

A Hospital Based Study to Assess the Usefulness of Using the Combination Regime of the Ferric Carboxy Maltose, Vitamin B12 and Folic Acid as a Treatment of Severe Anemia among Pregnant Women in a Rural Tribal Community of South Gujarat

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Abstract

Introduction: Anemia is most common morbidity in pregnancy and micronutrient deficiency is its most common cause in India. **Objective:** It is to assess the beneficiary effects as well as side effects of single parenteral administration of ferric carboxymaltose (FCM), Vitamin B12, and folic acid as treatment of severe anemia during pregnancy. **Methods:** This pre-post intervention study was done from April 2018 to March 2019 at a charitable hospital. 100 pregnant women were treated with one infusion of FCM (1000 mg), along with intramuscular Vitamin B12 (500 mcg) and folic acid (15 mg) followed by daily oral supplementation of iron (100 mg) up to delivery. **Results:** Compared to baseline, absolute increase in hemoglobin was 2.9 g/dl ($P < 0.001$) and 5.4 g/dl ($P < 0.001$) after 6 weeks of infusion and at delivery, respectively. 63.9% of women turned nonanemic and none had severe anemia at delivery. No serious side effect was reported and none needed blood transfusion at any time during the study. **Conclusion:** FCM along with Vitamin B12 and folic acid might be considered for treating severe anemia in pregnancy in resource-poor settings.

Keywords: Anemia, ferric carboxymaltose, pregnancy

INTRODUCTION

Severe anemia is an important reason for morbidity and mortality among pregnant women in India. Over 50% of pregnant women in the country are anemic.^[1] To treat severe anemia in pregnancy, iron sucrose is approved for administration requiring 200 mg twice weekly infusions with or without blood transfusion.^[2] Due to the need of multiple infusions and side effects, compliance is a major concern with parenteral iron sucrose.^[3] Ferric carboxymaltose (FCM) was developed for intravenous (IV) administration of large amount of iron requiring only one or two infusions. Many studies outside India have shown that FCM is more effective, easy to monitor, and safe, especially in pregnancy.^[4] In the absence of any studies on FCM among pregnant women in tribal Indian population, this study was done to assess its efficacy and safety among a cohort of pregnant women suffering from severe anemia during their pregnancy.

MATERIALS AND METHODS

Study was conducted at a hospital that functions as the first referral unit in predominantly tribal Jhagadia block of Bharuch district in Gujarat for 1980. It was a single group pre and postintervention design.

All severely anemic pregnant women with hemoglobin value between 4.0 g/dl and 7.0 g/dl seeking antenatal care from April 2018 to March 2019, aged 18 years and above, in the second

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trimester of pregnancy and ready to be delivered at study hospital were eligible. Women having microcytic-hypochromic anemia with high RDW suspicious of iron deficiency who were residing in nearby 3 blocks of Bharuch district (Jhagadia, Valia, Netrang) were included for easier follow-up. Women who had known hypertension, diabetes or other comorbidities, sickle cell disease, thalassemia, macrocytic anemia or hypersensitivity to IV iron solution were excluded from the study. Women who weighed < 35 kg, had blood transfusion during the first trimester, or clinically unstable were excluded from the study.

All participants received IV infusion of 1000 mg of FCM in 100 mL of 0.9% m/v NaCl over 15 min at enrollment. Based on the following equation, 1000 mg dose was established.^[4]

Hemoglobin iron deficit (mg) = body weight (kg) × (14-hemoglobin) × (2.145) + (iron to replenish stores)

Deficiency of Vitamin B12 and folic acid is also common causes of anemia in India.^[4] Therefore, along with FCM, folic acid and Vitamin B12 (cynocobalamin) were supplemented in the form of intramuscular injection vitcofol (Vitamin B12 500 mcg + folic acid 15 mg + niacinamide 200 mg) 2 ml for 5 days started immediately with FCM injection. However, typical pregnancy requirements are additional 1000 mg. Hence, iron tablet with zinc (Tablet Tonofolic XT: Ferrous ascorbate 100 mg + Zinc 22.5 mg) was orally administered once a day for 120 days. Participants were not charged for the treatment. The adhesiveness of this oral medication was monitored through the follow-up visit paid by participants to the hospital after 6 weeks of enrolment.

