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Research Article

A Comparative Study to Assess the Safety and Efficacy between Intravenous Iron Sucrose and Ferric Carboxymaltose in the Treatment of Iron Deficiency Anemia in Pregnancy – A Single Center Prospective Observational Study from a Tertiary Care Center.

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Abstract

Objective: To Compare the safety and efficacy between intravenous iron sucrose and ferric carboxy maltose in the treatment of iron deficiency anemia in pregnancy.

Methodology: A Prospective study was conducted on 100 antenatal women with iron deficiency anemia in department of Obstetrics and Gynecology of a tertiary care center in northern India from June 2021 to May 2022.

Results: The mean age in group A (Iron Sucrose group) was 25± 2.83 years and in group B (FCM group) was 24.08±4.45 years. In group A (IS group) the average increase in Hb level was about 1.24 ± 0.29 gm/dl at 3 weeks and 2.62 ± 0.2 gm/dl at 6 weeks. In group B (FCM group) the average increase was about 1.74 ± 0.42 gm/dl at 3 weeks and 4.15 ± 1.94 gm/dl at 6 weeks. In IS group the average increase in ferritin was about 18.83 ± 18.18 ng/dl at 3 weeks and 43.54 ± 31.71 ng/dl at 6 weeks. In FCM group the average increase was about 34 ± 19.83 ng/dl at 3 weeks and 96.62 ± 50.7 ng/dl at 6 weeks. P value at both time periods was 0.0001, which is highly significant. 43 patients (86%) in Group B as compared to 19 patients (38%) in group A showed improvement in anaemia in PBS findings over 3 week and 6 week period, which was statistically significant with a P value of 0.024. In Group A (IS group) only two patients complained of diarrhoea, two complained of headache, 1 patient complained of nausea ,vomiting, one complained of nausea only, In Group B (FCM group) total 3 patients (6%) complained of minor reactions like nausea, vomiting and itching. There were mild side effects only in both the groups.

Conclusion: Intravenous FCM is more efficient and better alternative than iron sucrose in the treatment of iron deficiency anaemia in pregnancy.

Key Words: IDA, FCM, IS, Ferritin, Haemoglobin.

Introduction

Anaemia is defined as decrease in the oxygen carrying capacity of the red blood cells. WHO defines anaemia as haemoglobin less than < 12g% in women and < 13g% in men. Anaemia due to nutritional deficiency – Iron deficiency anaemia is the most common type. Globally, anaemia affects 1.62 billion people which constitute 24.8% of the total population and the

group with the greatest number of individuals affected being pregnant women (41.8%). [1-4]

It is a global public health problem and is responsible for 40% of the maternal deaths in developing countries out of which it is responsible for 25% of direct maternal deaths. The prevalence of Iron deficiency anaemia (IDA) in pregnancy in India ranges from 23.6% to 61.4%. The prevalence of IDA among pregnant women increases from 6.9% in the first trimester to 14.3% and 28.4% in the second and third trimesters, respectively.[5]

The causes of anaemia in pregnancy and their frequency are dependent on multiple factors such as geography, ethnicity, nutritional status, socioeconomic factors, preexisting iron status, and prenatal iron supplementation. It is a leading cause for preterm labour, infections, poorly tolerated postpartum haemorrhage, cardiac failure in the mother. During the postnatal period, anaemia is associated with poor wound healing, postpartum depression and lactation failure. In India anaemia antedates pregnancy, it is aggravated during pregnancy by increased requirements and blood loss at delivery, infection during antenatal and postnatal period and with early advent of next pregnancy. The risk of anaemia is higher due to a wide range of factors such as inadequate diet, hemoglobinopathies, and infections such as HIV, malaria, and parasitic infestation.[6] Also, it is the second leading cause of maternal deaths in the country. [7-9]

The mainstay of treatment for iron deficiency anaemia is iron supplementation either oral or parenteral. Traditionally, oral iron replacement is used as the first-line therapy in patients with IDA due to its ease of administration, and early initiation of this treatment can correct anaemia. However, oral iron has some disadvantages such as GI side-effects, poor compliance, limited gastrointestinal absorption, and the long course required to treat anaemia and replenish iron stores.

