Research Article

Benefits of Ferric Carboxymaltose Administration for Enhanced Hemoglobin Levels in Urban Population of Sindh: BOFERIN® Observational Study

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Abstract: Background: Iron deficiency anemia is a major public health issue in developing countries, especially among women of reproductive age. Anemia is a major public health problem in women of reproductive age in rural Pakistan and a large proportion of women were found to have low levels of serum iron.

Materials and Methods: A multicenter observational cohort study was conducted at Karachi & Hyderabad from 8th February 2022 to 30th April 2022. Women with low hemoglobin level and age 18-45 years were included in this study. Patients were grouped according to 1-week assessment and 3-week assessment of hemoglobin concentration. A single dose of a generic substituent ferric carboxymaltose (Boferin®) was administered to the patients over 15 minutes infusion. Baseline hemoglobin levels were compared at 1 week and 3 weeks after administration of Ferric Carboxymaltose.

Results: A total of 104 patients were enrolled in this study. The mean hemoglobin levels at baseline were 9.22 ± 0.175 g/dl and 7.55 ± 0.329 g/dl for 1-week and 3-week, respectively. The mean hemoglobin increases after 1 week and 3 week was reported as 1.4211± 0.169 g/dl ($p< 0.001$) and 2.321± 0.335 g/dl ($p< 0.001$) respectively. Only three patients presented with mild to moderate adverse effect which included abdominal discomfort and nausea.

Conclusion: This is a first in class study has shown statistically significant increase in hemoglobin at 1-week and 3-week interval with minimal side effects. It is concluded that Boferin® is efficacious in increasing hemoglobin levels in patients with iron deficiency anemia with its safety being documented in pregnant Pakistani population as well.

Keywords: Anemia, Iron-Deficiency, Iron carboxymaltose, Generic drugs, Hemoglobin, Ferric carboxymaltose.

INTRODUCTION

Anemia is one of the most frequent dietary deficiencies worldwide. Nutritional anemia affects people of all ages and genders, but it is more common in women and relates to maternal morbidity and death, as well as low birth weight. Anemia in reproductive-age women is a worldwide public health issue. Anemia prevalence varies by geographic region and genetic background among women of reproductive age for a number of reasons. World Health Organization reported a 29.9% prevalence of anemia worldwide as of 2021, and a prevalence of 41.1% anemia in women of reproductive age of Pakistan [1, 2].

Iron-Deficiency Anemia (IDA) is the most common type of anemia, with the World Health Organization claiming that 50 percent of two billion anemic people had IDA [3, 4]. IDA can be caused by a long-term low iron balance or inadequate bioavailability/absorption of dietary iron. Iron deficiency normally develops over time, and until the anemia becomes severe, there are usually no evident clinical symptoms. IDA causes a loss of appetite, which exacerbates anemia. Iron deficiency causes impaired motor and sensory system function, as well as delays in cognitive and physical development, resulting in reduced labor capacity, which has an impact on the country's growth [5-7].

Iron deficiency anemia is defined as a Hemoglobin (Hb) level of less than 13.0 g/dL in male adults, less than 12.0 g/dL in female adults who are not pregnant, and less than 11.0 g/dL in pregnant women [8]. Hemoglobin synthesis is reduced in iron deficiency anemia, which results in the formation of hypochromic and microcytic RBCs. Reduced iron intake or absorption, increased iron requirement during adolescence and pregnancy, bariatric surgery, significant blood loss during menstruation, chronic gastrointestinal (GI) blood loss, polyps, or cancer are some of the factors that contribute to IDA [9, 10].

Pregnant women who have anemia are more likely to have poor

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perinatal outcomes such as preterm birth, intrauterine growth restriction, low birth weight, or neonatal anemia. Anemia also has negative effects on the mother, increasing her risk of pre-eclampsia and postpartum depression [11, 12].

