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To evaluate the efficacy and safety of intravenous ferrous carboxymaltose compared with Iron sucrose in treating iron deficiency anemia in postpartum period

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ABSTRACT

Background: Iron deficiency anemia continues to be a serious problem in developing countries resulting in spectrum of adverse events in pregnant women. The first choice for prophylaxis and treatment of mild IDA in pregnancy is oral iron therapy. However, in patients with moderate and severe anemia, oral therapy takes very long time and compliance could be a big issue in our country. Thus, pregnant women with moderate anemia should be better treated with parenteral iron therapy. Postpartum women were eligible for the study with hemoglobin level <10 g/dl, while those with sickle cell anemia, aplastic anemia, megaloblastic anemia, etc., or having allergy to parental iron were considered not eligible for this study. The eligible women were randomly categorized to receive intravenous iron sucrose and intravenous ferrous carboxymaltose. **Aims and Objectives:** (1) To Compare ferrous carboxymaltose with iron sucrose in treating iron deficiency anemia in postpartum period (2) To assess the adverse effects and patient compliance. **Materials and Methods:** A comparative, prospective, and randomized distributed in 50 patients within the Department of Obstetrics and Gynecology, MGM Medical College and Hospital, Navi Mumbai. The subjects were randomized into two group, first group receiving iron sucrose, whereas second group receiving ferrous carboxymaltose. **Results:** Study, 25 women received iron sucrose and 25 women received ferrous carboxymaltose. There was significant higher increase in hemoglobin levels at 6 weeks in ferric carboxymaltose (FCM) group as compared iron sucrose group hemoglobin levels. There was significant higher increase in ferritin levels at 2 and 6 weeks in FCM group as compared iron sucrose group hemoglobin levels. There was significant higher increase in reticulocyte count at 6 week in FCM group as compared iron sucrose group reticulocyte count. **Conclusion:** Ferric carboxymaltose is safe and efficient in treatment of iron deficiency anemia in postpartum women as compared to iron sucrose with lesser adverse effect and better patient compliance.

Key words: Center for disease control, Ferric carboxymaltose, Hemoglobin, intravenous, Intravenous iron sucrose complex, Recombinant human erythropoietin

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INTRODUCTION

Iron deficiency anemia is very much prevalent in the India, among women of child bearing age, especially in under privileged population.[1] Anemia is estimated to about 20% of all maternal deaths and 9 times higher risk of perinatal mortality. Postpartum anemia is observed in up to 27% of women.[2] It is a major contributing factor and indirect

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cause of maternal death. Postpartum anemia is associated with longer hospital stays, depression, anxiety, persistent ill health, and lactation failure in mother and delayed development in infants.[3] In view of fetal and maternal risk associated with iron deficiency anemia, the treatment of anemia would lead to considerable reduction in risk which affects pregnancy, fetal outcome, and postpartum period. Adequate and early treatment of anemia in postpartum period will have improved life quality in women in child bearing age group.[4] The treatment of choice for postpartum anemia depends on the severity and/or additional maternal risk factors or comorbidities. Puerperal patients who have iron deficiency anemia are likely to have high iron requirement.[5] In addition, an inflammatory reaction can occur, particularly following surgically assisted deliveries and cesarean section, leading to iron sequestration in macrophage. Hence, iron demand increses.[6] Parenteral iron therapy is more compliant, efficacious, better tolerance, rapid replenishment of iron stores and hence used in chronic blood loss, gastrointestinal disorders, and impaired iron absorption.[7,8] Type I complex has high incidence of anaphylaxis with slow release of iron, type II complexes are comparatively safer, and type III complexes are unstable and leads to tissue toxicity.[8] Iron sucrose (FeS) in November 2000 got FDA approved forming iron hydroxide sucrose complex in water with 34,000–60,000 Dalton molecular weight. It is administered as intravenous bolus injection over 5–10 min or as infusion in 100 ml normal saline over 15–20 min with no test dose and maximum daily dosage of 200 mg, not more than thrice a week.[7-9] Side effects include pain at injection site, dizziness, and local irritation.[10,11] Ferric carboxymaltose (FCM) is novel non-dextran with type I complex administered rapidly 500 mg in 100 ml NS over 6 min and 1000–1500 mg in 250 ml NS over 15 min as intravenous infusion.[11] It has faster controlled delivery raising Hb and replenishing iron stores at shorter duration with minimal toxicity and anaphylaxis have wider therapeutic index, better compliance, and tolerance.[9,11]

Aims and objectives

1. To Compare ferrous carboxymaltose with iron sucrose in treating iron deficiency anemia in postpartum period.
2. To assess the adverse effects and patient compliance.