The indications for parenteral iron treatment are intolerance to oral iron, noncompliance to oral iron and the need for rapid restoration of iron stores. Current intravenous iron formulations include ferric gluconate, iron sucrose, iron polymaltose and the recently introduced ferric carboxymaltose. [10]

Iron sucrose has been widely used due to its higher bio-availability for erythropoiesis than iron dextran and offers a good safety profile. But it cannot be given in higher doses and requires frequent doses for administration. [10-13]

Ferric carboxy maltose is a novel iron complex which has a near neutral pH , physiological osmolarity and increased bioavailability, which makes it possible to administer high single doses over shorter time periods (up to 1000 mg in a single dose infused in 15 minutes) with low pre-disposition to anaphylactic reactions since it has a low immunogenic potential. [14]

However, the availability of new preparations (iron sucrose, ferric gluconate, low-molecular weight iron dextran, and, more recently, ferric carboxymaltose, iron isomaltoside and ferumoxytol) with much better safety profiles, is changing the pattern of the use of IV iron in a number of clinical settings. [16]

Materials and Methods

This prospective study was conducted in the Department of Obstetrics and Gynecology, Sardar Patel Medical College & AGH, Bikaner (Rajasthan) from June 2021 to May 2022. A total of 100 antenatal women were studied. Two groups were made, 50 of whom were given Iron Sucrose infusion (Group A) and the remaining 50 were given Ferric Carboxy Maltose infusion (Group B). The study population was recruited by using simple random sampling method after obtaining informed written consent. Approval for study was taken by ethical committee.

Inclusion Criteria: Antenatal patients with gestation period between 14-28 weeks , Patients with Hb <10gm.

Exclusion Criteria: Patients with anaemia other than iron deficiency like sickle cell anaemia and thalassemia or with iron overload disorder, not willing to participate in the study, hypersensitivity reaction to any iron preparation. History of blood transfusion. history of bleeding tendency , Other medical conditions like chronic renal failure, CNS disorders, TB, Hepatitis B/C, HIV infection etc.

A detailed clinical history was taken i.e menstrual, obstetric, previous treatment history, including iron therapy, compliance with oral iron and chronic medical illness. Demographic data like age, education, socioeconomic status, height, weight were recorded in proforma. Complete general physical examination and obstetric examination was done. Routine antenatal investigations were done according to standard departmental protocol. Investigations related to anaemia like hemogram, peripheral blood smear, red cell indices (MCHC, MCV, and MCH), serum ferritin levels were done.

The total required dose was calculated on the basis of Hb deficit and body weight using Ganzoni's formulae. Target Hb level was taken as 11 gm/dl or %. Total Iron deficit in mg = Body weight in Kg x [Target Hb- Actual Hb] x 2.4 + Depot Iron (in mg) where, Depot Iron = 15mg/kg in body weight <35 kg and 500 mg in body weight >35 kg.

Group A: Iron Sucrose (IS) : Iron sucrose was given in a dose of 200 mg intravenously in 100 ml 0.9% Normal saline over a period of 30 mins on alternate days until the total dose was administered [not to exceed 600 mg per week]. The first few ml was infused intravenously over a period of 15 mins, if there were no adverse reactions remaining amount was infused over 30 mins period.

Group B: Ferric Carboxy Maltose (FCM)

Ferric carboxy Maltose was given in 0.9% Normal Saline as follows

100 - 500 mg in 100 ml NS - 15 mins duration

500 – 1000 mg in 200 ml NS - 30 mins duration,

Maximum dose per sitting was 1000 mg. Subsequent doses if needed were planned on 7th and 14th day.

The vitals of patients like, blood pressure, pulse rate were noted before infusion and every 5 mins during infusion. Fetal heart rate was monitored before and after infusion. Any minor and major adverse effects were noted. Hemoglobin level and serum ferritin level were done after 3 and 6 weeks post therapy.

Statistical Analysis:

The data analysis was computer based, SPSS - 22 was used for analysis . For categoric variables Chi – square test was used. For continuous variables independent sample's T - test was used. P value < 0.05 was considered as significant.

Observations:

All baseline characteristics were matched. Both groups were comparable at baseline. In group a 52 % patients were in age group 21-25 years and 42% were in age group 26-30 years and in group B 50% patients were in age group 21-25 years and 32% were in age group 26-30 years. In group A maximum no. of patients 43 (86%) belonged to rural area and 7 (14%) belonged to urban area and in group B maximum no. of patients 44(88%) belonged to rural area and 6 (12%) belonged to urban area which was comparable at baseline.

