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Safety and Efficacy of Ferric Carboxymaltose Therapy in Post-Partum Women with Iron Deficiency Anemia

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Abstract: ***World Health Organization has defined post-partum anaemia as haemoglobin of less than 10gm% during the post-partum period. WHO estimates two-thirds of maternal deaths occur after delivery. Post-partum haemorrhage being the most commonly reported complication and the leading cause of maternal death (29.6%). Post-partum anaemia has been associated with post-partum depression, stress, anxiety, cognitive impairment, poor mother-infant interactions and delayed infant development. Oral iron therapy is currently the treatment of choice for the majority of patients with iron deficiency anemia but it has disadvantages like poor absorption, poor compliance and gastro-intestinal (GI) side effects. Packed cell transfusion is reserved for cases with severe anaemia but carries significant risk of transmission of blood transmissible diseases as well as risk of anaphylactic and allergic reactions. Parenteral iron helps in restoring iron stores faster and more effectively than oral iron. Intravenous (IV) iron sucrose is safe, effective and economic in comparison to the repeated and painful intramuscular iron injections. Although the incidence of anaphylaxis and other adverse reactions with intravenous iron sucrose is markedly lower, multiple doses and prolonged infusion times are typically required. Ferric carboxymaltose is a novel molecule composed of poly-nuclear iron (III) hydroxide complexes to carboxymaltose. Intravenous ferric carboxymaltose has a neutral pH (5.0-7.0) and physiological osmolarity which makes it possible to administer its higher single dose over shorter time period (single dose up to 1000 mg over 15 min) than other parenteral preparations. Ferric carboxymaltose is cost effective with other positive benefits of fewer hospital visits and improved patient compliance.***

Keywords: Post-partum women, Iron deficiency anemia, Oral Iron, Intravenous Iron sucrose, Ferric Carboxymaltose

1. Introduction

World Health Organization has defined post-partum anemia as hemoglobin of less than 10gm% during the post-partum period.[1] About 29.8% of women who were not previously anemic during pregnancy become anemic after delivery.[2] Iron deficiency is the most common cause of anemia worldwide. Lack of iron intake, increased iron demand, faulty dietary habits, parasitic infections and malaria are common causes of iron deficiency anemia especially in post-partum period. In India, about 36% of the total maternal deaths are attributable to post-partum hemorrhage or anemia.[3] Iron deficiency is the most common cause of post-partum anemia, with rates as high as 50.0% reported in 1st postpartum week.[4] Iron deficiency anaemia during post-partum period leads to fatigue, cardio-respiratory problems, increased chances of infection, reduced immunity, lactation failure, increased postpartum depressive episodes, post-partum hemorrhage and requirement of packed cell transfusion as well as mortality.[5] .Patients with severe post-partum anemia have a longer hospital stay, are more likely to receive a blood transfusion and incur higher hospitalization costs.12Oral iron therapy is currently the treatment of choice for the majority of patients with iron deficiency anemia but it has disadvantages like poor absorption, poor compliance and gastrointestinal (GI) side effects. Packed cell transfusion is reserved for cases with severe anemia but carries significant risk of transmission of blood transmissible diseases as well as risk of anaphylactic and allergic reactions. Parenteral iron helps in restoring iron stores faster and more effectively than oral iron. Intravenous (IV) low-molecular-weight iron dextran has been associated with an incidence of anaphylaxis or anaphylactoid reactions as high as 1.7%. Newer parenteral iron products (iron sucrose and iron gluconate) do not contain the dextran moiety, and the incidence of anaphylaxis with these products is markedly lower. Ferric carboxymaltose is a novel molecule composed of poly-nuclear iron (III) hydroxide complexes to carboxymaltose. IV ferric carboxymaltose has a neutral pH (5.0-7.0) and physiological osmolarity which makes it possible to administer its higher single dose over shorter time period (single dose up to 1000 mg over 15 min) than other parenteral preparations.[6] Ferric carboxymaltose is cost effective with other positive benefits of fewer hospital visits and improved patient compliance. Ferric carboxymaltose does not contain dextran, therefore, the risk of anaphylaxis or serious hypersensitivity reactions is very low and a test dose is also not required.

