ORIGINAL ARTICLE

Comparison of Efficacy and Safety of Ferric Carboxymaltose Injection with IV Iron Sucrose Complex for Correction of Postpartum Iron Deficiency Anemia

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ABSTRACT

Aim: To compare safety and efficacy of IV iron sucrose complex (ISC) and parenteral ferric carboxymaltose (FCM) injection to correct postpartum iron deficiency anemia.
Study design: Randomized controlled trial
Place and duration of study: Obstetrics & Gynecology Unit 4, Sir Ganga Ram Hospital, Lahore from 1st September 2020 to 31st 2021.
Methodology: One hundred and sixty women were recruited and they were divided in two equal groups Group A received two doses intravenous iron sucrose complex 200 mg on day 2 and day 4 and Group B was given intravenous ferric carboxymaltose. Dosage of ferric carboxymaltose was given on weekly until the individual's calculated cumulative dose was achieved. There was follow up of the patients who were treated with ferric carboxymaltose and iron sucrose complex after being discharged from the hospital at day 21.
Results: The mean age of intravenous iron sucrose complex (Group A) was 26.16±5.17 years and Group B (ferric carboxymaltose) the mean age was 26.86±4.32 years. The mean BMI was 24.09±0.77 in Group A and 24.56±1.42 in group B. In group A, the mean percentage improvement was 36.42±7.61% and in group B it was 56.62±5.56% with statistically higher improvement in group B than group A (P<0.001). At 21st day, 18 (22.5%) females in group A and 65 (81.2%) females in group-B had Hb levels >12 g/dl which was statistically significant. In group A, only 6 (7.5%) females and 34 (42.5%) in group B females benefitted from the treatment with significantly higher efficacy in group B (P<0.0001). Complications in group A were seen in 67 (83.8%) in group A and 75 (93.8%) in group B respectively with higher safety profile in group B (P<0.05).
Conclusion: Ferric carboxyl maltose injection had higher improvement in hemoglobin and other parameters, higher efficacy and safety profile with negligible complications than Iron sucrose Complex. So, ferric carboxyl maltose injection can be utilized for correction of post-partum anemia that can help in delivering health benefits to the mother.
Keywords: Pregnancy, Postpartum blood loss, postpartum anemia, Ferric carboxymaltose, Iron sucrose complex, Efficacy

INTRODUCTION

Anemia is a condition in which RBC numbers and/or hemoglobin concentration are less than normal and lower to meet an individual's physical demands. World Health Organization (WHO) labels anemia in pregnancy as hemoglobin (Hb) less than 10.5 g/dl in the second trimester and hemoglobin (Hb) less than 11 g/dl in first and third trimesters of pregnancy**.** As reported by WHO anemia, particularly iron deficiency anemia (IDA) among pregnant women is a worry some issue having a prevalence of as much as 56% in under developed countries while 14% in developed countries. Iron deficiency anemia is recognized public health concern that impairs heath and is associated with poor reproductive outcomes in under privileged countries like Pakistan[1,2].

Also, postpartum anemia has been linked with various complications like depression and anxiety; increased days of hospital stay as well impaired infant development. It is associated with puerperal pyrexia and wound infection. Different clinical practices have been used for treating IDA during pregnancy. Oral supplementation is conventionally used as first line therapy while blood is transfused for severe cases. Though oral iron therapy has been most commonly prescribed but problems like difficulty in digesting the tablets or other side effects may preclude the use of this therapy especially in those having gastrointestinal disorders.[3-5]

Parenteral preparations like iron dextran and sorbitol are may result in anaphylactic reactions. Blood transfusions frequently result in viral infections cross and reactions and iron sucrose complex has been associated lesser side effects, low renal excretion and little tissue accumulation and toxicity high availability for erythropoiesis. Iron sucrose complex improves hemoglobin faster than oral iron but it is costly and needs hospitalization.[6]

There has been a revived interest in the use of ferric carboxymaltose (FCM), a polynuclear iron – hydroxide carboxymaltose complex, that has been approved in more than 70 countries for correction of IDA. Ferric carboxymaltose has several advantages of fewer doses, or administration of higher doses in shorter period of time. This leads to replenishment of iron stores by release into reticuloendothelial system in the spleen and liver in a controlled manner**.** It was basically developed for rapid

