ORIGINAL RESEARCH

Efficacy and safety of ferric carboxymaltose and iron sucrose in management of postpartum iron deficiency anemia-A comparative observational study

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ABSTRACT

Anemia is one of the major contributing factors in maternal mortality and morbidity in third world countries. Adequate and early treatment of anemia in post-partum period will have improved quality of life in women of child bearing age group. Parenteral iron treatment is expected to be advantageous in patients with postpartum anemia. **Objectives:** To compare efficacy and safety of intravenous ferric carboxymaltose with iron sucrose in treatment of postpartum iron deficiency anemia in postpartum mothers at Maternity Hospital SKIMS, Soura. To reduce the prevalence of postpartum anemia. **Methods:** The present prospective study was conducted in the department of Obstetrics and Gynaecology at Maternity hospital SKIMS Soura, in the northern region of India from September 2017 to March 2019. **Type of study:** Prospective comparative observational study. **Sample Size:** A total of 200 patients with postpartum iron deficiency anemia were taken up in the study. They were randomly distributed into two groups consisting of 100 cases each. **Group A:** 100 cases in this group received intravenous ferric carboxymaltose therapy. **Group B:** 100 cases in this group received intravenous iron sucrose therapy. **Results:** Our study indicates that postpartum anemia can be treated effectively by ferric carboxymaltose as compared to iron sucrose because ferric carboxymaltose results in a much more rapid resolution of iron deficiency anemia due to its ability to deliver a high dose of iron within a short period of time. **Conclusion:** The study concluded that ferric carboxymaltose is safe intravenous agent for the treatment of iron deficiency anemia in postpartum period in comparison to Iron Sucrose.

Keywords: Anemia, postpartum period, ferric carboxymaltose, iron sucrose.

INTRODUCTION

Anemia is widely prevalent in developing countries like India andthe most common affected group is women of child bearing age particularly pregnant women. According to the WHO, it contributes to 20% maternal deaths.[1]The main cause of anemia in pregnancy is found to be iron deficiency, i.e. 95%.[2] Causes of Iron deficiency in pregnancy include poor dietary intake, poor tolerance towards iron, the ability of fetus to extract its requirement of iron from mother.[3] This is aggravated by gastrointestinal effects of pregnancy like nausea and vomiting, motility disorder with reflux esophagitis, indigestion, constipation, and a tendency to develop hemorrhoids. These factors increase the severity of anemia. Therefore, more amount of iron, exceeding the daily requirement is to be supplemented.[4]

Postpartum anemia is observed in up to 27% of women.[5] Postpartum anemia is associated with longer hospital stay, depression, anxiety, and delayed infant development.[6] Adequate and early treatment of anemia in post-partum period will have improved quality of life in women of child bearing age group. 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.[7] In addition an inflammatory reaction can occur particularly following surgically assisted deliveries and caesarean section, leading to iron sequestration in macrophages. So Iron demand increases.[8] In most of these cases oral iron is not enough since the endogenous iron stores are already depleted and less iron is provided for

sufficient erythropoiesis. As compliance to oral iron therapy is very poor and also the results are unpredictable, parenteral iron therapy is better option to treat such patients.[9] However the standard approach to treatment in the majority of institutions is oral supplementation, with blood transfusion reserved for more severe or symptomatic cases,[10] but there are a number of hazards of blood transfusion including transfusion of wrong blood, anaphylaxis and risk of transmission of infections, any of which would be devastating for the young mother. Therefore, parenteral iron treatment is expected to be advantageous in cases in which treatment with oral iron is not possible due to gastrointestinal (GI) side effects, in patients with poor compliance, or in patients with severe anemia.[11]

PARENTRAL IRON PREPARATIONS

Treatment with IV iron is clearly superior to oral iron and presents several advantages such as faster and higher increase in hemoglobin levels and replenishment of body iron stores.

The ferric hydroxide preparation was the first iron compound for parenteral use introduced early in the 20th century.