2. Aims and Objectives

1) To evaluate the efficacy and tolerability of ferric carboxymaltose in comparison to oral iron and intravenous iron sucrose in women with post-partum iron deficiency anaemia.
2) To note down any adverse effects of ferric carboxymaltose.

3. Material and Methods

The present prospective randomized study was carried out in the Department of Obstetrics and Gynaecology, in collaboration with Department of Biochemistry, Pt. B.D. Sharma PGIMS, Rohtak in 90 post-partum anemic women.

All the post-partum women who were in the immediate postpartum period were subjected to haematological investigations namely, complete haemogram with absolute platelet count, red blood cell indices, peripheral smear and serum ferritin levels. Postpartum women having hemoglobin between 6-7.9 g/dl were included in the study.

These postpartum women were divided randomly into three groups, each having 30 postpartum women. They were give

iron supplementation. The first women received oral ferrous sulphate, second women received intravenous ferric carboxymaltose and third one received intravenous iron sucrose and so on. Group 1 (n=30) women were given oral ferrous sulphate 100 mg twice a day for 6 weeks; group 2 (n=30) women were given intravenous ferric carboxymaltose and group 3 (n=30) women were given intravenous iron sucrose.

Exclusion Criteria

Women having:

Sickle cell anemia, thalassemia, aplastic anemia, megaloblastic anemia. anemia due to liver disease, kidney disease, cardiovascular disease, history of previous one month blood transfusion, history of allergy to parenteral iron therapy and any personal or family history of bleeding disorder were excluded from the study.

Dosage

The dosage for intravenous ferric carboxymaltose and Intravenous iron sucrose were calculated by following formula:[7]

$2.4 \times W \times D + 500$ where W = weight in kg, D = (Target - actual haemoglobin)

The rise in hemoglobin and serum ferritin was measured after 3 weeks and 6 weeks.

Statistical Analysis

Statistical analysis was performed by the SPSS version 17.0. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

4. Observations

The present prospective randomized study was carried out in the Department of Obstetrics and Gynaecology in collaboration with Department of Biochemistry, Pt. B.D. Sharma PGIMS, Rohtak in 90 post-partum women having iron deficiency anemia (Hb between 6 to 7.9gm%). The following observations were made:

Table I: Age Distribution of Study Population

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	23.47 ± 4.14	24.33± 3.03	23.63 ± 3.93	0.635

The mean age of group 1, group 2 and group 3 was 23.47 ± 4.14 years, 24.33 ± 3.03 years and 23.63 ± 3.93 years respectively. Statistically, there was no significant difference in the mean age distribution (p value >0.05) among the three groups (Table I).

Table II: Parity Distribution of Study Population

O/H	Group 1	Group 2	Group 3	p value
	Frequency (%)	Frequency (%)	Frequency (%)	
P1	21 (70.0%)	9 (30.0%)	15 (50.0%)	
P2	5 (16.7%)	9 (30.0%)	9 (30.0%)	
P3	2 (6.7%)	8 (26.7%)	5 (16.7%)	
P4	1 (3.3%)	4 (13.3%)	0 (0.0%)	0.141
P5	1 (3.3%)	0 (0.0%)	0 (0.0%)	
P6	0 (0.0%)	0 (0.0%)	1 (3.3%)	
Total	30 (100%)	30 (100%)	30 (100%)	

Table II shows that in twenty one women (70%) in group 1, nine women (30%) in group 2 and fifteen women (50%) in group 3 were primipara. On statistical analysis, the difference among the three groups was not significant (p >0.05, Table II).

Table III: Mode of Delivery (MOD) in Study Population

MOD	Group 1	Group 2	Group 3	p value
	Frequency (%)	Frequency (%)	Frequency (%)	
LCSS	8 (26.7%)	5 (16.7%)	11 (36.7%)	
Vaginal	22 (73.3%)	25 (83.3%)	19 (63.3%)	0.216
Total	30 (100%)	30 (100%)	30 (100%)	

Maximum number of patients were delivered vaginally in group 1 (73.3%), group 2 (83.3%) and group 3 (63.3%) respectively. On statistical analysis, the difference among the three groups was not significant (p >0.05, Table III).

