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ORIGINAL ARTICLE

MANAGING POSTPARTUM ANEMIA WITH FERRIC CARBOXYMALTOSE AT TERTIARY LEVEL HOSPITAL: A RETROSPECTIVE STUDY

Surekha Narayan Khandale[1], Kshama Kedar[2]

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ABSTRACT: OBJECTIVE: 1) To evaluate safety and efficacy of Ferric Carboxymaltose (FCM) in the treatment of postpartum anaemia (PPA). 2) To assess the increase in Hb level after FCM. Design: This is a retrospective, study consisted of 121 women admitted in obstetrics ward with postpartum anemia who received FCM. **MATERIALS & METHODS:** Clinical records of patients with postpartum anemia who received FCM were analysed. **RESULTS:** Mean haemoglobin (Hb) increased significantly from baseline by 2.76±1.00 g/dl (n=121; p<0.0001). The change in Hb was maximum in patients having baseline Hb 6.1-8g/dL. Only 2 patients (1.65%) reported treatment-related adverse events headache, n=1; rash/urticaria, n=1]. **CONCLUSION:** FCM was effective in improving Hb in PPA patients & was well tolerated.

KEYWORDS: Ferric carboxymaltose, postpartum anemia.

INTRODUCTION: In developing countries anemia is a major cause for maternal mortality & morbidity. The prevalence of postpartum anemia (PPA) is 27% and a postpartum haemoglobin (Hb) level of less than 8g/dL is observed in 10% women. It is a common problem throughout the world. It is a major cause of maternal morbidity such as lethargy, headaches, tiredness, dizziness, lactation failure, and postpartum depression and mortality in resource–poor countries. Anemia may result from inadequate dietary intake, parasitic infection, or malaria, and may be exacerbated by the physiologic effect of pregnancy and blood loss at the time of birth.[1]

WHO has defined PPA as haemoglobin of less than 10 gm% during the postpartum period.[2] Lack of iron supplementation during pregnancy and postpartum haemorrhage (PPH) are important causes of PPA. Women with iron deficiency anaemia (IDA) especially during the third trimester of pregnancy are more likely to suffer from PPA. It is also because IDA increases the risk of PPH in these women. WHO estimates that, of the 529000 maternal deaths occurring every year, 136000 or 25.7% take place in India, where two-thirds of maternal deaths occur after delivery, postpartum haemorrhage being most commonly reported complication and the leading cause of death (29.6%).[3] The other risk factors identified to be associated with PPA is multigravidas, multiple pregnancies and closely spaced pregnancies. All these condition in turn increase the risk of PPH which can further complicate the issue.[4]

The traditional treatment for postpartum anaemia is oral iron supplementation, while blood transfusion is reserved for more severe cases of anaemia. High doses of oral iron usually cause side effects, including constipation, nausea, and gastric irritation, which affect compliance. On the other hand, though blood transfusion gives excellent results, it is associated with a high risk of infections particularly with hepatitis B, hepatitis C, and human immunodeficiency virus, and not to forget serious transfusion reactions. In such a scenario, intravenous iron has been considered as an alternative.

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In the past, iron dextran given intravenously was associated with severe anaphylactic reactions, but now iron preparations like iron- sucrose complex and ferric carboxymaltose are available with excellent safety profile.[1]

Although iron sucrose is rarely associated with anaphylactic reactions, it must be administered in lower doses as it is a less robust iron-carbohydrate formulation. The free iron that may accumulate in the blood might result in potential reaction (hypotension, gastrointestinal symptoms and pain in the back or chest).[5]

Guidelines[6] for treatment of postpartum IDA issued by Schweizerische Gesellschaft fur Gynakologie und Geburtshilfe and the network for Advancement of transfusion Alternatives recommend that IDA Should be treated by replenishing body iron deficits either by oral or i.v. administration of iron depending on the severity of anemia and how fast the anemia needs to be corrected. Of note, intravenous iron, alone or in association with recombinant erythropoietin (rHuEPO), has been considered in the management of severe iron deficiency (Table 1).