However severe toxic reactions led to it being recommended only in extraordinary circumstances. [12]

The first high-molecular-weight iron dextran [HMW-ID]) for intramuscular and IV use (Imferon) was introduced in 1954. The bioavailability of this iron occurs via uptake of iron dextran particles into the

reticuloendothelial system (RES) with subsequent breakdown. [12, 13]

However, the increased incidence of serious Adverse events reported with high molecular weight iron dextrose (HMW-ID), particularly the well-known dextran-induced anaphylactic reactions, led to its recommendation only when extreme clinical conditions were present and other options unavailable. Severe reactions by the conventional panrenteral iron preparations prevented their wider use.[2] For these reasons, modern formulations of IV iron have emerged as safe and effective alternatives for IDA management.[14-19]

Iron sucrose has been used for years for intravenous treatment of iron deficiency in second and third trimester of pregnancy and postpartum period. However, its use is limited to low dose due to local and systemic side effects in higher doses. Recently, ferric carboxymaltose has been introduced. This preparation can be used intravenously in high doses with up to 1000 mg infused in 15 min with low risk of side effects.[20]

Iron sucrose (IS) was FDA approved in November 2000. Iron sucrose is iron hydroxide sucrose complex in water. The molecular weight of iron sucrose is 34,000- 60,000 Dalton's. Iron sucrose is administered by intravenous bolus injection over 5-10 minutes or as short infusion in 100 ml of normal saline over 15-20 minutes. A maximum daily bolus dose of 200 mg can be given at a time, for not more than thrice a week. Once iron sucrose has been administered, it is transferred toferritin,the normal iron storage protein.[21] Then, it is broken down in the liver, spleen, and bone marrow. The iron is then either stored for later use in the body or taken up by plasma. The plasma transfers the iron to hemoglobin, where it can begin increasing red blood cell production.[22] A general side effect includes metallic taste, nausea, dizziness and local irritation.

Ferric carboxymaltose (FCM) is a novel non-dextran containing Type-I complex. It consists of ferric hydroxide core stabilized by a carbohydrate shell. IV ferric carboxymaltose (FCM) has a neutral pH (5.0-7.0) and physiological osmolarity, which makes it possible to administer its higher single doses over shorter time periods (single dose up to 1000 mg over 15 min) than other parenteral preparations.[23] Moreover, it does not contain dextran; therefore, the risk of anaphylaxis or serious hypersensitivity reactions is very low, and a test dose is also not required. Its design allows for controlled and fast delivery with minimal risk of acute toxicity and there is a much wider therapeutic window as compared to its other counterparts.

Intravenous administration of ferric carboxymaltose results in transient elevations in serum iron, serum ferritin and transferrin saturation, and, ultimately, in the correction of hemoglobin levels and replenishment of depleted iron stores.

The total iron concentration in the serum increased rapidly in a dosedependent manner after intravenous administration of ferric carboxymaltose. Ferric carboxymaltose is rapidly cleared from the circulation and is distributed primarily to the bone marrow (approximately 80%) and also to the liver and spleen. Repeated weekly administration of ferric carboxymaltose does not result in accumulation of transferrin iron in patients with iron-deficiency anemia. [24]

Ferric carboxymaltose injection leads to hemoglobin 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. Ferric carboxymaltose is cost effective with other positive benefits of fewer hospital visits, reduced interruption in lifestyle, improved patient compliance.[25]

Both these compounds (Iron sucrose and Ferric carboxymaltose) are safe in postpartum period and have less chances of hypersensitivity reactions.[2]

MATERIALS AND METHODS

The present prospective study was conducted in the department of Obstetrics and Gynaecology at Maternity hospital SKIMS Soura, in the northern region of India from September 2017 to March 2019.

Type of study: Prospective comparative observational study.

Study population: Study population included all women who delivered at Maternity Hospital SKIMS Soura during the study period.

Sample Size: A total of 200 patients with postpartum iron deficiency anemia were taken up in the study. They were randomly distributed into two groups consisting of 100 cases each.

Group A: 100 cases in this group received intravenous ferric carboxymaltose therapy.

Group B: 100 cases in this group received intravenous iron sucrose therap.

Inclusion criteria was postpartum patients with haemoglobin less than 10 gm/dl.World Health Organization (WHO) has defined postpartum anemia(PPA) as hemoglobin (Hb) of <10 gm% in postpartum period. However a group of patients was excluded from the study. This group comprised of patients withanaemia other than iron-deficiency anemia,patients who received blood transfusion in postpartum period, patients with known history of allergy to injection iron, patients with renal diseases, hepatic dysfunction, thromboembolism, seizures and drug abuse.

INVESTIGATIONS

Include complete hemogram, peripheral blood smear for cell morphology and baseline serum ferritin levels. These were done before administering iron injection. However the parameters of assessment were:

Peripheral blood smear (before treatment).

