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Efficacy and safety of ferric carboxymaltose in anemia in pregnancy

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Abstract
Objectives: To study the role, safety and efficacy of ferric carboxymaltose in antenatal women.
Methodology: This will be a prospective interventional study conducted in Obstetrics and Gynaecology department of AMC MET medical college. Study group of 40 antenatal women between 20 weeks to 32 weeks of gestation will be followed through. Haemoglobin level before infusion of FCM and after 2 weeks of infusion will be estimated. The efficacy of ferric carboxymaltose will be analysed in study group. The evaluation of safety and tolerance to mother will also be monitored.
Inclusion criteria: Gestational age > 20 weeks and < 32 weeks, Haemoglobin concentration of > 6 gm% and < 8 gm%.
Exclusion criteria: Hypersensitivity reaction to any iron preparation, History of blood transfusion, History of iron overload diseases, Concomitant medical or surgical diseases.
Results: A total of 40 antenatal patients were included in our study. It's observed that the incidence of anaemia was higher among the reproductive age group especially in pregnant women of 21 to 30 years of age, than so in age group less than 20 and more than 30. Out of which 35% were primigravida and 65% were multigravida. Among 40 patients who received Inj. Ferric carboxylate maltose, 3 patients developed drug reactions. The mean rise in haemoglobin was found to be 0.9gm/dl at the end of 15 days from treatment. Correspondingly the MCV and RDW values were up by 11fL and 4.3% respectively.
Conclusion: Ferric carboxymaltose is a safe and effective treatment option for iron deficiency anaemia in antenatal patients.

Keywords: Anaemia, pregnancy, haemoglobin, ferric carboxymaltose

Introduction

Anaemia is a major public health problem worldwide. The global prevalence of anaemia during pregnancy is estimated by the world health organisation to be 47.4% [1]. Anaemia during pregnancy is one of the most common issue encountered both in developing and developed areas [2]. Among anaemia, Iron deficiency anaemia is a prevalent condition during pregnancy and may result from different factors [3]. Many women have low or empty iron stores already at the start of pregnancy. During pregnancy, the physiological need for absorbed iron increases from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester [4]. Total iron demand in pregnancy is about 900mg of which about 500-600mg are lost in the blood loss at delivery and a similar amount is expended at lactation. Dietary iron intake does not compensate for this strongly increased iron demand, because of poor bioavailability. Consequently, the risk of iron deficiency and, ultimately, iron deficient anaemia increases during pregnancy.

As per WHO, anaemia during pregnancy is defined as haemoglobin concentration of less than 11 gm% and haematocrit less than 33% [5]. The centre of disease control and prevention defined anaemia as less than 11gm/dl in first and third trimester and less than 10.5 gm/dl in second trimester [6]. Progression from iron deficiency to IDA in pregnancy is common, due to the increased demand for iron during pregnancy (about 1000 mg), required to support maternal haemoglobin mass expansion as well as the growing fetus and placenta. All this makes iron supplementation, a necessity in all pregnant women.

Anaemia during pregnancy in India contributes as cause to 20% maternal death directly and 50% for associated causation [7]. The relative risk of maternal mortality associated with moderate anaemia (hb 4-8) was 1.35 and for severe anaemia (hb<4.7gm/dl) was 3.51 [8]. The important consequences of moderate to severe anaemia during pregnancy has susceptibility towards infection, Intrauterine growth retardation, premature delivery, increased perinatal morbidity and mortality [9].

Also during delivery the requirement for blood transfusion increases with increase in cardiovascular complications, longer hospital stay, reduced lactation, and postpartum mood disorders. Iron therapy can be administered orally or parenterally. Oral iron is the treatment of choice for the majority of patients with IDA because it is safe, effective, inexpensive, and readily available. However, the tolerability of oral iron therapy can be problematic, with up to 40% of patients reporting gastrointestinal adverse events [10, 11]. Intravenous (IV) low-molecular-weight iron dextran has been associated with an incidence of anaphylaxis or anaphylactoid reactions as high as 1.7% [12, 13]. The high incidence of these serious adverse events is believed to be caused by the formation of antibodies to the dextran moiety. Newer parenteral iron products (iron sucrose and iron gluconate) do not contain the dextran moiety, and the incidence of anaphylaxis with these products is markedly lower [12]. However, the physical characteristics of iron gluconate and iron sucrose limit the dose and administration rate.

