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Original Research Article

## Comparison of iron carboxy maltose and iron sucrose in pregnant females

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### ABSTRACT

**Background:** Maternal anaemia is a common problem worldwide. The aim of this study is to compare the efficacy and safety of FCM vs iron sucrose for correction of iron deficiency during pregnancy.

**Methods:** This study was conducted in Swasthya healthcare, Jammu for a period of ten months from Sep 2017 to June 2018. A total of 100 women with Hb 7-9.9g% enrolled. They were divided into two groups of 50 each. Group A were given Iron Carboxy maltose and Group B were given Iron Sucrose. These were compared for their efficacy and safety.

**Results:** In the present study, the rise in mean hemoglobin at 4 weeks in Group A was  $1.79 \pm 0.47$  and  $1.06 \pm 0.11$  in Group B which was highly significant ( $p$ -value  $< 0.0001$ ). Rise in mean serum ferritin level at 4 weeks in Group A was  $123.80 \pm 16.03$  and in Group B was  $84.78 \pm 10.53$ . Statistically, this rise was also highly significant ( $p < 0.0001$ ). In present study, adverse reactions were observed in 34% patients in Group A, while in Group B it was observed in 52% patients.

**Conclusions:** Iron carboxy maltose shows higher rise in hemoglobin and ferritin levels as compared to Iron Sucrose and incidence of adverse effects is also comparatively lower in the former.

**Keywords:** Anaemia, Iron carboxy maltose, Iron sucrose

### INTRODUCTION

Maternal anaemia is a common problem especially in developing countries like India. One of the studies conducted revealed that 87% of the women in India are anaemic.<sup>1</sup> According to the 2008 WHO analysis, anaemia affected 24.8% of the world's population.

Anaemia in pregnancy is defined as haemoglobin concentration  $< 11 \text{ gm/dl}$  and further categorised into three levels: mild:  $9-10.9 \text{ gm/dl}$ , moderate:  $7-8.9 \text{ gm/dl}$ ; severe:  $< 7 \text{ gm/dl}$ .<sup>2</sup> Maternal anaemia in pregnancy is commonly considered as risk factor for poor pregnancy outcomes like pre-eclampsia, antepartum haemorrhage, preterm deliveries and maternal mortality.<sup>3</sup> Maternal anaemia is

also associated with poor perinatal outcome like low birth weight babies, meconium stained liquor, low APGAR scores at one min and NICU admissions.<sup>4</sup> Among the pregnant women the most common type of anaemia is iron deficiency anaemia as shown by several studies.<sup>5</sup>

The mainstay of treatment for iron deficiency anaemia is iron supplementation either oral or parental. The indications for parental iron treatment are intolerance to oral iron, non-compliance to oral iron and patients who need rapid restoration of iron stores. Current intravenous iron formulations include ferric gluconate, iron sucrose, iron polymaltose and, recently, ferric carboxymaltose.<sup>5</sup> They have the same structure, but differ from each other by the size of the core and the surrounding carbohydrate.

Iron sucrose and ferric carboxy maltose (FCM) are dextran free intravenous iron alternatives. Iron sucrose has widely been used as it has a higher availability for erythropoiesis than iron dextran a good safety profile in pregnancy.<sup>6</sup> However, it cannot be administered in a higher dose and re-quires frequent visits to the hospital by a pregnant woman. Intravenous ferric carboxy maltose is a novel iron complex which consists of a ferric hydroxide core which is stabilised by a carbohydrate shell. It is not predisposed to anaphylactic reactions since it has a low immunogenic potential. Upon administration, it allows controlled delivery of iron within the cells of the reticuloendothelial system which further deliver to the iron-binding proteins ferritin and transferrin. Studies have shown that it is rapidly cleared from the circulation and is distributed primarily to the bone marrow and also to the liver and spleen and there is no risk of accumulation of iron in patients with iron-deficiency anaemia.<sup>7</sup> Ferric carboxy maltose also per-mits the administration of large doses (15 mg/kg; maximum of 1000mg/infusion) in a single and rapid session (15-minute infusion). The aim of this study is to compare the efficacy and safety of FCM vs iron sucrose during pregnancy for correction of iron deficiency during pregnancy.

## METHODS

This was a prospective, comparative study conducted in Swasthya healthcare, Jammu from 1<sup>st</sup> September 2017 to 30<sup>th</sup> June 2018 over a period of 10months.

### Inclusion criteria

- Hundred antenatal patients with gestational age more than 28 weeks and moderate anaemia with hemoglobin 7-9.9gm and S. Ferritin levels <30mcg were included in the study.