Hemoglobin estimation by Sahli's method (before and after treatment).

Serum ferritin (before and after treatment).

Calculation of total iron requirement Iron deficit was calculated by the formula:

Total iron dose required (mg) = 2.4 × Body weight (kg) × (Target Hb - Actual Hb in g/dl) + 500 mg.

Group A: They received intravenous injections of Ferric carboxymaltose complex, which are available as ampules of 10 ml containing 500 mg of elemental iron. Total 1000 mg/20 ml in 250 ml of 0.9% normal saline was infused over 15-20 min.

Group B: They received intravenous injections of iron sucrose complex. The iron sucrose was infused as 200 mg elemental Iron (2 ampules of 5 ml) in 200ml of 0.9% normal saline over 30 min, every alternate days up to 5doses. A maximum of 1000 mg iron sucrose was given per 10 days.

Ferric carboxymaltose and iron sucrose was provided free of cost under Janani Shishu Surakhsha Karyakaram (JSSK) scheme.

Patients were observed for any side effects like headache, nausea, diarrhoea, vomiting, pain and burning at injection site, rigors, fever, hypotension, tingling sensation, itching, rash or any other side effects for 1 hour. If there were any side effects, then the drip was immediately stopped and the patient was treated. Patients were advised to follow-up after 2 weeks from the last injection. Serum ferritin and hemoglobin levels were repeated after 2 weeks.

STATISCAL METHODS

Statistical package for social sciences ver.22 was used for data analysis. The result was expressed in percentages or mean SD as specified. Pearson's Chisquare test was used to analyse categorical data. P value less than .05 was taken statistically significant.

RESULTS

There was a satisfactory rise in hemoglobin and serum ferritin, good patient satisfaction, minimal side effects and easy administration of dose in patients who received intravenous ferric carboxymaltose.

Both the group were comparable on base line characteristics. Patients studied were from all the age groups and most of the patients (108) belonged to age group of 25-29. Total 68% and 72% patients in either groups respectively were from lower socio economic class according to Modified Kuppuswamy

Classification. Most of the patient were primipara in the both groups and most of the patients were residing at rural areas (137 patients) and on the ground of literacy majority of the patients (141) were illiterate.

Mean hemoglobin before starting of therapy in group A was (8.1± 0gm/dl) and in group B was (8.06± 0.5gm/dl). Mean hemoglobin after therapy in group A was (11.10±0.90gm/dl) and in group B was (10.11±0.68gm/dl). This was statistically significant (p value ≤ 0.0001). While comparing mean rise of hemoglobin level between groups A (3.0gm/dl) and B (2.1gm/dl), group A had significant rise of hemoglobin level after 2weeks of therapy.

In group A 68 patients and in group B 55 patients had Microcytic Hypochromic Anemia. Both the group were comparable on baseline hematological parameters.

Rise in serum ferritin level after 2 weeks of therapy was higher in group A (326.48±33.76) as compared to group B (187.5 ±24.04) which was significant (p value ≤ 0.0001). Hence, ferric carboxymaltose replenish the store faster .

The mean duration of hospital stay in group A was 3.3 days, which was very less as compared to group B 6.75 days. Adverse reactions were milder in both the groups and mostly affected to local reactions, rate of adverse effect is1% in ferric carboxymaltose group and 6% in case of iron sucrose group.

Table 1: Distribution of Patients According to Symptoms

Symptoms		Group A	Group B	Total
GW	Count	91	95	186
	% of Group	91%	95%	93%

Palpitations	Count	9	5	14
	% of Group	9%	5%	7%
Total	Count	100	100	100
	% of Group	100.0%	100.0%	100.0%

Table 1: shows generalized weakness in 91 patients in group A and 95 patients in group B and remaining complained of palpitations. This is statistically insignificant.

Table 2: Distribution of Patients According to Signs

Signs		Group A	Group B	Total
Pallor	Count	87	89	176
	% of Group	87%	89%	88%
PE	Count	11	8	19
	% of Group	11%	8%	9.5%
PK	Count	2	3	5
	% of Group	2%	3%	2.5%
Total	Count	100	100	100
	% of Group	100.0%	100.0%	100.0%

Table 2: shows in group A 87 patients and in group B 89 patients have only pallor which is a subjective observation and is insignificant.