Hemoglobin was tested using Sysmex-i800-5-part-cell-counter in hospital's laboratory at enrollment, after 6 weeks of enrollment, and at the time of the delivery. The data on side effects and birth outcomes were collected. The data collection was done by a trained data collector, recorded in register, and entered in MS Excel. The reminders for the follow-up were sent to the mothers 2 days prior the concerned date.

Sample size was calculated to estimate the difference of 1 g/dl in hemoglobin for paired sample. At 95% confidence interval with 90% power, 99% alpha, and a standard deviation (SD) of 2.11, it came to be 66. The nonresponse was assumed to be around 10%, considering the 1 year of follow-ups so the registration was done for 100 females. The final sample size was 72 women whose pre and postintervention hemoglobin was measured.

The primary indicator for this study was improvement in hemoglobin level. The tested hypothesis was whether the treatment led to increase in hemoglobin level of women during pregnancy. Paired *t*-test was used to test the differences. Frequency of adverse events, low birth weight, and newborns having congenital anomalies were also reported. Frequency, proportions, and mean with confidence interval were calculated. Statistical Software SPSS-20 was used to perform the final analysis (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

Ethical consideration

Institutional Ethics Committee approved this study. Informed written consent was taken from all the participants after explaining them the intervention, its benefits, and risks.

RESULTS

Table 1 shows the background characteristics of the participants. 95% of them were tribal, all in their second trimester of pregnancy.

Figure 1 shows that 100 participants were enrolled and 28 participants were lost to follow-up by the time they delivered.

Table 2 shows that mean improvement in hemoglobin was 2.9 g/dl (95% CI: 2.74–3.18, *P* < 0.001) and 5.4 g/dl (95% CI: 5.11–5.74, *P* < 0.001) at 6 weeks and delivery respectively, compared with baseline. No woman needed blood transfusion at any time during their pregnancy.

Figure 2 shows that none of the women had severe anemia and almost two-third women were no more anemic at the time of delivery.

There were no side effects reported at the first follow-up or at the time of delivery except only nausea in two participants at the time of FCM administration. None of the neonates had congenital anomalies. All 72 mothers had live births. Mean birth weight was 2719 g (SD: 442), mean gestational weeks were 38.1 (SD: 2.33), and no congenital anomalies.

DISCUSSION

The use of FCM for the treatment of severe anemia is relatively new. Our study suggested that combination of FCM,

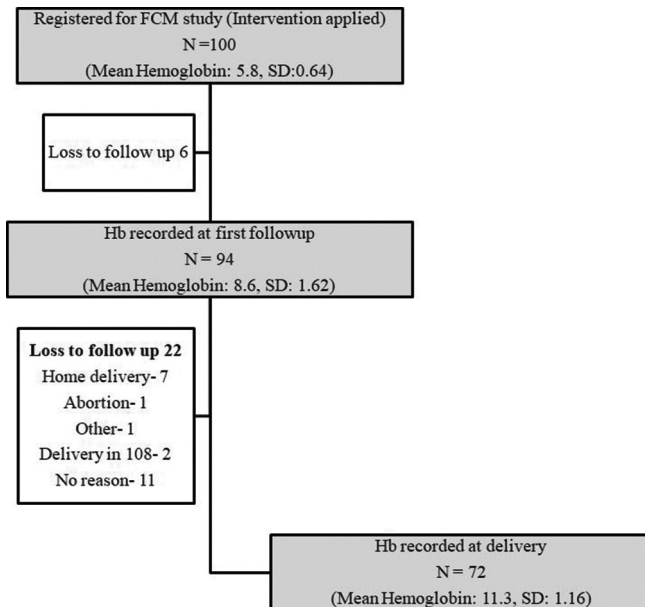
Table 1: Participant's characteristics at the time of enrollment (n=100)