### Exclusion criteria

- Patients with history of blood transfusion, hypersensitivity reaction to any iron preparation, history of bleeding tendencies, history of iron overload disorders, thalassemia's or haemochromatosis or medical disorders like chronic renal failure, cardiovascular disorder, tuberculosis, hepatitis B/C or HIV infection were excluded from the study.

These patients were evaluated for CBC, PBF and S. Ferritin levels. These patients were divided into a group of 50 each: Group A and Group B. Group A were given ferric carboxy maltose and Group B subjects were given iron sucrose.

The dose of intravenous iron was calculated by the following formula:

Total iron requirement=2.4 x body weight (in kgs) x hemoglobin deficit+500mg (iron stores).

Hemoglobin deficit was calculated by subtracting from 11gm%.

FCM was administered by intravenous drip infusion. The iron requirement dose was rounded down to nearest 100 mg if body weight <66kg and rounded up to nearest 100 mg if body weight >66kg. FCM was diluted to a maximum single dose of 1000mg iron in 250ml normal saline and given over a period of 15minutes. Iron sucrose was given as an infusion of 200mg in 200ml of normal saline over 15minutes on alternate days till the required dose was met. After the iron infusion the patients were observed for adverse reactions like itching, headache, nausea, fever, pain at injection site or severe anaphylactic reaction. Complete blood count and S. Ferritin levels were repeated 2weeks after the last dose of FCM or iron sucrose.

## RESULTS

The data was analysed, and following observations made.

**Table 1: Distribution of patients according to age.**

Age (years)	Group A No. (%)	Group B No. (%)
15-19	01 (02)	0 (0)
20-24	23 (46)	17 (34)
25-29	22 (44)	22 (44)
30-34	03 (06)	11 (22)
35-39	01 (02)	0 (0)
Total	50 (100.00)	50 (100.00)
Mean±SD (years)	26.46±3.58	24.64±2.87
Statistical inference	Unpaired t value=2.80; p=0.006; Not significant	

As shown in Table 1, mean age of Group A was 26.46±3.58years and mean age of Group B was 24.64±2.87 years, which was comparable (p=0.006). 44% of patients in Group A and 38% in Group B were primigravidae, while 56% of patients in Group A and 62% in Group B were multigravida; both groups being statistically comparable (p=0.54) (Table 2).

**Table 2: Gravidity of patients.**

Gravidity	Group A No. (%)	Group B No. (%)	Statistical inference
Primigravida	22 (44)	19 (38)	Chi square =0.37 p=0.54; Not significant
Multigravida	28 (56)	31(62)	
Total	50 (100.00)	50 (100.00)	

Table 3 shows the pre-treatment haemoglobin in the two groups. Patients with haemoglobin level of moderate range (7-9.9gm/dl) were included in the study.

Most patients in Group A (46%) and in Group B (46%) had their haemoglobin in the range of 8 to 8.9gm/dl.

Mean values of haemoglobin in both the groups were comparable statistically ( $p=0.69$ ).

**Table 3: Pre-treatment haemoglobin (gm/dl) of the patients.**

Pretreatment Hb	Group A No. (%)	Group B No. (%)
7-7.9	14 (28.00)	10 (20.00)
8-8.9	23 (46.00)	23 (46.00)
9-9.9	13 (26.00)	17 (34.00)
Total	50 (100.00)	50 (100.00)
Mean Hb (g/dl)	8.45±0.64	8.40±0.64
Statistical inference	Unpaired t test value=0.39; $p=0.69$ ; Not significant	

Patients with serum ferritin less than 30 mcg/L were included in the study. Mean serum ferritin of Group A was 14.09±6.05mcg/L and that of Group B was 14.74±5.82mcg/L, the difference being statistically not significant ( $p=0.58$ ) (Table 4).

As shown in Table 5, the rise in mean haemoglobin level at 4 weeks was also more in Group A as compared to Group B (1.79 vs 1.06gm/dl).

**Table 6: Post-treatment rise in serum ferritin (mcg/L) at 4 weeks.**

Mean rise in S. ferritin (mcg/L) at 4 weeks	Group A	Group B	Statistical interference
	123.80±16.03	84.78±10.53	Unpaired t test: $t=14.38$ ; $p<0.0001$ ; Highly significant

As shown in Table 5, the rise in mean haemoglobin level at 4 weeks was also more in Group A as compared to Group B (1.79 vs 1.06 gm/dl). Statistically, the rise was highly significant ( $p<0.0001$ ).