Table 3: Comparison of Pre-Treatment and Post-Treatment Hb& Serum Ferritin Levels

	Group	N	Mean	Std. Deviation	Std. Error Mean	p-value
Age	A	100	29.110	3.9181	.3918	
	B	100	29.350	3.6108	.3611	0.65
Pretreatment HB	A	100	8.109	0.6898	.0690	
	B	100	8.081	0.7099	.0710	0.77
Pretreatment FERRITIN	A	100	9.941	1.9327	.1933	
	B	100	10.059	2.2391	.2239	0.69
Post-treatment HB	A	100	11.107	0.9060	.0906	
	B	100	10.111	0.6899	.0690	≤0.0001*
Post-treatment FERRITIN	A	100	326.480	33.7604	3.3760	
	B	100	187.500	24.0448	2.4045	≤0.0001*

Table 3: shows mean hemoglobin 8.1 g% pretreatment and 11.1g% posttreatment in group A and therefore, a rise by 3.0 g% in 2 weeks. The mean hemoglobin 8.0 g% pre-treatment and 10.1 g% post-treatment in group B and therefore, a rise by 2.1g% post-treatment. This is statistically significant.

Table 4: Distribution of Cases According to Adverse Drug Reaction

Side Effects		Group		Total
		A	B	
None	Count	99	94	193
	%of group	99.0%	94.0%	96.5%
Pain at	Count	0	1	1
injection site	%of group	0.0%	1.0%	0.5%
RASH	Count	0	5	5
	%of group	0.0%	5.0%	2.5%
Tingling	Count	1	0	1
	%of group	1.0%	0.0%	0.5%
Total	Count	100	100	200
	%of group	100.0%	100.0%	100.0%

Table 4: shows minor adverse reaction in 1 patient out of 100 patients in group A and 6 patients out of 100 patients in group B, which is statistically insignificant. They continued with the study.

DISCUSSION

Anemia in pregnancy and postpartum period is a major public health problem especially in India and most common is iron deficiency anemia. Postpartum anemia arises frequently and imposes a substantial disease burden during the critical period of maternal-infant interactions and can be very debilitating, especially when caring for a newborn. Hence, postpartum iron deficiency anemia require attention and high quality care.

Currently intravenous iron has been considered as an alternative in the management of iron deficiency anemia.

The present study conducted in the department of Obstetrics and Gynaecology SKIMS Soura compared the two intravenous iron preparations for the treatment of iron deficiency anemia in postpartum period.The aim of our study was to compare the efficacy and safety of Ferric Carboxymaltose and Iron Sucrose in postpartum Iron deficiency anemia. The safety and efficacy of Ferric Carboxymaltose and Iron Sucrose in the treatment of postpartum Iron deficiency anemia have been tested in a number of randomized, multicenter studies.

In our study total 200 post-partum women with iron deficiency anemia were divided randomly in two groups, out of which one received ferric carboxymaltose (Group A) and the other received iron sucrose (Group B), with 100 patients in each group. A uniform dose was given to all women with postpartum Iron deficiency anemia.In both the groups, serum ferritin, hemoglobin and peripheral blood film was done at day 0. Follow up was done after two weeks of therapy and hemoglobin and serum ferritin level were repeated.

Our study indicates that postpartum anemia can be treated effectively by ferric carboxymaltose in comparison to iron sucrose as ferric carboxymaltose results in early and significantly higher rise in hemoglobin and serum ferritin levels. Iron sucrose has undoubtedly been the standard of care in parentral iron therapy for treatment of anemia, however its main disadvantage is the limited maximum permissible dose per week and hence the need for maximum visits to deliver the required iron dose. On the other hand, ferric carboxymaltose can be administered in larger amount in single visit with lesser side effects and better patient compliance. The overall satisfaction reported by the patients was better as the drug involves minimum hospital stay with time of infusion only 15 minutes.

In our study, majority of cases were of lower socioeconomic status (68% in group A and 72% in group B), illiterate (69% in group A and 72% in group B), rural areas (64% in group A and 73% in group B), younger than 30 years of age (68.5%), thus showing that there is high prevalence of early marriage and early childbearing in rural and economically backward areas of India. Low socioeconomic status causes poor maternal health.

It has been seen that illiteracy, wrong customs and rigid beliefs, refusal for taking nutritional and health services provided by government, lower status of women, poor nutrition and lack of personal hygiene etc, compromise the quality of life of women.

