COMPARISON OF ORAL IRON, IRON SUCROSE AND FERRIC CARBOXYMALTOSE (FCM) TO TREAT POST PARTUM ANAEMIA

Sipra Singh[1], Rakesh Kumar Singh[2], Shanti Singh[3]

[1]Professor, Department of Obstetrics & Gynaecology, Katihar Medical College, Katihar.
[2]Professor, Department of Anaesthesiology, Katihar Medical College, Katihar.
[3]Professor, Department of Obstetrics & Gynaecology, Katihar Medical College, Katihar.

ABSTRACT

BACKGROUND

Iron deficiency anaemia in post-partum period is associated with poor maternal and foetal outcome. Oral iron though convenient to use, is associated with annoying gastrointestinal side effects. Parenteral iron may present a substitute to both oral iron in patients who cannot take oral iron, and also to blood transfusion. Aim of the present study is to compare the efficacy of oral iron with intravenous iron sucrose and intravenous ferric carboxymaltose and also the safety profiles of these preparations.

MATERIALS AND METHODS

Ninety anaemic patients who had delivered in last seven days, were allocated in to three groups of thirty patients each to receive either oral iron, intravenous iron sucrose or intravenous v ferric carboxymaltose. Haemoglobin (Hb) and serum ferritin were measured at the start of the study and at two weeks' and six weeks' intervals. Side effect were observed, recorded and treated. Continuous data were analyzed using analysis of variance (ANOVA) and categorical data were analyzed using Chi squared test. SPSS 20 was used for statistical analyses. p value<0.05 was taken as significant.

RESULTS

Blood haemoglobin (Hb) and serum ferritin level were significantly higher in ferric carboxymaltose group as compared to blood sucrose and oral iron group at two weeks' and six weeks' intervals. Significantly higher percentage (66.67%) of patients in ferric carboxymaltose group achieved target Hb level of 12 gm/dl.

CONCLUSION

Treatment with ferric carboxymaltose result in comparatively better outcome with regard to rise in haemoglobin(Hb) and serum ferritin level. Safety profile of parenteral iron sucrose and ferric carboxymaltose is comparable.

KEYWORDS

Iron Deficiency Anaemia, Parenteral Iron Therapy, Ferric Carboxymaltose, Iron Sucrose.

HOW TO CITE THIS ARTICLE: Singh S, Singh RK, Singh S. Comparison of oral iron, iron sucrose and ferric carboxymaltose (FCM) to treat post-partum anaemia. J. Evid. Based Med. Healthc. 2016; 3(20), 832-835. DOI: 10.18410/jebmh/2016/190

INTRODUCTION: Iron deficiency anemia is the most common cause of anemia during pregnancy and in the post-partum period.[1] 90% cases of anemia have iron deficiency anaemia.[2,3] 20% 0f maternal death occurs due to anaemia.[4] WHO has defined anemia as hemoglobin level <11 gm/dl irrespective of cause and <10 gm/dl in post-partum period.[5,6] Iron deficiency anemia may adversely affect the cognitive function, physical activity, immune response of the mother and physical and mental development of exclusively breast fed newborn baby. Correction of anemia in post-partum period is essential for mother as well as the new born babies. Different kinds of treatments ranging from oral iron preparation, parenteral iron preparation to blood transfusion are used to correct anemia in post-partum period. Aim of the treatment is to return both hemoglobin and iron stores to normal level. Oral iron therapy is the most common treatment modality for correction of anemia due to ease of administration but oral iron administration is associated with frequent gastrointestinal side effects adversely affecting the compliance of the patient.[7] Oral iron is often not found to be capable of replenishing the depleted iron stores.[8] Blood transfusion may be chosen to correct the iron deficiency anemia but is associated with transmission of infection, immunological impact and transfusion reaction. Parenteral iron administration appears to be a suitable alternative to oral iron as well as blood transfusion. First generation intravenous iron preparation iron dextran has been used to treat iron deficiency anemia but has been found to be associated with serious fatal immunological anaphylactic reaction.[9,10] Second generation intravenous iron preparations like iron sucrose and iron ferric gluconate have been introduced which are devoid of iron dextran ring and hence the immunological fatal anaphylactic reaction but associated with dosing limitation. Higher drug administration can result in a reaction called labile iron reaction characterized by hypotension, cramping diarrhea and chest pain.[11] Iron sucrose can be administered as a maximum

Submission 09-02-2016, Peer Review 23-02-2016,
Acceptance 02-03-2016, Published 10-03-2016.
Corresponding Author:
Dr. Rakesh Kumar Singh,
Professor, Department of Anaesthesiology,
Katihar Medical College, Katihar-854105.
E-mail: drrakeshsingh2008@yahoo.co.in
DOI: 10.18410/jebmh/2016/190

bolus dose of 200 mg daily and maximum weekly dosing should not exceed 600 mg.