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correction of anemia in high dosages. It is due to high stability of FCM compared to other sources like Iron sucrose complex or the ferric gluconate that allow slow but controlled and effective delivery of iron.[6-8]

Because of the stability of FCM, high dosage of iron can be delivered in much reduced period of time that will sufficiently replete the storage of iron with fewer dosages compared to Iron sucrose Complex where longer period of times for infusion and more dosage is typically needed. Ferric carboxymaltose is also considered safe for postpartum anemia due to good compliance of the treatment, better normalization of the iron storage, low incidence of gastrointestinal side effects and comparatively short period of treatment. As published in one recent RCT, the mean change in hemoglobin level from baseline to the maximum value was 0.8 g/dl with oral iron, 1.9 g/dl with Iron sucrose complex, 2.0 g/dl with any iron and 2.2 g/dl with FCM. Also, side effects related to drugs were also least noted in category of ferric carboxymaltose.[3]

Another study has published equal safety of IV ferric carboxymaltose compared to Iron sucrose complex as far as managing the IDA postpartum is concerned irrespective of the fact that its dosage is quite high. Ferric carboxymaltose and ISC are both equally effective in management and normalization of hemoglobin levels postpartum. Also advantages such as low incidence of local site reaction and better compliance have been observed after one supplication of FCM.[9] Literature search has shown that both ferric carboxymaltose and iron sucrose complex are equally effective. However as far as ferric carboxymaltoseis concerned test dose in not required, it is dextran free and has a better safety profile. It can be administered in single doses up to 1000 mg over 15 minutes.

MATERIALS AND METHODS

This randomized controlled trial study was conducted at Obstetrics & Gynecology Unit 4, Sir Ganga Ram Hospital Lahore from 1st September 2019 to 31st April 2021. One hundred and sixty women were included in the study (80 in each group). The patients with hemoglobin between 6-10 g/dI after 24 to 48 hours of delivery, serum ferritin level less than 15ng/I, history of placentaprevia and placental abruption during index pregnancy were included. The patients with non-iron deficiency anemia (hemolytic anemia), anemia not linked to blood loss during delivery, clotting disorders, peri-partum blood transfusion, intolerance to derivatives of Iron, history of asthma, thromboembolism, eczema and atopic allergy or drug use and women with signs of infection or evidence of renal or hepatic dysfunction were excluded. After complete workup including history, examination and investigations, other causes of anemia were ruled out. Baseline iron status of the patient was assessed by the clinical examinations and by `complete blood picture and serum ferritin levels. These women were randomly divided into two group. Group A received two doses of intravenous Iron sucrose Complex 200 mg on day 2 and day 4 after enrolment.

The dose was calculated by means of the formula: total iron dose in mg – 2.4 x W x deficit + iron depot (mg), where W is the body weight in Kg, deficit is target Hb – actual Hb in gm. Total required dose of iron was administered as 100-200mg. Iron sucrose complex as a single dose was repeated thrice weekly. Iron sucrose complex was diluted in 250 ml of 0.9% NaCl and administered within 2 hours slowly in order to avoid any anaphylactic episode. Patients were monitored for 30 minutes for anaphylactic reactions, urticaria, hypotension, headache, chest pain, dyspnea, tachycardia, breathlessness skin rash, facial flushing, metallic taste etc. The treatment was stopped after the administrating a total of 400mg. Group B was given parenteral ferric carboxymaltose. Dosage of ferric carboxymaltose was given weekly until maximum of 2500 mg of ferric carboxymaltose was given or the calculated cumulative dose of the individual was reached the maximum weekly single dose of ferric carboxymaltose was 15 mg/kg, not more than 1000 mg/dose, administered intravenously around 15 minutes. The patients who were treated with ferric carboxymaltose and Iron sucrose complex were followed-up at day 21.

The data was entered and analyzed through SPSS-20. Hemoglobin level was compared in both treatment groups at baseline and 21 days with repeated measures ANOVA/Freidman test. Side effects in the treatment groups were compared using Chi-square and Fisher exact test. P-value<0.05 was taken as significant.

RESULTS

The mean age in group A was 26.16±5.17 years and in group B the mean age was 26.86±3.32 years (Table 1).

