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INTRAVENOUS IRON THERAPY IN PREGNANCY: A COMPARISON BETWEEN INTRAVENOUS FERRIC CARBOXYMALTOSE AND INTRAVENOUS IRON SUCROSE

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ABSTRACT

Background: Anemia being the most common nutritional deficiency disorder in the world affects the pregnancy and its outcome, more so in the developing countries. With the prevalence of more than 60%in India, it needs an effective and novel tool for treatment of anemia in pregnancy which has deleterious effects on the mother and the baby. Ferric carboxymaltose formulation is safe and effective in treating iron deficiency anemia. **Objective:** To compare the safety, efficacy and tolerance of Ferric carboxymaltose and Iron sucrose in iron deficiency anemia in pregnancy. **Methods:** 100 pregnant women were allocated into two groups. Group A IV FCM group subjects were given 1000mg FCM at single setting. Group B IV Iron sucrose subjects were given multiple doses of 200mg per day on day 0,2,4,6,8 total of 1000mg iron sucrose. Both groups Hb%, PCV, Red cell indices, Peripheral smear were done on day 0 and after 4weeks of parenteral iron therapy. Rise in Hb, Red cell indices along with side effects and tolerability were noted. **Results:** There was statistically sifnificant rise in Hb (P<0.001)in FCM group of 2.09g/dl when compared to Hb in Iron sucrose group 1.82g/dl. No serious adverse effects were noted either in FCM group or Iron sucrose group. **Conclusion**: FCM can be used an effective alternative to afford the efficacy of IV Iron administration without the inconvenience of multile small doses, with less side effects and better tolerance in pregnancy.

KEY WORDS: Anemia in pregnancy, Ferriccarboxymaltose, Iron sucrose, Iron deficiency.

INTRODUCTION

Anemia is the most common nutritional deficiency disorder in the world. WHO has estimated that prevalence of anaemia in pregnant women is 14% in developed, 51% in developing countries and 65-75% in India.[1] About one third of the global population (over 2 billion) are anemic.[2] Anemia in pregnancy is a condition with effects that may be deleterious to mothers and fetuses. Maternal anemia causes severe maternal morbidity and mortality[4]. Studies suggest that a fall in maternal haemoglobin below 11g/d1 is associated with a significant rise in perinatal mortality rate.[3, 4, 5] There is usually a 2 to 3-fold increase in perinatal mortality rate when maternal haemoglobin levels fall below 8g/d1 and 8-10 fold increase when maternal haemoglobin levels fall below 5g/dl.[6,7] A significant fall in birthweight due to increase in prematurity rate and intrauterine growth retardation has been reported when maternal haemoglobin levels were below 8 g/d1.

Iron is available in various forms, oral and parenteral for supplementation. Oral iron agents are inexpensive and modestly effective. However,GI complaints afflict up to 20% of patients taking ferrous iron salts.[8,9] As many as 30% of unselected patients may be totally nonadherent to prescribed therapy[10] and efficacy hinges, of course, on prolonged, successful adherence to a twice or thrice-daily pill-taking regimen.[11] Intravenous (IV) iron preparations are promising. They 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.[12] Although the incidence of anaphylaxis and other adverse reaction with newer agents [iron sucrose, ferric gluconate] is markedly lower, prolonged infusion times are typically required and multiple clinic visits for the calculated dosage administration are challenging to the patients compliance.

Ferric carboxymaltose does not contain dextran and the risk of hypersensitivity reaction is very low and a test dose is not required. It has several advantages over iron sucrose like it overcomes the low dosage limitation of iron sucrose, rapid infusion rate i.e., 1000mg within 15 min, fewer clinic visits and safe option at higher doses.

This also adds to potential cost savings to the health care providers.

METHODS

We performed a prospective observational study to analyze the efficacy, side effects and tolerance of intravenous ferriccarboxymaltose(IV FCM)and intravenous iron sucrose(IV IS) in pregnant women. Study was conducted at the Department of OBG, VIMS, Ballari between January 2013 and March 2013.

