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Original Article

Intravenous Iron Treatment in Pregnancy: Ferric Carboxymaltose for Correction of Iron Deficiency Anaemia

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Abstract:

Iron deficiency is the most common nutritional deficiency state of women in childbearing age. Peri-partum iron deficiency anaemia (IDA) is associated with significant maternal, fetal and infant morbidity. An effective management is needed to prevent adverse outcomes. Current options for treatment are limited; these include oral iron supplements, which are usually ineffective and poorly tolerated, and whole blood transfusion, which carries an inherent risk, should be avoided during pregnancy. Intravenous ferric carboxymaltose is a new treatment option and it is better tolerated with a good result. The study was designed to assess the safety and efficacy of intravenous ferric carboxymaltose for correction of IDA in pregnant women in third trimester. It was a prospective study; 260 anaemic pregnant women received Injection ferric carboxymaltose, as a total dose of 500-1000 mg between 28 to 36 weeks of pregnancy. Safety was assessed by analyzing adverse drug reactions. Ferric carboxy maltose significantly increased Hb level ($p<0.001$) in all women in this study group. Increased Hb value was observed 3-4 weeks after infusion. None of the women felt worse. No serious adverse effects were found and minor side effects occurred in 34(13%) patients.Our study revealed that the Hb level increased significantly, was well tolerated and without significant side effects.

Key words: Iron Deficiency Anaemia, Infusion Ferric Carboxy maltose, Pregnancy, Haemoglobin, Serum Ferritin.

Introduction:

Anaemia in pregnancy is one of the most common clinical conditions in Obstetrics practice.The most common cause of anaemia in pregnancy is iron deficiency in both the developed and developing world[1]. Peri-partum iron deficiency anaemia (IDA) is associated with significant maternal, fetal and infant morbidity[2]. Iron deficiency anaemia in pregnancy has been defined as low serum ferritin level together with low blood hemoglobin values[3].

The clinical manifestations of anaemia includes skin or mucosal pallor, lack of energy and shortness of breath, fatigue, lack of concentration which may present in different grades depending on the severity of anaemia[4]. Consequences of anaemia in pregnancy are susceptibility to infection and premature delivery, intrauterine growth restriction and consequences of prematurity are increased perinatal morbidity and mortality[5,6]. Anemia in pregnancy is an important indirect cause of maternal death in developing countries.The common consequences are cardiac failure, anesthetic hazards, shock, postpartum haemorrhage, sepsis, venous thrombosis and pulmonary embolism[7]. During pregnancy,the needs of the growing fetus and placenta as well as the increasing maternal blood volume and red cell mass, impose such a demand on maternal iron stores that iron supplementation of daily required dose between 18 and 100 mg from 16 weeks of gestation onwards can't completely prevent the depletions of maternal iron storage at term[8]. This is further aggravated by blood loss during pregnancy and delivery. Deliveries by caesarean section is associated with more blood loss than normal vaginal delivery. All these make women vulnerable for peri-partum blood transfusion, chronic iron deficiency anemia and iron storage depletion[9].

Iron deficiency is potentially preventable and treatable. For many decades the mainstay of treatment for IDA has been oral iron and blood transfusion.However, oral iron supplementation drugs can lead to significant side effects resulting in non-compliance in many patients[10]. The risk of whole blood transfusion is well described

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and should be avoided where possible during pregnancy period[11]. Intravenous iron formulation is an alternative approach for correction of anaemia in third trimester of pregnancy[12]. But intravenous iron was less commonly used as fear of anaphylaxis with iron dextrose formulations, and long infusion time with iron polymaltose[12]. A test dose is also required in iron dextrose due to high risk of hypersensitivity.

The development of dextrose free parenteral iron formulations with an improved safety profile and more rapid delivery time suggests that intravenous iron should be considered as a mainstay treatment of choice for IDA[10].

A novel intravenous iron agent ferric carboxymaltose is a non-dextrose containing drug with a near neutral p^H(5-7), physiological osmolarity and increased bio-availability[13]. It is possible to administer ferric carboxymaltose at higher dose over short period of time than other parenteral preparations[6]. A single dose as large as 500-1000 mg can safely be injected within a period of 15 minutes without a test dose. Because it doesn't contain dextran and chance of anaphylaxis is very low. That makes ferric carboxymaltose a potentially ideal alternative for treating anaemia associated with pregnancy.

Till date, there are few clinical studies using ferric carboxymaltose in pregnant women. The primary aim of our study was to assess the efficacy of ferric carboxymaltose in the correction of IDA in pregnancy. The secondary aims were to determine the extent and severity of adverse effects of ferric carboxymaltose.

Materials and Methods:

This was a prospective study carried out in a private obstetrics clinic, at Faridpur, Bangladesh between July 2014 and June 2015 (one year). A total of 260 pregnant women with diagnosed IDA were treated with intravenous ferric carboxymaltose. Informed written consent was taken from all patients & ethical clearance was taken from appropriate authority. All pregnant women in this group were between the gestational ages of 28 to 36 weeks. They were screened for presence of anaemia.Here anaemia was defined by Hb level less than 10gm/dl. Further it was subdivided as 8-10gm/dl(mild), 6-8gm/dl (moderate) and <6gm/dl (severe). At the same time serum ferritin level was estimated.Serum ferritin level less than 30ng/ml was considered as low iron storage. All women in this study group (n=260) were treated with intravenous ferric carboxymaltose as a single dose (500-1000mg) in an infusion time of 15-20minutes. Maternal blood pressure was recorded at every five minutes interval during infusion and fetal heart rate was assessed before and after the infusion. After infusion oral iron supplementation was withheld for next seven days. All patients were reassessed after 3-4 weeks clinically, by Hb level. Any adverse effect happened during infusion was recorded and a telephone interview was conducted after 48 hours for any complaints related to injection. In this study we used Inj. ferinject (500mg) from Vifor Pharma, Switzerland marketed by UniHealth Limited, Bangladesh. The inclusion criteria were all patients at their gestational age of 28-36 weeks and patients having Hb level below 10gm/dl. The exclusion criteria was patients having renal function impairment. The variables were summarized by their frequency with percentage and by their mean ± SD. Paired t-test was used for comparison of means for clinical parameters. All statistical tests were considered statistically significant at 5% level of significance. Statistical Package for Social Sciences (SPSS) version 20.0 was used.