MATERIALS AND METHODS

This prospective comparative study was conducted in Indian pregnant women "To evaluate the efficacy and safety of intravenous FERROUS CARBOXYMALTOSE compared with IRON SUCROSE in treating iron deficiency anemia in postpartum period." This study has been carried out for 2 years in MGM Medical College and Hospital, KALAMBOLI in OPD and IPD basis. Patients were included after matching inclusion and exclusion criteria. Institutional ethics committee permission was taken before study.

Study groups

Iron sucrose

Twenty-five postpartum pregnant women with iron deficiency anemia received available intravenous IRON SUCROSE in hospital.

Ferrous carboxymaltose

Twenty-five postpartum pregnant women with iron deficiency anemia who received intravenous FERROUS CARBOXYMALTOSE compared with IRON SUCROSE.

Study duration

The total duration of study is approximately up to 2 years or until required number of patients is completed whichever is earlier.

Study population

Inclusion criteria

The following criteria were included in the study:

- Postpartum women with hemoglobin level <10 g/dl
- They will be randomly categorized to receive intravenous iron sucrose and intravenous ferrous carboxymaltose.

Exclusion criteria

The following criteria were excluded from the study:

- Patient having sickle cell anemia, thalassemia, aplastic anemia, megaloblastic anemia, and anemia due to liver disease or kidney disease should be excluded
- History of blood transfusion in current pregnancy
- History of allergy to parental iron
- Not consenting.

Methodology

The Institutional Ethics Committee permission was taken. This is hospital-based prospective comparative study; total 50 patients were enrolled after matching inclusion and exclusion criteria. These women were divided in two groups, in which Group A will be treated with intravenous iron sucrose and Group B will be treated with intravenous ferrous carboxymaltose. After detailed history and examination, laboratory investigation performed, where HB, PCV, red cell indices, reticulocyte count and peripheral smear, and serum ferritin will be measured to diagnose iron deficiency anemia.

Dose calculation for intravenous iron sucrose and intravenous ferrous carboxymaltose by Ganzoni Formula.

Iron deficit = body weight (kg) × D × 2.4 + iron storage (mg)

D= Target hemoglobin-Actual hemoglobin
W = weight in kg

Iron sucrose is given by 300 mg elemental iron iv injection in 300 ml ns as slow infusion over 30 min every alternate days until the required dose is completed.

i. Ferrous carboxymaltose is administered as intravenous drip infusion, max dose of 1000 mg (20 ml) diluted in 250 ml ns over 15 min.
ii. Patients were observed for side effects like pain and burning at injection site, fever, itching and rash, dizziness, and vitals for 1 h.

End points

Primary end points

Target Hb in postpartum anemia is 12 g/dl, 500 mg for body stores in lactation.

Secondary end points

To determine following safety parameters from baseline to end of treatment.

Questionnaires: Local reactions (such as pain and rashes at injection site) systemic effects (such as transient hypotension, dizziness, heart palpitation, nausea, and headache).

Statistical analysis

All the collected data were entered in Microsoft Excel sheet and then transferred to SPSS software ver. 22 for analysis. Qualitative data were presented as frequency and percentages and analyzed using Chi-square test. Quantitative data were presented as mean and SD and compared by t-test. P<0.05 was taken as level of significance.

RESULTS

As shown in Table 1, the most common age group among study population was 21–25 years (52%) followed by 26–39 years (34%) and <20 years (14%). The mean age of the study population was 23.48±3.34 years.

In the above Table 2, it was observed that most of the study population were multigravida (58%) followed by primigravida (42%)

In the above Table 3, it was observed that 38% of study population were registered, while 62% were unregistered.

As shown in Table 4, in iron sucrose group, 44% cases (n=22) were primigravida and 56% (n=28) were multigravida, while in the FCM group, 42% cases (n=21) were primigravida and 58% (n=29) were multigravida. There was no statistically significant difference between parity status and different study population (P>0.05).

As shown in Table 5, in iron sucrose group, 10% cases (n=5) belong to age group of <20 years, 54% cases (n=27) belong to age group of 21 to 25 years, and 36% cases (n=27) belong to age group of 26 to 39 years, while in the FCM group, 14% cases (n=7) belong to age group of <20 years, 46% cases (n=23) belong to age group of 21 to 25 years, and 40 % cases (n=20) belong to age group of 26 to 39 years. There was no statistically significant difference between age group and different study population (P>0.05).