A total of 100 pregnant women presenting to antenatal clinic who gave informed consent were included for the study. All were randomly assigned to either Group-A IV FCM or Group-B IV Iron Sucrose. After detailed history and examinations, lab investigations were performed. Haemoglobin, PCV, red cell indices, red cell count, and peripheral smears were performed. Group-A subjects were given IV FCM single dose, 1000mg diluted in 200 ml of 0.9% NS over 15 mins. Group-B received IV Iron Sucrose in multiple doses, 200mg per day on Day 0, 2, 4, 6, 8, total of 1000mg. Each 200mgiron sucrose was diluted in 100ml of 0.9% NS and given over 20 mins. Side effects like pain, fever, rashes, urticaria and anaphylactoid reactions like pain at injection site were looked for during the procedures. Patients were observed for one hour after the infusion. Mild allergic reactions were managed by stopping the infusion and giving Chlorpheniramine 10mg IV slowly. All emergency drugs (adrenaline, hydrocortisol etc.) to manage any adverse reactions were kept ready. Both the groups Hb%, PCV, red cell indices, red cell count and peripheral smears were repeated after four weeks of the last dose parenteral Iron.

The endpoint of the study was to evaluate efficacy, the raise in haemoglobin, red cell indices, side effects and tolerability. Statistical analysis were performed.

RESULTS

A total of 100 pregnant women were included in the study. 50cases received ferric carboxymaltose and 50 received iron sucrose. Demographic characteristics and general characteristics are summarized in Table l and 2 respectively. Demographic data showed significant difference between the two groups in the age and weight parameters.

Table 1: Agewise distribution of study subjects

Age group	FCM group	Iron sucrose group	Total
15 – 20 years	19 (38%)	07 (14%)	26 (26%)
21 – 25 years	23 (46%)	19 (38%)	42 (42%)
26 – 30 years	07 (14%)	19 (38%)	26 (26%)
>30 years	01 (02%)	05 (10%)	06 (06%)
Total	50 (100%)	50 (100%)	100 (100%)

Chi square – 14.12 df-3 p value – 0.003

Table 2: General characteristics of study subjects

Variables	FCM group		Iron sucrose group		P value*
	Mean	Std.deviation	Mean	Std.deviation	
Age (years)	22.56	3.3	25.10	3.9	0.001 (S)
Weight (Kgs)	49.84	7.8	53.90	4.4	0.02 (S)
Height (cms)	150.80	6.3	150.46	3.4	0.73 (NS)

*independent‘t’ test

Efficacy of IV Iron Treatment: In the group treated with Ferric Carboxymaltose, women received 1000 mg IV Iron and group treated with iron sucrose received 5 doses of 200mg of intravenous iron. The mean haemoglobin rise in the group receiving FCM was 11.47g/dl and 11.22g/dl in the group receiving Iron Sucrose. The mean follow up time was 4 weeks after the last dose of IV Iron administration in both the groups. This difference is statistically significant. Blood parameters in both the groups before and after drug intervention are summarized in table 3,4,5.

Table 3: Comparison of blood parameters between two groups before drug intervention

Blood parameters	FCM group		Iron sucrose group		P value*
	Mean	Std.deviation	Mean	Std.deviation	
Haemoglobin (gm%)	9.37	0.8	9.39	0.7	0.89 (NS)
RBC (mcells/cmm)	3.58	0.4	3.71	0.4	0.14 (NS)
PCV	28.96	3.4	28.13	2.2	0.15 (NS)
MCV (fl/dl)	79.03	9.9	83.42	2.3	0.003 (S)
MCHC (gm/dl)	31.81	3.4	32.32	1.6	0.35 (NS)
MCH (pg/dl)	26.15	3.8	31.24	1.8	0.001 (S)
TC	6663.72	280.6	5895.62	334.4	0.21 (NS)
Platelet count	242.16	82.6	298.24	84.9	0.001 (S)

*independent ‘t’ test

Table 4: Comparison of blood parameters between two groups after drug intervention

