Original Article

Efficacy and Safety of Ferric Carboxymaltose for Iron-Deficiency Anemia (IDA) in Postpartum Women: An Observational Study

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ABSTRACT

Objective: To assess the efficacy and safety of ferric caboxymaltose in postpartum women with iron deficiency anemia using single dose infusion in a tertiary care hospital.

Study Design: A single center, single-arm observational study

Place and Duration of Study: This study was conducted at the Ziauddin Hospital Keamari, Karachi which is affiliated with Ziauddin University, Karachi from April, 2014 and November, 2014.

Materials and Methods: A single center, single-arm observational study was conducted at Ziauddin Hospital Keamari, Karachi which is affiliated with Ziauddin University between April, 2017 and November, 2017. A total of 60 women 10 days or less after delivery with postpartum Hb less than 9g/dl diagnosed as iron deficiency anemia. The dosage of ferric carboxymaltose was fixed as 1000mg diluted in 100 ml normal saline infused in 30 minutes or less, for all the patients. CBC, serum iron, serum ferritin, TIBC were performed prior to administration of ferric carboxymaltose and then repeated after week 2 and week 4. The primary efficacy end point was the change in Hb from baseline to week 4.Secondary efficacy endpoints included change in Hb and other serum iron parameters. A secondary outcome measure was occurrence of adverse events from baseline to week 4.

Results: There was a statistically significant improvement in haemoglobin levels over a period of 4 week (day 0 - 14 $p<0.001$, day 0 - 28 $p<0.001$). The mean MCV was not found to be statistically significant between baseline and week 2 and week 4 ($p = 0.158$, $p = 0.658$).We found a statistically significant improvement in TSAT and serum ferritin from baseline to week 2 and week 4 ($p <0.001$).

Conclusion: In conclusion, ferric carboxymaltose seems to be the drug of choice if I/V iron treatment during postpartum period becomes necessary. Our study shows that the tolerance of ferriccarboxymaltose in pregnancy is excellent, and prevalence of side effects is low, in the postpartum period.

Key Words: Post partum anemia, iron deficiency anemia, blood loss

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INTRODUCTION

Anemia is defined by World Health Organization as hemoglobin of less than 12g/dl. It is a global public health issue[1,2]and its most common cause is iron deficiency[3].Postpartum anemia occurs in 50-80% of mothers in the developing countries[4] and is common even in the developed world.[5,6]

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Iron deficiency is most prevalentin the developing countries[7]. Furthermore postpartum anemia is associated with depression in the postpartum period, stress, anxiety, cognitive impairment and poor mother child bonding with consequent delay in the infant development[8,9].Mothers who are anemic also have increased risk of infections including infections of breast and urinary tract, delayed healing of the wounds and diminished supply of milk[10,11].Postpartum anemia in postpartum patients is caused primarily by inadequate iron intake prior to and during pregnancy[2], and by peripartum blood loss.[12,13]

Patients with postpartum anemia have a longer average length of hospital stay, are more likely to receive a blood transfusion, and there is an increased hospital cost. For many decades the mainstay of treatment of iron deficiency anemia has been oral or conventional parenteral iron and red blood cell (RBC) transfusions. However, oral iron supplementation can lead to significant gastrointestinal side effects resulting in non-compliance in many patients. The conventional

parenteral iron supplements including iron sorbitol citrate, and iron sucrose are associated with allergic reactions which may prove to be lethal. Moreover multiple doses make parenteral iron non-convenient for the patient. The risks for blood transfusion are well established and it should be avoided whenever possible[14].

Ferric carboxymaltose (FCM)is a newer dextran-free iron formulation with a near neutral pH, physiological osmolarity and increased bioavailability which allows for single dose, short fifteen minute infusion time and higher dosing (upto 1000 mg) These properties make ferric carboxymaltose an attractive alternative to iron sucrose in terms of risk profile, efficacy, patient comfort and convenience, staff and institutional resource utilization. It facilitates effective treatment of iron deficiency as well as rapid replacement of iron stores.

Postpartum anemia is widespread in Pakistan, but there is paucity of local studies and there is a serious need for developing a proper protocol and management strategy for treatment of anemic mothers. This will help in reduction of morbidity associated with anemia and improve maternal health situation in our country. The total drug infusion concept with third-generation parenteral iron molecules is convenient for the patient and can save resources in the health care system, especially when compared with oral therapy and blood transfusions.

