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A PROSPECTIVE STUDY OF INTRAVENOUS FERRIC CARBOXYMALTOSE COMPARED WITH ORAL IRON IN THE TREATMENT OF POSTPARTUM IRON DEFICIENCY ANEMIA – A RANDOMIZED CONTROLLED STUDY

Gynaecology

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ABSTRACT

WHO has defined postpartum iron deficiency anemia (PPIDA) as hemoglobin (Hb) of <10 gm% during the postpartum period. The prevalence of PPA varies from 4% to 27%. Ferric carboxymaltose (FCM) is a non – dextran containing type 1 complex designed to be administered in large doses by rapid (over 15 minutes) intravenous infusion6. The FCM complex is composed of a polynuclear iron(III) hydroxide complexed to carboxymaltose. Aim of the study was to compare the efficacy and safety of FCM injection with oral iron in treatment of PPIDA.425 women between day 1 to day 10 of normal delivery with moderate anemia (Hb 7-10 g/dl) underwent the screening tests at JMMCRI, Thrissur, Kerala. On the basis of Peripheral blood smear examination and/or RBC indices, 140 subjects with PPIDA were finally recruited in the study. Pre-treatment baseline hematological parameters were comparable in both the groups. Mean Hb was 8.4 vs 8.4 g/dl, mean serum iron was 49.5 vs 54.3 mg/dl mean ferritin was 12.7 vs 12.8 ng/ml in parenteral and oral groups respectively. Significantly higher number of women in parenteral group achieved Hb rise>3 gm/dl (75.7% vs 15.7%, p value < 0.001) after 6 weeks of therapy but this difference was not statistically significant at 3 weeks (10.0% vs 2.9%, p value 0.085). FCM was better tolerated than ferrous sulphate with low incidence of gastrointestinal adverse effects, rapid normalization of iron stores, better compliance and shorter treatment period.

KEYWORDS

PPIDA, FCM

INTRODUCTION

WHO defines postpartum anemia (PPA) as hemoglobin (Hb) of <10 gm% during the postpartum period. The prevalence of PPA in India is 4% to 27%. In India, about 36% of the total maternal deaths are attributable to postpartum hemorrhage or anemia. In healthy women after normal delivery, the prevalence of anemia 1-week postpartum is 14% in iron-supplemented women and 24% in non-supplemented women. Anemia is the most common hematologic abnormality diagnosed in pregnancy1.Pregnant women are recommended to take one iron tablet per day for at least 100 days (each tablet containing 100 mg of elemental iron and 500 mcg of folic acid) after first trimester of pregnancy; a similar dose applies to lactating women. Oral iron is an effective, cheap and safe way to replace iron. After oral iron therapy, Hb starts rising from third week but replenishment of iron stores may take up to three months. Iron salts may cause nausea, epigastric discomfort, constipation or diarrhea. Non- compliance and intolerance to oral iron can limit its efficacy .

Parenteral iron therapy is indicated when there is non-compliance or intolerance to oral iron, impaired iron absorption, chronic blood loss, and gastrointestinal disorders. Parenteral iron therapy ensures good compliance, rapid correction of anemia and replenishment of iron stores. FCM is a non dextran containing type 1 complex designed to be administered in large doses by rapid (over 15 minutes) intravenous infusion2. The FCM complex is composed of a polynuclear iron (III) hydroxide complexed to carboxymaltose. As FCM is a strong robust iron complex, it can be administered in high doses, does not release large amounts of reactive (free) iron into the circulation and does not trigger dextran –associated immunogenic reactions3. Its design allows for controlled delivery and minimal risk of acute toxicity and there is a much wider therapeutic window. The three major clinical trials (cited later in literature review)in PPIDA show consistent results regarding comparative efficacy of FCM injection and oral iron in increasing Hb. FCM injection leads to Hb rise along with replenishment of iron stores in much shorter time. Also, there is better tolerability with low risk of anaphylaxis and other adverse effects. A sub study on breast milk has been done showing it to be safe for infants4. Thus, FCM seems promising in the treatment of PPIDA.

