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INTRAVENOUS FERRIC CAROXYMALTOSE FOR ANAEMIA IN PREGNANCY

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ABSTRACT

Background: Iron deficiency is a very common nutritional deficiency amongst women of reproductive age. Peripartum iron deficiency anaemia (IDA) is associated with significant maternal, fetal and infant morbidity. Currently for treatment are limited: these include oral iron supplementation, which can be ineffective and poorly tolerated, and red blood cell transfusions, which carry an inherent risk and should be avoided. Ferric carboxymaltose is new treatment option that may be better tolerated.

The study designed to assess the safety and efficacy of iron deficiency anaemia (IDA) correction with intravenous ferric carboxymaltose in pregnant women with mild, moderate and severe anaemia in pregnancy.

Methods: retrospective observational study; 43 anaemic pregnant women received ferric carboxymaltose up to 15 mg/kg between 24 and 40 weeks of pregnancy . Treatment effectiveness was assessed by repeat haemoglobin (Hb) and serum ferritin measurements and patient report of well-being at3rd week. Safety was assessed by analysis of adverse drug reactions and fetal heart rate monitoring during the infusion.

Results: Intravenous ferric carboxymaltose infusion significantly increased Hb values ($p < 0.01$) above baseline levels in all women. Increased Hb values were observed at 1and 3 weeks post infusion a. Ferritin values increased significantly after the infusion. Fetal heart rate monitoring did not indicate a drug related negative impact on the fetus. Follow-up interview during revisit was conducted on 43 (100%) women at3weeks. Of these women, 35 (81.3%) reported an improvement in their wellbeing (48% reported feeling "much better", 15% reported "a little better", and 8(18) reported feeling "no different") after the infusion. None of the women re- ported feeling worse.

Conclusions: Our retrospective data is consistent with existing observational reports of the safe and effective use of ferric carboxymaltose in the treatment of iron deficiency anaemia in pregnancy.

KEYWORDS : Pregnancy, Iron deficiency, Intravenous ferric carboxymaltose, Red blood cell transfusion

BACKGROUND

Anemia Of pregnancy is defined as Hb<10.g/dL with a slight variation according to trimester of pregnancy. However a hemoglobin level of <10g/dL indicates anemia at any stage during pregnancy. Nutritional iron deficiency anemia (IDA) is a most common disorder in the world affecting more than two billion people. In a singleton gestation, maternal need for iron averages about 1000mg. Of this, 300mg is for fetus and placenta, 500mg for maternal for maternal Hb mass expansion and 200mg that is shed normally through gut, urine and skin. This is further aggravated by blood loss associated with delivery. According to WHO data, the prevalence of IDA in pregnancy in pregnancy ranges from an average of 14% in developed countries to average of 56% in developing countries. IDA in pregnancy can be associated with serious maternal complications. Studies have shown that low Hb during pregnancy is associated with increased risk of low birth weigth, preterm birth, IUD and incidence of which increases as severity of anemia increases. New approaches are leading to more effective management of this condition. Patients with IDA are commonly prescribed oral iron preparations because of low cost and convenience but the efficacy of these agents is limited by their decreased absorption rate and GI side effects. Peripartum iron deficiency anemia is associated with significant maternal, fetal and infant morbidity. Women with iron deficiency anemia are also at risk of adverse effects requiring medical interventions such as red blood transfusion, cardiovascular problems, reduced physical and cognitive performance, reduced immune function, tiredness and increased depressive episodes. Peripartum maternal iron deficiency has been associated with childhood developmental problems and negative mother infants interactions such as an increase in negative statements and decreased responsiveness. Deliveries by both cesarean section and vaginal deliveries that require instrumentation/intervention represent an even greater risk increasing women vulnerability for peri- partum blood transfusion, chronic iron deficiency anemia and iron store depletion, all compromising maternal wellbeing. However, this recognition has not resulted in a universal approach of iron supplementation.

