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A Comparative Study Of Efficacy And Safety Of Intravenous Ferric Carboxymaltose Versus Intravenous Iron Sucrose In The Treatment Of Iron Deficiency Anaemia Of Pregnancy

Prof. Dr. SangeetaShah , M.D. (OB.GYN), Dr. K. Swapna , M.S. (OB.GYN)
Professor-Ob.Gyn- Gandhi Medical College
Corresponding author: Prof. Dr. SangeetaShah

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I. Background

Iron deficiency anaemia is the most common nutritional deficiency in women of reproductive age[1] India has high prevalence of anaemia in pregnancy according to WHO[1]. Anaemia is a major contributor to maternal mortality. The effects of iron deficiency anaemia in pregnancy during antenatal, intrapartum and postnatal period are very much significant. These women suffer from fatigue, cardio respiratory problems, risk of haemorrhage, infections and even death. [2] The fetus of the iron deficient woman also may not be spared and is at risk of preterm PROM, intrauterine growth restriction, stillbirth, low birth weight, and even poor growth trajectory after birth. Dietary deficiency of of iron and folic acid along with poor bioavailability of iron is responsible for high prevalence of anemia in pregnancy. Various iron preparations are available for treatment of iron deficiency anemia. Intravenous iron preparations like iron dextran, iron sucrose and ferric carboxymaltose are available for treatment of IDA. Iron dextran has commonly been associated with allergic reactions. Iron sucrose requires multiple intravenous infusions to achieve the target hemoglobin concentration. Ferric carboxymaltose is a novel compound of polynuclear iron(III) hydroxide complexed to carboxymaltose which can be given in a single maximum dose of 1000mg infusion and thus avoids multiple infusions. Very few comparative studies have been done comparing the second generation i.v. ironsucrose therapy with the third generation i.v. FCM therapy regarding efficacy and safety profile of these drugs in pregnancy. The result would definitely help us in deciding the better of the two drugs in the treatment of iron deficiency anemia in pregnancy after weighing all the pros and cons.

II. Methodology

The present study was conducted in the Department of Obstetrics and Gynecology, Gandhi Medical College/ Hospital, Secunderabad., a tertiary care centre in the state of Telangana

This was a Comparative Observational Prospective Study done over a period of one year (2016-2017)The Antenatal women attending Department of Obstetrics and Gynaecology were the source of our sample. 60 antenatal women were studied, 30 of whom were given ferric Carboxymaltose infusion and the remaining 30 were given iron sucrose infusion.

Inclusion criteria: Antenatal women between 12 to 34 weeks of gestational age with hemoglobin between 7 to 9.9g% and microcytic hypochromic anaemia were included in the study.

Exclusion criteria: Women not willing to participate, anemia other than microcytic hypochromic anemia (iron deficiency), women with medical disorders ,women with known hypersensitivity or history ofhypersensitivity to parenteral iron infusion, womenwith history of blood transfusions in the present pregnancy and within 4 weeks after infusion were excluded from the study.

Pregnant women fully satisfying the above said inclusion and exclusion criteria were briefed about the study and their consent taken. The study was approved by Institutional Ethics Committee of Gandhi Medical College, Secunderabad.

Demographic data like age, education, qualification, socio economic status and obstetric history, general health, including weight and height was recorded on predesigned and pretested proforma.

The participants were subjected to iron infusion, iron sucrose or ferriccarboxymaltose according to randomization, after peripheral smear and hemoglobin estimation was done and the iron deficit was calculated according to formula:

Deficit = (11-Hemoglobin of the patient) x 2.4 x Weight + 500mg (storage)

Routine deworming of all the participating subjects was done with

oralAlbendazole tablets.

Group – Iron sucrose (IS):

Iron sucrose was given in a dose of 200 mg intravenously in 200 ml normal saline over a period of 15-20 min on alternate days until the required total dose was administered; not exceeding the maximum dose of 1000 mg/week.

