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EFFECTIVENESS OF IRON SUCROSE AND FERRIC CARBOXYMALTOSE IN THE MANAGEMENT OF POSTPARTUM IRON DEFICIENCY ANEMIA: A SOUTH INDIAN PERSPECTIVE

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ABSTRACT

BACKGROUND: Postpartum iron deficiency anemia is considered as one of major public health problem with a high prevalence in developing country like India .It is associated with significant morbidity.

AIM AND METHOD: This perspective observational study was carried out to estimate the safety and effectiveness of iron sucrose and ferric carboxymaltose in treatment of postpartum iron deficiency anemia. Total 100 participants diagnosed with postpartum anemia were allotted to receive either iron sucrose complex (n=50) or ferric carboxymaltose (n=50).

RESULTS: Hemoglobin improvement was significantly higher in ferric carboxymaltose than iron sucrose complex group (4.37 vs. 3.85 gm/dl, p<0.001), but rise in ferritin levels was comparable between the groups (116.59 vs. 110.48 ng/ml, p=0.330). Most of the patients tolerated the preparation well, minor side effects were observed in 12% and 48% of cases among iron sucrose and ferric carboxymaltose group respectively

CONCLUSION: Even though oral iron is considered as a first line therapy, it requires a prolonged administration and is associated with suboptimal response due to gastric intolerance and poor compliance. Intravenous iron preparations are safer, more convenient and effective alternative for treatment of postpartum iron deficiency anemia.

KEYWORDS : post partum anemia, iron deficiency, iron sucrose, ferric carboxy maltose

INTRODUCTION:

Globally, anemia after delivery (postpartum anemia, PPA) is considered as one of major public health problem.[1] Magnitude of problem reported in literature varies depending upon the factors like cut-off levels or critical limit of hemoglobin used to define anemia, the timing of sample collection in post partum period and consumption of iron supplementation in antepartum period etc. Prevalence of postpartum anemia varies from 10-80%, and is more in developing countries (50-80%) as compared to western nations.[2-4] In India the prevalence of PPA is as high as 94.6%.[5]These figures are quite alarming and need greater attention as well as timely intervention.

The hemoglobin (Hb) cut-off value for anemia proposed by WHO is less than 12 g/dl for pre-pregnancy and 11g/dl for 1st and 3rd trimester of pregnancy.[6] For second trimester 10.5 g/dl is considered as cut-off. Peripartum hemorrhage and hemodynamic changes after delivery need to be considered before reliable diagnosis of PPA can be made. Considering the physiological changes during puerperium, Milman et al. suggested the definition of Postpartum anemia as, hemoglobin less than 11 g/dl at 1 week of postpartum (similar to cut off level during pregnancy) and less than12 g/dl at 8 weeks of postpartum period (similar to pre-pregnancy level). [3] For diagnostic clarification, serum ferritin assay should be performed and a value of less than 30µg/L is evidence of iron deficiency store and iron deficiency anemia.[7]

The major cause of postpartum anemia reported is pre-existing prepartum iron deficiency and/or iron deficiency anemia (IDA) in combination with post partum haemorrhage.[7]Other infrequent causes are folate and vitamin B_{12} deficiency, inflammatory conditions, infectious disorders, haemoglobinopathies etc.

Postpartum period is the most neglected period and anemia during this period is associated with significant morbidity and mortality. Postpartum anemia can result in weakness, decreased work performance, easy fatigability, breathlessness, palpitations, infections specifically urinary tract infection, reduced cognitive performance, emotional instability and increased risk of postpartum depression leading to compromise in the bonding with child.[3,8] Oral iron is considered as first line therapy for iron deficiency anemia. But it has been associated with disadvantages like reduced absorption, poor compliance and gastro-intestinal (GI) side effects.[9] On the contrary; parenteral therapy restores iron stores more rapidly and effectively than oral iron. Three parenteral preparations available in India are iron dextran, iron sucrose and ferric carboxymaltose (FCM). Use of intramuscular iron dextran preparation is restricted because of high rate of side effect, including anaphylatoid reaction. Intravenous preparations produce faster and greater increase in the hemoglobin concentration. Furthermore, the total dose can be infused in a short span of time to yield replenishment of body iron reserve within a few days.[1] IV iron sucrose requires multiple doses and prolonged infusion times, whereas because of a nearly neutral pH (5.0-7.0) and physiological osmolarity of FCM, it is possible to administer a higher single dose over a shorter time period (single dose of up to 1000 mg can be given over 15 min).[10]

Limited studies have addressed this issue in South India. Present study was planned to estimate the safety and effectiveness of iron sucrose and ferric carboxymaltose in treatment of postpartum iron deficiency anemia in Telangana.