Ferric carboxymaltose (FCM) is a novel iron preparation having a stable ferric hydroxide nucleus in a carbohydrate shell. After intravenous administration, parenteral iron preparation is taken by reticulo-endothelial system of liver spleen and bone marrow.[12] From this stable molecule iron is delivered slowly avoiding toxicity and oxidation so large amount can be administered as a single I.V. bolus. Thus safety profile of IV ferric carboxymaltose appears promising. Recent Cochrane Systemic Review shows inconclusive results regarding the safety of intravenous administration over oral preparation. So, the present study was done to compare the efficacy of oral iron with intravenous iron sucrose and intravenous ferric carboxymaltose and safety profile of these preparations.

MATERIAL AND METHODS: This prospective randomized controlled trial was done in the Department of Obstetrics and Gynecology at Katihar Medical College, Katihar during the period July 2014 to June 2015. After obtaining the institutional ethical committee approval, 90 anemic patients of hemoglobin level less than 10 gm/dl who had delivered in the last seven days were included in the study. Patients were randomized in to three groups of thirty patients each by using a random number table to receive either oral iron or parenteral iron sucrose or parenteral ferric carboxymaltose (FCM). Group concealment was done using the sealed envelope technique. Patients with hypersensitivity to any component of oral iron, iron sucrose or ferric carboxymaltose, having anemia due to other causes than iron deficiency, blood transfusion in the recent past, renal disease, kidney disease, hemochromatosis or other iron storage diseases, receiving erythropoietin stimulating drug in last 30 days were excluded from the study. Hemodynamically unstable patient i.e. systolic blood pressure > 180 or < 80 mm of Hg or diastolic blood pressure >100 mm of Hg or < 40 mm of Hg were excluded from the study.

Patient in the oral iron group (group O) received 100 mg of ferrous ascorbate three times daily throughout the study period.

Iron deficit for parenteral iron administration was calculated with Ganzoni formula.

Iron Deficit (mg)={Weight in Kg× (Target Hb – Current Hb)×2.4}+500. Target Hb for post-partum patients were taken to be 12 gm/dl. In group receiving iron sucrose (group S), Iron sucrose was given by intravenous infusion as per the calculated deficit and rounded to nearest multiple of 100. 200 mg of iron sucrose was diluted in 200 ml of normal saline and given over 30 minutes. Repeat dose if needed was given on alternate days keeping in mind the total dose per week not to exceed 600 mg/week. In the group receiving Ferric carboxymaltose (group F), calculated cumulative dose was rounded up to nearest multiple of 100. Calculated dose was diluted in 250 ml of normal saline and transfused over 15 minutes. Single maximum dose allowed was 1000 mg. if additional doses were required; they were given after one week, after dilution in 250 ml of normal saline. Hemoglobin and serum ferritin level were recorded at the start of the treatment and at 2 weeks and 6 weeks after start of treatment. Side effect and adverse reaction group were noted and treated. All the data were analyzed using SPSS 20. Continuous data were analyzed using Analysis of Variance (ANOVA) and categorical data were analyzed using Chi Squared test. P value <0.05 was taken as significant.

RESULTS: All the three groups were comparable with regard to age, height, weight, parity, mode of delivery, baseline hemoglobin and baseline ferritin value and severity of anemia (Table 1). Delivery by caesarean section, post-partum hemorrhage, pregnancy induced hypertension and multiple gestation were the leading factor for post-partum anemia and were equally distributed between the groups.

Parameters	Group O	Group S	Group F	p value
Mean age (years)	22.36±5.79	22.73±5.58	23.26±5.91	0.831
Height (cm)	146.73±10.65	145.93±7.65	148.40±9.95	0.513
Weight (kg)	53.06±5.67	52.16±6.33	53.06±6.29	0.547
Parity (Primi/Multi)	13/17	10/20	10/20	0.650
Mode of delivery (LSCS/SVD)	7/23	7/23	9/21	0.792
Baseline Hb (g/dl)	8.20±0.76	8.23±0.77	8.25±0.75	0.782
Baseline Ferritin (ngm/ml)	37.36±2.90	37.43±3.20	37.51±2.80	0.143
Severity Mild (Hb>9 gm/dl) Moderate (Hb= 7.1-9 gm/dl) severe (Hb<7 g/dl)	 6 12 12	 5 14 11	 5 15 10	0.958