The goal of treatment for IDA patients should be to replenish iron reserves and restore normal Hb levels. This has been demonstrated to enhance QoL, morbidity, chronic illness prognosis, and pregnancy outcomes [13]. IDA is often treated with a range of orally administered ferrous (sulphate, fumarate, gluconate, glycine-sulfate) or ferric (protein-succinylate, mannitol-ovoalbumin, polymaltose complex) iron supplements, which are widely accessible, secure, and reasonably priced. However, oral iron absorbs poorly and may be further decreased by some drugs (such as proton pump inhibitors) and meal consumption, making therapy time-consuming (months to correct anemia and replenish iron stores). Chronic and acute inflammation may make it more difficult for people to absorb iron from food. It has been shown that parenteral iron is not only better, but also essential, and that avoiding IVI is not only ineffective but also possibly harmful. Ferric carboxymaltose (FCM), ferric gluconate (FG), ferumoxytol (FXT), iron isomaltoside 1000 (ISM), iron sucrose (IS), and low-molecular weight iron dextran (LMWID) are the six parenteral iron products that are primarily used in clinical practice [14].

Ferric carboxymaltose is a novel dextran-free intravenous iron that has a ferric hydroxide core and a carbohydrate shell to stabilize it. This enables for the controlled transport of iron to the reticuloendothelial system's cells, as well as the following delivery of iron-binding proteins. Because it delivers a large dose of iron in a short amount of time, ferric carboxymaltose is beneficial in the treatment of IDA. It can deliver up to 1500 mg of iron in just two 750 mg doses administered at least a week apart [15].

The carbohydrate shell is incompletely broken down in the circulation after intravenous administration of Ferric carboxymaltose by α-amylase. The Ferric carboxymaltose is then taken by macrophages via an endocytic mechanism in which the carbohydrate shell and polynuclear iron core are entirely broken down in endolysosomes and $Fe3^+$ is released. The liberated $Fe3^+$ is therefore expected to be reduced to $Fe2^+$ by the six-transmembrane epithelial antigen of the prostate. Divalent metal transporter-1 activity extrudes $Fe2^+$ from endolysosomes to the cytosolic labile iron pool, and Ferroprotein activity extrudes $Fe2^+$ from the cytosol to the plasma. It is then delivered to the liver, bone marrow, and other tissues by Transferrin [16].

Generic substituents are encouraged in the healthcare system to aid the patients according to the budget constraints. In terms of active ingredients, generic medications are the same as their brand-name counterparts, but inactive substances can differ. Inactive substances are added during the production process for stability and preservation, as well as to obtain a specific consistency, form, color, or taste. This implies that a generic and a brand-name medicine are interchangeable [17].

The majority of generic drugs have the same quality, safety, and efficacy as the original brand name product, but they are often 20-90 percent less expensive. Various studies have shown that generic medicine offer equivalent therapeutic outcomes compared to their brand name counterpart [18, 19]. The aim of this study is to evaluate the efficacy and safety of a generic substituent of ferric carboxymaltose manufactured by a national pharmaceutical industry in Pakistan.

MATERIALS AND METHODS

This is a multicenter, single drug evaluation, observational cohort conducted at different hospitals of Karachi and Hyderabad. Institutional Review Board (IRB) approval had assigned the study no. of 22/MAMJI/IRB/03. The study was started after IRB approval on 8th February 2022 and concluded on 30th April. During the timeline, patients complying with the inclusion criteria were included in this study i.e., anemia due to iron deficiency and with a screening hemoglobin level of less than 10 g/dl. Informed consent was taken from all the patients participating in the study. Patients were administered a single dose of a generic substituent of ferric carboxymaltose at doses according to their body weight. The medicine was administered as intravenous infusion diluted in normal saline as per guidelines. The infusion was as 15 minutes infusion.