Table 6 shows the rise in mean serum ferritin level at 4 weeks which was also more in Group A as compared to Group B (123.80 vs 84.78mcg/L). Statistically, the rise was also highly significant ( $p<0.0001$ ).

Table 7 shows the adverse effects noted in the two groups. Only mild side effects were noted after administration of the drugs. None of the patients presented with more than one side effect.

In Group A, 12% patients had skin discoloration, while 6% each had headache and constipation. 4% had diarrhoea and 2% each had nausea, injection site reactions and vomiting. In Group B 12% patients complained of diarrhoea, 8% each had constipation and injection site reactions, 6% had vomiting, 6% each had nausea, constipation, abdominal pain and injection site reactions. 4% each had abdominal pain, headache, dysgeusia and skin discoloration.

**Table 4: Pre-treatment serum ferritin (mcg/L) of the patients.**

Serum ferritin (mcg/L)	Group A No. (%)	Group B No. (%)
0-9.9	14 (28.00)	14 (28.00)
10-19.9	25 (50.00)	25 (50.00)
20-29.9	11(22.00)	11(22.00)
Total	50 (100.00)	50 (100.00)
Mean±SD	14.09±6.05	14.74±5.82
Statistical inference	Unpaired t test value $t=0.54$ ; $p=0.58$ ; not significant	

Statistically, the rise was highly significant ( $p<0.0001$ ).

**Table 5: Rise in mean haemoglobin (gm/dl) level at 4 weeks.**

Variable	Hemoglobin (gm/dl)		Statistical inference (unpaired t test)
	Group A Mean±SD	Group B Mean±SD	
Rise at 4 weeks	1.79±0.47	1.06±0.11	$t=10.97$ ; $p<0.0001$ ; highly significant

**Table 7: Adverse drug reactions.**

Adverse drug reactions	Group A No. (%)	Group B No. (%)	Statistical inference
Diarrhea	2 (4.00)	6 (12.00)	Chi-square value=3.30 48; $p=0.69$ ; Not significant
Nausea	1 (2.00)	1 (2.00)	
Constipation	3 (6.00)	4 (8.00)	
Abdominal pain	0 (0.00)	2 (4.00)	
Injection site reactions (pain, swelling, burning, irritation)	1 (2.00)	4 (8.00)	
Headache	3 (6.00)	2 (4.00)	
Dysgeusia	0 (0.00)	2 (4.00)	
Skin discoloration	6 (12.00)	2 (4.00)	
Vomiting	1 (2.00)	3 (6.00)	
Hypersensitive reaction	0 (0.00)	0 (0.00)	
Hypertension	0 (0.00)	0 (0.00)	
Hot flushing	0 (0.00)	0 (0.00)	
Hypotension	0 (0.00)	0 (0.00)	
Total	17 (34.00)	26 (52.00)	

In Group A, adverse reactions were observed in 34% patients, while in Group B it was observed in 52% patients. However, the difference in number of episodes in the two groups was statistically not significant ( $p=0.69$ ). No anaphylactic reactions or any other serious side effects were noted after the infusions in either group.

**Table 8: Comparison of two groups according to the results obtained.**

Variable (Mean±SD)	Group A	Group B
Baseline hemoglobin (gm%)	8.45±0.64	8.40±0.64
Hemoglobin (gm/dl) rise at 4 weeks	1.79±0.47	1.06±0.11
Baseline serum ferritin (mcg/l)	14.09±6.05	14.74±5.82
Serum ferritin (mcg/l) rise at 4 weeks	123.80±16.03	84.78±10.53
Adverse drug reactions (%)	34	52

Table 8 sums up the comparison between the two groups. As is shown in the table, iron carboxy-maltose group leads to a higher rise in the haemoglobin and serum ferritin levels and lower incidence of adverse drug reactions as compared to the iron sucrose group.

## DISCUSSION

In the present study, the mean age of Group A was 26.46±3.58 years and mean age of group B was 24.64±2.87 years, which was comparable ( $p=0.006$ ) (Table 1). Metgud MC et al, conducted a study in the Gynae department of a hospital in Karnataka, India where the mean age was 25.33±3.53 in FCM group vs 24.85±4.18 years in Iron Sucrose group.<sup>8</sup> Joshi SD et al, conducted a similar prospective study on 100 antenatal patients in VIMS, Karnataka with the mean age group in the FCM group 22.56 years and 25.1 years in Iron Sucrose group, with the majority of patients belonging to the age group of 21-25 years of age.<sup>9</sup> The age group of 20-29 years is found to be more prone to anaemia probably because of increased demand, improper dietary habits, lack of health education and iron deficiency during the adolescence period. 44% of patients in Group A and 38% in Group B were primigravidae, while 56% of patients in Group A and 62% in Group B were multigravida. In the study conducted by Metgud MC et al, 56.86% of females were multigravida in FCM group and 76.9% in the iron sucrose group.<sup>8</sup> Higher incidence of anaemia in multigravida is because multiple pregnancies especially without proper spacing leads to consumption of iron stores without adequate time for replenishment.