Table 1: Demographic and baseline characteristic in various groups

There was increase in Hb level in all the groups at 2 weeks' and 6 weeks' interval as compared to baseline Hb level (Table 2). Post hoc analysis showed that increase in iron sucrose (Group S) and FCM group (Group F) is significantly higher than oral iron group at 2 weeks and 6 weeks' interval. Increase in Hb level was significantly higher in group F as compared to iron sucrose at 6 weeks (p=0.000) but not at 2 weeks (p=0.066). Mean rise in Hb level at 2 weeks in Group F was 1.56±0.41

gm/dl as compared to 0.64±0.32 gm/dl in oral iron group and 1.33±0.41 gm/dl in group S. Mean rise in Hb was 2.95±0.61 gm/dl in group F, 2.64±0.55 gm/dl in group S and 1.31±0.41 gm/dl in group O at 6 weeks' interval.

Hb level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Baseline Hb	8.20±0.76	8.23±0.77	8.25±0.75	0.782		
At 2 weeks	8.84±0.612	9.55±0.56	9.90±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.066
At 6 weeks	9.50±0.56	10.69±0.47	11.23±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.000

Table 2: Hemoglobin(Hb) level in various groups at various time intervals

Rise in Hb level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Rise over 2 weeks	0.64±0.32	1.31±0.41	1.56±0.41	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.038
Rise over 6 weeks	1.30±0.48	2.64±0.55	2.95±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003

Table 3: Rise in Hemoglobin (Hb) level in different groups at various time intervals

Rise in serum ferritin was significantly higher in group F as compared to group O and group S at 2 weeks' interval and 6 weeks' interval(p=0.000), Table 4. Rise in serum ferritin in Group S was significantly higher than rise in group O at 2 weeks' and 6 weeks' interval(p=0.000) Table 4.

Ferritin level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Baseline Ferritin	37.36±2.90	37.43±3.20	37.51±2.80	0.867	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.995 0.871 0.912
Ferritin at 2 weeks	55.86±7.48	147.33±17.24	300.86±35.75	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003
Ferritin at 6 weeks	49.26±6.23	119.033±15.10	256.50±30.75	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003

Table 4: Serum ferritin in different groups at various time intervals

Target Hb was 12 g/dl. 20 (66.67%) patients in group F achieved Hb> 12 gm/dl in group F as compared to 16(53.33%) in group S and 4(13.3%) in group O (p=0.000) Table 5.

Mode of iron therapy	Number of patients with Hb level <12 g/mdl after treatment n (%)	Number of patients with Hb level >12 gm/dl after treatment n (%)	p value
Oral iron (Group O)	26 (86.7%)	4 (13.3%)	0.000
Iron Sucrose (Group S)	14 (46.67%)	16 (53.33%)	
FCM (Group F)	10 (33.33%)	20 (66.67%)	

Table 5: Patients achieving target Hb level (12 g/dl)

Gastrointestinal side effects comprising mainly of constipation (13.3%), nausea and vomiting (13.3%) and abdominal pain (10%) were the common side effects in oral iron group (Table 6). 1(3.3%) patient each in group S and group F complained of pain at injection site, Table 6. 1(3.3%) patient each in group S and group F developed hypotension and complained of giddiness but responded well to conservative therapy. No patient in any group developed any serious adverse effect.

Complication	Group O	Group S	Group F	p value
Pain at injection site	0	1(3.33%)	1 (3.33%)	0.600
Urticaria	0	3(10%)	2(6.67%)	0.277
Nausea and vomiting	4(13.33%)	1(3.3%)	1(3.3%)	0.200
Constipation	4 (13.3%)	0	0	0.015
Abdominal pain	3(10%)	1	0	0.160
Giddiness and hypotension	0	1(3.33%)	1(3.33%)	0.600

Table 6: Adverse effects

DISCUSSION: Iron deficiency anemia (IDA) is the commonest cause of anemia in post-partum period. Oral iron is the most common modality of treatment of iron deficiency anemia due to ease of administration. Various studies have reported increase of 2-3 gm/dl within 4-12 weeks.[13,14] Rise in Hb level was found to be 1.30±0.49 gm/dl after 6 weeks of oral iron therapy in our study. Richard Dillon and Ibrahim Momoh reported a rise of 2.4 (1.99-2.74) gm/dl in Hb level with iron sucrose and a rise of 2.7(2.30-3.03) gm/dl with FCM at 6 weeks' interval, which is similar to findings of our study.[1,5] Iftikar Hussain and Jessica Bhoyroo compared the safety of FCM and iron dextran and found a Hb rise of2.8±1.44 gm/dl with FCM and 2.4±1.71 gm/dl with iron dextran[15]. Purpose of supplemental iron therapy is to replenish the depleted iron stores. Breyman et al reported serum ferritin level to rise from 39.9 ngm/ml to 568.2 ng/ml at first week and to the level of 161.2 ngm/dl at 12 weeks. Changes in ferritin level were significantly higher as compared to control group ($p<0.001$).[16]