Ferric carboxymaltose (FCM) is novel non-dextran with type I complex administered rapidly 500mg in 100ml NS over 6 mins and 1000-1500 mg in 250 ml NS over 15 mins as intravenous infusion [14]. It has faster controlled delivery raising Hb and replenishing iron stores at shorter duration with minimal toxicity and anaphylaxis have wider therapeutic index, better compliance and tolerance.

The FER-ASAP (Ferric carboxymaltose-Assessment of Safety and efficacy in Pregnancy) study was the largest prospective randomised study conducted in pregnant women with IDA, and its results showed that intravenous FCM was effective and well tolerated during late-stage pregnancy [15]. In the FER-ASAP study, pregnant women (gestational weeks 16-33) with IDA were randomised in a 1:1 ratio to FCM or ferrous sulphate (FS) for 12 weeks [15]. Haemoglobin (Hb) levels improved at comparable rates in both treatments; however, significantly higher number of women achieved anaemia correction within a shorter time frame with FCM (84%) than with FS (70%; P = 0.031). FCM treatment significantly improved the quality of life (QoL) from baseline up to delivery, and there were markedly fewer gastrointestinal treatment-related adverse events with FCM (11%) than with FS (15%).

The aim and objective of our present study is to study the role and efficacy of ferric carboxymaltose in antenatal women and to study the safety of the same.

Methods

This was an interventional prospective study conducted among 40 pregnant women visiting in department of obstetrics and gynaecology at LG hospital, Maninagar. Ethical clearance was taken from Institutional review board following which detailed demographic and clinical details were taken from patients fulfilling the selection criteria, and a valid written consent was obtained. Patients were admitted in the ward. Upon clinical examination, skin and mucosal pallor was noted and investigations which were evaluated included complete blood count, peripheral blood smear. IV infusion of FCM over 20 mins given. Pretreatment n post treatment vitals were monitored. Patient was asked if having any complain during or after infusion. Repeat CBC was obtained after 15 days of infusion. Values from the pre treatment and post treatment were analysed and documented in spreadsheet. The efficacy of ferric and of carboxymaltose will be analysed in study group. The evaluation of safety and tolerance to mother will also be monitored.

Inclusion Criteria

- Gestational age > 20 weeks and < 32 weeks
- Haemoglobin concentration of > 6 gm% and < 8 gm%

Exclusion Criteria

- Hypersensitivity reaction to any iron preparation
- History of blood transfusion
- History of iron overload diseases
- Concomitant medical or surgical diseases

Results and Discussion

A total of 40 antenatal patients were included in our study. As per Table 1 it's observed that the incidence of anaemia was higher among the reproductive age group especially in pregnant women of 21 to 30 years of age, than so in age group less than 20 and more than 30. A total of 18 patients had haemoglobin >=6 -7gm/dl and 22 patients had haemoglobin 7.1-8gm/dl. Out of which 14 were primigravida and 26 were multigravida. Among our 40 patients who received Inj. Ferric carboxylate maltose, 1 of them had local skin reaction, 1 of them had hypotension and 1 had fever. They were treated conservatively and had an uneventful recovery. The mean rise in haemoglobin was found to be 0.9gm/dl at the end of 15 days from treatment. Correspondingly the MCV and RDW values were up by 11fL and 4.3% respectively.