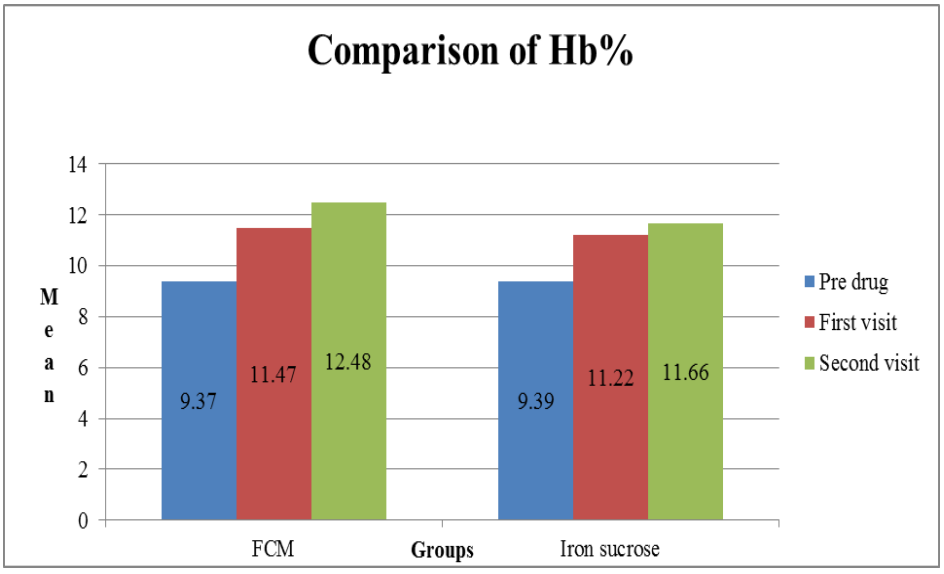
Blood parameters	FCM group		Iron sucrose group		P value*
	Mean	Std.deviation	Mean	Std.deviation	
Haemoglobin (gm%)	11.47	0.6	11.22	0.8	1.00 (NS)
RBC (mcells/cmm)	4.01	0.4	3.89	0.4	0.22 (NS)
PCV	33.78	3.0	32.41	2.8	0.02 (S)
MCV (fl/dl)	84.63	7.6	84.52	2.2	0.91 (NS)
MCHC (gm/dl)	34.18	3.3	32.94	1.6	0.02 (S)
MCH (pg/dl)	28.85	3.9	31.94	1.5	0.001 (S)
TC	5286.62	259.4	5621.60	205.7	0.47 (NS)
Platelet count	225.87	69.2	265.28	92.6	0.01 (S)

*independent‘t’ test

Table 5: Comparison of mean difference (before and after first visit of drug intervention) of blood parameters between two groups

Blood parameters	FCM group		Iron sucrose group		P value*
	Mean (difference b/w pre drug & post drug I visit)	Std Deviation	Mean (difference b/w pre drug & post drug I visit)	Std Deviation	
Haemoglobin (gm%)	2.09	0.7	1.82	0.2	0.01 (S)
RBC (mcells/cmm)	0.43	0.05	0.17	0.01	0.001 (S)
PCV	4.82	3.2	4.28	1.5	0.28 (NS)
MCV (fl/dl)	5.60	0.9	1.10	0.1	0.001 (S)
MCHC (gm/dl)	2.37	0.4	0.62	0.09	0.004 (S)
MCH (pg/dl)	2.70	0.4	0.70	0.09	0.002 (S)
TC	1377.10	345.4	274.02	41.0	0.14 (NS)
Platelet count	16.30	10.8	32.96	11.5	0.45 (NS)

