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Comparative Study between intravenous iron Sucrose and ferric carboxymaltose for the treatment of Postpartum Anemia in rural women

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ABSTRACT
Anemia is the most common haematological abnormality diagnosed during pregnancy. The prevalence of Postpartum Anemia in developing countries ranges from 50-95%. Postpartum anemia has been defined as Hemoglobin of <10 gm/dL and Serum Ferritin <15 microgram/L, in 24-48 hours post delivery. Aim of the study was to compare efficacy and safety of Intravenous Ferric Carboxymaltose and Intravenous Iron sucrose in treatment of Iron deficiency Anemia. A Comparative, interventional, prospective study was carried out in 50 postpartum patients with Haemoglobin ≥ 7gm/dL to ≤ 10 gm/dL with Serum Ferritin < 15 µg/L in the Department of Obstetrics and Gynaecology from January 2018 to June 2019. The subjects were randomized in two groups . First group received 500 mg of Intravenous Iron sucrose in 3 divided doses(200 mg on Day 0, 2 and 100 mg on Day 4) and Second group received a single dose of 500 mg of Intravenous Ferric Carboxymaltose. Maximum number of patients in our study belonged to Low socio-economic group, significantly higher number of women achieved rise oh Hb > 2gm/dL in FCM group. 32% women in FCM group achieved Hb rise of > 2 gm/dL as compared to 4% in iron sucrose group, which was significant (p=0.023). Mean rise of Hb was 1.88 gm/dL and 1.12 gm/dL respectively for FCM and Iron sucrose group which was also significant. Mean rise of Serum Ferritin level in FCM group was 67.68 µg/L as compared to 51.92 µg/L in Iron sucrose group which was statistically significant. Adverse drug reactions were significantly less in FCM group. In our study, FCM was very effective in improving Hb concentration as well as in early replenishment of iron stores in patients with Postpatum anemia. It has an added advantage of single dose administration, well tolerated, offers better compliance and reduces length of hospital stay.
Keywords- *Iron deficiency anemia, Iron Sucrose, Ferric carboxymaltose, Postpartum anemia*

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INTRODUCTION

Major contributor to the maternal mortality and morbidity is the anemia in the third world countries. The WHO Data says that it accounts to 20% of the maternal deaths (1). Anaemia is the most common haematological abnormality diagnosed during pregnancy. The prevalence of postpartum anemia in developing countries ranges from 50-95% (2). WHO defines, anaemia during pregnancy as condition in which less than 11 gm% (7.45 mmol/L) haemoglobin concentration and less than 33% haematocrit. Postpartum anemia is a condition described when haemoglobin is less than 10 gm/dl and serum ferritin less than 15 miocrogram/L, in 24-48 hours post-delivery(3). Statistics accounts explains low intake of essential nutrient, predominantly vegetarian diet, repeated pregnancies at short intervals and chronic blood loss due to infection such as malaria, hookworm infestation, young mothers not taking iron folic acid supplement in pregnancy are the main factors which contributes to anemia in third trimester. The most common type of anaemia during pregnancy and puerpurium is dimorphic anaemia due to isolated or combined nutritional deficiency of iron, vitamin B12, and folic acid(4). Studies conducted postpartum anemic female have shown postpartum depression, stress, anxiety and cognitive impairment are associated with it.(5,6) Oral Iron is safe way to replace iron and is practiced in government policies for anemia prevention and treatment. Oral iron therapy should be given in a dose of 60 mg elemental iron twice daily during the 2nd and 3rd trimester of pregnancy and then for 6 months postpartum. Nausea, epigastric discomfort, metallic taste non-compliance are the main side effects of the Iron salts preparation. This intolerance to oral iron limits its efficacy. The haemoglobin level starts to rise after 3rd week of oral iron

therapy and it takes 3 months to replenishment of iron stores. Parenteral iron therapy is indicated when there is no compliance or intolerance to oral iron, impaired iron absorption, chronic blood loss, and gastrointestinal disorders limiting the therapeutic effects of oral iron therapy. Parenteral iron therapy ensures good compliance, rapid correction of anemia and replenishment of iron stores.(7)

Parentral therapy- **Iron sucrose (IS)** Iron sucrose is administered as 200 mg dose diluted in 100 ml normal saline in outpatient basis as short infusion of 30 min (200 mg diluted in 100 ml normal saline infuse slow in 15-30 min). No test dose is required and there is less anaphylactic reaction and better bioavailability. Haemoglobin rises at rate of 1 gm/ week. IV sucrose infusion should be given in a day care setting with facilities to handle emergencies under the supervision of a medical officer. The woman is to be kept under observation atleast for 2 hours after infusion.