As shown in Table 6, in iron sucrose group, 36% cases (n=18) had previous H/O iron supplementation, while in the FCM group, 26% cases (n=13) had previous H/O

Table 1: Age group among study population

Age group (years)	Frequency (%)
<20	7 (14)
21–25	26 (52)
26–39	17 (34)
Total	50 (100)

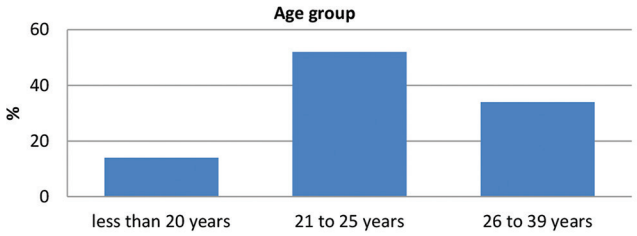


Table 2: Parity status among study population

Parity status	Frequency (%)
Primigravida	21 (42)
Multigravida	29 (58)
Total	50 (100)

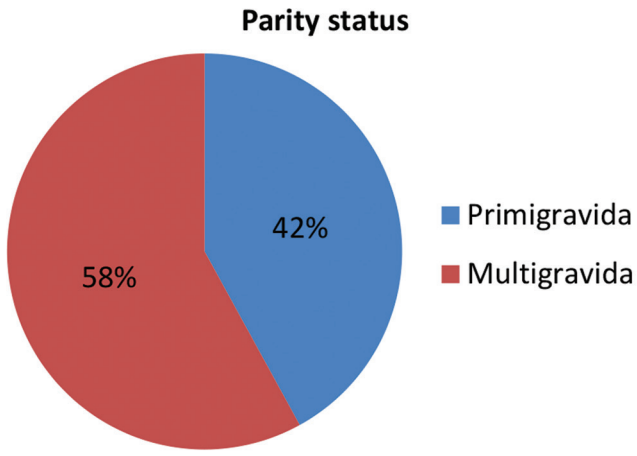


Table 3: Registered/unregistered status among study population

Registered/unregistered	Frequency (%)
No	31 (62)
Yes	19 (38)
Total	50 (100)

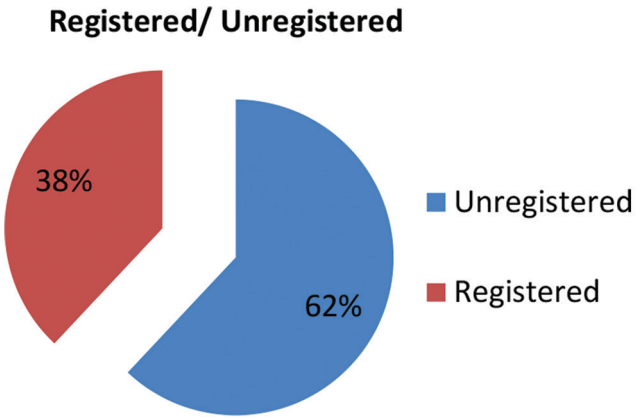
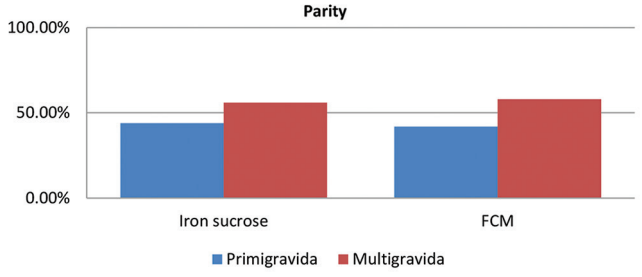


Table 4: Comparison of parity status among different study population

Parity	Groups		Total
	Iron sucrose	FCM	
Primigravida			
Count	11	10	21
Percentage	44.00	42.00	43.00
Multigravida			
Count	14	15	29
Percentage	56.00	58.00	57.00
Total			
Count	25	25	50
Percentage	100.00	100.00	100.00

χ^2 – 0.04, P – 0.833. FCM: Ferric carboxymaltose



iron supplementation. There was no statistically significant difference between previous H/O iron supplementation and different study population (P>0.05).