Mean values of hemoglobin pre-infusion in Group A was 8.45±0.64gm/dl and in Group B 8.40±0.64gm/dl, the difference being statistically insignificant ( $p=0.69$ ) (Table 3). This is consistent with the study conducted by Metgud MC et al, where the pretreatment mean Hb was 8.70±0.84

gm/dL in FCM group while in IS group it was 8.82±0.84 gm/dL.<sup>8</sup> Mean serum ferritin of Group A was 14.09±6.05 mcg/L and that of Group B was 14.74±5.82 mcg/L, the difference being statistically insignificant ( $p=0.58$ ) (Table 4).

The rise in mean hemoglobin at 4 weeks in Group A was 1.79±0.47 and 1.06±0.11 in Group B which was highly significant ( $p$ -value <0.0001) (Table 5). These results were consistent with the study of Garg R et al, who found the mean increase in Hb after 4 weeks to be 2.48 gm/dL in FCM group and 2.10 gm/dL in IS group.<sup>10</sup> Similarly, Metgud MC et al, also reported higher rise in Hb in the patients receiving FCM (2.27 gm/dL) versus Hb in the patients receiving IS infusion (2.17 gm/dL).<sup>8</sup> Joshi SD et al, also found the mean increase in Hb after 4 weeks of treatment to be 2.09 in the FCM group and 1.82 in the IS group and Maheshwari B et al, found it to be 3.59gm/dL in the patients receiving FCM vs 2.34gm/dL in the patients receiving IS infusion.<sup>9,11</sup>

Rise in mean serum ferritin level at 4 weeks in Group A was 123.80±16.03 and in Group B was 84.78±10.53. Statistically, the rise was also highly significant ( $p<0.0001$ ) (Table 6). Boughton S et al, found the post transfusion rise of S. ferritin in their study to be 296 mcg/L in FCM group whereas it was only 105 mcg/L in the IS group after 4 weeks of treatment. Maheshwari B et al, found the rise in S. ferritin after 4 weeks to be only 22.54 mcg/L in case of FCM and 5.05 mcg/L in case of IS infusion i.e. more in case of FCM infusion.<sup>11-13</sup> Patel J et al, found the rise to be 9.4 mcg/L for patients transfused with FCM and 9.1 mcg/L for those who got IS after 2 weeks of treatment. Serum Ferritin is the measure of iron stores the body.<sup>13</sup> In present study authors found its rise to be more in case of FCM infusion.

In present study, adverse reactions were observed in 34% patients in Group A, while in Group B it was observed in 52% patients. Group A, 12% patients had skin discoloration, while 6% each had head-ache and constipation. 4% had diarrhea and 2% each had nausea, injection site reactions and vomiting. In Group B 12% patients complained of diarrhea, 8% each had constipation and injection site reactions, 6% had vomiting, 6% each had nausea, constipation, abdominal pain and injection site reactions. 4% each had abdominal pain, headache, dysgeusia and skin discoloration. Garg R et al, in their study found adverse effects in 16% of patients in FCM group and 20% of patients in IS group, the most common being pain at injection site (8%) in IS group and transient hypotension (4%) in FCM group, while Maheshwari B et al found the same in 28.96% of patients receiving FCM and 31.58% of patients receiving IS.<sup>10,11</sup> Boughton S et al, in their study found adverse effects in 16% of patients in FCM group and 34% of patients in IS group while Joshi SD et al found 14% adverse drug reactions in FCM group and 20% in IS group.<sup>9,12</sup> Hence, the incidence of side effects was less with FCM as compared to iron sucrose group.

Table 8 shows a comparison of both the drugs in terms of baseline parameters i.e. mean hemoglobin levels and mean serum ferritin taken before infusion and how they were affected post infusion of ferric carboxy maltose and Iron Sucrose along with the percentage of the adverse effects noted.

## CONCLUSION

Ferric carboxymaltose has shown to increase haemoglobin and serum ferritin levels significantly more than Iron Sucrose and has lesser incidence of adverse drug reactions making it a better choice for the treatment of iron deficiency anaemia in pregnant women.

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