Advantages of iron sucrose- Less tissue peroxidation, less oxidative injury, less tissue injury by free iron, better increase in erythropoiesis, less side effects, Hb rise within 5 days, allergic reactions are rare as compared to iron dextran (8.7 vs. 3.3 allergic events per 1,000,000 doses).

Ferric carboxymaltose is a Type 1 polynuclear iron hydroxide carbohydrate complex that produces a slow and sustained delivery of the complexed iron to endogenous iron binding site.8,9 IV ferric carboxymaltose (FCM) has a neutral pH (5.0 - 7.0) at physiological osmolarity, which makes it possible to administer its higher single doses over shorter time periods (single dose up to 1000 mg over 15 minutes) than other parenteral preparations.11 Due to its stability, Ferric carboxymaltose releases iron gradually which is delivered to the endogenous iron-binding proteins. It does not release ionic iron into the serum. After intravenous administration, the iron is distributed mainly in the liver, in the spleen, and in the bone marrow.10 The carbohydrate moiety is metabolized via glycolysis into simple oligo-glucose units such as maltotriose, maltose and glucose.

MATERIAL AND METHODS

Study duration : This was a cross sectional study conducted on the patient admitted postnatal care ward in the over a period of 18 months from January 2018 to June 2019.

Study population: The population in this study consisted of postpartum patients (postnatal or post caesarean) within 10 days of delivery with haemoglobin ≥7 g/dL to ≤ 10g/dL with serum ferritin < 15 nanogram/ml.

Study design: This is a multicentric hospital based prospective comparative study conducted on rural population of postpartum patients with anemia admitted in postnatal ward, Department of Obstetrics and Gynecology, UPUMS, Saifai, Etawah & Faculty of medicine and health sciences SGT University

Sample Size : On evaluation of statistics of the study conducted in 2016 by Singh Shakun comparing efficacy and safety of intravenous Ferric carboxymaltose and intravenous Iron sucrose in Iron deficiency anaemia during post-partum period, data used and sample size calculated using formula

$$N \geq [55\ (5-55)+55(1-55)]/\Delta 2$$

$\otimes = 51\_52$

51 = *Percentage of subjects achieving rise of ≥ 2 gm/dl at 21 days in Iron Sucrose group. (24%)*

52= *Percentage of subjects achieving rise of ≥ 2 gm/dl at 21 days in Ferric Carboxymaltose group. (88%)*

k = 7.8 (constant)

Calculated minimum sample size is 6.

Sample size in current study was 25 for each group **Patient selection**

Inclusion criteria:

- Postpartum women aged 18-40 years.
- Postnatal/Post caesarean within 10 days of delivery
- Hb = 7 - 10 gm/dL

Exclusion criteria:

- Women with significant vaginal bleeding in prior 24 hours.
- Non-Iron deficiency anemia.
- Previous blood transfusion within 120 days.
- Bleeding disorder or coagulopathies.
- Chronic renal/ liver disease
- Severe cardiovascular disease or failure.
- Previous surgeries of intestinal resection/bypass.

Methodology

The postpartum cases both primi and multipara (postnatal as well as post caesarean) within 10 days of delivery with Hb less than 7 - 10 g/dl with Serum Ferritin <15ng/ml were included in the study. Each case

meeting the selection criteria signed a written informed consent after explaining the procedure required for the study and then a preliminary assessment was done by detailed history and clinical examination. Diagnosis was confirmed by Complete Blood Count, Serum.ferritin and Peripheral blood smear.