Group – Ferric Carboxymaltose (FCM):

Ferric Carboxymaltose was given as per the total required dose in normal saline infusion as follows:
IVdrip infusion : Dilute in 0.9% sodium chloride
100 to 200 mg: 50 ml NS,
200 to 500 mg : 100 ml NS - 6 min duration,
500 to 1000mg : 250 ml NS - 15 min duration, not exceeding the maximum dose of 1000 mg / day/ week.
All the doses in both groups were given in the ward where equipment for cardiopulmonary resuscitation was available. Patients were observed for side effects or anaphylactic reactions. Any minor or major side effects were documented. Hemoglobin test was repeated at the end of 4 weeks interval.

Statistical Analysis: The categorical data was expressed in terms of frequencies and percentages while continuous data was expressed as mean ± standard deviation (SD). The two groups were compared using chi-square test for categorical data and independent sample 't' test was used to compare the means of different parameters. A 'p' value of less than or equal to 0.05 was considered as statistically significant.

III. Observation And Results

The study was conducted on 60 antenatal women, 30 women in each of the two groups were observed and following results were observed. All the demographic parameters in the two groups like age distribution, occupation, educational status, socioeconomic status, parity status, period of gestation and body mass index in the two groups were comparable with a p value of>0.05. When the pre-treatment haemoglobin was compared, majority of women in group IS(66.7%) and group FCM (70%) had hemoglobin levels between 8.5 to 10 g% (p>0.05) **(Table-1)**

The mean pre treatment hemoglobin levels in both the groups were comparable (8.75±0.78 vs. 8.61±0.71; p>0.05)**.(Table-2)**

The mean requirement in group IS was 786.23±88.85 compared to 820.1±100.42 in group FCM and this difference was statistically not significant (p>0.05). Even the doses were comparable (p>0.05). **(Table -3)**

The post treatment hemoglobin levels were found to be above 10.5 g% in group IS in 73.3% of women and in group FCM in 66.67%. This difference was statistically not significant (p>0.05) **.(Table -4)**

However the post treatment hemoglobin levels in group IS was 11.06±0.71 and group FCM was 11.0133±0.164 (p value was less than 0.05) which was significant. **(Table- 5)**

In the present study post treatment increase in hemoglobin levels above 2.5g% is found in 40% of women in group IS compared to 53.34% in group FCM (p>0.05) statistically not significant**.(Table-6)**

But the mean increase in hemoglobin levels post treatment in group IS was 2.35±0.41 vs. 2.52±0.073 in group FCM which was statistically significant (p<0.05) **(Table-7)**

In the present study 16.6% of women in group IS were found to have increase in hemoglobin percentage above 25% compared to 73.3% in FCM. The p value being <0.001 indicates the higher efficacy of drug in group FCM**.(Table-8)**

In this study mean percentage change in hemoglobin levels post treatment in group IS was 21.34±3.73 compared to 29.5001±0.999 in group FCM . This was statistically significant with p value being < 0.0000001 **(Table-9)** In the present study side effects were noted in 36.7% of women in group IS and 33.3% of women in group FCM, however the difference was statistically not significant (p>0.05**).(Table-10)**

Regarding the side effects noted in group IS and group FCM, it was noted that significantly higher number of women had nausea in group FCM while group IS has higher incidence of diarrohea and headache. Patients had more than one side effects**. (Table-11)**

IV. Tables

TABLE-1 : Pre Treatment of Hemoglobin vs percentage of women

Hemoglobin %	Group IS		Group FCM		P- Value
	Frequency	Percentage	Frequency	Percentage	
7.0 - 8.5	10	33.3	9	30	>0.05
8.5 - 10.0	20	66.7	21	70	
Grand Total	30	100	30	100	

Chi square test p>0.05 (not significant)

TABLE-2 : Mean of Pre Treatment Hemoglobin levels

	Group IS		Group FCM		P- Value
Pre Hb	Mean	SD	Mean	SD	>0.05
	8.75	0.78	8.61	0.71	

't' test p> 0.05 (not significant)