Ferric carboxymaltose (FCM) is a parenteral, dextran free iron formulation, which overcomes the limitations of existing i.v. Preparations. The FCM complex is composed of a polynuclear iron (III) hydroxide complexed to carboxymaltose. As FCM is a strong and robust iron complex, it can be administered in high doses, does not release large amounts of reactive ('free') iron into the circulation and does not trigger dextran- associated immunogenic reactions.[7] The safety and efficacy of FCM in patients with heavy uterine bleeding or postpartum IDA with significant improvements in Hb and iron profile have been documented previously. FCM is cost effective with other positive benefits of fewer hospital visits, reduced interruption in lifestyle, improved patient compliance.[8]

OBJECTIVES: 1) To evaluate safety and efficacy of Ferric Carboxymaltose (FCM) in the treatment of postpartum anaemia (PPA). 2) To assess the increase in Hb level after FCM.

MATERIALS AND METHODS: This was a retrospective study of FCM. Data were collected from patient records who were admitted in the department of obstetrics with post-partum IDA who were administered IV FCM at the discretion of the physician and as per the product's prescribing information. Data was collected from January to December 2014 for a period of 1 year. The following details were recorded: patient's age, weight, history of postpartum haemorrhage, co-morbidities, total iron deficit, actual FCM dose and method of administration (Injection/Infusion), blood transfusion, if any in postpartum period and results of laboratory investigation (Hb, RBC count as done) pre and post treatment. Patient's name and address were not recorded. Primary outcome measures were increase in Hb from baseline after FCM injection. Adverse events observed if any were reported.

Stastistical Analysis: Continuous variables like age, birth weight and haemoglobin were presented in mean±SD, categorical variables were expressed in percentage, and continuous variables were compared between groups by performing paired t-test. Categorical variables were compared by Chi-square statistics. $P < 0.05$ was taken as statistical significance.

Results: Patients' Demography {Table 2}: Total 121 patients with mean (± SD) weight of 52.26±14.34 kg and mean baseline Hb of 7.78±0.90 g/ dl were treated with FCM injection. 59.50% delivered by vaginal route while 40.49% were delivered by Caesarean section. 7 patients (5.78% had history of PPH, there were no other co-morbid conditions documented.

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Change in Hb: In overall patient population, mean (±SD) Hb at baseline was 7.78±0.90 g/dl, which increased to 10.45±1.31 g/dl after FCM injection (difference=2.69±1.00; p <0.0001; Table3). The time interval for change in haemoglobin after FCM was mean 14.8 ±9.6 days.

Change in Hb in different Baseline Hb Strata: In patients having Hb 6.1-8g/dl the change in haemoglobin was maximum (2.9±1.00 g/dl; p<0.0001). The change in haemoglobin of 2.61±0.85g/dl; p<0.0001 and 2.86±1.09g/dl; p<0.0001 was observed in patients with haemoglobin <6g/dl and ≥8g/dl respectively [Table].

Adverse Events: FCM was well tolerated. Adverse effects were recorded in 2 patients (1.65%), namely headache (n=1) and rash/urticaria (n=1). These were expected events reported in previous literature. There was no serious adverse event reported.

DISCUSSION: Postpartum anaemia arises frequently and imposes a substantial disease burden during the critical period of maternal- infant interactions and can be very debilitating, especially when caring for a newborn. Furthermore, anaemic puerperia have a longer average length of hospital stay, are more likely to receive a blood transfusion, and incur higher hospitalization costs, Hence, postpartum IDA require attention and high quality care.[9] The most reliable parameter to assess postpartum IDA is Hb, because ferritin levels may vary and indicate falsely elevated values after delivery. The traditional treatment s, i.e. oral iron therapy and blood transfusion, involve significant drawbacks. Oral iron intake is limited by gastrointestinal complaints and patients non-adherence. Due to risk of infections, blood transfusions are reserved for the most severe cases and particularly in life threatening situations.[10]

In addition, an inflammatory reaction can occur, particularly following surgically assisted deliveries and Caesarean section, leading to iron sequestration in the macrophages and decrease of intestinal absorption, so that the administered iron is not available for hemopoiesis.[10]