METHODOLOGY:

This prospective observational follow up study was carried out in the Department of Obstetrics and Gynecology during the period of December 2018 to March 2020. Institutional review board and ethical committee approval was obtained. From previous studies, the minimum sample size was estimated to be 90 participants and with an expected attrition rate of 10%, we kept the sample size to 100.[11] All postpartum women with moderate to severe iron deficiency anemia (Hb level between (6 to 9.9mg/L) were enrolled for this study after obtaining informed written consent. Hundred participants were recruited by convenient and consecutive sampling method and enrolled to one of the study groups by lottery method. Group A (n=50) received iron sucrose infusion and Group B (n=50) received ferric carboxy maltose. Women not willing to participate, high risk pregnancy conditions like hypertensive disorders , medical disorders like hepatic or renal disorders, tuberculosis, diabetes, connective tissue disorders, acute infections, malignancies, known hypersensitivity to iron derivatives and parenteral iron treatment and anemia due to other causes like hemolytic anemia, thalassemia and megaloblastic anemia were excluded from the study.

Data regarding demography, detailed history and examination findings were collected. Baseline investigations like peripheral smear, hemoglobin and serum ferritin were obtained. The participants were subjected to iron transfusion, either with iron sucrose or iron ferric carboxymaltose, with an intention to increase the target hemoglobin to 12g/dl. Total dose of iron infusion was calculated according to Ganzoni's formula.[12]

Total dose infusion (in milligram) = (target Hb-actual Hb in g/dl) x 2.4 x body weight in kg +body iron store. The target Hb was set as 12g/dl, correction factor of 2.4 was considered from patient's blood volume (7% of body weight) and iron content of Hb (0.34%).In addition extra 500mg was considered to replenish body iron stores. For convenience total dose was rounded to nearest multiple of hundred.

Iron sucrose was given intravenously in a dose of 200 mg in 200 ml of 0.9% of sodium chloride solution(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.

Ferric Carboxymaltose was given as intravenous infusion, with 500 mg of FCM diluted in 100ml of normal saline administered over a period of 6 min and 1000mg of FCM diluted with 250 ml of normal saline given over 15 min duration, not exceeding the maximum dose of 1000 mg/day/week. Participants requiring more than 1000mg of FCM, repeat dose were administered weekly, not exceeding total cumulative dose of 2500mg.

Parenteral iron infusion was given under availability of equipments for cardiopulmonary resuscitation. Patients were observed for side effects or anaphylactic reactions. Any minor or major side effects were documented and treated. Hemoglobin and serum Ferritin level were again measured at the end of 8 weeks.

All the data were collected and tabulated in Microsoft excel spreadsheet and analyzed using IBM SPSS statistics (Version21). 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 or fisher exact test for categorical data and independent sample't' test or Mann Whitney U test for comparing the means of different parameters. A 'p' value of less than or equal to 0.05 was considered as statistically significant. The objectives of the present study were to estimate the safety and efficacy of ISC and FCM in treating PPA. To access the safety of drugs, we recorded the vitals of patient and adverse events of drugs during and after administration of the preparations. Patients were asked to report any untoward medical events at onset and appropriate steps were taken to manage the events as per the hospital protocol. We followed up the participants till 8weeks post transfusion. The efficacy was accessed by estimating the post-transfusion improvement in level of hemoglobin, serum ferritin as well as by measuring the proportion of participants achieved hemoglobin of more than 12 gm/dl and increase in Hb of more than 2gm/dl.

RESULTS:

Demographic and clinical characteristics were tabulated in table-1. Both ISC and FCM groups were comparable with respect to sociodemographic and baseline characteristics. The mean age was 25.5 ±2.5 years; most of the women belong to lower and lower middle class. Majority of the patients were of lower socioeconomic status and most of them were unbooked. Mean hemoglobin was 8.5 gm /dl with majority of them having moderate anemia.