TABLE-3 : Mean Iron requirement and Doses

	Group IS		Group FCM		P- Value
Iron Requirement	Mean	SD	Mean	SD	
	786.23	88.85	820.1	100.42	>0.05
Doses	778.33	90.67	813.33	93.71	>0.05

't' test p> 0.05 (not significant)

TABLE-4 : Post Treatment Hemoglobin vspercentage of women

Hemoglobin %	Group IS		Group FCM		P- Value
	Frequency	Percentage	Frequency	Percentage	
9.5 - 10.5	8	26.7	10	33.33	>0.05
10.5 - 11.5	14	46.7	10	33.33	
11.5 - 12.5	8	26.6	10	33.33	
Grand Total	30	100	30	100.0	

Chi square test p>0.05 (not significant)

TABLE-5 : Post Treatment Hemoglobin levels

,	Group IS		Group FCM		P- Value
	Mean	SD	Mean	SD	<0.05
Post Hb	11.06	0.71	11.0133	0.164	

't' test p<0.05 (significant)

TABLE- 6: Increase in Hemoglobin levels in post treatment vs % of women

Hemoglobin %	Group IS		Group FCM		P- Value
	Frequency	Percentage	Frequency	Percentage	
1.5 - 2.0	6	20.0	4	13.334	>0.05
2.0 - 2.5	12	40.0	10	33.334	
2.5 - 3.0	10	33.3	12	40	
3 ≤	2	6.7	4	13.334	
Grand Total	30	100.0	30	100.0	

Chi square test p>0.05 (not significant)

TABLE- 7 : Post treatment Mean Increase in Hemoglobin levels

	Group IS		Group FCM		P- Value
	Mean	SD	Mean	SD	<0.05
Rise in Hb(%)	2.35	0.41	2.52	0.073	

't' test p<0.05 (significant)

TABLE-8 : Increase in Hemoglobin level percentage after treatment vs % of women

Percentage Change	Group IS		Group FCM		P- Value
	Frequency	Percentage	Frequency	Percentage	
< 15	2	6.7	0	0	<0.001
15 – 25	23	76.7	8	26.67	
25 – 35	5	16.6	22	73.33	
Grand Total	30	100	30	100	

Chi square test p value <0.001(highly significant)

TABLE - 9 :

Mean Increase in Hemoglobin level percentage at post treatment compared to pre treatment

	Group IS		Group FCM		P- Value
	Mean	SD	Mean	SD	<0.001
Percent Change	21.34	3.73	29.5001	0.999	

t test p value <0.001(highly significant)

TABLE - 10 : Specific Side Effect

Side Effect	Group IS		Group FCM		P- Value
	Frequency	Percentage	Frequency	Percentage	
Present	11	36.7	10	33.3	>0.05
Absent	19	63.3	20	66.7	
Grand Total	30	100	30	100	

Chi square p value >0.05 (not significant)

TABLE - 11 : Specific Side Effect

Side Effect	Group IS		Group FCM	
	Frequency	Percentage	Frequency	Percentage
abdominal pain	1	3.3	2	6.7
Chestpain	2	6.7	1	3.3
Diarrhea	3	10.0	2	6.7
Headache	3	10.0	1	3.3
Pyrexia	2	6.7	2	6.7
Nausea	0	0.0	3	10.0
Myalgia	0	0.0	1	3.3
Constipation	0	0.0	1	3.3
Hypertenssion	0	0.0	1	3.3

V. Discussion

IV iron sucrose (IS) has been used for many years to treat iron deficiency in pregnant women after the first trimester. However its use is limited by a low maximum dose due to side effects at higher doses. IV ferric carboxymaltose (FCM) can be administered at a higher doses and has a good side-effect profile. Ferric carboxymaltose is approved for use in pregnancy in the second and third trimesters. 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).