Patient data including patient age, weight, vitals (Blood pressure, respiratory rate, heart rate), concomitant drugs administered, pregnancy status and smoking status was recorded. Patient sensitive data was kept confidential and excluded from the analysis. The patients were categorized into pregnant and non-pregnant. Patients with comorbidities such as diabetes, primary hypertension, cancer, autoimmune disease, post-surgical recovery, and hepatitis B & C were excluded from the study. Only patients with iron deficiency anemia, with or without pregnancy were included in the study.

Patients were administered ferric carboxymaltose single dose diluted in 100ml normal saline over 15 minutes infusion. Patients were observed for any adverse effect during administration. According to investigator's advice and discretion, patient's hemoglobin was followed at 1-week interval or 3-week interval (as per physician's discretion) to assess the increase in hemoglobin and therefore placed as separate groups. The data was tabulated and analyzed using Minitab version 20.3 by Minitab LLC. Two-sample t-test for mean was applied to analyze the significance of change in hemoglobin at 1-week and 3-week interval.

STATISTICAL ANALYSIS

Sample size calculation was not necessary as all the patients complying with the inclusion criteria were included in the study, that has also been done by Toledano *et al.* & Bach *et al.* [20, 21]. Two sample t-test for sample mean at 0.01 level of significance was used to statistically analyze the mean difference of hemoglobin level at baseline to 1-week and 3-week after drug administration.

RESULTS

A total of 104 female patients having serum hemoglobin less than 10g/dl were enrolled in this study. Out of which 38 patients were followed for upto 1 week after administration of dose and 66 patients were followed upto 3 weeks. The age group of patients observed was 18-47 years with an average age of 29.9 years. Among these patients, 28 were pregnant (third trimester) and 76 non-pregnant. The baseline variables and their value are mentioned in Table **1**. According to which, the mean baseline blood pressure and pulse was found to be within the normal range. The mean weight of participants was 63.45Kg ± 1.43.

event were reported among the patient being administered ferric carboxymaltose generic substituent.

The mean increase in hemoglobin after single dose administration of generic substituent of ferric carboxymaltose was found to be 1.41 ($p<0.001$) after 1-week and 2.32 ($p<0.001$) after 3 weeks from baseline as mentioned in Table **3** and Table **4**.

DISCUSSION

In a variety of disorders associated with absolute or functional iron shortage with or without anemia, the therapeutic efficacy of parenteral Ferric Carboxymaltose has been examined in various

Table 1. Baseline Characteristics of Participants Observed in the Study.

Variable	Mean ± SE
Age	29.96 ± 1.09
Weight	63.45 ± 1.43
Pulse (beats per minute)	86.490 ± 0.975
Blood Pressure (mmHg)	113.4/74.1 ± 1.19/0.978

Table 2. List of Concomitant Medications Used.

S. No	Concomitant Medication	Occurrence in Patients
01	Calcium Supplements	n=5
02	Vitamin D Supplements	n=4
03	Vitamin B6 Supplements	n=3
04	Vitamin C Supplements	n=3
05	Alpha Methyldopa	n=1
06	Multivitamin Supplements (Including vitamin A, B-complex, C, D, E) and Minerals (Iron Phosphorus, Iodine, Magnesium Selenium Molybdenum, Chromium, Potassium Chloride)	n=3

Table 3. Two Sample t-test for Sample Mean for Hemoglobin Assessed at 1-week after Administration of Ferric Carboxymaltose.

Variable		Mean ± SE	p-value
Hemoglobin (g/dl) N=38	Before Infusion	9.221 ± 0.175	
	After Infusion	10.642 ± 0.169	
	Mean Difference	1.421	<0.001

Table 4. Two Sample t-test for Sample Mean for Hemoglobin Assessed at 3-week after Administration of Ferric Carboxymaltose.