Table 1: Demographic And Baseline Clinical Characteristics

Characteristics	ISC group (n=50)	FCM group (n=50)	P-value
Age (in years)	25.24 ± 4.20	26.28 ± 4.39	0.508
Socioeconomic status			
Lower Lower middle Middle Upper middle Upper	17(34%) 18(36%) 07(14%) 07(14%) 01(2%)	14(28%) 19(36%) 09(18%) 06(12%) 02(4%)	0.914
Booking			
Booked Unbooked	14(28%) 36(72%)	09(18%) 41(82%)	0.234
Parity			
Primi Multi	24(48%) 26(52%)	28(56%) 22(44%)	0.423
Mode of delivery			
Vaginal Instrumental delivery Cesarean Section	26(52%) 06(12%) 18(36%)	27(54%) 02(4%) 21(42%)	0.324
BMI (Kg/m^2)	24.18 ± 3.92	23.61±3.5	0.332
Mean Hb (gm %)	8.53±0.87	8.51±0.95	0.896
Degree of anemia			
Mild (9.1-10gm %) Moderate (7.1-9gm %) Severe (6-7gm %)	19(38%) 27(54%) 4(8%)	20(40%) 25(50%) 5(10%)	0.898

ISC: Iron Sucrose Complex, Fcm: Ferric Carboxy Maltose; Hb: Hemoglobin

Baseline and 8 week post treatment hematological parameters were tabulated in table-2. Treatment with iron sucrose increased the mean hemoglobin from 8.53 gm/dl to 12. 38 gm/dl (MD, 3.85 gm/dl; 95% CI, 3.66-4.0; p<0.001) and also improved the serum ferritin from 26.38 ng/ml to 136.87ng/ml (MD, 110.48 ng/ml; 95% CI, 102.1-118.9; p <0.001). Conversely, the mean hemoglobin increase after FCM infusion was from 8.51 gm/dl to 12.88gm/dl (MD, 4.37gm/dl; 95%CI, 4.2-4.55; p<0.001) and corresponding ferritin improved from 27.69 ng/ml to 144.29 ng/ml (MD, 116.59 ng/ml; 95%CI, 107.3-125.8; p<0.001). Statistically significant improvement in hemoglobin and ferritin levels was observed in both iron sucrose and ferric carboxymaltose as compared to its baseline values. However between group comparison revealed, hemoglobin improvement was significantly higher in FCM than ISC group (p<0.001), but rise in ferritin levels was comparable between the groups (p=0.330). The target hemoglobin of more than 12gm/dl was achieved in 74% of ISC group and 86% of FCM group. In both the treatment groups a rise of hemoglobin of more than 2gm/dl was observed in all patients.

Table 2 Change In Hematological Parameter

Outcomes	ISC group (n=50)	FCM group (n=50)	Between group comparison P-value [b]
Hb(gm/dl) [a]			
Baseline	8.53±0.87(8.28-8.78)	8.51±0.96(8.23-8.78)	0.896
8 weeks	12.38±0.93 (12.12-12.64)	12.88±0.95 (12.61-13.15)	0.009
Change in Hb	3.85±0.66(3.66-4.0)	4.37±0.62(4.2-4.55)	<0.001*
P-Value [c]	t=41.24,df=49, p<0.001	t=49.81,df=49, p<0.001	
Ferritin(ng/ml) [a]			
Baseline	26.38±7.49(24.2-28.5)	27.69±12.27(24.2-31.2)	0.520
8 weeks	136.87±31.06(128.0-145.7)	144.29±30.96(135.5-153.1)	0.235
Change in ferritin	110.48±29.68(102.1-118.9)	116.59±32.6 (107.3-125.8)	0.330
P Value [c]	t=26.31,df=49,p<0.001	t=25.24,df=49,p<0.001	

Note: Hb: Hemoglobin; FCM: ferric carboxy maltose; ISC: Iron sucrose complex

[a] hemoglobin and ferritin expressed in mean ± standard deviation with 95% confidence interval in closed bracket

[b] Between group comparison of mean by student's t test

[c] Intra group comparison of mean, before and after treatment by paired t test

* Statistically Significant

Table-3 is showing the change of hemoglobin level among different degree of anemia. Statistically significant improvement in post-treatment hemoglobin levels was observed among different grade of anemia in both ISC and FCM treatment groups. Similarly between the groups (ISC Vs FCM) comparison revealed a statistically significant rise in hemoglobin level among women treated with FCM as compared to ISC group except the women with severe degree of anemia, where the difference was not statistically significantly different.

Table 3: Change In Hemoglobin Level With Respect To Degree Of Anemia

ISC group					FCM group				Between group
Degree of anemia	Hb1	Hb2	MD	P value	Hb1	Hb2	MD	P value	P value
Mild	9.31	12.97	3.66	<0.001	9.36	13.59	4.22	<0.001	0.02*
Moderate	8.38	12.30	3.91	<0.001	8.28	12.71	4.42	<0.001	0.04*
Severe	6.32	10.47	4.15	<0.001	6.40	11.10	4.70	<0.001	0.12

Note: Hb1: baseline hemoglobin; Hb2:post-treatment hemoglobin FCM: ferric carboxymaltose; ISC: Iron sucrose complex; MD: mean difference; Mild anemia: 9.1-10g/dl, Moderate: 7.1-9g/dl, Severe: 6-7 g/dl

* Statistically Significant

Post-treatment ferritin levels were significantly greater across

different degree of anemia when compared to its baseline values in both ISC and FCM treatment groups (table-4). However the mean difference in ferritin levels between ISC and FCM across different degree of anemia were comparable (P>0.05).