To overcome these problems, IV iron preparations [e.g., Iron dextran, or iron sucrose (IS)] are used. However, the latter either require multiple administrations of low doses to replenish stores (IS) or are associated with hypersensitivity reactions (Iron dextran).[9] FCM represents a novel iron preparation that overcomes the limitations of existing IV preparations, is effective in the correction of Hb and rapidly replenishes iron stores with large iron doses and minimal risks of hypersensitivity or other adverse effects. The safety & efficacy of FCM in the treatment of postpartum IDA have been tested in a number of randomized, multicenter studies.[9]

In this study, mean (±SD) total iron deficit was 1061.11±259.11 mg against which mean (±SD) actual elemental iron administered through FCM injection/infusion was 1060.14±257, 46mg, representing 100% replenishment of deficit. Treatment with FCM increased mean Hb by 2.67g/dl in all patients, which was statistically significant (p<0.0001). The mean Hb raised from 7.78±0.90 at baseline to 10.45±1.31g/ dl (p<0.0001) after mean 14.8 days in all patients evaluated for time interval faster change in haemoglobin from baseline. Our results correlate with several randomized, controlled multicenter trials in postpartum patients where FCM was considered to be very effective in the treatment of PPA.

In a randomized trial[11] to assess safety and efficacy of intravenous FCM in the treatment of postpartum IDA, 227 women were assigned to IV FCM with 1000mg maximum dose (up to 3 weekly doses) versus 117 women who received oral ferrous sulphate 100 mg twice daily.

Intravenous FCM was as effective as oral ferrous sulphate with no statistically significant differences between groups at any point despite the shorter treatment period and a lower total dose of iron (mean 1.3 g IV iron versus 16.8 g oral iron).[11] In the similar line, rise in Hb of 2.54 g/dl in this study was achieved with mean FCM dose of 1.06gm.

In a multicenter randomized, controlled study by Seid et al.,[12] 291 women after delivery with Hb ≤10 g/dl were randomized to receive 1000 mg IV FCM (143 women), repeated weekly to a calculated replacement dose (Maximum dose 2.5g), or ferrous sulphate (148 women) 325 mg orally three times daily for 6 weeks (Total dose 40.9g). FCM treated women achieved a Hb>12g/dL in a shorter period of time with a sustained Hb>12 g/dL at day 42. Furthermore, the achieved Hb rise of ≥3g/dL was significantly more rapid in the IV group [median 15 vs. 28 days; p <0.0001] than the oral group. Patients with Hb levels ≤8g/dL showed greatest difference in the responder rate between FCM and ferrous sulphate group [78.9% vs. 43.5%; p= 0.0286].[12]

In our study, patients having Hb 6.1-8gm/dL; the change in Hb is maximum (p value <0.0001) (Hb increased from 7.39±0.36 to 10.26±1.06; p<0.0001).

In another randomised trial[13] by et al. Van Wick 174 women who received IV FCM with a mean total dose of 1.4g versus 178 women who received 325 mg ferrous sulphate three times daily for 6 weeks (Total dose 40.9 gm) were assessed. Patients assigned to FCM achieved a Hb rise >2 gm/dl faster than oral iron group (7 days compared with 14 days in the oral group, The IV iron group significantly achieved Hb rise >3g/dl at any time (86.3% compared with 60.4% faster than oral group, p<0.0001), were more likely to achieve Hb >12 g/dL (90.5% compared with 60.4% in the oral iron group, p<0.001).

Compared with oral sulphate, FCM was better tolerated, prompted a more rapid Hb response, thus providing a reliable solution for correction of IDA anemia.[13] In our study, mean Hb raised by 2.67g/dL (pvalue <0.0001) in all patients, but did not reach the target level of 12 g/dl. The reason for the same could be that % of patients in our study were having severe PPA (Baseline Hb≤8g/dL) which necessitates use of erythropoietin along with intravenous iron in these patients.