MATERIALS AND METHODS

A single center, single-arm observational study was conducted at Ziauddin Hospital Keamari, Karachi which is affiliated with Ziauddin University between April, 2014 and November, 2014. An institutional review board approved the study protocol for the center prior to initiation. All subjects gave written informed consent before enrollment. A total of 60 subjects was considered as sufficiently powered to detect differences in Hb levels at week 4 versus baseline ($\alpha = 0.05$, two-sided; 90% power).Women 10 days or less after delivery with postpartum Hb less than 9g/dl diagnosed as iron deficiency anemia, with peripheral smear showing microcytic hypochromic anemia, low serum ferritin levels and intolerance to oral iron supplementation were enrolled in our study after they gave informed consent. Patients with concomitant severe hepatic, cardiovascular or renal disorder, asthma or atopic allergy, severe psychiatric disorders, severe infection, and who had received parenteral iron therapy or blood transfusion for anemia within last 20 days were excluded from this study.

After obtaining informed consent patients were administered ferric carboxymaltose. The dosage of ferric carboxymaltose was fixed as 1000mg diluted in 100 ml normal saline infused in 30minutes or less, for all the patients. CBC, serum iron, serum ferritin, TIBC were performed prior to administration of ferric carboxymaltose and then repeated after week 2 and week 4. All laboratory data for efficacy analysis were collected and analyzed at the hospital laboratory. A pre designed Performa was filled that included patients bio data and initial and subsequent hematological values.

The primary efficacy end point was the change in Hb from baseline to week 4.Secondary efficacy endpoints included change in Hb and other serum iron parameters. A secondary outcome measure was occurrence of adverse events from baseline to week 4. Adverse events were classified using the Medical Dictionary for Regulatory Activities Terminology. For the purpose of this study, allergic reactions (hypersensitivity) were classified by grade according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. An AE was classified as serious if it met any one of the following: death, life-threatening, hospitalization, disability, or important medical events.The data was analyzed using SPSS version 19. Paired t-test and Wilcoxon signed-rank test was used to compare the changes in parameters from baseline to week 2 and 4. A p-value <0.05 was considered as significant.

RESULTS

A total of 60 post-partum women who delivered at our tertiary care hospital were included in the study. Most common age group included women between 28-32 years of age (n = 26, 43.3%). About 55% (n=33) of women were multigravida and 45% (n=27) were primigravida. At screening (day 0),mean hemoglobin, mean MCV, mean TSAT and mean serum ferritin were 8.13± 0.9 g/dL, 79.8± 9.5 fL, 9.7% and 52.7 ng/ml. At day 14, mean hemoglobin, mean MCV, mean TSAT and mean Serum ferritin were 10.5 ± 1.2 g/dL, 82.6± 15.4 fL, 25.8% and 777.3ng/ml. At day 30, mean hemoglobin, mean MCV, mean TSAT and mean Serum ferritin were 11.8 ± 1.02 g/dL, 80.9± 19.5, 26.3% and 316.1 ng/ml.

Table No. 1: Demographic Characteristics of Study Participants (n=60)

Age (years)	Mean ±sd	32.1 ± 4.3
Gravidity	Mean ±sd	2.1± 1.2
Parity	Mean ±sd	1.6±0.8
Delivery Method n(%)		
Vaginal		38 (63.3)
Caesarean		18 (30)
Forceps		03 (5)
Vaccum		01 (1.7)
Weight (kg)	Mean ±sd	72.4 ± 17.8

There was a statistically significant improvement in haemoglobin levels over a period of 4 week (day 0 - 14 $p<0.001$, day 0 - 28 $p<0.001$) Figure 1. The mean MCV was not found to be statistically significant between baseline and week 2 and week 4 ($p = 0.158$, $p = 0.658$)

but still a small rise of 1.1 fL. We found a statistically significant improvement in TSAT and serum ferritin from baseline to week 2 and week 4 (p <0.001). Other parameters like TIBC and Iron showed marked improvement after FCM administration.(Table 2).

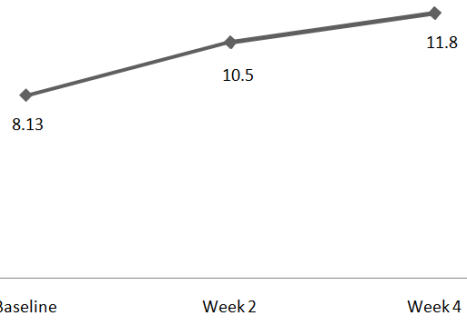

Figure No. 1: Hemoglobin values before and after treatment

Table No.2: Hematological values at baseline, week 2 and week 4(n=60)

Parameters		Screening				
		Baseline	Week 2	P value*	Week 4	P value**
Hemo-globin	g/dL	8.13	10.5	<0.001	11.8	<0.001
MCV	fL	79.8	82.6	0.158	80.9	0.658
TSAT	%	9.7	25.8	<0.001	26.3	<0.001
S. ferritin	ng/ml	52.7	777.3	<0.001	316.1	<0.001

* Baseline and week 2 **Baseline and week 4

During the first 24 hours of the treatment period in the study subjects, The most common treatment-emergent adverseevents after receiving FCM were nausea (3.3%), headache (5%), palpitations (5%) and dizziness (1.6%)Figure 2.However, no serious ADR was reported in any patient.