Christoph et al.[3] undertook a retrospective analysis of 206 pregnant women who were treated either with FCM (n=103) or IS (n=103) to assess maternal tolerability and safety and to exclude safety concerns for the foetus. The incidence of drug-related adverse events was low and mostly mild in both groups, patients treated with FCM had fewer side effects (FCM - 7.8%; IS - 10.7%,). The mean rise of haemoglobin was 15.4 g/L for FCM and 11.7 g/L for IS. This study nevertheless showed that the tolerance of FCM in pregnancy is good and that side effects are rare, even when administered in a much higher dose than IS and it also offers the advantage of requiring less administrations thereby increasing patient comfort. The authors concluded that FCM would seem to be the drug of choice if IV iron treatment is necessary in the second or third trimester of pregnancy. The findings of the present study were in agreement with the results of Christoph et al.[3] except the mean haemoglobin levels which were 11.0133± 2.52 in the present study compared to 15.4 g/L.

In a prospective observational study done by Bernd Froessler et al.[4] in Australia 65 anaemic pregnant women received ferriccarboxymaltose up to 15 mg/kg between 24 and 40 weeks of pregnancy. Intravenous ferric carboxymaltose infusion significantly increased Hb values ($p<0.01$) above baseline levels in all women. Increased Hb values were observed at 3 and 6 weeks post infusion and up to 8 weeks post-infusion. Fetal heart rate monitoring did not indicate a drug related negative impact on the foetus. No serious adverse effects were found and minor side effects occurred in 13 (20%) patients. Even though the rise in

haemoglobin in our study was comparable to this study, the incidence of adverse side effects in our study was more.

Myers B et al.[5] conducted a retrospective analysis of pregnant women treated with ferric carboxymaltose and iron dextran. Of the 92 women, 44 received i.v FCM and 48 received i.v Iron Dextran . At two weeks, the mean Hb rise in the FCM group was 1.73 g/dL and 1.34 g/dL in the Iron Dextran group. At four weeks, the total rise in Hb was 2.57 g/dLwith FCM, 2.34 g/dLwith Iron Dextran. At six weeks the rise was 3.01 g/dL and 3.2 g/dL respectively for FCM and Iron Dextran. The rise in Hb at the end of four weeks was comparable to our study.

In the present study 33.33% of the pregnant women had side effects in group FCM compared to 36.7% in group IS suggesting that the safety of intravenous iron carboxymaltose is comparable with intravenous ferric sucrose. The common side effects noted with iron sucrose were headache (10%), diarrohea (10%), pyrexia (6.7%), chestpain (6.7%) and abdominal pain (3.3%). The common side effects with women who underwent treatment with intravenous ferric carboxymaltose were nausea (10%), abdominal pain (6.7%), diarrohea (6.7%), pyrexia (6.7%), hypertension (6.7%).

Bailie GR[6] showed in a review paper, including nine randomized studies with more than 3000 patients, that ferric carboxymaltose had a good tolerability and efficiency profile.

Overall, the data from this study is consistent with existing data that intravenous iron carboxymaltose administration in pregnancy is likely to be safe and effective. However the limitation of the study was that due to the limited financial assistance, blood indices like serum ferritin, transferin saturation and other indices for iron deficiency anaemia was not feasible in our study. Ideally measuring serum ferritin levels would have been a better marker for noting the efficacy of the treatment. Furthermore the follow up of patients was done only at the end of four weeks. Serial follow ups at the end of two, four, six and eight weeks would have been better in observing the trend in rise of haemoglobin values. Since the duration of our study was only one year, follow up of the neonates and infants was not included in the study.

The cost of the Ferric Carboxymaltose drug is relatively high when compared to other available parentral iron preparations. This high cost of the drug is very well compensated when the number of visits and number of days of hospital admission is taken in to account. However studies for observing the cost effectiveness of the treatment needs to taken up. Further studies including large number of women in a randomized controlled trial along with the long term follow up of the neonates would extend the effectiveness, safety and efficacy of intravenous ferric carboxymaltose in the treatment of iron deficiency anaemia in pregnancy.

VI. Conclusion

Based on the results of this study it may be concluded that, the intravenous iron carboxymaltose is more effective in the treatment of iron deficiency anaemia among pregnant women compared to intravenous iron sucrose. Further it is well tolerated in pregnant women as side effects are comparable to that of iron sucrose.

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