

Pregnant women who had Hb of 7-9g/dl, were infused with FCM. A total of 50 women were included. Patient was infused with FCM (500mg/10ml) diluted with 100ml of 0.9% NaCl solution over a period of 20 minutes. Maternal vital signs and systemic reactions were monitored every five minutes during infusion and foetal heart rate was monitored during infusion. Blood samples were collected to measure haemoglobin, ferritin levels, PCV prior to infusion and then repeated 3 weeks after infusion, immediately after delivery and six weeks post partum. Sodium lauryl sulphate (SLS) method was used for Hb analysis. Women were observed for 4 hours post infusion, before being discharged home. All 50 patients were followed up by phone call to assess their well-being after infusion of FCM. Patients were asked to express their well-being as worse, no change, some improvement or much better which reflected change in symptomatology since infusion.

The data were analysed using, p values (of <0.05 to indicate significance) and standard deviation. Available pre-infusion, post-infusion and post-partum haemoglo-bin and ferritin levels were analysed.

Results

A total of 50 women received a ferric carboxy-maltose infusion for antenatal Fe deficiency

anaemia, with pre-infusion haemoglobin data available for all 50 women. Following infusion, haemoglobin values were repeated as required and data were available for 88% of women: 31 women (48%) at visit 1 (3 weeks post infusion), 26 women (40%) at visit 2 (after delivery) and a total of 20 (31%) women had a blood test at visit 3 (6 weeks post-partum). All women responded to the treatment with in-creased Hb values.

Table 1 discusses about the mean Hb and ferritin values at baseline, third week post infusion, immediately after delivery and six weeks post partum.

Table 1: comparison of outcome measures at various periods of study

Time of Measurement	HB Mean	HB SD	Ferritin Mean	Ferritin SD
Base line	8.19	.48	91.52	24.82
3rd week	10.75	.64	158.88	26.29
After delivery	10.18	.65	152.68	39.05
6 weeks after delivery	9.85	.49	132.92	30.25

The mean HB was improved from 8.19 +.48 at base line to 10.75 +.64 after 3 weeks of treatment .But after delivery the value is further reduced to 9.85+.49 .The Hb values at different times were never lesser than base line values.

Likewise, the mean ferritin at baseline was 91.52 +24.82 and it was improved to 158.88 + 26.29 after 3weeks of treatment. After delivery it was dropped to 152.68+39.05 and at 6weeks following delivery it was further reduced to 132.92 +30.25.

Table 2

Time of Measurement	HB	Ferritin
Wilks lamda	.05	.203
F Value	281.56	61.34
P Value	.001	.001

Repeated measures ANOVA shows that there significant difference (wilks lambda .5, f= 281.56, p = .001) in the HB measurements at different study periods.

Repeated measures ANOVA is statically significant (wilks lambda =.203, f=61.34, p=.001) suggesting that the measurements are statistically different at various times.

Table 3: Haemoglobin levels (mg/dl) and ferritin levels across the testing period for women in the stud

Comparison – Different times	HB Mean Difference	HB P Value	Ferritin Mean difference	Ferritin P value
Base line				
3rd week	2.56	.001	67.36	.001
After delivery	1.99	.001	61.16	.001
6 weeks after delivery	1.65	.001	41.40	.001
3rd week				
After delivery	.57	.001	6.2	.726
6weeks after delivery	.91	.001	25.96	.001
After delivery				
6weeks after delivery	.34	.001	19.76	.008

In table 3, post –HOC comparisons using bonfferroni is shown. The mean difference in HB from baseline to 3rd week was highest 2.56 followed by after delivery, 1.99 and 6 weeks after delivery, 1.65. the P value is significant at all three comparison levels suggesting that Hb is significantly improved from baseline measures to other periods of measurements . The difference in ferritin was also much higher at 3rd week (67.36) followed by after delivery (61.16) and 6 weeks after delivery (41.40) when compared to baseline. but the comparision is statistically significant at different times

The drop in Hb (.57) is statistically significant from third week after delivery and third week to 6 weeks after delivery. The drop in ferritin is not

statistically significant from third week to after delivery(6.2) but it is statistically significant from third week to six weeks after delivery(25.96) suggesting that ferritin values were not dropped significantly from 3rd week values to after delivery, but it is significantly dropped at 6th week following delivery. Both Hb and ferritin was significantly dropped from delivery to 6 weeks following delivery.

Table 4 Number of women experiencing a drug related adverse events following infusion with FCM (total number of women infused n = 50)

Adverse event	N (%)
Any adverse event	2(4)
Systemic	
Headache	1(2)
Pruritus	1(2)

All adverse reactions are presented in Table 4. No ser-ious adverse effects were recorded in any of the 50 women receiving an infusion. Minor side effects occurred in 2 (4%) patients. One patient required medication with Paracetamol for headache, pherniramine for pruritus. All adverse events were self-limiting. Fetal heart rate monitoring did not indicate a drug related adverse effect on the fetal heart pattern. Red blood cell transfusion was required by 1 women (2%) in the study cohort, who had a significant ante-partum haemorrhage.

