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INTRAVENOUS FERRIC CARBOXYMALTOSE IN THE MANAGEMENT OF PREGNANT WOMEN WITH IRON DEFICIENCY ANEMIA: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

INTRODUCTION: Iron-deficiency anemia during pregnancy and postpartum occurs frequently and may lead to severe maternal complications. The aim of the study was to assess the safety and efficacy of Intravenous ferric carboxymaltose in the management of anemia in pregnant women during the 3rd trimester.

METHODS: Prospective observational study; 60 anemic pregnant women received 1000mg of ferric carboxymaltose between 29 and 34 weeks of pregnancy. Treatment effectiveness was assessed by repeat hemoglobin (Hb) measurement after 2 weeks. Safety was assessed by analysis of adverse drug reactions during the infusion and 2 hours after infusion.

RESULTS: Intravenous ferric carboxymaltose infusion significantly increased hemoglobin values ($p < 0.001$) above baseline levels in all women. None of the women developed serious adverse events during the study period.

CONCLUSIONS: Intra venous ferric carboxymaltose can be used safely in moderate to severe iron deficiency anemia diagnosed later in

KEYWORDS

Pregnancy, Iron Deficiency Anemia, Ferric Carboxymaltose, Oral Iron Therapy

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Iron deficiency anemia is a common condition during pregnancy in developing countries. The prevalence of anemia in pregnant women is high, affecting 41.8% of all pregnant women. The prevalence of anemia in pregnancy is much more in developing countries. Such high prevalence indicates that, by and large, dietary uptake of iron and supplementation of oral iron therapy are insufficient to meet physiological requirements during pregnancy. The main reason for anemia in pregnancy is increased demand for iron during pregnancy, required to support maternal hemoglobin mass expansion, as well as the growing fetus and placenta. Iron deficiency anemia (IDA)in pregnancy can cause various kinds of gestational complications, as well as increased maternal and infant morbidity and mortality. Maternal consequences include cardiovascular symptoms, reduced physical, mental and immune function and peripartum reserves. Apart from these complications concerns regarding safety and availability of donor blood have promoted avoidance of inappropriate transfusion and encourage use of transfusion-free strategies wherever possible.

UK guidelines published in 2012 defines anemia in pregnancy is defined as: a hemoglobin (Hb) of less than 11 g/dL in first trimester, 10.5 g/dL in second and third trimesters and ,10 g/dL in postpartum period.

Most common options for treatment of IDA in pregnancy include oral iron supplementation . For the majority of women with IDA in pregnancy, oral supplements are adequate, but for a significant minority oral iron therapy has failed. This may be due to malabsorption, poor tolerance or non-compliance. In these circumstances, and late pregnancy with severe grade of anemia requires intravenous iron therapy. Iron (intravenous) IV formulations contain more or less tightly bound ferric iron. Of these formulations 1st generation products include low molecular weight iron dextran and iron sorbitol citrate. These compounds can be given in higher doses but are associated with anaphylactic reactions. A 2nd generation compounds like iron sucrose require multiple injections to supplement 1000 mg of iron. Thus, a new parenteral iron molecule with the advantages of both the parenteral preparations is needed. It is important to find a better way of treating the pregnant patients with IDA. At present, the principle treatment for anemia is oral iron supplementation.

Ferric carboxymaltose is a novel intravenous molecule which can be infused high single doses over a short time period, (typically 15 minutes). It is administered as a single dose of 1000 mg for total body infusion (TBI) dose. This dose provides quick replenishment of body iron stores. Randomized controlled trials of ferric carboxymaltose in the postpartum period have shown either noninferiority or superiority to oral ferrous sulphate in the treatment of iron deficiency anemia, with rapid and sustained increases in Hb. The risk of allergic reaction appears to be exceedingly low with this agent. The evidence for safety and efficacy of ferric carboxymaltose in pregnant women with IDA is currently lacking.

The aim of this prospective observational study was to evaluate the efficacy, safety and tolerability of IV ferric carboxymaltose, in pregnant women with IDA whose gestational age more than 28 weeks and less than 34 weeks and Hb <10gm/dL.

METHODS

After ethics committee approval this prospective study was performed between July 2015 and may 2016. Informed consent was not taken from the patients, as ferric carboxymaltose was being used as our routine clinical treatment modality in this setting.

Pregnant women between 29 and 34 weeks of pregnancy with documented IDA, defined as Hb < 9 g/dl, who consecutively presented as outpatients in our institute to receive ferric carboxymaltose infusions were recruited to this study. A total of 60 women were included. All patients received 1000 mg of ferric carboxymaltose (Ferium by Emcure Pharmaceuticals Ltd, INDIA) either single setting or two doses of 500 mg ferric carboxymaltose 48hours apart.

Baseline data were collected on maternal age and weight, gestational age, adverse events during IV iron treatment. IV iron was administered by nurses, and they were instructed to document the procedure and any side effects during and after administration of the drug. Women were observed for two-hour post infusion, before being discharged home. During this period all women were monitored with noninvasive blood pressure, heart rate and SpO2. The primary outcome of the study was the change in Hb from baseline to week 2.

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STATISTICALANALYSIS

All data were analyzed by student t test (independent samples t test) and Chi-squared test where ever applicable. For all analyses, P-values < 0.05 were considered statistically significant. The statistical analysis was performed with SPSS® 17.0 software (SPSS® Inc., Chicago, IL, USA).