Serum Ferritin Level (Apoferritin + Iron = Ferritin). Values in non-pregnancy state = 50 to 150 mcg/L. Serum ferritin less than 12 mcg/dl is diagnostic of depleted iron stores in pregnancy, cutoff value up to 50 mcg/dl have been used and if values <35 mcg/L iron deficiency should be suspected. Categorization of Women Using Hb and Ferritin

Category	Sr.Ferritin(mcg/ L)	Hb (gm/dL)	Diagnosis
I	>12	>11	Normal – no iron deficiency
II	<12	>11	Storage iron depletion
III	<12	<11	IDA

Subjects were randomized and divided into 2 groups by chit system.

Group 1-Subjects were given Intravenous iron sucrose in three doses, 200 mg/day on day 0, 2 and 100 mg on day 4, total of 500 mg. (iron Sucrose 200 mg diluted in 100ml of 0.9% normal saline and given over 20 to 30 min.). During first five minutes, infusion should be given at the rate of 20-30 drops/min and then increased to 80-90 drops/min. **Group 2-** Subjects were given Intravenous ferric carboxymaltose 500 mg single dose (Carboxymaltose 500 mg diluted in 100ml of 0.9% NS given in 20 to 30 min). In both groups complete blood counts and serum ferritin were done on 0 and after 2 weeks of last dose of parenteral iron. Side effects like headache, myalgia, arthralgia, nausea, vomiting, epigastric discomfort and anaphylactoid reactions will be looked for during the procedure. The patients were observed for one hour after infusion.

Table-1 Demographic Profile

Demographic variables		Group A (n=25)	Group B (n=252)	P value
Age group (years)	20-24	10 (40%)	8 (32%)	0.407
	25-29	11 (44%)	14 (56%)	
	30-34	4 (16%)	3 (12%)	
Socioeconomic status	Lower	18 (72%)	12 (48%)	0.222
	Lower middle	5 (20%)	9 (36%)	
	Middle	2 (8%)	4 (16%)	
Booking status	Booked	8 (32%)	11 (44%)	0.382
	Unbooked	17 (68%)	14 (56%)	
Parity	P1	7 (28%)	6 (24%)	0.979
	P2	12 (48%)	12 (48%)	
	P3	4 (16%)	5 (20%)	
	P4	2 (8%)	2 (8%)	

Table-2 Distribution of cases according to Mode of delivery

Mode of delivery	Group A (n=25)	Group B (n=25)	P value
LSCS	6 (24%)	9 (36%)	0.596
NVD	11 (44%)	12 (48%)	
NVD with episiotomy	4 (16%)	1 (4%)	
Repeat LSCS	2 (8%)	1 (4%)	
VBAC	2 (8%)	2(8%)	

Table-3 Haemoglobin levels before intervention in both groups

Pre-treatment haemoglobin	Group A (n=25)	Group B (n=25)	P value
7.0-8.0	7 (28%)	7 (28%)	1.000
8.1-9.0	13 (52%)	13 (52%)	
9.1-10.0	5 (20%)	5 (20%)	

Table-4 Post-treatment levels of Haemoglobin in both groups

Post-treatment haemoglobin	Group A (n=25)	Group B (n=25)	P value
8.0-9.0	5 (20%)	1 (4%)	0.055
9.1-10.0	14 (56%)	10 (40%)	
10.1-11.0	5 (20%)	8 (32%)	
11.1-12.0	1 (4%)	6 (24%)	

Table-5 Comparison of mean haemoglobin among the two groups

Haemoglobin levels	GroupA(n=25) Mean ± SD	GroupB(n=25) Mean ± SD	P Value
Haemoglobin (Pre-treatment)	8.45±0.63	8.42±0.66	0.845
Haemoglobin (Post-treatment)	9.58±0.73	10.29±0.85	0.003
Haemoglobin (Difference)	1.12±0.27	1.88±0.29	<0.001