Characteristic	Frequency (%)
Age (years)	
18-24	73
>25	27
Education (standard)	
Illiterate	16
1-8	47
9-12	37
Status of gravid	
Primi	42
1-3	44
>3	14
Hemoglobin at enrollment (g/dl)	
4-4.9	8
5-5.9	47
6-6.9	45
Mean gestational weeks at enrollment (weeks)	20
Mean patient weight (kg)	44
Median systolic BP (mmHg)	110
Median diastolic blood pressure (mmHg)	64

Table 2: Mean difference of hemoglobin between defined time interval

	Mean difference in hemoglobin (SD)	95% CI of the difference	Significance
At first follow-up and enrollment	2.96 (1.08)	2.74-3.18	<0.001
At delivery and enrollment	5.42 (1.33)	5.11-5.74	<0.001
At delivery and at first follow-up	2.51 (1.39)	2.17-2.84	<0.001

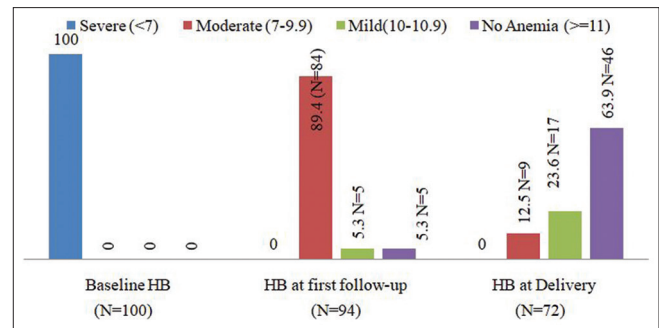
SD: Standard deviation, CI: Confidence interval

**Figure 1:** Flow chart

Vitamin B12, and folic acid might be an effective and pragmatic approach for severely anemic pregnant women in remote areas where blood transfusion is not easily available, and compliance to multiple doses of iron sucrose is challenging. It showed significant improvement in hemoglobin with minimal side effects.

Bernd Froessler (2014), Anouk Pels and Wessel Ganzevoort (2015), and Rafael Aporta Rodriguez (2016) showed that IV FCM was effective and safe in the treatment of iron deficiency anemia during pregnancy.^[5-7] Our study showed that persistently higher rise in Hb with no women remained severely anemic at the time of delivery and no serious side effects. Studies from India by Mohinuddin (2019) and Patel (2015) reported very few mild side effects as it was seen in our study.^[3,8]

Patricia Christoph (2012) had compared FCM and iron sucrose for treating severe anemia in pregnancy and concluded that the FCM was better tolerated. Although FCM has a comparable safety profile as iron sucrose, a much higher single dosage of FCM reduces the need for repeated administration.^[9] Christian Breymann (2016) concluded that during the last stage of pregnancy, FCM was a more appropriate option than first-line iron for rapid and effective anemia correction.^[10] In the present study, such comparison with either oral or parenteral iron sucrose was not done.

**Figure 2:** Proportion of woman at enrolment, after 6 weeks of treatment and at the time of delivery according to their status of anemia

Limitations of the study

We did not investigate levels of micronutrients; however, such investigations are not routinely available in resource-poor settings. FCM is costlier than iron sucrose; it avoided the need and cost for blood transfusion. Randomized control trials are required to establish effectiveness of the combination regimen.

CONCLUSION

Our study was conducted in remote tribal area which has high prevalence of severe anemia among women. The combination of single infusion of FCM, parenteral Vitamin B12, and folic acid may provide an efficient, effective, safe, and practical option to treat severely anemic pregnant women, especially in resource-poor settings. However, more studies with robust study design are required to compare effectiveness and costing with iron sucrose.

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Conflicts of interest

There are no conflicts of interest.

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