The characteristics of patients in group A and in group B were statistically comparable in relation to age. In the study majority of women were in the age group of 25-29 years. Mean age of the patients was 28 years. Majority of the patients were primipara (75% and 65%) in either groups respectively, which indicated the high prevalence of anemia in adult females from preconceptional period. Among 200 patients studied most of the patients presented with the chief complaint of generalized weakness (91%) in group A and (95%) in group B, while the rest presented with palpitations (9% and 5%) in either groups, respectively.

Majority of them were showing the presence of pallor on general physical examination, (87%) in group A and (89%) in group B. Mode of delivery was caesarean section in majority patients,70% in group A and 74% in group B ,delivered by cesarean section. Higher percentage of anemia is seen in patients delivered by cesarean section as there is more blood loss in it (1000ml) as compared to vaginal delivery (500ml). The mean duration of hospital stay was lesser in group A (3.30days) as compared to group B (6.75days).

In our study, mean hemoglobin before starting of therapy in Group A and Group B was 8.1 ±0.68 versus 8.08±0.70. After 2 weeks of therapy, mean hemoglobin in Group A and Group B was 11.10±.09 versus 10.11±0.68, which was significant (P value <0.001). The mean rise of hemoglobin in ferric carboxymaltose group and iron sucrose group was 3gm/dl versus 2.03gm/dl, which was significant.

Serum ferritin, which indicates iron store of body, increased significantly in ferric carboxymaltose group than iron sucrose group, 326.48±33.76 versus 187.50±24.04 (P value ≤0.0001),which was significant. Hence, ferric carboxymaltose results in quick rise in hemoglobin and early replenishment of iron stores thereby preventing the recurrence of IDA and improving the quality of life.

Adverse reactions are known to occur with various parentral iron preparations.

However in our study both drugs did not show any serious Adverse Drug Reactions. In iron sucrose group, 6% of the patients had adverse reactions in the form of rash (5%) an pain at injection site (1%). In ferric carboxymaltose group only 1% of the patients reported adverse reactions in the form of a rash at the injection site. Therefore the most common adverse effect in parenteral group was a localized rash.

These adverse events were mild, mostly restricted to local reactions at the infusion site. These reactions were reversible. There were no treatment-related serious adverse events. No anaphylactic reaction was

detected. No venous thrombosis was registered. There was no life threatening complications in either groups. Many studies that have been done previously have compared the cost of ferric carboxymaltose and iron sucrose. It has been found that the overall cost in the ferric carboxymaltose group is significantly less.[26,27] In our study, the drug was provided free of cost to the patients under the JSSK (Janani Shishu Suraksha Karyakram) scheme by the Indian Government. The total cost of drug was analyzed in both the groups in the present study and showed significantly higher cost in ferric carboxymaltose group. However, the overall cost of therapy including the travel costs and the number of working days lost due to travel would have been more in ISC group. This is because of the need of multiple visits required to receive the complete dosage in iron sucrose group.

Our study indicates that postpartum anemia can be treated effectively by ferric carboxymaltose as compared to iron sucrose because ferric carboxymaltose results in a much more rapid resolution of iron deficiency anemia due to its ability to deliver a high dose of iron within a short period of time. It has minimal sideeffects, lesser number of dosing, better compliance, lesser side effects and lesser days of hospital stay. Anemia in postpartum period is debilitating and ferric carboxymaltose is a revolution in its treatment. We highly recommend the use of ferric carboxymaltose in postpartum iron deficiency anemia.

Our study is consistent with other reported comparative studies with Iron sucrose or other preparations.

LIMITATIONS

FCM was provided free of cost in our study but its high cost indeed needs special attention. It should be included world wide in free maternity schemes so that women can avail it's benefit.

CONCLUSION

The study concluded that ferric carboxymaltose is safe intravenous agent for the treatment of iron deficiency anemia in postpartum period. In comparison to Iron Sucrose, it has an advantage of large dose administration per sitting, early and significantly higher rise in hemoglobin and serum ferritin levels, lesser total number of dosing, lesser days of hospital visits, lesser discomfort caused to the patient by multiple needle pricks, fewer adverse reactions. The overall cost of ferric carboxymaltose therapy (including the travel and visits) is less than that of iron sucrose. It has a patient friendly dosing and better compliance. It results in early recovery and better sense of wellbeing in patients.

From our study we recommend its use in postpartum iron deficiency anemia, indeed it is a revolution in the treatment of iron deficiency anemia.

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CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

Not required

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