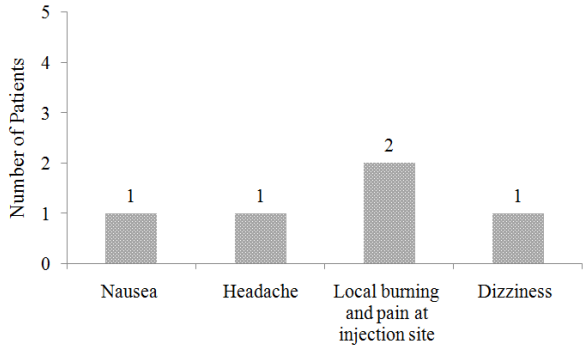

Figure No.2: Treatment Related Adverse Events

DISCUSSION

Postpartum anemia is a common problem in our population. In the vast majority of patients the underlying cause is iron deficiency as a result of either noncompliance of patients with iron preparation or a non-booked status during pregnancy. Occurrence of postpartum hemorrhage further complicated the picture. The conventional treatment is either blood transfusion, iron supplementation in the form of oral iron or multiple doses of intravenous iron which is largely dependent on patient's compliance. Use of ferric carboxymaltoseprovides us the opportunity to treat iron deficiency anemia with a large dose of intravenous iron in a single administration. This is important as the patient can be loaded with iron during her hospital stay and thus is independent of the patient's compliance. However, safety and tolerability of this preparation is important in addition to its efficacy. Since the oral compliance is a problem in post partum females the 1000mg dose seems a promising option in order to maintain the hemoglobin level, and meet the iron need in lactation.

In this study we found that after a single dose administration of ferric carboxymaltose the mean hemoglobin increased from 8.13 on day 0 to 10.69 on day 10 and 11.64 on day 30 which means an increase of 2.56g/dl after 10 days and 3.51g/dl after 4 weeks. This is in accordance with the study done by Froessler who found an increase in hemoglobin levels at 3 and 6 weeks post infusion of ferric carboxymaltose ,however his cohort was of pregnant mothers[15].Setu Rathood reportsthe mean increase in Hb after 2 weeks as 3.2 g/dLand 4.4 g/dL at 6 weeks In post partum females, afterthey received ferrous carboxymaltose[16].

In our study we found that the rise in ferritin at day 30 was 238.5microgram above the baseline and the mean end of trial (day 30). Mean T SAT (transferrin saturation) was 25.36% after 30 days as compared to 10.69% of baseline.Vikrant has also reported similar trends in T SAT. In his subjects the TSAT increased from baseline of 19.5 % to 25.5 % at follow up[17].Bailie reported that serum ferritin increased in theferrous carboxymaltose treatment group[18].Our results are also consistent with the results of a meta-analysiswhich showed an end-of-trial increase over oral iron of hemoglobin and ferritin[19].We did not find any adverse reactions in our study subjects. Vikrant also didn't find any significant minor or major side effects in his study participants. Overall, both drugs (FCM & IS) did not show any serious ADR and these are expected events that are reported in previous literature.[20-23]

CONCLUSION

Intravenous ferric carboxymaltose was safe and well tolerated and an effective treatment option for postpartum and postoperative anemic women. Advantages included achievement of normal haemoglobin levels in a shorter duration, single administration with no relevant clinical safety concerns and a single dose infusion can avoid multiple visits.

Author's Contribution:

Concept & Design of Study:	Shahina Ishtiaq, Urooj Malik, Minahil Majid
Drafting:	Muhammad Athar Khan
Data Analysis:	Minahil Majid, Mehreen Yousaf Rana, Rozina Khaskheli
Revisiting Critically:	Muhammad Athar Khan, Shahina Ishtiaq, Mehreen Yousaf Rana, Rozina Khaskheli
Final Approval of version:	Shahina Ishtiaq, Urooj Malik, Minahil Majid

Conflict of Interest: The study has no conflict of interest to declare by any author.

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