Table 1: Distribution according to age

Age (years)	No. of women
Less than 20	3
21-30	35
More than 30	2

Table 2: Distribution according to severity of anemia

Hb level in gm/dl	No. of women (Total=40)
>=6-7 gm/dl	18
7.1-8gm/dl	22

Table 3: Prevalence of IDA depending on parity

Parity	No. of pregnant women
Primigravida	14
Multigravida	26

Tablet 4: Adverse drug reactions

Laboratory Parameters	Pre treatment (average)	After 15 days (average)
Hb	7.4 gm/dl	8.3 gm/dl
MCV	67 fL	78 fL
RDW	15%	19.3%

Table 5: Rise in Laboratory parameters after 15 days

Adverse reaction	No. Of pregnant
Injection site reaction	1
Fever	1
Hypersensitivity reaction	0
Hypotension	1
Nausea	0
Vomiting	0

Anaemia in the pregnant women is a serious global health concern [16]. As per WHO, about 32.4 million pregnant women suffer with anaemia out of which 0.8 million are severely anaemic [3]. 50% anaemic cases are attributable to iron deficiency anaemia [6]. Of 1000 Indian women, half of them were anaemic at some point and 40% were throughout pregnancy [17]. IDA during pregnancy increases the risk of low

birth weight, preterm labour, maternal and perinatal mortality with poor Apgar score [7]. WHO estimated about 591000 perinatal deaths and 1150000 maternal deaths globally due to IDA directly or indirectly [16].

Maternal mortality increases if anaemic mothers have postpartum haemorrhage [18]. Anaemia below 8g% doubles the risk of infection and increases maternal morbidity when hb <5 gm%. [14]. Estimated maternal deaths due to IDA in India is approximately 326000 and associated DALYs (Disability adjusted life years) is 12497000 [19]. IDA results in decrease in GDP (Gross domestic product) up to 4.05% in developing countries and 1.18% of India's GDP [19].

Christoph *et al*. conducted a retrospective study on 206 pregnant women (103=FCM, 103=IS) which gave results of rise in haemoglobin by FCM 15.4g% and IS 11.7g%. [20]. FCM was found more efficacious and safer than IS [20]. Similarly Froessler *et al*., carried out prospective observational study in Australia with 65 anaemic pregnant women who received FCM showing significant raise in baseline haemoglobin level [21]. IDA during pregnancy is associated with low birth weight, intrauterine growth restriction (IUGR), intrauterine fetal death (IUFD), fetal distress, low Apgar score and increased perinatal mortality [5]. These significantly occurs in women with mild maternal anaemia, with 2 to 3 folds increase with moderate maternal anaemia and 8 to 10 folds with Hb less -than 5 g%. [5]. Lower iron stores in the IDA can cause poor mental performance or behavioural abnormalities in lately. Significant difference is present in the infants mean birth weight born to anaemic and non-anaemic mothers. Anaemia in second trimester associated with preterm birth which increases by 5 folds in anaemia due to iron deficiency and by 2 folds in anaemia due to other causes [5]. Hence, correction of iron deficiency anaemia during pregnancy with parenteral therapy has role in better neonatal outcome with decreased perinatal mortality [22].

Parenteral iron helps in restoring iron stores faster and more effectively than oral iron. Intravenous (IV) iron sucrose is safe, effective, and economic in comparison to the repeated and painful intramuscular iron injections. Although the incidence of anaphylaxis and other adverse reactions with IV iron sucrose is markedly lower, multiple doses and prolonged infusion times are typically required. IV ferric carboxymaltose (FCM) has a neutral pH (5.0-7.0) and physiological osmolarity, which makes it possible to administer its higher single doses over shorter time periods (single dose up to 1000 mg over 15 min) than other parenteral preparations [23]. Moreover, it does not contain dextran; therefore, the risk of anaphylaxis or serious hypersensitivity reactions is very low, and a test dose is also not required. FCM though reported in the literature is yet to find its place in India for routine use.

Conclusion

Treatment of iron deficiency anaemia should begin early in pregnancy in order to ensure a good iron status prior to delivery. FCM is a safe and effective treatment option and the ability to administer 1000 mg doses in a single sitting, fewer adverse reactions and better compliance makes FCM the first-line drug in the management of antenatal iron deficiency anaemia causing a faster and higher replenishment of iron stores and correction of Hb levels.

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