As shown in Table 7, side effects such as pain at injection site, itching and rash, fever, dizziness, and no complications were observed in 12% cases (n=3), 8% cases (n=2), 0% cases (n=0), 0% cases (n=0), and 80% cases (n=20),

Table 5: Comparison of age group among different study population

Age group (years)	Groups		Total
	Iron sucrose	FCM	
<20			
Count	3	4	7
Percentage	10.00	14.00	14
21–25			
Count	14	12	26
Total	54.00	46.00	52
26–39			
Count	8	9	17
Total	36.00	40.00	34
Total			
Count	25	25	50
Total	100.00	100.00	100.00

χ^2 – 0.75, P – 0.68. FCM: Ferric carboxymaltose

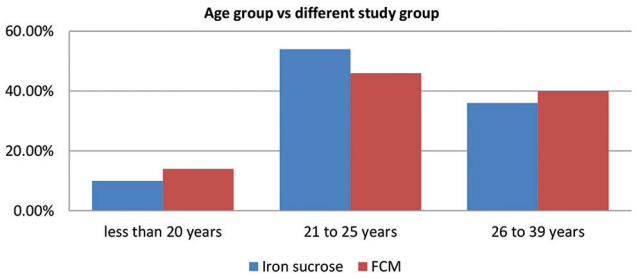
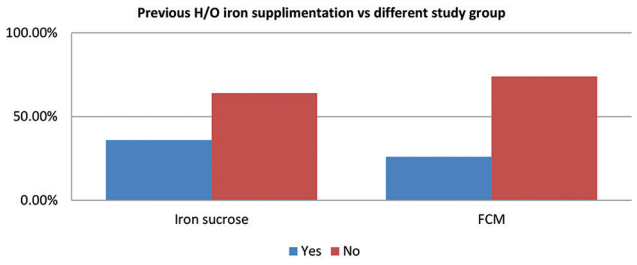


Table 6: Comparison of previous history of iron supplementation among different study population

Previous history of iron supplementation	Groups		Total
	Iron sucrose	FCM	
Yes			
Count	9	7	16
Percentage	36.00	26.00	32.00
No			
Count	16	18	34
Percentage	64.00	74.00	68.00
Total			
Count	25	50	100
Percentage	100.00	100.00	100.00

χ^2 – 1.16, P – 0.27. FCM: Ferric carboxymaltose



respectively, in iron sucrose group, while it was observed in 0% cases (n=0), 0% cases (n=0), 4% cases (n=1), 4% cases (n=1), and 92% cases (n=23), respectively, in FCM group.

There was statistically significant difference between side effects and different study population (P<0.05).

As shown in Table 8, on intragroup comparisons, there was significant increase in hemoglobin levels at 6 week in iron sucrose group as compared to day 1 hemoglobin levels, while there was significant increase in hemoglobin levels at 2 weeks and 6 weeks in FCM group as compared to day 1 hemoglobin levels.

On intergroup comparisons between iron sucrose and FCM group, there was significant higher increase in hemoglobin levels at 6 week in FCM group as compared iron sucrose group hemoglobin levels.

As shown in Table 9, on intragroup comparisons, there was significant increase in ferritin levels at 2 and 6 weeks in iron sucrose group as compared to day 1 ferritin levels and there was significant increase in ferritin levels at 2 weeks and 6 weeks in FCM group as compared to day 1 ferritin levels.

On intergroup comparisons between iron sucrose and FCM group, there was significant higher increase in ferritin levels at 2 and 6 weeks in FCM group as compared iron sucrose group hemoglobin levels.

As shown in Table 10, on intragroup comparisons, there was significant increase in reticulocyte count at 6 and 2 weeks in iron sucrose group as compared to day 1 reticulocyte count, while there was significant increase in reticulocyte count at 2 weeks and 6 weeks in FCM group as compared to day 1 reticulocyte count.

Table 7: Comparison of side effects among different study population

Side effects	Groups		Total
	Iron sucrose	FCM	
Pain at injection site			
Count	3	0	3
Percentage	12.00	0.00	6
Itching and rash			
Count	2	0	2
Percentage	8.00	0.00	4
Fever			
Count	0	1	1
Percentage	0.00	4.00	2
Dizziness			
Count	0	1	1
Percentage	0.00	4.00	2
No complications			
Count	20	23	43
Percentage	80	92	86
Total			
Count	25	25	50
Percentage	100.00	100.00	100.00

$\chi^2 - 19.8$, P – 0.001. FCM: Ferric carboxymaltose

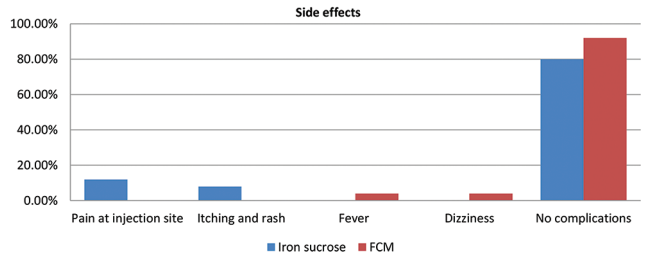


Table 8: Comparison of hemoglobin at various time interval among different study population