Table IV: Red Blood Cell Indices of Study Population

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
MCV (fL)	66.15 ± 5.51	66.307± 6.9	67.513 ± 3.5	0.578
MCH (pg)	19.52 ± 1.09	19.94 ± 1.53	20.01 ± 1.05	0.251
MCHC (g/dL)	30.783 ± 0.78	29.977 ± 1.6	30.36± 1.11	0.061

The mean MCV in group 1, group 2 and group 3 was 66.157 ± 5.51 fL, 66.309 ± 6.90 fL and 67.513 ± 3.50 fL respectively. The mean MCH in group 1, group 2 and group 3 was 19.52±1.09 pg, 19.94 ± 1.53 pg and 20.01 ± 1.05 pg respectively. The mean MCHC in group 1, group 2 and group 3 was 30.783 ± 0.78 g/dL, 29.977 ± 1.6 g/dL and 30.36 ± 1.11 g/dL respectively. On statistical analysis, the difference among the three groups was not significant (p >0.05, Table IV).

Table V: Hemoglobin Levels among Different Groups

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
Hb at start of treatment(g/dL)	7.22 ± 0.49	6.96± 0.69	7.08 ± 0.48	0.203
Hb after 3 weeks(g/dL)	7.97 ± 0.46	9.88 ± 0.62	9.08 ± 0.61	<0.001
Hb after 6 weeks(g/dL)	9.00 ± 0.46	11.01 ± 0.61	10.03± 0.60	<0.001

The mean hemoglobin at the start of treatment in group 1, group 2 and group 3 was 7.22 $\pm$ 0.49 g/dL, 6.96 $\pm$ 0.69 g/dL and 7.08 $\pm$ 0.48 g/dL respectively. The mean hemoglobin after 3 weeks of treatment in group 1, group 2 and group 3 was 7.97 ± 0.46 g/dL, 9.88 ± 0.62 g/dL and 9.08 ± 0.61 g/dL respectively. The mean hemoglobin after 6 weeks of treatment in group 1, group 2 and group 3 was 9.00 ± 0.46 g/dL, 11.01 ± 0.61 g/dL and 10.03 ± 0.60 g/dL respectively (Table V).

Table VI: Serum Ferritin Levels among Different Groups

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
S. ferritin at start of treatment (ng/mL)	10.31 ± 1.64	13.24 ± 10.06	10.29 ± 1.63	0.094
S. ferritin after 3 weeks(ng/mL)	13.07 ± 1.95	271.17 ± 9.76	160.7 ± 3.49	<0.001
S. ferritin after 6 weeks(ng/mL)	23.20 ± 2.46	107.51 ± 6.76	58.18 ± 3.13	<0.001

In the group 1, the mean serum ferritin levels at the start of treatment, 3 weeks after treatment and 6 weeks after treatment were 10.31 ± 1.64 ng/mL, 13.07 ± 1.95 ng/mL and 23.20 ± 2.46 ng/mL respectively (Table VI).

In the group 2, the mean serum ferritin levels at the start of treatment, 3 weeks after treatment and 6 weeks after treatment were 13.24 ± 10.06 ng/mL, 271.17 ± 9.76 ng/mL and 107.51 ± 6.76 ng/mL respectively (Table VI).

In the group 3, the mean serum ferritin levels at the start of treatment, 3 weeks after treatment and 6 weeks after treatment were 10.29 ± 1.63 ng/mL, 160.70 ± 3.49 ng/mL and 58.18 ± 3.13 ng/mL respectively (Table VI).

The rise of mean serum ferritin in group 1, group 2 and group 3 at three weeks after treatment was 2.76 ng/mL, 257.93 ng/mL and 150.41 ng/mL respectively and at six weeks after treatment was 12.89 ng/mL, 94.27 ng/mL and 47.89 ng/mL respectively. On statistical analysis, the difference among the three groups was found to be highly significant (p <0.001, Table VI).