LITERATURE REVIEW

Clinical trials using FCM in Postpartum Iron Deficiency Anemia (PPIDA) Van Wyck et al (2007)5 conducted a multicentric open-label, phase 3 randomized controlled trial comparing FCM with oral iron in 352 postpartum anemic women. Of these, 174 patients were given FCM given weekly up to calculated dose and 178 patients were given FeSO4 as 325 mg tablet three times daily for 42 days. They found that FCM injection is as effective as oral iron in achieving Hb rise of more than 2g/dl (96.4% compared with 94.1%, 95% CI -2.19 to 6.88; p=0.443), but median time to achieve this increment was shorter in FCM group than oral iron group (7.0 days compared with 14.0 days; p<.001). Also, the proportion of patients who achieved rise in Hb 3.0 g/dl or more, and proportion of patients who experienced correction of anemia (achieving Hb >12g/dl) were higher in FCM group than oral iron group (90.5% compared with 68.6%; p<0.001). Serum ferritin increased promptly in FCM treatment group. Adherence rate to treatment was greater in FCM group (98%) than oral iron group (83%). Breymann et al (2008)4 did a multicentric study spread over 20 centres in 3 countries in a 12 week study period on 348 postnatal women, in which they found almost similar findings. In FCM group there was significant increase in serum ferritin (p<0.001), and transferring saturation (p <.004), but no change in red cell indices in both the groups.

Seid et al (2008)6 conducted an RCT on 291 postpartum anemic women. They found FCM superior to oral iron in causing greater and sustained increase in Hb in a significantly shorter period of time and in improving iron stores. The percentage of patients who achieved Hb greater than 12 g/dl and increase in Hb 3g/dl or more were significantly more in FCM group than in oral iron group (91.4 vs 66.7%; p <0.0001). Also, the median time to achieve Hb greater than 12 g/dl (14 days vs 27 days; p=0.0002) and the median time to achieve an increase in Hb 3g/dL or greater (15 days vs 28 days; p <0.0001) were significantly shorter in subjects treated with FCM. Increased ferritin level was noted in FCM group than oral iron group (238 ng/ml vs 21 ng/ms p<0.0001). Rathod et al (2015)7 did a study to compare the safety and efficacy of FCM, intravenous (IV) iron sucrose and oral iron in the treatment of PPIDA in 366 women admitted to SCB Medical College, Cuttack ,India ,between September 2010 and August 2012 suffering from PPIDA hemoglobin (Hb) <10 g/dL . An increase in Hb and serum ferritin level was observed in all three groups, but the increase in FCM group was significantly higher (P < 0.0001) than conventional iron sucrose and oral iron group.

Joshi et al (2016)8 did a study to compare the safety and efficacy of FCM with Fe sucrose to treat IDA in the post-partum in 200 women in India. Both groups Hb%, and serum ferritin were done on 0 and day 30

of last dose of parenteral iron. There was statistically significant rise (P <0.001) of Hb in FCM group 4.68 g/dl compare to iron sucrose group 3.92 g/dl. Mean rise of serum ferritin was 71.07±27.23 and 95.39±45.84 in iron sucrose and FCM group.

Mishra et al (2015)9 did a prospective study in India which included 39 antenatal women >20-36 weeks gestation and 119 women with PPIDA. FCM was administered and improvement in hemoglobin and iron stores was assessed after 3 weeks. They found a significant improvement in hemoglobin over a period of 3 weeks from mean Hb 8.97±1.05 gm/dL to 11.34±0.90 gm/dL with p value < 0.001 which was statistically significant.

Chaurasia A et al (2016)10 did a prospective study conducted at MLN Medical College, Allahabad, India from 2014 to 2015 in 350 postpartum anemic women given different iron preparation and changes in various hematological parameters . They concluded that parenteral irons are definitely better chosen with preferences for FCM.

MATERIALS AND METHODS

- The present study was a prospective Randomised control study with an objective to compare the efficacy and safety of FCM with oral iron for treatment of PPIDA, conducted in Jubilee Mission Medical College and Research Institute, Thrissur, Kerala, between January 2015 to June 2016.
- A total of 425 postpartum women between day 1 to day 10 of normal delivery with moderate anemia (Hb 7-10 g/dl) underwent the screening tests.
- On the basis of peripheral blood smear examination and RBC indices, 140 subjects with iron deficiency anemia were randomized in 1:1 ratio into two groups.
- After an informed written consent, all subjects underwent detailed history, general physical and systemic examination. Group 1 subjects (n=70) received intravenous FCM and Group II subjects (n=70) received oral ferrous sulfate.
- Total dose of IV FCM was calculated by Ganzoni formula11 and was given as intravenous infusion; 1000 mg/dose weekly up to calculated dose or maximum of 2500 mg.
- Second group of subjects was instructed to take ferrous sulfate tablet 200 mg (containing 60 mg elemental iron) 3 times daily 1 hour before meal for 6 weeks. Both the groups were given deworming therapy along with folic acid 5 mg tablet once a day.
- All subjects were followed at 3 and 6 weeks. Repeat Hb estimation was done at 3 and 6 weeks while RBC indices and serum iron parameters were repeated at 6 weeks. 97% subjects in parenteral group and 76% subjects in oral group completed the study. Data was analyzed as per intention to treat.

