Role of Ferric Carboxy Maltose (FCM) in Treatment of Anemia among Women in Postpartum Period

NCEAR-A Working Paper Series, Issue 2, 2019

Reported prevalence of postpartum anemia ranges between 50-75%. Under Anemia Mukt Bharat (AMB) guidelines, in postpartum period, daily one tablet of Iron Folic Acid containing 60 mg of elemental iron and 500 µg of Folic Acid is recommended as prophylactic dose for 180 days. Ferric Carboxy Maltose (FCM) is effective and safe for the treatment of moderate to severe anemia (hemoglobin levels between 5.0-9.9 gm/dL) among women in postpartum period.

Introduction:

Anemia is a condition in which the number of red blood cells or their oxygen carrying capacity is insufficient to meet the physiological needs of the body. [1] Postpartum period is defined as the period beginning just after childbirth throughout the subsequent six weeks. World Health Organization defines anemia in non-pregnant women (15-49 years) as hemoglobin level <12 gm/dL.[1] Anemia Mukt Bharat (AMB) guidelines also use the same cut off for defining anemia in lactating women. However, many studies suggest that anemia in postpartum period (first six weeks after delivery) should be defined as hemoglobin level <10 gm/dL.[2,3] Prevalence of postpartum anemia (PPA) reported by different studies varies from 50-75%.[4,5] Postpartum anemia is associated with postpartum stress, depression, anxiety, poor cognitive interaction, delayed infant development and sometime even maternal death. [6]

Anemia in postpartum period is defined as hemoglobin concentration <12.0 gm/dL.

Management of anemia in postpartum period:

Under the Anemia Mukt Bharat (AMB) guidelines, in postpartum period, daily one tablet of Iron Folic Acid containing 60 mg of elemental iron and 500 µg of Folic Acid is recommended as a prophylactic dose for 180 days. However, AMB guidelines do not specify the therapeutic regimen for anemia in postpartum period.

National Centre of Excellence and Advanced Research on Anemia Control (NCEAR-A) recommend injection Ferric Carboxy Maltose for treatment of moderate to severe anemia among women in postpartum period (hemoglobin levels between 5.0-9.9 gm/dL).

FCM-molecular structure and mechanism of action[7]:

The Ferric Carboxy Maltose (FCM) molecule has an outer covering of carboxymaltose over a core of iron. Due to its unique structure, the dissociation of the iron carbohydrate complex is very low in the blood stream. Strongly bound parenteral iron carbohydrate complexes, e.g., FCM, are taken up through endocytosis by the macrophages of the reticulo-endothelial system. In a further step, the endosome fuses with a lysosome and the acidic and reducing environment in the endolysosome leads to cleavage of iron from the complex. The Fe2+ is incorporated into ferritin, and remains transiently stored within the macrophage, or can be transported out of the macrophage by the trans-membrane protein, ferroportin (as Fe2+). The exported Fe2+ is immediately oxidized by ceruloplasmin to Fe3+ which is sequestered by transferrin for transport in the serum to the sites of utilization, e.g., in the bone marrow for hemoglobin synthesis. FCM has high molecular weight and a high structural homogeneity, and, thus, deliver iron from the complex to transferrin in a regulated way via macrophages endocytosis and subsequent controlled export. Therefore FCM can be administered intravenously and is clinically well-tolerated even at high doses.

FCM is safe and clinically well tolerated even at high doses.

Pharmacokinetics:

FCM has a strong iron and carbohydrate bond. After intravenous administration, FCM is distributed mainly in the blood stream with the volume of distribution equivalent to the plasma volume (around three liters).[6] Within 5–10 minutes of the infusion it reaches the liver, spleen and bone marrow, where it is taken up by the reticulo-endothelial system. Its concentration from the liver and spleen decreases gradually after 15 minutes, but the bone marrow concentration increases steadily. Serum half-life (t1/2) of FCM is about 7.4 to 12.3 hours, whereas it becomes undetectable after 60–96 hours post infusion. [8]

Due to slow dissociation in the blood stream after administration, very small amounts of FCM saturate transferrin and other non-transferrin molecules. FCM has physiological osmolarity and neutral pH. All these properties lead to fewer side effects. Therefore, large amount of iron can be infused in a single dose (up to 1,000 mg). In addition, FCM administration in postpartum period has been found to be safe for breastfed neonates. [9]

Impact of FCM on hemoglobin level and other related parameters

A. **Increase in hemoglobin level following FCM administration:** Studies conducted in different parts of India report a rise in hemoglobin level ranging from 3.2 gm/dL to 4.4 gm/dL six weeks after FCM administration among women in postpartum period. [10,11]

The rise in hemoglobin level ranges from 3.2-4.4 gm/dL six weeks after FCM administration.