Table 1: Descriptive statistics of age in both groups

Group	Age (years)
Intravenous iron sucrose complex	23.16±5.17
Ferric carboxymaltose	26.86±4.32
Total	26.15±4.77

Table 2: Frequency of parity, gravidity and abortion in both groups

Variable	Group A	Group B	Total
Parity			
<3	61(76.2%)	55(68.8%)	116(72.5%)
3 or more	19(23.8%)	25(31.2%)	44(27.5%)
Gravida			
<4	56(70%)	45(56.2%)	101(63.1%)
4 or more	24(30%)	35(43.8%)	59(36.9%)
Abortion			
Never	61(76.2%)	56(70%)	117(26.9%)
≥1 times	19(23.8%)	24(30%)	43(26.9%)

The mean weight in group A and group B was 60.95±1.58 kg and 62.96±2.47 kg respectively. The mean height in Group A and group B was 1.59±0.02 meters and 1.60±0.03 meters respectively. The mean BMI was 24.09±0.77 kg/m^2 in Group A and in group B was 24.56±1.42 kg/m^2in. The parity, gravidity and abortion in both groups is shown in Table 2.The comparison of hemoglobin at 48 hours and day 21 of treatment, the mean MCV at 48 hours and at 21 days interval was 66.82±6.14 fland 80.38±2.10 fl for Group A and 64.08±6.3 fl and 81.33±3.08 fl respectively for group B. The mean improvement in MCV for group A was 21.16±9±.96% and for Group B was 27.94±11.45%. The

mean MCV at 21st day and mean improvement was statistically higher in group B than group A respectively (P<0.05). The mean MCH at 48 hours and at 21 days interval was 23.63±2.99 and 29.84±0.98 pg/cell in Group A and 22.85±3.04 pg/cell and 30.39±0.97 pg/cell respectively for group B. There was statistically insignificant difference in MCH at 48 hours but for MCH at 21 days there was a significant difference. Percentage of improvement in MCH for group A was 28.27±16.30and for Group B was 35.23±17.41 with statistically significant differences (P<0.01). The mean MCHC at 48 hours in group A and group B was 26.26±2.16 g/dl and 26.01±1.77 g/dl while the mean MCHC at 21st day in group A and group B was 32.5±6.35 g/dl and 33.33±1.42 g/dl respectively. The mean percent improvement in group A and group B was 25.75±9.38 and 27.77±11.52 respectively. The mean MCHC and percent improvement in group B was statistically significantly higher as compared to group A (P<0.05) [Table 3].

At 21st day, 18(22.5%) females in Group A and 65(81.2%) females in group B had Hb level >12 g/dl. At 21st day, 134(42.5%) females in Group A and 40(50%) of females in group B had MCV >80 fl (Table4).

Table 3: Comparison of hemoglobin levels, MCV levels, MCH levels and MCHC levels at 48 hours and 21st day of treatment and percentage improvement in both groups

Variable	Group A	Group B	t-test	P value
Hemoglobin (g/dl) level				
At 48 hours	8.65±0.46	7.98±0.48	8.954	0.058
At 21 days	11.78±0.57	12.48±0.59	-7.732	<0.001
Improvement (%)	36.42±7.61	56.62±5.56	-19.158	< 0.001
MCV (fl) levels				
At 48 hours	66.82±6.14	64.08±6.31	2.781	0.06
At 21 days	80.38±38	81.33±3.08	-2.271	0.024
Improvement (%)	21.16±9.96	27.94±11.45	-3.996	0.000
MCH (pg./cell) levels				
At 48 hours	23.63±2.99	22.85±3.04	1.637	0.104
At 21 days	29.84±0.98	30.39±0.97	-3.531	0.001
Improvement (%)	28.27±16.30	35.23±17.41	-2.611	0.010
MCHCH (g/dl) levels				
At 48 hours	26.01±1.77	26.26±2.16	-795	0.428
At 21 days	32.56±1.35	33.33±1.42	-3.486	0.001
Improvement (%)	25.75±9.38	27.77±11.52	-1.218	0.225

Table 4: Comparison of Hb (g/dl) and MCH (g/dl) levels >12 at 21st day in both groups

Variable	Group A	Group B	Chi square	P value
Hb (g/dl)				
>12	18(22.5%)	65(81.2%)	55.303	0.001
12 or less	62(77.5%)	15(18.8%)		
MCV (fl)				
>80	34(42.5%)	40(50.0%)	0.905	0.341
80 or less	46(57.5%)	40(50.0%)		