Hemoglobin	Groups		P
	Iron sucrose	FCM	
Day 1	7.32±0.55	7.47±0.6	0.177
2 weeks	8.1±0.63	9.2±0.52	0.761
	0.52	0.0001	
6 weeks	9.12±0.7	10.23±1.1	0.0001
	0.0001	0.0001	

FCM: Ferric carboxymaltose

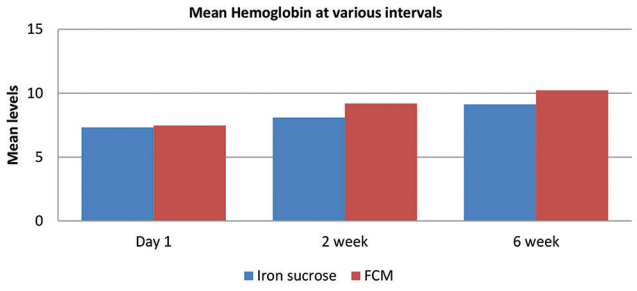


Table 9: Comparison of ferritin level at various time interval among different study population

Ferritin level	Groups		P
	Iron sucrose	FCM	
Day 1	20.49±4.7	21.11±5.1	0.87
2 weeks	46.01±7.8	78.77±13.5	0.0001
	0.01	0.0001	
6 weeks	62.32±8.1	109.05±21.2	0.0001
	0.0001	0.0001	

FCM: Ferric carboxymaltose

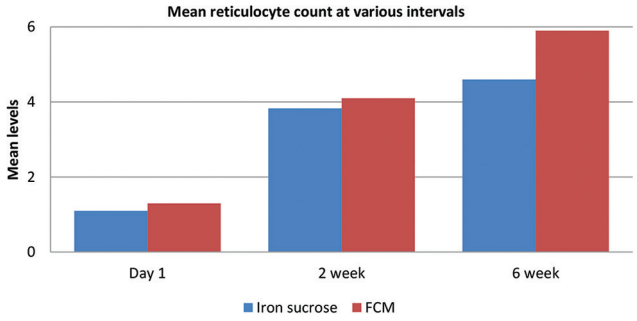
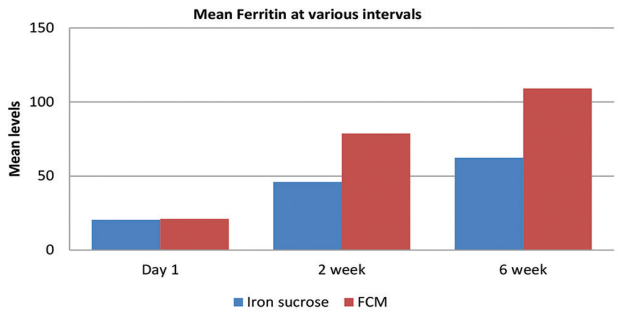


Table 10: Comparison of reticulocyte count at various time interval among different study population

Reticulocyte count	Groups		P
	Iron sucrose	FCM	
Day 1	1.1±0.4	1.3±0.6	0.834
2 weeks	3.83±0.9	4.1±1.3	0.541
	0.01	0.0001	
6 weeks	4.6±1.3	5.9±1.7	0.0001
	0.0001	0.0001	



On intergroup comparisons between iron sucrose and FCM group, there was significant higher increase in reticulocyte count at 6 week in FCM group as compared iron sucrose group reticulocyte count.

DISCUSSION

Postpartum anemia occurs frequently and causes a relevant disease burden at the time of critical period of maternal-infant interactions. Anemic women have vast average length of hospital stay, are more commonly receive a blood transfusion, and incur higher hospitalization costs; Hence, postpartum IDA requires prime quality attention and high quality care.[12]