Table 4: Change In Ferritin With Respect To Degree Of Anemia

ISC group					FCM group				Betwen group
Degree of anemia	F1	F2	MD	P value	F1	F2	MD	P value	P value
Mild	30.69	142.5	111.8	<0.001	27.76	162.45	134.69	<0.001	0.23
Moderate	25.88	138.8	113.0	<0.001	26.07	136.78	110.71	<0.001	0.63
Severe	21.36	134.9	113.6	<0.001	23.20	114.32	91.12	<0.001	0.94

F1: baseline ferritin (ng/ml); F2: post-treatment ferritin

Table-5 depicts the adverse events of iron sucrose and ferrous carboxymaltose. Most of the patients tolerated the preparation well. Minor side effects like burning pain at site of injection, nausea, vomiting , fever, rigor and transient hypotension observed in 6(12%) and 4(8%) cases among ISC and FCM group respectively, which was managed medically and no serious adverse drug reaction or anaphylaxis was observed in any of the patients.

Table 5: Adverse Reactions Of Iron Preparation

Adverse events	ISC group n (%)	FCM group n (%)
Burning or pain at site of injection	2(4%)	1(2%)
Hypotension	1(2%)	1(2%)
Headache	2(4%)	2(4%)
Nausea, vomiting	2(4%)	1(2%)
Fever, rigor	1(2%)	0(0%)
Severe anaphylaxis	0(0%)	0(0%)
Total adverse events*	6(12%)	4(8%)

* Some patients had more than one adverse event

DISCUSSION:

Postpartum iron deficiency anemia is a most neglected entity, more so in developing countries. Treatment modalities include oral / injectable iron preparation and blood transfusion is reserved for more severe cases of anemia. Oral ferrous sulphate is the cheapest oral preparation readily available all over India and also supplied free of cost by govt of India under Janani Shishu Suraksha Karyakrama(JSSK).[13] Oral iron is always considered as first line treatment option for mild to moderate anemia, however oral iron use has a limitation of suboptimal response or non-response, which could be due to noncompliance as consequence of psychological cause or gastric intolerance(at a frequency of 20%). Thus intravenous iron therapy should be considered as an alternative in this women.[1] Oral iron also has a disadvantage of requirement of prolonged administration to achieve target haemoglobin and replenish stores.[12]

Injectable preparations recently available are low molecular weight iron dextran (LMW-ID), ferric gluconate, iron sucrose complex, ferrous carboxymaltose and iron isomaltoside.[14] Indication of injectable preparations are failure of standard oral therapy, gastric intolerance, severe anemia and condition where rapid correction of anemia is required.[7] Intramuscular preparations are less popular than intravenous (IV) and has a disadvantage of pain and permanent discolouration at site of injection.[14] Intravenous preparation has been observed to be superior to oral iron for improvement of haemoglobin as well as ferritin level more rapidly, improve fatigue score and lower rate of gastro-intestinal side effects.[1] In a narrative review of 14 randomised controlled trials of 2913 women treated with either oral iron or intravenous iron preparation for treatment of uterine bleeding and postpartum anemia, Daniilidis et al. ,concluded that IV preparations are more effective than oral supplements in achieving target haemoglobin and ferritin levels within a shorter period of time.[14] However some randomised controlled trials did not find any difference between the two treatment regimens in achieving target level of haemoglobin. But IV iron is better tolerated than oral supplement because of less gastrointenstinal side effects.[10,15] Similarly Sultan et al., in their systematic review of 15 randomised controlled trial of 2182 women in postpartum period who received oral iron (n=1001) and IV iron (n=1181) , reported a higher hemoglobin concentrations at 6 weeks postpartum among the IV iron group compared to the oral iron group (MD, 0.9 g/dL; 95% CI , 0.4-1.3; P =0.0003).[16] In addition IV iron has been reported to have a decreased likelihood of constipation and dyspepsia as compared to oral iron but an increased likelihood of skin flushing. They reported the rate for anaphylaxis among women receiving IV iron was 0.6%. A recent parallel-group, open-label, randomized controlled phase 3 trial of 230 women, randomly assigned to a study group (114 to intravenous iron, 116 to oral iron). Authors observed that intravenous ferric carboxymaltose was safe and yielded a better hemoglobin response than oral iron in postpartum period.[17]