B. Increase in serum ferritin level following FCM administration: Studies done in India report a rise in serum ferritin level, six weeks after FCM administration, ranging from 44 ng/mL to 219 ng/mL among women in postpartum period.[11–13]

Calculation of dose of iron requirement:

Total dose of iron requirement should be calculated using Ganzoni's formula[11] i.e. Total iron requirement (in mg) = Body weight (in kgs.) X (Target Hb- Actual Hb in gm/dL) X 2.4 + allowance for Iron stores. Target Hb can be set at 12.0 gm/dL, and allowance for iron stores as 500 mg.

How to administer FCM:

FCM is to be administered as intravenous infusion of 500 mg to 1000 mg dose based on calculated dosage diluted in 100 mL of 0.9% Normal Saline solution over 15 minutes. Maximum dose of 1000 mg can be given in a single setting. If needed, the second dose can be given after one week later to make up the remaining of the calculated FCM dose.

Follow-up:

The hemoglobin level of postpartum women should be checked at 4-6 weeks after the administration of FCM. If there is no improvement in the hemoglobin levels at the end of the FCM treatment, other causes of anemia should be investigated.

Hemoglobin estimation is sufficient to monitor the progress after administration of FCM. In hospitals with advanced laboratory facilities, serum ferritin should be the biomarker of choice.

Adverse events following FCM administration:

The rise in hemoglobin level ranges from 3.2-4.4 gm/dL six weeks after FCM administration.

FCM, as outlined above, releases a very small amount of iron into the blood stream. Therefore, there is a low saturation level of transferrin and non-transferrin protein. This feature enables the administration of a large dose of FCM in a single go with minimal side effects. Animal study conducted by Ballie et al showed lowest oxidative stress (measured by nitrotyrocine and dinitro phenyl) by iron sucrose followed by FCM.[14] Toblli et al., in animal studies found no significant difference in oxidative stress (indicated by pro-

inflammatory markers like TNF-α, IL6) when compared to control after infusion of FCM.[15] Many studies conducted throughout the world among humans have documented that FCM is safer than other available alternatives. The reported minor adverse reactions with FCM infusion are:

Local reactions:

urticaria, local burning sensation, pain at injection site, and rash.

Generalized reactions:

headache, nausea, vomiting, constipation and dizziness.

Other less common side effects are generalized discomfort, shivering, hyperpyrexia, epigastric pain, abdominal pain.

Safety profile:

FCM has been approved for clinical use in India and abroad (USFDA). It was approved on 11.02.2011 for clinical use in India by the Drug Controller General of India. Since then, tertiary care centres have used FCM in antenatal and postpartum women.

Conclusion:

FCM is safe and effective in the treatment anemia among women in postpartum period. FCM may be used for the treatment of moderate and severe anemia among women in postpartum period.

The hemoglobin level of postpartum women should be checked at 4-6 weeks after administration of FCM.

Summary of the existing guidelines on use of FCM for treatment of anemia among postpartum women

S.no	Data Source	Indication	Contra-indication	Other remarks
1.	Anemia – guidelines for use of Ferinjet in pregnancy and postpartum period for the treatment of iron deficiency anemia Version: V4.2 Date of approval: October 2018 NHS Foundation Trust, Royal Berkshire, UK[16]	- Hb level 7-9 gm/dL and asymptomatic - Hb >9gm/dL and symptomatic	Patients with thalassemia and sickle cell diseases	Maximum single dose of 1000 mg or 15 mg/kg as a single dose
2.	Guideline for administration of Ferinjet infusion for management of iron deficiency anemia (IDA) Version: 1.1 Date of approval: February 2016 Worcestershire Hospital Services NHS Trust, UK[17]	Hb level <10 gm/dL	Non-iron deficiency anemia and history of drug hyper sensitivity	Maximum single dose of 1000 mg or up to 20 mg/kg as a single dose
3.	Ferinject in pregnancy and postpartum period for treating iron deficiency anemia Version:2.0 Date of approval: October 2018 Mid Essex Hospital Services NHS Trust, UK[18]	Where there is a need to correct iron deficiency and ensuing anemia urgently	Hepatic impairment, thalassemia or sickle cell anemia	Maximum single dose of 1000 mg or 15 mg/kg as a single dose

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National Centre of Excellence and Advanced Research on Anemea (NCEAR-A) is established in All India Institute of Medical Science (AIIMS), New Delhi with the support of Ministry of Health and Family Welfare (MOHFW), GoI, and UNICEF. The mandate of NCEAR-A is to develop and provide technical support to the Ministry of Health and Famity Welfare, Government of India, for incorporating scientific, policy and community perspective in policy and programmatic decisions for control of anemia.

Suggested Citation:
Kant S et al. Role of Ferric Carboxymaltose (FCM) in Treatment of Anemia in Postpartum Period, NCEAR-A, AIIMS, New Delhi, 2019

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