OBSERVATIONS AND RESULTS:

Demographic profile was comparable in both the groups. Mean age was 25.53.6 years in group 1 versus 25.4 3.8 years in group 2 and mean BMI was around 22 in both the groups. Majority of patients were Hindu by religion (61.4% vs 45.7%), belonged to upper socio-economic status (45.7% vs 52.9%), and had received high school education (51.4% vs 42.93%).

- Majority of women in study groups were para 2 (about 50% in each group) and had a mean gestational age of 38 weeks at the time of delivery.
- Pre-treatment baseline hematological parameters were comparable in both the groups. Mean Hb was 8.4 vs 8.4 g/dl, mean serum iron was 49.5 vs 54.3 g/dl (Table 1) mean ferritin was 12.7 vs 12.8 ng/ml in parenteral and oral groups respectively. (Table 1).
- Significantly higher number of women in parenteral group achieved Hb rise>3 gm/dl (75.7% vs 15.7%, p value < 0.001) after 6 weeks of therapy but this difference was not statistically significant at 3 weeks (10.0% vs 2.9%, p value 0.085).
- Significantly higher percentage of women in the parenteral group as compared to oral group achieved correction of anemia i.e. Hb>11gm/dl, both at 3 weeks (40.0% vs 10.0%; p<0.001) and 6 weeks (77.1% vs 38.6%, p<0.001).
- Both groups showed significant improvement in all hematological parameters post treatment (Table 1)
- Significantly higher number of women in parenteral group achieved Hb rise>3 gm/dl (75.7% vs 15.7%, p value < 0.001) after 6 weeks of therapy but this difference was not statistically significant at 3 weeks (10.0% vs 2.9%, p value 0.085).
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- Both groups showed significant improvement in all hematological parameters post treatment (Table 1).

TABLE 1

HEMATOLOGICAL PARAMETERS AT BASELINE AND AT 6 WEEKS

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Baseline reticulocyte count (%)	FCM	70	2.165	1.0265	.1227
	Ferrous sulfate	70	2.174	.8116	.0970
Reticulocyte count at 6 weeks (%)	FCM	70	2.109	.7120	.0851
	Ferrous sulfate	70	2.001	.5825	.0696
Baseline serum iron (mg/dl)	FCM	70	49.53	26.609	3.180
	Ferrous sulfate	70	54.30	21.426	2.561
Serum iron at 6 weeks (mg/dl)	FCM	70	114.61	21.396	2.557
	Ferrous sulfate	70	88.33	30.731	3.673
Baseline total iron binding capacity (mg/dl)	FCM	70	416.24	38.818	4.640
	Ferrous sulfate	70	419.60	36.920	4.413
Total iron binding capacity at 6 weeks (mg/dl)	FCM	70	323.23	44.810	5.356
	Ferrous sulfate	70	385.24	46.554	5.564
Baseline transferrin saturation (%)	FCM	70	12.279	5.7106	.6826
	Ferrous sulfate	70	12.684	4.5950	.5492
Transferrin saturation at 6 weeks (%)	FCM	70	23.713	5.1421	.6146
	Ferrous sulfate	70	16.649	6.5596	.7840
Baseline serum ferritin (ng/ml)	FCM	70	12.79	6.833	.817
	Ferrous sulfate	70	12.83	7.050	.843
Serum ferritin at 6 weeks (ng/ml)	FCM	70	147.51	35.413	4.233
	Ferrous sulfate	70	14.87	6.846	.818

- The change from baseline was highly significant in all hematological parameters in parenteral group as compared to oral group (p=0.001), except for the reticulocyte count (-0.06 vs -0.17%) (p=0.418) (Table 2, 3).
- Mean rise in Hb was 3.35 g/dl in parenteral versus 2.12 g/dl in oral group which was highly significant (p<0.001) (Table 2).
- Serum ferritin which rose multifold in parenteral group and only marginally in oral group (134.7 ng/ml vs 2.04 ng/ml p<0.001). There was a fall in total iron binding capacity due to iron therapy in both the groups (-93.01 g/dl vs -34.36 g/dl) (Table 2).
- Overall incidence of side effects was found lower in parenteral group than oral group. (Figure1)

TABLE 2: CHANGES IN HEMATOLOGICAL PARAMETERS FROM BASELINE TILL COMPLETION OF STUDY PERIOD (6 WEEKS)