Table-6 Comparison of post-treatment Haemoglobin in both groups

Post-treatment Hb	Group A (n=25) Number (%)	Group B (n=25) Number (%)	P Value
<11	23 (92.0 %)	19 (76.0 %)	0.247
>=11	2 (8.0 %)	6 (24.0 %)	
Total	25 (100.0 %)	25 (100.0 %)	

Table-7 Comparison of post-treatment rise of Haemoglobin in both groups

Rise of Haemoglobin	Group A (n=25) Number (%)	Group B (n=25) Number (≥%)	P Value
<2	24 (96.0 %)	17 (68.0 %)	0.023
>=2	1 (4.0 %)	8 (32.0 %)	
Total	25 (100.0 %)	25 (100.0 %)	

Table-8 Comparison of Serum Ferritin values before and after intervention in both groups

	Serum Ferritin levels	N	Mean ± SD	Mean Difference ± SD	P Value
Group A	Serum Ferritin (Pre-treatment)	25	10.48 ± 2.36	(-) 51.92 ± 7.04	<0.01
	Serum Ferritin (Post-treatment)	25	62.40 ± 7.49		
Group B	Serum Ferritin (Pre-treatment)	25	10.60 ± 2.35	(-) 67.68 ± 6.42	<0.01
	Serum Ferritin (Post-treatment)	25	72.28 ± 6.35		

Table-9 Comparison of Post-treatment adverse reactions in both study groups

	Group A (n=25)		Group B (n=25)	
	Present	Absent	Present	Absent
Local reactions	7 (28.0%)	18 (72.0%)	3 (12.0%)	22 (88.0%)
Rashes	1 (4.0%)	24 (96.0%)	0 (0.0%)	25 (100.0%)
Nausea/Vomiting	3 (12.0%)	22 (88.0%)	0 (0.0%)	25 (100.0%)
Giddiness/Hypotension	3 (12.0%)	22 (88.0%)	1 (4.0%)	24 (96.0%)
Chest discomfort/Breathlessness	2 (8.0%)	23 (92.0%)	0 (0.0%)	25 (100.0%)

In this study,a total of 50 women with postpartum anemia were studied who were randomized into two groups, 25 cases were given Iron sucrose (Group A) and 25 cases were given Ferric carboxymaltose (Group B). Both the groups were compared for age,socio economic status and parity and were comparable.The mean age in Iron sucrose group (Group A) was 25.84± 3.05 years and in Ferric carboxymaltose (Group B)

was 25.72± 3.16 years, with no statistical difference between the two groups. Most of the patients in the study, in both the groups belonged to Lower socio economic status.Parity of most patients in the study was 2, 48% each in both the groups.In present study most of the patients delivered vaginally (44% in Iron sucrose group and 48% in Ferric carboxymaltose group),i.e. no significant relationship between mode of delivery and the interventions used. Mean haemoglobin before starting of therapy in group A groups A (1.12±0.27 gm/dl) and B (1.88±0.29 gm/dl), Group B had significant rise of haemoglobin level after 2 weeks.was 8.45±0.63 and in group B was 8.42±0.66.While comparing mean rise of haemoglobin level between Haemoglobin level of ≥11gm/dl was achieved in 24% patients in FCM group as compared to 8% in Iron sucrose group which was significant.Similarly,In Group B (FCM Group) 32% of patients had rise of Haemoglobin ≥2 gm/dl as compared to 4% in Group B (Iron sucrose Group).Increment in the levels of Serum Ferritin level after 2 weeks of therapy was higher in group B (67.68±6.42) as compared to (51.92±7.04) which was significant.Adverse reactions were significantly less in Ferric carboxymaltose as compared to iron sucrose.