Iron deficiency is potentially both preventable and treatable. Effective management strategies that allow women to replenish iron stores, both antenatal or during labour, restore hemoglobin values and are likely to enhance the health of health of the mother and infant. For many decades the mainstay treatment of IDA has been oral iron and red cell transfusion. However oral iron supplementation can lead to significant side effects resulting in non-compliance in many patients and risks for RBC transfusion are well described and should be avoided whenever possible. Intravenous iron formulations offer an alternative approach in the presence of moderate or severe anemia, intolerance of or non –adherence to oral iron and malabsorption states. Intravenous iron is less commonly used as fear of anaphylaxis with iron dextran formulations with and long infusion time with iron polymaltose, have led reluctance amongst clinicians. The development of dextran 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 for moderate to severe IDA.

Iron sucrose and ferric carboxymaltose are dextran free intravenous iron alternatives. When compared to oral iron in pregnancy iron sucrose is superior with respect to the rate of both hemoglobin increases and iron store replenishment, combined with a good safety profile. Serious adverse effects are rare with iron sucrose, however minor side effects occur in up to 18%of patients which may in part be attributed to its non-physiological properties. Ferric carboxymaltose is a newer dextran free iron formulation with a near neutral pH, physiological osmolality and increased bioavailability which allows for single dose, short 15minutes infusion time and higher dosing up (up to 1000mg). 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. To date, there are few clinical studies using ferric carboxymaltose in pregnant women. The primary aim of this study was to assess the use of intravenous ferric carboxymaltose in correction of iron deficiency anemia in pregnant women. The secondary aims were to determine the extent and severity of adverse effects of ferric carboxymaltose and to evaluate the perceived quality of life of women in the post-partum period

METHODS:

This retrospective study was performed between Jan 1st 2015 and december 2015. Informed consent was waived for data collection, as ferric carboxymaltose was being used as our routine clinical treatment modality . Pregnant women with documented IDA, defined as Hb < 10 g/dl, who consecutively presented as outpatients in the Kanachur medical college derlakatte to receive ferric carboxymaltose infusions were recruited my study. A total of 43 women were included. As there is limited availability of safety data for its use in pregnancy, adopted a longer infusion protocol (30 min) than recommended by the manufacturer (15 min). Blood pressure was taken every five minutes during infusion and also foetal heart rate was assessed before and after infusion. According to routine antenatal care blood samples were collected to measure haemoglobin, and ferritin levels, prior to infusion and then again after three post-infusion visits. Haemoglobin and ferritin concentrations were determined in the hospital laboratory. Women were observed for one hour post infusion, before being discharged home. Data were collected from case notes and electronic laboratory reports, as well as transfusion data linkage reports. In resist the patient interview was conducted after all 43 patients delivered to evaluate well-being after the infusion. Patients were asked to place themselves into 1 of 4 allocated categories (worse, no different, better or much better), which reflected degrees of perceived change in symptomatology since infusion.

The data were analysed using p values of ≤0.05 to indicate significance. Available preinfusion, post infusion haemoglobin and ferritin.

RESULTS:

Characteristics of the women receiving ferric carboxymaltose for iron deficiency anaemia are outlined in Table 1. A total of 43 women received a ferric carboxymaltose infusion for antenatal iron deficiency anaemia, with preinfusion haemoglobin data available for all 43 women. Following infusion, haemoglobin values were repeated as required and data were available: 43 women (100%) at visit 1 (1week post infusion), 43 women (100%) at visit 2 (3weeks post infusion). All women responded to the treatment with increased Hb values.

43 women entered into the study, 15(35%) women were defined as having severe anaemia (Hb <7 g/dl), while 18 women (42%) were defined as having moderate anaemia (7-9 g/dl) and the remaining 10(23.2%) women had mild anaemia (9-10 g/dl)

The pre infusion haemoglobin level was significantly lower than haemoglobin values measured at all subsequent visits ($p < 0.01$ in each case). There was a significant increase in haemoglobin levels from 1 to 3 weeks post-infusion (average increase 12 g/dl; $p < 0.01$).