Iron replenishment in post-partum anemia is important to prevent anemia in future pregnancy and should be started just after delivery. Oral iron is convenient to administer but because of annoying gastrointestinal side effects, patient compliance is often poor resulting in poor outcome. Parenteral iron therapy may be a good substitute of oral iron preparation in patients with severe anemia and in patients who cannot tolerate oral iron therapy. Parenteral iron preparations can replenish the depleted iron store and avoid unnecessary blood transfusion. As Ferric Carboxymaltose can be used in large single dose (up to 1000 mg in single setting over 15 minutes), less hospitalization is required. Only 200 mg of iron sucrose can be transfused in a day and not more than 600 mg can be transfused in a week, so treatment with iron sucrose requires longer hospital stay. Though Ferric Carboxymaltose is costlier than Iron Sucrose, due to shorter hospital stay, treatment with Ferric Carboxymaltose (FCM) is cheaper than treatment with Iron Sucrose.

CONCLUSION: Both iron sucrose and ferric carboxymaltose (FCM) are good alternatives to treat severe post- partum anemia and can avoid unnecessary blood transfusions. Treatment with ferric carboxymaltose result in comparatively better outcome with regard to rise in hemoglobin (Hb) and serum ferritin level. Oral iron therapy results in poor outcome and is associated with high incidences of gastrointestinal side effects. Safety profile of parenteral iron sucrose and ferric carboxymaltose is comparable.

BIBLIOGRAPHY:

1. Cuervo LG, Mohamed K. Treatment of iron deficiency anemia in pregnancy. Cochrane Database systemic review 2015.
2. Viteri FE. A new concept in control of iron deficiency: community based preventive supplementation of at risk group by the weekly intake of iron supplements. Biomed Environment Science 1998;11(1):46-60.
3. Singh K, Fong YF, Arunkumaran S. Anemia in pregnancy-a cross sectional study in Singapore. European journal of clinical nutrition 1998;52(1):65-70.
4. Malagi U, Reddy M, Naik R. Evaluation of nutritional control programme in Dharwar (Karnataka). Human Ecology 2006;20(4):279-81.
5. Nutritional anemia. Report of a WHO group of experts. World health organization technical report. 1972;503:1-29.
6. Milman N. Postpartum anemia l: definition, causes and consequences. Hematology 2011;90(11):1247-53B.
7. Danielson G, Geisser P, Schneider W. Iron therapy with special emphasis on intravenous administration. Vifor (International) Inc. 1996.
8. Silverstein SB, Gilreath JA, Rodgers GM. Intravenous iron therapy: a summary of treatment options and review of guidelines. Journal of Pharmacy Practice 2008;21(6):431–443.
9. Anonyme. "Ferric carboxymaltose: a breakthrough treatment for iron deficiency anaemia." European Journal of Hospital Pharmacy Practice 2009;15:62–65.
10. VanWyck DB, Martens MG, Seid MH, et al. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. Obstetrics and Gynecology 2007;110(2):267–278.
11. Van Wyck DB, Anderson J, Johnson K. Labile iron in parenteral iron formulations: a quantitative and comparative study. Nephrology Dialysis Transplantation 2004;19(3):561–565.
12. Kulnigg S, Stoinov S, Simanenkov V, et al. Anovel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. American Journal of Gastroenterology 2008;103(5):1182–1192.
13. Breymann C, Gliga F, Bejenariu C, et al. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Int J Gynaecol Obstet 2008;101:67–73.
14. Giannoulis C, Daniilidis A, Tantanasis T, et al. Intravenous administration of iron sucrose for treating anemia in postpartum women. Hippokratia 2009;13:38–40.
15. Iftikhar Hussain, Jessica Bhoyroo, Angelia Butcher, et al. Direct comparison of the safety and efficacy offerric carboxymaltose versus iron dextran in patientswith iron deficiency anemia. Anemia 2013;Article ID 169107:P-10.
16. Breymann C. Iron deficiency and anemia in pregnancy: modern aspects of diagnosis and therapy. Blood Cells Mol Dis 2002;29:506-16.