	Group			
	FCM		Ferrous sulfate	
	Mean	SD	Mean	SD
Change in Haemoglobin at 6 weeks (g/dl)	3.35	.77	2.12	1.01
Change in Packed cell volume at 6 weeks (%)	9.46	4.33	4.99	4.19
Change in Mean corpuscular volume at 6 weeks (f1)	13.04	8.50	4.77	6.62
Change in Mean corpuscular haemoglobin at 6 weeks (pg)	5.22	3.69	2.79	3.23
Change in Mean corpuscular haemoglobin concentration at 6 weeks (g/dl)	2.80	2.42	1.14	2.23
Change in Red blood cells count at 6 weeks (million/cumm)	.89	.49	.48	.45
Change in Peripheral smear at 6 weeks	1.73	.51	1.11	.88
Change in Reticulocyte count at 6 weeks (%)	-.06	.96	-.17	.71
Change in Serum iron at 6 weeks (mg/dl)	65.08	27.45	34.03	30.50
Change in Total iron binding capacity at 6 weeks (mg/dl)	-93.01	37.75	-34.36	38.79
Change in Transferrin saturation at 6 weeks (%)	11.43	6.14	3.96	5.66
Change in Serum ferritin at 6 weeks (ng/ml)	134.73	34.46	2.04	1.97

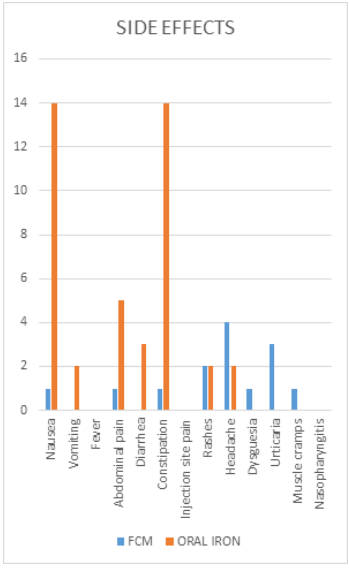
TABLE 3 Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Change in Haemoglobin at 6 weeks (g/dl)	Equal variances assumed	5.040	.026	8.060	138	.000	1.2257	.15207	.92503	1.52640
	Equal variances not assumed			8.060	129.022	.000	1.2257	.15207	.92484	1.52658
Change in Packed cell volume at 6 weeks (%)	Equal variances assumed	.271	.603	6.206	138	.000	4.4700	.72025	3.04584	5.89416
	Equal variances not assumed			6.206	137.836	.000	4.4700	.72025	3.04583	5.89417
Change in Mean corpuscular volume at 6 weeks (f1)	Equal variances assumed	3.582	.060	6.424	138	.000	8.2686	1.28707	5.72365	10.81349
	Equal variances not assumed			6.424	130.170	.000	8.2686	1.28707	5.72230	10.81485
Change in Mean corpuscular haemoglobin at 6 weeks (pg)	Equal variances assumed	2.426	.122	4.146	138	.000	2.4300	.58615	1.27101	3.58899
	Equal variances not assumed			4.146	135.540	.000	2.4300	.58615	1.27082	3.58918
Change in Mean corpuscular haemoglobin concentration at 6 weeks (g/dl)	Equal variances assumed	.039	.845	4.233	138	.000	1.6643	.39313	.88694	2.44163
	Equal variances not assumed			4.233	137.117	.000	1.6643	.39313	.88689	2.44168
Change in Red blood cells count at 6 weeks (million/cumm)	Equal variances assumed	.446	.505	5.134	138	.000	.4101	.07988	.25219	.56809
	Equal variances not assumed			5.134	136.824	.000	.4101	.07988	.25218	.56811
Change in Peripheral smear at 6 weeks	Equal variances assumed	42.044	.000	5.069	138	.000	.6143	.12118	.37467	.85390
	Equal variances not assumed			5.069	110.676	.000	.6143	.12118	.37415	.85442
Change in Reticulocyte count at 6 weeks (%)	Equal variances assumed	3.951	.049	.812	138	.418	.1163	.14326	-.16698	.39955
	Equal variances not assumed			.812	127.029	.418	.1163	.14326	-.16720	.39977
Change in Serum iron at 6 weeks (mg/dl)	Equal variances assumed	3.900	.050	6.332	138	.000	31.0557	4.90475	21.35754	40.75389
	Equal variances not assumed			6.332	136.497	.000	31.0557	4.90475	21.35660	40.75483
Change in Total iron binding capacity at 6 weeks (mg/dl)	Equal variances assumed	.485	.487	-9.067	138	.000	-58.6571	6.46905	-71.44843	-45.86586
	Equal variances not assumed			-9.067	137.898	.000	-58.6571	6.46905	-71.44851	-45.86577
Change in Transferrin saturation at 6 weeks (%)	Equal variances assumed	2.993	.086	7.484	138	.000	7.4700	.99818	5.49629	9.44371