Table 1 Demographic information of women

		numbers	percentage
age	<20	15	35%
	20-30	16	37%
	>30	12	28%
BMI			
	underweight	16	37%
	normal	29	67.4%
	overweight	5	12%
	obese	2	5%
parity			
	primigravida	12	28%
	multigravida	15	35%
	grand multi	16	37.2%
mode of delivery			
	vaginal	15	35%
	emergency LSCS	10	23%
	elective LSCS	11	25.5%
	vaccum	7	16.2%
Hb at booking			
	mild	23	53.4%
	moderate	13	30.2%
	severe	7	16.2%
ferritin levels below 17microgrmz/l		26	60.4%

When IDA severity was included in the analysis, a similar pattern of results emerged (Table 2). Haemoglobin levels increased post infusion at 1and 3 weeks, to be significantly higher than baseline levels ($p < 0.01$ in all cases).

	pre infusion	increase in 1st week	increase in 3week
mild	23	13(56%)	10(43%)
moderate	13	7(53%)	6(46%)
severe	7	2(28%)	5(71%)

$p<0.01$

Ferritin values increased significantly after the infusion (Table 3).

ferritin levels <17microgrms/dl	at booking	at 1 week increased	at 3weeks
	26	14(54%)	12(46%)

All adverse reactions are presented in Table 4.

		number	Percentage
local(injection site irritation)		4	4%
systemic	hypotension	3	3%
	headache	1	1%
	nausea/vomiting	1	1%
	pruritus	1	1%

No serious adverse effects were recorded in any of the 43 women receiving an infusion. Minor side effects occurred in 10 (30%) patients. One patient required medication with Metoclopramide for nausea and vomiting. All other ad- verse events were self-limiting. Fetal heart rate monitoring did not indicate a drug related adverse effect on the fetal heart pattern. Red blood cell transfusions were required by 7 women (16%) in the study.

Follow-up interview during revisit was conducted on 43 (100%) women at3weeks. Of these women, 35 (81.3%) reported an improvement in their wellbeing (48% reported feeling "much better", 15% reported "a little better", and 8(18) reported feeling "no different") after the infusion. None of the women re- ported feeling worse.

Discussion

This is the retrospective study reporting on ferric carboxymaltose infusions in pregnancy. key finding of our study is that in women presenting with IDA in pregnancy, a ferric carboxymaltose infusion prior to delivery significantly increased haemoglobin levels and improved iron stores. Also its demonstrate 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.

Many women develop iron deficiency during pregnancy, a condition that can have serious maternal and fetal implications [1]. In this study, first trimester booking bloods showed only discrete anaemia with mean Hb of 10 g/dL, but all women studied developed moderate to severe IDA. The low mean ferritin at booking of 17 µg/L represent pro-found iron deficiency and reiterates the importance of ferritin as a screening tool. This finding should generally result in the initiation of iron supplementation. 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 supple- mentation .To date

no prospective, controlled clinical study has been performed using ferric carboxymaltose in pregnant women. A recent Cochrane review concluded that large, good quality trials, assessing clinical outcomes (including adverse effects) as well as the effects of treatment by severity of anaemia are required [2]. In the absence of these studies, observational safety and efficacy data may help identify potential benefits and risks. Two recent retrospective observational studies comparing ferric carboxymaltose to different intravenous iron preparations highlighted the safety and efficacy of ferric carboxymaltose [3,4].

The rapid delivery option of a large single dose of ferric carboxymaltose offers a promising treatment modality for pregnant women who need correction of iron deficiency and anaemia, over other IV iron formulations that have low dosage limits, such as iron sucrose (200 mg). The properties of ferric carboxymaltose may also reduce the burden on the patient and the health care system.

Conclusion

The data from this retrospective study is consistent with existing retrospective data that ferric carboxymaltose administration in the second and third trimester of pregnancy is likely to be safe and effective. In our study ferric carboxymaltose successfully corrected IDA prior to delivery. No serious adverse events were recorded. Well-being also improved for the majority of women after the infusion.

Abbreviations

IDA: Iron deficiency anaemia; Hb: Haemoglobin;

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