DISCUSSION

Insufficient intake of iron in pregnancy and peripartum blood loss are primary causes of postpartum IDA. Women with low socio economic status and with less nutritional intake are more at risk of developing ID. ID not only predisposes several health risks for mother's wellbeing during important time of mother child bonding, but can also become a hurdle in care of child. Moreover, anemia could lead to more blood transfusions and prolonged hospitalization. Hemoglobin is the best parameter for managing IDA. This is because ferritin level can give different results leading to fake values. Intravenous iron should be used as a first line therapy in routine practice for treating postpartum anemia in order to reduce postpartum morbidity and mortality.[10]

Efficacy and safety of FCM in the treatment of postpartum IDA have tested in number of trials. It has always demonstrated more safety and efficacy as compared to with oral and parenteral iron agents.FCM has very few gastrointestinal side effects. Moreover it has offered many benefits such as more patient comfort, less hospitalization time and is cost effective[11,12].

Rathod et al reported that mean Hb increased the most in FCM group as compared to oral and ISC group within two weeks respectively. The same trend was shown by serum ferritin for oral, Iron sucrose Complex and FCM group respectively. Adverse iron drug reactions were significantly lesser in FCM group when compared with other two groups. The study concluded that FCM is more effective than both oral iron and IV iron formulation for both Hb level serum ferritin.[13]

In 2018, a comparative interventional prospective trial compared the effectiveness and safety FCM versus iron sucrose complex in postpartum IDA. Subjects in IV Iron sucrose Complex group were administered with several doses 200 mg/day on 0, 2, 4, 6, and 8 completing 1000 mg. In FCM group, IV FCM of 1000 mg was given as one dose. Hemoglobin and serum ferritin was repeated on day 0 and 30. Mean increase was significantly more in ferric carboxymaltose group. Another study concluded that FCM was safer and well tolerated as compared to oral ferrous sulphate in postpartum iron deficiency anemia with a superior efficacy.[14-16]

In the current study, at day 21, 65 (81.2%) females in iron carboxymaltose had Hb levels more than 12 g/dl which were statistically significant. One prospective trial comparing oral and parenteral forms of iron therapy

reported that parenteral iron especially FCM was more successful in restoring iron stores and had the advantage of few doses and lesser side effects. Another randomized controlled trial compared safety and effectiveness of parenteral iron in postpartum IDA. One group was given 1000mg iron FCM on day 1 and if required repeated on day 7 and 10, the other group was given ISC in a dose of 300 mg up to twice weekly. The mean rise of Hb in FCM group was much higher at 12 weeks. FCM was associated with greater improvement in fatigue scores. No serious side effects were noted in either group.[7,17] Another study like ours, reported that in India, mean increase in Hb after giving FCM versus iron sucrose complex to patients was 9.69±0.49 g/dl and 12.22±0.43 mg/dl respectively. By FCM, the increase in Hb was 9.8±0.43 g/dl and 12.22±041 g/dl at week 2 and 6 respectively. Serum ferritin was also higher in IV FCM group compared with Iron Sucrose Complex at 2 and 6 weeks (p=0.049; p=0.023). A prospective open label, randomized controlled study conducted at Australia favored the use of intravenous FCM in the management of post-operative anemia with impressive results[18,19].

Studies report less adverse side effects are seen when FCM is given to patients. Another study reported that despite of five time's higher dose, safety and efficacy of FCM is equal to oral iron therapy or IV iron. IS and FCM can rapidly replace Hb after delivery. Patient satisfaction, lesser side effects and short hospital stay are also advantages of FCM. Joshi et al has also published that FCM has only few side effects and can be considered as standard treatment for postpartum IDA.[20-22] Verma et al[21] have also shown consensus that use of FCM is safe, well tolerated, highly effective, low cost and easy to manage IDA in postpartum women suffering with this problem. Another recent study supports the use of single dose of FCM in the post-partum period with evidence of improved efficacy and minimal side effects[23,24].

CONCLUSION

This study found that ferric carboxyl maltose injection led to marked improvement in Hb and other parameters, higher efficacy and safety with minor complications than iron sucrose complex. So, there stands a need to conduct more trials over larger number of subjects in the country to encourage the use of IV FCM for correction of post-partum anemia.

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