A retrospective study by Pfenniger A et al.[9] compared the safety and efficacy of intravenous (IV) high dose FCM with iron sucrose (IS) for the treatment of postpartum anaemia in 210 inpatient women in postpartum period who received IV high dose FCM (15mg/kg; maximum 1000 mg) or IS (2×200mg), respectively. Rapid administration of IV FCM was as safe as IS in the management of PPA despite five times of higher dosage. FCM was as effective as IS in changing Hb levels from the baseline. There was no difference in the mean daliy Hb increase between the groups. Women with severe anemia 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.[9]

As such, postpartum period is considered to be characterized by physiologically low iron requirements, particularly because the expanded red cell mass contracts after delivery and its iron can be utilized and stored. But low iron stores during pregnancy may be carried over into the postpartum period, and therefore iron supplements after delivery enhance the postpartum recovery of haematological values.[14] Previously, in PPA IV FCM has shown significant increase in serum ferritin levels than with ferrous sulphate (p value<0.0001) indicating a successful repletion of iron stores and accessibility for erythropoesis.[11]

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In our study only 2 patients (1.65%) needed blood transfusion, reflects positive benefits of FCM. Thus, intravenous FCM undoubtedly allows blood transfusion to be avoided in postpartum women, even though the need for blood transfusion is unquestionable in life threatening situations.[1]

Present results validate previous studies and have shown significant increase in Hb of 2.76 gm/dl in PPA patients in shorter time period of just 14.8 days. Overall, FCM was well tolerated with only two (1.65%) patients reporting minor side effects of headache, rash/urticaria. This observation correlates with previous studies that have investigated the safety profile of intravenous FCM.

CONCLUSION: To conclude intravenous FCM offers rapid normalization of Hb in postpartum anemia without any significant adverse effects. FCM should be offered to all women with PPA to minimize maternal mortality and morbidity. It will help in mother baby bonding by decreasing maternal morbidity in anaemic women.

Schweizerische Gesellschaft fur Gynakology und Gubertshilfe
• Slight IDA = Hemoglobin 95-120g/l Oral iron 80-200 mg/day
• Moderate IDA= Hemoglobin 80-95g/ dl -IV iron 500-1000 mg
• Severe IDA= Hemoglobin <80g/l -IV iron 500-1000mg -Consider erythropoietin 10, 000-20, 000 U subcutaneously
Network for Advancement of Transfusion
• Moderate to severe IDA= Hemoglobin 80-95g/dl -IV iron 500-1000mg -Consider erythropoietin 10, 000-20, 000 U subcutaneously
• Very severe IDA = Hemoglobin <60g/l -Consider blood transfusion

Table 1: Guidelines for treatment of postpartum IDA associated with blood loss

Parameter	**Value**
Total number of patients (n)	121
Age (yrs; mean ±SD)	27±4.42
Weight (kg; mean ± SD)	52.26±14.34
Type of delivery (n; Vaginal vs. Cesarian)	72(59, 50%) vs. 49(40.49%)
History of PPH (n; %)	7(5.78%)
Total iron deficit (mg; mean± SD)	1061.11±259.11

Table 2: Patient's demography

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Parameter	N	Base line	After FCM therapy	Change from baseline	p-value*
Overall	121	7.78±0.90	10.45±1.31	2.69±1.00	<0.0001
Change in Hb (g/dl) over mean 14.7 days	121	7.78±0.90	10.45±1.31	2.69±1.00	<0.0001

Table 3: Mean values of haemoglobin (g/dl) before and after FCM

*T-test, p <0.05 is statistically significant.

Different Hb (g/dl) strata	N	Base line (mean±SD)	After FCM therapy (mean± SD)	Change from baseline (mean± SD)	p-value*
≤6	9	5.67±0.26	8.32±0.91	2.61±1.15	<0.0001
6.1-8	61	7.39±0.36	10.26±1.06	2.9 ±1.00	<0.0001
≥8.1	51	8.59±0.38	10.62±1.18	2.86±1.09	<0.0001

Table 4: Mean values of Hb (g/ dl) before and after FCM

*T-test, p < 0.05 is statistically significant

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AUTHORS:

1. Surekha Narayan Khandale
2. Kshama Kedar

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Obstetrics & Gynaecology, Indira Gandhi Government College, Nagpur, Maharashtra.
2. Associate Professor, Department of Obstetrics & Gynaecology, Indira Gandhi Government College, Nagpur, Maharashtra.

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NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Surekha Narayan Khandale,
#310, Chandralok Building,
Central Avenue Road,
Nagpur-440018.
E-mail: drsurekha.narayankhandale@gmail.com

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