Results:

A total 260 anemic pregnant women ageing 16 to 45 years were studied and their gestational age was between 28 to 36 weeks. Most of the patients were from middle and low socioeconomic conditions. Among them 13% (34) experienced some sorts of minor adverse effects such as injection site irritation with slight burning sensation, headache, nausea or vomiting etc. Of them, moderate and mild anaemia were 7.69% and 82.31% respectively (Table I).

Table I: Demographic and clinical characteristics of the study Population (n=260)

Variables		Number (%)
Adverse Event:	Adverse event	34 (13%)
	No adverse event	226 (87%)
Anaemia {Hb	Moderate (6-8)	20 (7.69%)
level (gm/dl)}:	Mild (8-10)	240 (82.31%)

Table II represent the maternal and clinical characteristics of the study population. In this table we found that the mean±SD of age, gestational age, Hb level and S. Ferritin levelat initial stage of the study subjects were 25.23 ± 4.99, 31.60 ± 1.73, 8.98 ± 0.05 and 55.39 ± 36.66 respectively.

Table II: Maternal and clinical characteristics of the study population.

Variables	Mean ± SD
Age (years)	25.23 ± 4.99
Gestational age before infusion (weeks)	31.60 ± 1.73
Hb (gm/dl) level before infusion	8.98 ± 0.05
S. Ferritin (ng/ml)	55.39 ± 36.66

Clinical and maternal characteristics compared between before and after infusion of the study population were shown in table III. Compared with the Hb (mean 8.9gm/dl) level before infusion, the Hb (mean 10.53gm/dl) level after infusion had significantly ($p<0.001$) increased. So ultimate increase in Hb level is mean 1.55 gm/dl within 3-4 weeks after infusion of ferric carboxymaltose. It is clearly evident that Inj. Ferric Carboxymaltose significantly ($P<0.001$) increased Hb level among the study participants and it is safe and effective for pregnant women.

Table III: Clinical and maternal characteristics compared between before and after infusion of the study population.

Variables		Mean ± SD	p-value
Hb (gm/dl):	Before Infusion	8.98 ± 0.56	<0.001
	After Infusion	10.53 ± 0.68	

Discussion:

IDA in pregnancy is one of the important causes of maternal and neonatal morbidity in both developed and developing countries. So diagnosis for IDA is important and all pregnant women should be corrected of anaemia before delivery. IDA is also an important indirect cause of maternal death.

In majority of cases anemia can be treated effectively with oral iron preparations. Many patients can tolerate oral iron supplements well; however, up to 40% have side effects. The incidence of adverse effects is also dose dependent. Another important factor is irrational use of anti-ulcerant drugs, which reduces iron absorption[14]. Intolerance to oral iron leads to a greater percentage of failure in correction of iron deficiency anemia during pregnancy.

In third trimester of pregnancy IDA can also be treated with safe blood transfusion. In spite of all clinical tests for safe blood transfusion, still there are lots of adverse effects and should ideally be avoided.

There is little number of clinical studies on using ferric carboxymaltose in pregnant women. A recent Cochrane review concluded that large, good quality trials are required to assess the efficacy and adverse effects of ferric carboxymaltose[15]. There are recent retrospective observational studies comparing ferric carboxymaltose with different intravenous iron preparations that highlighted the safety and efficacy in favor of ferric carboxymaltose[16].

Our results are in line with a number of randomized control studies which have shown the safety and efficacy of ferric carboxymaltose. It permits a much higher single dose over a short period of time. Drug related adverse events are 20% in a study[17] which is 13% in our group. There was a significant ($p<0.01$) increase in haemoglobin level from 3-6 weeks post infusion period but in our study there is also significant ($p<0.001$) increase in Hb level within shorter interval e.g. 3-4 weeks after infusion. In a recent study shows the increase of mean Hb level was 2.48 gm/dl, 4 weeks after infusion of ferric carboxymaltose[17] which is 1.55 mg/dl in our study group.

Ferric Carboxymaltose has been available in Europe since its approval in 2007 and in USA in 2009; it is recently marketed in over 50 countries and is also available in Bangladesh[18].

Thus rapid infusion option of a large single dose of ferric carboxymaltose offers a promising treatment modality for pregnant women with iron deficiency anaemia. This property of ferric carboxymaltose can reduce the IDA related burden of the perinatal patients' complications and improve the health care system.

Conclusion:

Administration of ferric carboxymaltose for correction of IDA in third trimester of pregnancy is likely to be safe and effective and hemoglobin level increased significantly according to previous studies. In this study we also found, correction of IDA by single large dose of ferric carboxymaltose is significant. No serious adverse were observed in this study. Our findings suggested that corrections of anemia with ferric carboxy maltose before labour can reduce the maternal and neonatal morbidity significantly.

Conflicts of interest:

The authors don't have any financial conflicts of interest except the data collection and compilation was assisted by UniHealth Pharmaceutical Limited, Bangladesh personnels, they are the local marketing agent of Vifor Pharma, Switzerland.

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