Variable		Mean ± SE	p-value
Hemoglobin (g/dl) N=66	Before Infusion	8.551 ± 0.175	
	After Infusion	10.872 ± 0.169	
	Mean Difference	2.321	<0.001

Patients were also taking additional medications which are highlighted in Table **2**. Only one pregnant patient aged 21 years was suffering from gestational hypertension was prescribed alpha methyldopa to control her high blood pressure. Only 3 patients presented with mild to moderate adverse effect which included abdominal discomfort and nausea. No severe or harmful adverse

multicenter trials. Patients with IBD, abnormal uterine bleeding (AUB), postpartum IDA, chronic heart failure (CHF), anemia in the second and third trimesters of pregnancy, post-partum anemia (PPA), and chronic kidney disease patient with or without hemodialysis are among those included in the trials. The majority of these studies used oral iron as a comparison, and

Ferric Carboxymaltose was found to be more effective than oral iron in terms of improving Hb levels, especially when it came to body iron replenishment [22-24].

This is a first in class study to evaluate the safety and efficacy of a generic substituent of ferric carboxymaltose on manufactured by a national pharmaceutical of Pakistan. Our study was aimed to assess the increase in hemoglobin concentration after the administration of generic substituent of ferric carboxymaltose. This study revealed that single dose administration of ferric carboxymaltose resulted in hemoglobin increase of ~1.4g/dl after 1-week of drug administration and ~2.3 g/dl after 3-week. These findings are in accordance with the global finding of hemoglobin increase at 3 weeks after administration of Ferric carboxymaltose [25-29].

The study population was stable as evident by the baseline characteristics and did not possess any comorbidities (only one patient had gestational hypertension) which may prove to affect the study results. No effect of concomitant medication was observed as reported in Table **2**. Patients were evaluated for their smoking status as smoking affects iron uptake. No patient was reported to smoke in the study population [30].

Our study also revealed that few patients were suffering from severe anemia (baseline hemoglobin ~3g/dl) in 3-week group and single dose ferric carboxymaltose was not sufficient to elevate the hemoglobin level to normal range but produced significant increase in hemoglobin concentration. This finding reveals that more doses are required to correct low hemoglobin in severe anemia to acceptable range. Our study revealed that ferric carboxymaltose is safe to use in pregnant population as well. Only nominal adverse events were observed during administration of ferric carboxymaltose.

CONCLUSION

This is a first in class study to assess the effect of generic substituent of ferric carboxymaltose (Boferin®) on hemoglobin concentration in Pakistani population. The study has shown statistically significant increase in haemoglobin at 1-week and 3-week interval with minimal side effects. It is concluded that Boferin® (ferric carboxymaltose) is efficacious in increasing haemoglobin levels in patients with iron deficiency anaemia with its safety being documented in pregnant Pakistani population as well.

LIMITATION

This only reported the effect of generic ferric carboxymaltose in a limited number of patients and on a single variable of hemoglobin. Further studies should be conducted in larger population and different laboratory parameters to further assess the safety and efficacy of generic Ferric carboxymaltose in Pakistani population.

ETHICS APPROVAL

Institutional review board of MAMJI Hospital provided the ethical approval to conduct this study (No. 22/MAMJI/IRB/03).

FUNDING

Generic Ferric Carboxymaltose (Boferin®) samples was provided by Bosch Pharmaceuticals Pvt. Ltd. free of cost to the study population. Bosch Pharmaceuticals had no influence in any part of the study.

AUTHORS' CONTRIBUTION

- **Jahanara Ainuddin, Syed Saad Hussain, Sarmad Iqbal**: Conception or design of the work.
- **Jahanara Ainuddin, Raheel Sikander, Azra Aslam, Nasreen Majid**: Data collection.
- **Jahanara Ainuddin, Raheel Sikander, Azra Aslam, Nasreen Majid**: Data analysis and interpretation.
- **Syed Saad Hussain, Sarmad Iqbal**: Drafting the article.
- **Syed Saad Hussain**: Critical revision of the article.
- **Jahanara Ainuddin, Syed Saad Hussain**: Final approval of the version to be published.

CONFLICT OF INTEREST

Declared none.

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