Follow-up interview by telephone was conducted on 30 (60%) women in the post-partum period. Of these women, 50% reported an improvement in their wellbeing, 35% reported feeling "much better", 12% reported "a little better", and 3% reported feeling "no different" after the infusion. None of the women reported feeling worse.

Discussion

This is the first prospective study reporting on FCM infusions in pregnancy in south India. We also show that FCM appears to be a secure and effective treatment modality for the correction of IDA, as no severe side effects and minor side effects reported. Patients improvement in perceived wellness assessed in the postnatal period was high.

In our study, first trimester baseline bloods showed Hb of 8.19mg/dl. The ferritin levels of 91.52ng/ml represents profound Fe deficiency and conveys the significance of ferritin as a screening tool. Routine oral Fe supplementation initiated for all ladies seems to be enough for a few women to maintain adequate Fe stores. However many women develop mild to extreme IDA in spite of oral Fe supplementation, For these intravenous Fe administration may be a greater effective remedy. Fe dextran, Fe sucrose and Fe ferrigluconate are usually used IV Fe formulations commercially. Fe dextran is associated with hazard of hypersensitive reaction that has resulted in serious detrimental results within the beyond. Fe sucrose is widely used cheaper parentral Fe which doesnot include dextran, therefore may be given as bolus or infusion without previous test dose.

The new shape of intravenous Fe, FCM has been advanced to combine the advantageous traits of Fe dextran and Fe sucrose. It avoids dextran precipitated allergic reaction and overcomes low dosage obstacles of Fe sucrose and gluconate.

FCM formulations have nearly neutral pH and physiological osmolarity unlike Fe sucrose which has high pH and excessive osmolarity (Funk F et al, 2010). It can be given by fast infusion upto a thousand mg of elemental Fe.

Table 4 Dosage of FCM

Hb (g/dl)	**Patients with body weight ≥ kg and < 70 kg**	**Patients with body weight ≥ 70 kg**
< 10	1500 mg	2000 mg
≥ 10	1000 mg	1500 mg

The rapid delivery option of a large single dose of FCM offers a promising treatment modality for pregnant women who need correction of Fe deficiency and anaemia, over other IV Fe formulations that have low dosage limits, such as Fe sucrose (200 mg). The properties of FCM may also reduce the burden on the patient and the health care system.

Salient Features of FCM Injection

- FCM is a new third generation intravenous Fe preparation with high stability and low toxicity (Port J Nephrol Hypert 2009; 23(1): 11-16).
- FCM combines the positive characteristics of Fe dextran and Fe sucrose but is not associated with dextran-induced hypersensitivity reactions (PortJ Nephrol Hypert 2009; 23(1): 11-16).
- FCM can be administered in much higher doses than Fe sucrose or Fe gluconate (Port J Nephrol Hypert 2009; 23(1): 11-16).
- The chemical characteristic of the Fe-carbohydrate complex in FCM means that Fe is released slowly, avoiding toxicity and oxidative stress (Port J Nephrol Hypert 2009;23(1):11-16).
- Up to 1000 mg Fe can be given as a single infusion of FCM thus speeding up the delivery of Fe and saving time and resources (Drugs 2009; 69 (6): 739-756).
- FCM can be given by rapid infusion over 15 minutes - this reduces administration time (Drugs 2009; 69 (6): 739-756).
- With FCM, a test dose is not required unlike Fe dextran (Drugs 2009; 69 (6): 739-756).
- FCM minimizes the number of clinic visits required for parenteral Fe infusion and reduces number of venous punctures (Port J Nephrol Hypert 2009; 23(1): 11-16).
- Amongst the new IV Fe preparations FCM is dextran-free unlike ferumoxytol and Fe isomaltoside 1000 and does not possess the risk of dextran-induced anaphylactic reactions (Port J Nephrol Hypert 2011; 25(3): 000-000).
- Clinical efficacy and safety shown in wide variety of indications including anemia associated with kidney disease, inflammatory bowel disease, postpartum anemia associated with abnormal uterine bleeding and chemotherapy induced anemia.
- Hemoglobin response and normalization observed with FCM in FERGIcor study was found to be superior to Fe sucrose (Gastroenterology 2011; 10.1053/ j.gastro.2011.06.005).
- In cost-minimization studies, use of FCM was found to be less expensive than Fe dextran and Fe sucrose (Therapeutics and Clinical Risk Management 2011:7 501-509).

Conclusion

We infer from the study that FCM can be safely and effectively used in treatment of anemia in child bearing period. Despite being pricey for a setup like India it could be attempted in rare blood groups, avoidance of blood transfusion related complication and improvement in patients wellbeing.

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