DISCUSSION

Both the study groups were similar in demographic profile i.e. age,pariry,socio economic status etc. The mean age in Iron sucrose group (Group A) was 25.84± 3.05 years and in Ferric carboxymaltose (Group B) was 25.72± 3.16 years.This study was comparable to Ruchika Garg et al. where mean age of patients in both groups was 25.50 and 25.56 years respectively in Iron sucrose and Ferric carboxymaltose group. In our study,most of the patients in both groups were unbooked and lower socio economic status.The mean haemoglobin level before starting therapy in Group A was 8.45±0.63 and 8.42±0.66 (Table-5),there was increase of 1.12±0.27gm/dl in haemoglobin level after 2 weeks of therapy and mean haemoglobin level was 9.58±0.73 gm/dl in group A,whereas in group B there was increase of 1.88±0.29 gm/dl in haemoglobin and the haemoglobin level was 10.29 ±0.85 gm/dl at 2 weeks after therapy (Table-5).Statistically significant difference was found in post-treatment haemoglobin values in both the groups which is similar to the study conducted by Lunagariya et al.in which the pre-treatment values of haemoglobin in Iron sucrose and Ferric carboxymaltose group were 8.536±0.45 and 8.385±0.56 gm/dl and the post-treatment values were was 10.29 ±0.42 and 10.28±0.70 gm/dl respectively.Mean rise of haemoglobin after iron sucrose and Ferric carboxymaltose was 1.66 gm/dl and 1.9 gm/dl respectively in study conducted by Lunagariya et al. In our study 8% and 24% of cases achieved a post treatment haemoglobin value of ≥11 gm/dl respectively in group A and group B. 4% and 32% of cases had a rise of ≥2 gm/dl in haemoglobin level respectively in group A and group B, i.e. larger number of cases who received Ferric carboxymaltose achieved a rise of haemoglobin level which was more or equal to 2 gm/dl. Nalini Sharma et al in 2017 conducted a prospective,comparative study on 120 postpartum women with iron deficiency anemia. A fixed dose of 1000 mg of Ferric carboxymaltose or Iron sucrose was given.Haemoglobin and Serum Ferritin were repeated 14 days post-transfusion. The mean haemoglobin after treatment with Iron sucrose and Ferric carboxymaltose was 9.2 and 10.46 gm/dl,respectively which was statistically significant (P value 0.000 and 0.000).They concluded Ferric carboxymaltose was very effective in improving haemoglobin concentration as well as in early replenishment of iron stores.

In our study mean values of Ferritin before intervention were 10.48±2.36 and 10.60±2.35 in group A (Iron sucrose)and group B (FCM) respectively, however post-treatment the values were 62.40±7.49 and 78.28±6.35 in group A and group B respectively. The difference between post-treatment values of both the groups were statistically significant, (P<0.001).The mean rise in Serum Ferritin in group A and group B was 51.92±7.04 and 67.68±6.42 respectively. This shows that Ferric carboxymaltose is more efficient and causes faster replenishment of iron stores. Suyajna D et al. in 2016 performed study on 200 women to compare multidose Iron sucrose (200 mg/day in 5 divided doses ; alternate day) and single dose Ferric carboxymaltose (1000 mg) for treatment of postpartum anemia. Haemoglobin and Serum Ferritin values were repeated after 30 days post-treatment.They concluded that there was statistically significant rise (P<0.001) of haemoglobin in Ferric carboxymaltose group (4.68 gm/dl) as compared to iron sucrose (3.92 gm/dl). Also the mean rise in serum ferritin was more in ferric caboxymaltose group (95.39±45.84) as compared to iron sucrose group (71.07±27.23).

In our study, subjects in group A had significantly higher incidence of adverse effects.Local reactions (28% verses 12%), rashes (4% verses 0%), nausea/vomiting (12% verses 0%), hypotension/giddiness (12% verses 4%), breathlessness (8% verses 0%). Similarily in study conducted by Lunagariya et al., Singh S et al., Suyajna D et al. and other studies have shown thar Ferric carboxymaltose has less side effects than Iron sucrose.

CONCLUSION

From our study we conclude that Ferric carboxymaltose causes significantly higher rise in haemoglobin as compared to Iron sucrose. Notably, Serum ferritin which is a marker of iron stores increased Statistically significant in FCM group in comparison to Iron sucrose group, which prevents recurrence of iron deficiency anemia. Ferric carboxymaltose has an additional advantage of single dose administration improves compliance of the patient and also reduces length of hospital stay. Intravenous Ferric carboxymaltose is more effective than Iron sucrose for correction of postpartum iron deficiency anemia with minimal side effects.

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