Table VII: Distribution of Adverse Effects in Various Groups

Adverse effects	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	Total	p value
abdominal pain	2(6.7%)	0(0%)	0(0%)	2(2.2%)	0.129
arthralgia	0(0%)	0(0%)	2(6.7%)	2(2.2%)	0.129
Constipation	4(13.3%)	0(0%)	0(0%)	4(4.4%)	0.064
Epigastric pain	1(3.3%)	0(0%)	0(0%)	1(1.1%)	0.364
Headache	0(0%)	0(0%)	1(3.3%)	1(1.1%)	0.364
Nausea and vomiting	5(16.7%)	0(0%)	0(0%)	5(5.6%)	0.005
Slight burning sensation	0(0%)	2(6.7%)	3(10%)	5(5.6%)	0.117
Tingling sensation of feet	0(0%)	0(0%)	1(3.3%)	1(1.1%)	0.364

5. Discussion

Nutritional anemia in pregnancy and post-partum period is a public health problem especially in developing countries and commonest in iron deficiency anemia. Anemic women have a longer average length of hospital stay and are more likely to receive a blood transfusion and incur higher hospitalization costs. Hence, post-partum iron deficiency anemia requires attention and high quality care.

Parity

Multiple pregnancies are known cause of anemia in women, especially in low socioeconomic status, due to lack of awareness and resources to consume balanced diet during pregnancy and post-partum period.

Mode of delivery

Maximum number of patients delivered vaginally in group 1 (73.3%), group 2 (83.3%) and group 3 (63.3%) in the present study. In a study by Damineni et al 48.88% patients underwent vaginal delivery and 51.1% patients underwent LSCS in the oral iron group, where as in FCM group 73.33 % patients had vaginal delivery and 26.7% had undergone LSCS.[8]

Hemoglobin levels among different groups

The mean hemoglobin at the start of treatment in group 1, group 2 and group 3 was 7.22 ± 0.49 g/dL, 6.96 ± 0.69 g/dL and 7.08 ± 0.48 g/dL respectively in the present study. The rise of mean hemoglobin in group 1, group 2 and group 3 at three weeks was 0.75 g/dL, 2.92 g/dL and 2.0 g/dL respectively. The rise of mean hemoglobin in group 1, group 2 and group 3 at six weeks was 1.78 g/dL, 4.05 g/dL and 2.95 g/dL respectively in the present study. Van Wyck et al compared FCM with oral iron in 477 subjects at 2, 4 and 6 weeks with baseline hemoglobin of 9.4g%. It was found that a greater proportion of patients assigned to IV ferric carboxymaltose, compared to those assigned to oral iron, achieved the primary endpoint, an increase in hemglobin level of 2.0 g/dl or more, within 42 days after baseline (82.0% vs. 61.8%; 95% CI of treatment difference, 12.2%-28.3%; $p < 0.001$).[7]

Ferritin

The rise of mean ferritin in group 1, group 2 and group 3 at three weeks after treatment was 2.76 ng/mL, 257.93 ng/mL and 150.41 ng/mL respectively and at six weeks after treatment was 12.89 ng/mL, 94.27 ng/mL and 47.89 ng/mL respectively in present study. Singh et al found that serum ferritin, which is a marker of iron stores rises much higher 67.6 ng/mL in ferric carboxymaltose group as compared to 47.88 ng/mL for iron sucrose group.[9]

Adverse Events

In the group 1, the most common side effects was nausea and vomiting in 5 (16.7%) women, constipation in 4 (13.3%), epigastric pain in 1 (3.3%) and abdominal pain in 2 (6.7%) women. In the group 2, burning at Injection site was noted in 2 (6.7%) women. In the group 3, burning at Injection site was observed in 3 (10%) women, Arthralgia in 2 (6.7%), tingling sensation of feet in 1 (3.3%) and Headache in 1 (3.3%) women. Van Wyck et al studied the adverse drug events in the FCM and oral iron groups and they found that nausea is seen 3.5% and 11.9% respectively and constipation in 3.0% and 4.2% and reported a higher incidence of skin problems like pruritus and rashes with parenteral iron although they are transient and subsided within 5-15 min.[7]

6. Conclusion

Pregnancy is a state characterized by many physiological hematological changes, which may appear to be pathological in the non-pregnant state. Many hematological changes also, occurring during these periods are physiological and care should be taken in their interpretation during anaemia especially during postpartum. Ferric carboxymaltose is a safe and an effective alternative to oral iron and iron sucrose. Ferric carboxymaltose restores iron stores faster and more effectively than oral iron and iron sucrose (as evident in present study) in terms of rise in hemoglobin and serum ferritin levels without any serious adverse effects. In the present study it was found that ferric carboxymaltose is significantly better than oral iron and iron sucrose in rising the hemoglobin faster and replenishing the iron deficit in post-partum women.

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