RESULTS

A total of 60 pregnant women were included in the study. Demographic characteristics and basic data are summarized in Table 1. Of the 60 women entered into the study, 11 (18.3%) women were defined as having moderate anemia (Hb 9 - 10gm/dL) and 49 (81.7%) women were defined as having severe anemia. Changes in hemoglobin concentration over the postinfusion period are presented in table 2. The pretreatment hemoglobin level was significantly lower than hemoglobin values measured at 2 weeks. The mean increase in hemoglobin after 2 weeks of initiation of treatment was 2.685gm/dL. All adverse reactions are presented in Table 3. No serious adverse effects were recorded in any of the 60 women receiving ferric carboxymaltose infusion. Minor side effects like injection site irritation occurred in 4 patients. One patient required medication with Metoclopramide for nausea and vomiting. All other adverse events were self-limiting.

Table 1: Demographic data

Variable	Mean ±SD or number (ratio %) (n=60)
Age (years)	22.50 ± 2.703
Maternal weight (kg)	49.32 ± 3.675
Gestational age (weeks)	31.27 ± 2.201
Hemoglobin before treatment (gm/dL)	8.25 ± 0.69
Gravida (primi/multi)	23/37 (38.3/61.7%)
Moderate anemia (Hb 9-10 gm/dL)	11 (18.3%)
Severe anemia (Hb < 9gm/dL)	49 (81.7%)

Table 2: Hemoglobin values before and after treatment

Variable	Mean ±SD	p value
Hemoglobin before treatment (gm/dL)	8.25 ± 0.69	<0.001
Hemoglobin after 2 weeks (gm/dL)	10.94 ± 0.415	
Rise in hemoglobin value (gm/dL)	2.685 ± 0.551	
Hemoglobin >10 gm/dl after 2 weeks	60 (100%)	
Hemoglobin >11 gm/dl after 2weeks	34 (56.7%)	

Table 3: Number of women experiencing a drug related adverse events following infusion with ferric carboxymaltose (total number of women infused n = 60)

Adverse event	Number of patients
Any adverse event	7
Local reaction	4
Systemic reactions	
Hypotension	1
Headache	1
Nausea and vomiting	1
Pruritus	0

DISCUSSION

The main finding of our study is that all women responded to the IV ferric carboxymaltose with increased hemoglobin values higher than their pretreatment values. The another important is that ferric carboxymaltose appears to be a safe and effective treatment modality for the correction of IDA, as no serious adverse events and only few minor adverse events reported. In our study all pregnant women hemoglobin improved >10gm/dL 2 weeks after IV infusion of ferric carboxymaltose, whereas only in 34 (56.7%) pregnant women hemoglobin level improved >11gm/dL (table 2). Similar positive findings also observed by many authors.[11-14]

Many women develop iron deficiency during pregnancy, a condition that can have serious maternal and fetal implications.[15] For some women oral iron supplementation appears to be sufficient to maintain adequate iron stores. However, many women develop moderate to severe IDA despite oral iron supplementation (as demonstrated in the current study where 48% of women were on oral iron), or due to drug intolerance, non-adherence or pre-disposing pathology such as malabsorption or inflammatory bowel disorders. For those women intravenous iron administration may be a more effective treatment modality. IV iron preparations are also increasingly being recommended for women with severe IDA and when IDA is diagnosed later in pregnancy and rapid intervention is required. [16] Intravenous iron provide a greater and more rapid iron supply than oral iron therapy without the gastrointestinal side effects of oral substitution and make it possible to avoid blood transfusion with associated risks.[2] Iron sucrose has been used for years for IV treatment of iron deficiency in pregnant women after the first trimester. However, its use is limited to low dose due to local and systemic side effects in higher doses.

Ferric carboxymaltose is a dextran-free IV iron preparation that allows rapid administration of high single doses of iron (up to 1000 mg iron in 15 min) once a week. Malek et al have previously shown that ferric carboxymaltose does not cross the placental barrier in an in vitro dual perfusion model, and its use is approved in the second and third trimesters of pregnancy.[17] Our results suggest that the larger the amount of iron that can be administered in the form of ferric carboxymaltose, the more effective the replenishment of the iron stores is and the more effective the correction of the anemia is. This, however, needs to be confirmed in appropriately designed multicenter randomized studies.

The main advantage of IV simple Ferric carboxymaltose is it's dosing regime, a large single dose can be given with greater patient compliance compared with iron sucrose which requires multiple doses for complete iron correction.[13] Thus Ferric carboxymaltose reduces the burden on patients to have multiple hospital visits.

The limitations of this study include the fact that it is prospective observational study. A further limitation of our study was the potential for missed adverse events, as this is a small study.

CONCLUSIONS

In summary, our study shows that intravenous ferric carboxymaltose is a safe and effective for management of iron deficiency anemia in late-stage pregnancy, when time to delivery is a limiting step. IV ferric carboxymaltose may be a more appropriate option than oral iron for rapid and effective correction of anemia. IV Ferric carboxymaltose can be considered for pregnant women who are non-compliant with, or are intolerant of oral iron treatment, as well as those who have severe IDA. Further research including randomized trials is needed to confirm usefulness of ferric carboxymaltose in late-pregnancy.

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