	Equal variances not assumed			7.484	137.065	.000	7.4700	.99818	5.49618	9.44382
Change in Serum ferritin at 6 weeks (ng/ml)	Equal variances assumed	39.992	.000	32.157	138	.000	132.6829	4.12608	124.52434	140.84138
	Equal variances not assumed			32.157	69.453	.000	132.6829	4.12608	124.45250	140.91321

All the hematological parameters showed improvement by the end of study period in both the groups. The change from baseline was highly significant in group 1 as compared to group 2 (p=0.00), except for the reticulocyte count. Mean rise in Hb was 3.35 g/dl in parenteral versus 2.12 g/dl in oral group which was highly significant (p value 0.000). Notably, serum ferritin which is a marker of iron stores rose multifold in parenteral group and only marginally in oral group (134.73 ng/ml vs 2.04 ng/ml; p=0.000) (Table 2). As expected, there was a fall in total iron binding capacity due to iron therapy in both the groups (-93.01 g/dl vs -34.36 (g/dl; p=0.000)

Figure 1 Side effects in both the groups



Subjects in oral group had significantly higher incidence of nausea (20% vs 1.4%; p=0.001) and constipation (20% vs 1.4%; p =0.001) than parenteral group. Vomiting and diarrhea were seen only in oral group. Urticaria, muscle cramps and dysguesia were present only in parenteral group. However, there was no statistical difference between the groups. No patient in parenteral group complained of post treatment injection site pain. Figure 1

CONCLUSION

FCM seems promising in PPIDA. FCM was better tolerated than ferrous sulphate with low incidence of gastrointestinal adverse effects, rapid normalization of iron stores, better compliance and shorter treatment period.

REFERENCES

1. Dutta DC. Medical and surgical illness complicating pregnancy In:Konar H.editor. Textbook of Obstetrics, 7th ed. London: New Central Book Agency (P) Ltd; 2010: 260-261
2. Breymann C. Treatment of iron-deficiency anaemia in pregnancy. And postpartum. In: Studd J, Tan SL, Chervenak FA, Editors. Current Progress in Obstetrics and Gynaecology, 1st ed. Mumbai: Tree Life Media; 2012: 135-148.
3. Covic A, Mircescu G. The safety and efficacy of intravenous ferric carboxymaltose in anaemic patients undergoing haemodialysis: a multicentre, open-label, clinical study, Nephrol Dial Transplant 2010;25 (8): 2722 – 30.
4. Breymann C, Gliga F, Bejenariu C, Strizhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Int J Gynaecol Obstet 2008; 101 (1): 67-73.
5. Van Wyck DB, Martens MG, Seid MH, Baker JB, Mangione A. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. Obstet Gynecol 2007;110 (2 Pt 1): 267-78.
6. Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, Rogers R. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. Am J Obstet Gynecol 2008;199 (4): 435. E 1-7.
7. Rathod S, Samal SK, Mahapatra PC, Samal S. Ferric carboxymaltose: A revolution in the treatment of postpartum anemia in Indian women. Int J ApplBasic Med Res. 2015 Jan-Apr; 5(1): 25–30.
8. Joshi SD, Chikkagowdra S, CM V K. Comparative study of efficacy and safety of intravenous ferric carboxy maltose versus iron sucrose in treatment of postpartum iron deficiency anemia. Int J Reprod Contracept Obstet Gynecol. 2016; 5(8): 2566-2570
9. Mishra V V, Chaudhary S, Gandhi K, Sharma U, Patel U. Study of intravenous ferric carboxy maltose in iron deficiency anemia during pregnancy and postpartum period-safety and efficacy. Indian Journal of Obstetrics and Gynecology Research, April-June 2015;2(2):69-72.
10. Chaurasia A, Singh N, Gupta V, Beenu. A prospective study comparing the efficacy of oral iron, intra-venous Iron sucrose and Ferric-carboxy- maltose in postpartum anemia. Int J Med Res Health Sci. 2016, 5(8):107-111.
11. Ganzoni AM. Intravenous iron – dextran: therapeutic and experimental possibilities. Schweiz Med Wochenschr 1970;100 (7): 301-3.