*independent‘t’ test



Side Effects and Tolerance

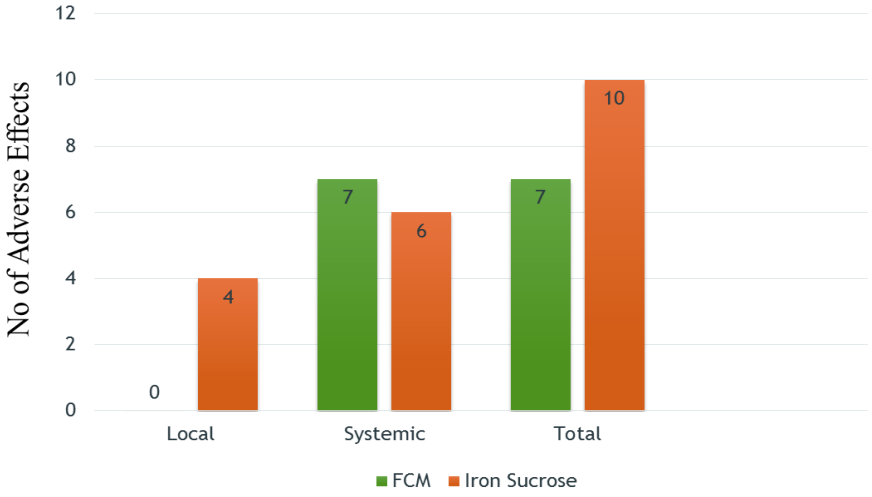
As summarized in Table 6, patients treated with Ferric Carboxymaltose had fewer side effects than those receiving Iron Sucrose, but the difference did not reach statistical significance. Total of 7 adverse events were noted. Mild reactions in the form of skin rashes in 2 patients and urticaria in 1 patient were noted in FCM group. 2 patients experienced breathlessness and 2 patients complained of giddiness, none needing medical intervention.

In the group receiving Iron Sucrose a total of 10 adverse events were reported, 4 were local reactions, 6 mild systemic reactions. In local reaction pain at the injection site, the difference between the two groups was statistically significant.

Table 6: Distribution of study subjects based on adverse effects in both the groups

Local Adverse Effects	FCM group	Iron sucrose group	P value*
Pain	00	04 (08%)	0.01
Swelling	00	00	-----
Systemic Adverse Effects	**FCM group**	**Iron sucrose group**	**P value***
Fever	00	00	----
Breathlessness	02 (04%)	02 (04%)	1.00
Palpitation	00	00	----
Sweating	00	00	----
Wheezing	00	00	----
Stridor	00	00	----
Giddiness	02 (04%)	04 (08%)	0.40
Diarrhea	00	00	----
Syncope	00	00	----
Hypotension	00	00	----
Skin rash	02 (04%)	00	0.15
Urticaria	01 (02%)	00	0.31

Figure depicting graphically the differences between groups with respect to adverse effects



DISCUSSION

Anemia is one of the most prevalent nutritional deficiency problems affecting pregnant women.[13] The high prevalence of iron and other micronutrient Deficiencies among women during pregnancy in developing countries is of concern and maternal anaemia is still a cause of considerable perinatal morbidity and mortality. The problem of anemia during pregnancy in developing countries is compounded by the fact that most women consume diets of low iron bioavailability and therefore, enter pregnancy with no iron stores and less than optimal hemoglobin concentrations. Poor nutrition, closely and frequently spaced pregnancy, infections play additional important role. Hence iron deficit that must be met is greater. Most cases can be effectively treated with oral iron replacement. Oral iron efficacy is limited which may be explained in part by frequent GI complaints and high rates of nonadherence with prescribed therapy. Nonadherence to oral iron prescription is directly related to severity of GI symptoms,[14] and efficacy is known to diminish as nonadherence increases.[15,16] Its use is also limited by poor absorption, poor compliance, low efficacy and the long time period required to replete iron stores.

Use of parenteral iron therapy for the treatment of anaemia dates back to 1932 when it was administered by Heath et al. Since then, there has been quest for the ideal iron preparation that would overcome the issues regarding safety related to anaphylaxis, release of free labile iron, fear of oxidative stress(lipid peroxidation) induced injury.

The challenge of treating iron deficiency with a parenteral preparation is related to the toxicity of iron in its elemental state, the required dose, and desired rate of repletion. Early parenteral formulations, now withdrawn in many countries, were associated with untoward effects that limited their use.[17] These were surpassed with the introduction of iron sucrose and modified formulations of iron dextran (and ferric gluconate complex in some countries).[18,19,20] These formulations had much improved safety profiles and lower rates of adverse events. The next inevitable challenge was to address the

issue of eliminating the need for a test dose and being able to administer larger amounts of iron in a shorter period of time, thereby potentially improving the convenience of treatment.