Studies compared oral iron and FCM, oral iron, and iron sucrose and found that both iron sucrose and FCM were independently simpler, more effective, and safe than oral preparations.[13] During a randomized trial to assess safety and efficacy of intravenous FCM within the treatment of postpartum IDA, 227 women were assigned to IV FCM with 1000 mg maximum dose (up to 3 weekly doses) versus 117 women who received oral ferrous sulfate 100 mg twice daily. Intravenous FCM was as effective as oral ferrous sulfate with no statistically significant differences between groups at any point despite the shorter treatment period and a lower total dose of iron (mean 1.3 g IV iron versus 16.8 g oral iron). Similarly in our study, on intra-group comparisons, there was significant increase in hemoglobin levels at 6 week in iron sucrose group as compared to day 1 hemoglobin levels, while there was significant increase in hemoglobin levels at 2 week and 6 week in FCM group as compared to day 1 hemoglobin levels. On intergroup comparisons between iron sucrose and FCM group, there was significant higher increase in hemoglobin levels at 6 weeks in FCM group as compared iron sucrose group hemoglobin levels. On intragroup comparisons, there was significant increase in ferritin levels at 2 and 6 weeks in iron sucrose group as compared to day 1 ferritin levels and there was significant increase in ferritin levels at 2 weeks and 6 weeks in FCM group as compared to day 1 ferritin levels. On intergroup comparisons between iron sucrose and FCM group, there was significant higher increase in ferritin levels at 2 and 6 weeks in FCM group as compared iron sucrose group hemoglobin levels.

In a multicenter randomized controlled study, 13 women got that postpartum anemia were given FCM 1000 mg/wt max 2.5 g and 325 mg of ferrous sulfate tablets thrice a day for 6 weeks and found shorter period to achieve hemoglobin of 12 g/dl with sustained level at 42 days compare to ferrous sulfate. Patients with Hb levels ≤8 g/dL showed greatest difference in the responder rate between FCM and ferrous sulfate group (78.9% vs. 43.5%; P=0.0286).[14] Retrospective study was conducted to assess the efficacy and safety of FCM and found effective.[15] In a prospective trial, FCM was better tolerated than iron sucrose in postpartum anemia with superior efficiency.[16] A retrospective study compared the safety and efficacy of intravenous (IV) high dose FCM with iron sucrose (IS) for the treatment of postpartum anemia in 210 inpatient women in postpartum period who received IV high dose FCM (15 mg/kg; maximum 1000 mg) or IS (2×200 mg), respectively. Rapid administration of IV FCM was as safe as IS in the management of postpartum anemia despite 5 times of higher dosage. FCM was as effective as IS in changing.

Hb levels from the baseline. There was no difference in the mean daily Hb increase between the groups. Women with severe anemia showed the foremost effective responsiveness. The single application of FCM shows advantages of lower incidence of side effects at the injection site, a shorter treatment period, and better patient compliance.[12]

In our study, among both the group, there was significant rise of Hb and ferritin after 1 month of the therapy which was comparable with the other opposite studies. Like others severe anemia showed the foremost effective response in both the groups. In iron sucrose group, 44% cases (n=22) were primigravida and 56% (n=28) were multigravida, while, in the FCM group, 42% cases (n=21) were primigravida and 58% (n=29) were multigravida with no statistically significant difference. In iron sucrose group, 10% cases (n=5) belong to age group of <20 years, 54% cases (n=27) belong to age group of 21 to 25 years, and 36% cases (n=27) belong to age group of 26 to 39 years, while in the FCM group, 14% cases (n=7) belong to age

group of <20 years, 46% cases (n=23) belong to age group of 21 to 25 years, and 40% cases (n=20) belong to age group of 26 to 39 years with no statistically significant difference. In iron sucrose group, 36% cases (n=18) had previous H/O iron supplementation, while in the FCM group, 26% cases (n=13) had previous H/O iron supplementation with no statistically significant difference.

Limitations of the study

Sample size determination is most essential component of every research, the larger the sample size the higher the degree of accuracy. But this is limited by resources available, and it was the limitation for the large sample use in this study.

CONCLUSION

Intravenous iron sucrose and intravenous ferric carboxymaltose both results in increase in the hemoglobin and serum ferritin levels among the study participants. Ferric carboxymaltose is safe and efficient in treatment of iron deficiency anemia in postpartum women as compared to iron sucrose with lesser adverse effect and better patient compliance. Due to properties like ultra-short duration of treatment, that is, ability to administer 1000 mg doses in a single sitting, fewer adverse reactions and better compliance makes FCM the first-line drug in the management of postpartum iron deficiency anemia causing a faster and higher replenishment of iron stores and correction of Hb levels.

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AG[1]- Concept and design, review of manuscript and treating doctor; **AG[2]**- Concept and design, revision of manuscript and treating doctor; **UG[3]**-Manuscript Preparation, **AG[4]**- Manuscript preparation and Revision of manuscript

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