There was no significant difference in socioeconomic status, residential area and mean gestational age of both groups. In terms of gravidity both groups were comparable with maximum multigravida patients (58 % in group A and 62 % in group B). (Table 1)

There was significant improvement in post treatment haemoglobin values in both the groups. In group A the average increase was about 1.24 ± 0.29 gm/dl at 3 weeks and 2.62 ± 0.2 gm/dl at 6 weeks and in group B the average increase was about 1.74 ± 0.42 gm/dl at 3 weeks and 4.15 ± 1.94 gm/dl at 6 weeks with P value at both time periods being <0.0001, which was highly

significant. There was significant Improvement of Serum Ferritin in both groups at 3 and 6 weeks post treatment. In group A the average increase in ferritin was about 18.83 ± 18.18 ng/dl at 3 weeks and 43.54 ± 31.71 ng/dl at 6 weeks. In group B the average increase was about 34 ± 19.83 ng/dl at 3 weeks and 96.62 ± 50.7 ng/dl at 6 weeks with P value at both time periods < 0.0001, which was highly significant. Improvement of MCV and MCH at 3 week and 6 weeks was not significant, while individual mean MCV and MCH values in both group A and group B show significant improvement over 3 weeks and 6 weeks of treatment. (Table 2)

All the study participants in both group A and group B had peripheral blood smear parameters done pretreatment and after 3 weeks and 6 weeks post treatment. 43 patients (86%) in Group B as compared to 19 patients (38%) in group A showed improvement in anaemia in PBS findings over 3 week and 6 week period, which was statistically significant with a P value of 0.024.(Table 3)

In group A 7 (14%) patients showed side effects, while 43 (86%) had no significant complaints whereas in group B 3 (6%) patients showed side effects, while 47 (94%) had no significant complaints. P value was found to be 0.317 which showed that there was no significant difference between both the groups. There were mild side effects only in both the groups. (Table 4)

Table 1: Base line characters of study participants

Parameters	**Group A (IS)**		**Group B (FCM)**		**P Value**
Age	25.00	2.83	24.08	4.45	0.220
Hb (g/dl)	7.81	1.32	7.83	0.85	0.320
MCV	74.02	12.67	70.62	12.52	0.180
MCH	22.72	3.44	22.34	7.26	0.739
Serum ferritin	7.49	2.64	7.89	3.99	0.556

Table 2: Variables - Pretreatment and post treatment at 3 and 6 weeks

Parameter	**Group A (IRON)**		**Group B FCM**		**df**	**t value**	**p value**
	Mean	**Sd**	**Mean**	**Sd**			
Hb Level							
Pre treatment	7.81	1.32	7.83	0.85	98	0.090	0.320
At 3 Week	9.05	1.03	9.57	1.27	98	2.249	0.027
At 6 Week	10.43	1.12	11.98	2.79	98	3.646	0.0001
MCV							
Pre treatment	74.02	12.67	70.62	12.52	98	1.350	0.180
At 3 Week	80.73	9.01	81.56	9.78	98	0.441	0.660
At 6 Week	85.30	8.01	86.21	8.52	98	0.550	0.583
Sr. Ferritin							
Pre treatment	7.49	2.64	7.89	3.99	98	0.591	0.556
At 3 Week	26.32	20.82	41.89	23.82	98	3.480	0.0001
At 6 Week	51.03	34.35	104.51	54.69	98	5.855	0.0001
MCH							
Pre treatment	22.72	3.44	22.34	7.26	98	0.334	0.739
At 3 Week	24.44	3.20	25.85	4.05	98	1.932	0.056
At 6 Week	26.75	3.15	27.45	4.76	98	0.867	0.388

Table 3: Peripheral blood smear comparison between group A and group B

Time period	Group A (IS)		Group B (FCM)		p Value
	No.	%	No.	%	
Pre treatment					
MCHC	50	100	50	0	
NCNC	0	0	0	0	
Post treatment (3 Weeks)					
MCHC	50	100	50	100	
NCNC	0	0	0	0	
Post treatment (6 Weeks)					
MCHC	31	62%	7	14%	0.002
NCNC	19	38%	43	86%	0.024

MCHC: Microcytic hypochromic NCNC: Normocytic and normochromic

Table 4: Specific adverse reactions

Adverse reactions	Group A (IS)	Group B (FCM)	Total
Pain at inj. site	0	0	0
Swelling at inj. site	0	0	0
Nausea	1	1	2
Nausea, vomiting	1	1	2
Headache	2	0	2
Diarrhoea	2	0	2
Flushing	1	0	1
Itching	0	1	1
Total (%)	7 (14%)	3 (6%)	10 (10%)

Discussion

Iron deficiency anemia is the most common medical condition during pregnancy in developing countries, the prevalence being 41.8% of all pregnant women. The progression from iron deficiency to IDA is common in pregnancy due to increased iron demand as well as haemodilution . it is associated with unfavorable consequences both for mother, perinatal mortality and morbidity. The timely detection of anemia in pregnancy and its effective management is available , affordable and possible. Although IDA can be treated with oral iron preparations, many women develop moderate to severe IDA despite oral iron supplementation due to drug intolerance, non-adherence or any predisposing pathology such as malabsorption or IBD, where IV iron administration may be a more effective modality. Hence, our study was aimed to compare between the two most commonly used parenteral iron preparations, ie. IV iron sucrose and IV FCM on the basis of their efficacy and side effects.