In the present study we observed a statistically significant improvement in hemoglobin and ferritin levels at 8weeks in both iron sucrose and ferric carboxymaltose as compared to its baseline values. Post treatment hemoglobin improvement was significantly higher in FCM than ISC group (4.37gm/dl Vs3.85 gm/dl; p<0.001), but the mean rise in ferritin levels was comparable between the groups (116.59 vs. 110.48; p=0.330).All the participants achieved increase in Hb level of more than 2gm/dl and higher proportion of participants among FCM group attended an absolute value of Hb of more than 12gm/dl (86% vs. 74%). FCM is more effective in correcting anemia with less frequency of hospital visit. Thus it may be considered as more convenient way of treating postpartum iron deficiency anemia.

Analogous result of superiority of FCM over ISC in management of PPA was observed by Pfenniger A et al., Sharma N et al., Rathod S et al. and Joshi SD et al., in their studies. In a retrospective cohort study, 210 women with postpartum anemia received IV high-dose FCM (15 mg/kg; maximum, 1000 mg) or ISC (2dose of 200 mg), Pfenniger A et al. concluded that FCM is as safe as ISC in the management of postpartum IDA despite being given in a five times higher dosage.[18] Both drugs are effective and offer a rapid normalization of Hb after delivery .Furthermore a single infusion of FCM has advantages of lower incidence of injection site complication, a shorter treatment period, and better patient compliance. Sharma N et al., Rathod S et al. and joshi SD et al. in their studies for management of post partum IDA, reported a superiority of FCM over ISC in improving hemoglobin and replenishment of iron store over a short period of time.[9,19,20] A recent systematic review and meta-analysis of 9 randomized controlled trials with 910 patients randomized to receive ISC (n=454) or FCM(n=456) reported a better efficacy of FCM in increasing Hb and ferritin levels , a favorable safety profile with fewer adverse events compared with ISC group for IDA treatment among obstetric and gynecologic patients.[21] Because of greater safety and efficacy, Ferric carboxymaltose is considered as first-choice among available intravenous preparation in postpartum women with iron deficiency anemia.[7] FCM has a practical benefit of single large dose administration which reduces the overall cost of treatment and improves patient comfort.

Intravenous preparations were formulated with a polynuclear-iron-oxyhydroxide core surrounded by a carbohydrate shell. This carbohydrate shell controls the release of free iron from the complex and also limits the serum concentration of free iron even after a bulk dose. The iron carbohydrate complex particles are taken up by macrophage in the reticuloendothelial system (RES) with subsequent breakdown and delivery of iron to transporter protein Transferrin without large amount of ionic iron being released in to serum.[1,22] Dextran containing preparation is associated with more adverse events and it's not preferred now a days. Newer second generation products like low molecular weight iron dextran and iron sucrose as well as more recently introduced third generation compounds like ferric carboxymaltose and ferric iron isomaltoside have better safety profiles.[1,22]

No serious adverse effect was observed in our study; however minor adverse events were encountered in 12% and 8% cases of ISC and FCM groups respectively which were managed by observation and/or medical management. Similar findings was reported in a systematic review and meta-analysis of 9 RCTs with 910 patients (FCM group, n=456; ISC group, n=454). FCM group showed a lower incidence of adverse events than ISC group (risk ratio, 0.53; 95% CI, 0.35–0.80; I2=0%; P=0.003) and serious adverse events were not reported in any group.[23] Several systematic studies failed to document any safety advantage of any injectable iron preparation over the other.[24,25] Free iron has been associated with unacceptable high toxicity inducing

severe, haemodynamically significant symptoms, however newer preparations like ISC and FCM contain the iron as an iron carbohydrate nanoparticle, does not release much free iron and thus the serious adverse events are rare.[26] Overall rates of serious or moderate to severe hypersensitivity reaction were low (0.2%-1.7%).[25]

CONCLUSION:

Postpartum period is a neglected period in women's life and postpartum iron deficiency anemia is a common entity and is associated with significant maternal morbidity. Even though oral iron is considered as a first line therapy, it requires a prolonged administration and is associated with suboptimal response due to gastric intolerance and poor compliance. Intravenous iron preparations are safe alternative and more convenient than oral iron for treatment of postpartum iron deficiency anemia. Ferric carboxymaltose is a third generation iron preparation and can be administered as a large bolus dose, requires lesser time of hospitalization, and is more efficacious, safer alternative in postpartum anemia.

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