Ferric carboxymaltose (FCM), is a polynuclear iron (III)-hydroxide carbohydrate complex. Ferric carboxymaltose has been designed to enable controlled, systemic release of iron within the cells of the reticuloendothelial system, minimizing the risk of releasing large amounts of iron into the serum.[31] The structure of the polynuclear iron(III)-hydroxide core resembles that of ferritin: the iron is trapped in the core in a non-redox active form and, therefore, toxic effects derived from weakly-bound iron are limited[32]. The complex has an average molecular weight of approximately 150,000 Da[33]. Ferric carboxymaltose is a type I complex[33]. Thus, following I.V. administration, FCM is metabolised by the RES in the spleen and the liver, and the iron is delivered to the bone marrow[34]. This is reflected in an efficient increase in Hb levels, an increase in transferrin saturation (TSAT) and ferritin levels[33,35,36]. The pharmocodynanmic and pharmacokinetic properties make FCM a safe and effective option at high doses. Intravenous preparations are effective in treating iron deficiency. An efficient increase in hb levels, transferin saturation and feritin levels are noted with ferric carboxymaltose.[33,35,36]

Our study did show a statistically significant raise in Hb and red cell indices in Ferric Carboxymaltose group. Although it cannot be concluded if the raise is faster and higher in comparison to iron sucrose from these data and needs well designed prospective studies.

The tolerance and safety profile of Ferric carboxymaltose is demonstrated in various studies for its use in iron deficiency anemia.[23,24,25,26,27,28,29] No safety concerns have been identified in breast fed infants of mothers receiving ferric carboxymaltose.[25] Its use is approved in second and third trimesters in pregnancy.[19] Our study shows that FCM is well tolerated in pregnant women and has fewer number of side effects as compared to iron sucrose in much higher dose. The incidence of drug related adverse effects was low.

Iron sucrose group had higher incidence of pain at injection site, while urticaria was noted as main drug related reaction with ferric carboxymaltose group. There were no treatment-related serious adverse events. No anaphylactic or anaphylactoid reaction was detected. No venous thrombosis was registered. None of the adverse events required further medical intervention.

As opposed to more frequent small-dose administrations, infrequent high-dose administrations of intravenous iron reduce the frequency of hospital or clinic visits, thereby causing less disruption to patients' lifestyle, especially if working, the overall time spent attending a hospital or clinic can be reduced.[21,22] This is likely to be more convenient for both patients and health care professionals and to improve patient compliance.[22] Such high-dose administrations have been shown to reduce waiting lists, travel costs are reduced, which may benefit patients and the health care economy, and the insurance company.[21] From a practical clinical perspective, target hemoglobin and ferritin levels may be achieved more rapidly, allowing hematinic levels to achieve stability earlier than when using multiple small doses.[21] Reduced frequency of venous access also reduces the risk of infection.

Strength of the study

This is one of the few studies available assessing the efficacy, side effects and tolerability of in IV FCM in pregnancy. Data on side effects are reliable as they are collected during and after the procedure. FCM was used on outpatient basis and patients were monitored for 1 hour post procedure to ensure maximal safety, observation and monitoring.

Limitations of the study

Other forms of anemia were not evaluated. Ferritin is most specific investigation to measure iron status in the body. Considering the cost factor ferritin levels were not measured and efficacy analyzed through Hb and red cell indices. A standard of 1000 mg of parental iron was given irrespective of the requirements considering the cost factor in terms of drug and hospital visits. Study doesn't include long term follow up to measure fetal outcome in terms of Hb, ferritin, birth weight etc.

CONCLUSION

Ferric carboxymaltose complex seems to afford the efficacy of IV iron administration without the inconvenience of multiple small-dose injections, the long infusion times and risk of adverse drug effects associated with higher IV iron doses, and the inconvenience, adverse GI effects, and risk of nonadherence associated with thrice-daily oral iron therapy. While further research including randomized trials is needed, ferric carboxymaltose seems to be the drug of choice if IV iron treatment during pregnancy becomes necessary in the second or third trimester.

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