In our study, majority of cases were in the age group 21-25 years, both in Group A (IS) and Group B (FCM). In group A (IS), the mean age of participants was 25.00 $\pm$ 2.83 years. While in Group B (FCM),the mean age was 24.08 $\pm$ 4.45 years. The least common age group in both the groups was > 30 years. Similar age group distribution was reported by **Agarwal et al'** in their study with 56 out of the 100 participating women falling in the 21-25 years age group. [17] The early age group that came in our study could be due to social factor of early marriage in this region of north India. More prevalence of IDA in multigravida women could be due to less interspacing between pregnancies, economic burden and self-negligence.

In our study the mean change of Hb level and serum ferritin level from a period of pretreatment to 3 weeks and 6 weeks post treatment was found to be highly significant in both the groups. Similar results were obtained in study by **Sangeeta Shah et al**. [18], where post treatment mean increase in Hb and serum ferritin after a 4 week treatment (p value < 0.05) was significant. **Agarwal D et al**.[17] study also showed similar significant increase in both these variables after 3 weeks of treatment. Our study findings were also consistent with that of **Beena Mahaur et al**.[19] who noted a significant rise in mean Hb and serum ferritin in FCM (1.56gm, 2.6gm) as compared to IS (0.64gm, 1.82gm) at 3 and 6 weeks.

Treatment with IV FCM results in faster replenishment of iron stores and a significantly higher rise in Hb as compared to iron sucrose group . The rise in Hb was noted in both the groups but the rise was significantly more in the FCM group which could be due to better bioavailability, convenient dosing and better compliance. The mild reduction in absolute value of mean serum ferritin could be due to redistribution of iron after saturation of receptors. This infers that IV iron infusion results in a rapid replenishment of iron stores.

The most common anaemia found in iron deficient states is microcytic hypochromic anaemia with low MCV. Treatment of iron deficiency results in rise of MCV, and the same is reflected in our study. Low MCH (>27%) indicates that RBCs are deficient in Hb concentration, which is seen in IDA. In our study, an improvement in mean MCH values was noted over 3 weeks and 6 weeks of both the modes of IV iron treatment.

We also noted the changes in terms of correction of Microcytic Hypochromic (MCHC) red cells to Normocytic normochromic (NCNC) red cells after administration of IS (Group A) and FCM (Group B). All the study participants in both group A and group B had MCHC anaemia pretreatment and after 3 weeks post treatment anaemia persisted. Group B 43 patients (86%) showed significant improvement as compared to group A 19 patients (38%)in terms of peripheral blood picture findings over 3 week and 6 week period. Contrary to our study, **Khatun F et al**[20]. noted no significant difference in PBS at post treatment 3 weeks and 6 weeks.

We also aimed at comparing the safety profile of both the modes of IV iron administration in terms of presence of side effects. In group A (I.S. group) 7 (14%) patients showed side effects, while 43 (86%) had no significant complains. In group B (FCM group) 3 (6%) patients showed side effects, while 47 (94%) had no significant complains. In group A, only two patients complained of diarrhoea, two complained of headache, 1 patient complained of nausea vomiting and 1 complained of nausea only and in group B, total 3 patients (6%) complained of minor reactions like nausea, vomiting and itching. Side effects were mild and comparable in both the groups. In a study by **Beena Mahaur et al**.[19], 28% participants in IS group were observed to have side effects as compared to 16% in FCM group. These data were also comparable to our study.

Strength

The participating antenatal women had the advantage of timely diagnosis and correction of iron deficiency anaemia of pregnancy by either of the two intravenous modes free of cost under government scheme. They were counselled regarding importance of frequent antenatal visits, importance of anaemia and its correction and its implications in next pregnancies. There were no patients lost to follow up in our study.

Limitations

It was a single center study with limited sample size.

Conclusion

Our study concluded that IV FCM is a more efficient and better alternative than IV Iron sucrose, in the treatment of IDA of pregnancy. It

resulted in significantly higher and faster rise of hemoglobin, improvement in serum ferritin levels and PBS findings as compared to IS. It offered an additional advantage of convenient single dose regimen and hence better patience compliance. However, the side effects noted were comparable to that of iron sucrose.

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