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Original Research Article

Efficacy and safety of intravenous iron sucrose, ferric carboxymaltose and iron isomaltoside in gynaecological patients: a comparative study

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ABSTRACT

Background: Anaemia is a serious global public health problem that particularly affects young children, menstruating adolescent girls, pregnant and postpartum women. Parental iron therapy with iron sucrose or ferric carboxy maltose or iron isomaltoside results in faster and higher replenishment of iron stores with correction of Hb and ferritin levels and better patient compliance compared to oral drugs.
Methods: This was a prospective, randomized comparative study conducted over 18 months in Department of Obstetrics & Gynaecology, Hind Institute of Medical Science, Barabanki, Uttar Pradesh. Total of 87 female patients of age group 18-50 years with haemoglobin level of <10gm/dl and serum ferritin <100ng/dl in Gynaecology OPD and IPD were assigned to 3 groups of Iron Sucrose (IS) group, Ferric Carboxymaltose (FCM) group and Iron Isomaltoside (IIM) group. Each group included 29 women with a ratio of 1:1:1. Iron requirement was calculated by Ganzoni formula and parenteral iron was given intravenously. Baseline values of haemoglobin and serum ferritin was noted and repeated at the end of 4 weeks of therapy. The observed values were compared and analysed.
Results: The rise in haemoglobin and ferritin was higher with iron isomaltoside and ferric carboxymaltose (p value 0.000, statistically significant) when compared with iron sucrose group. However, rise was statistically not significant when compared between FCM and IIM group (for hemoglobin, p=0.32 and ferritin, p=8.18). The occurrence of adverse reactions was seen more commonly in iron sucrose but it was not found to be statistically significant.
Conclusions: The ability to deliver a high dose of iron within a short time, with single prick and less adverse effects make FCM and iron isomaltoside suitable for patients requiring quicker restoration of iron stores.

Keywords: Ferric carboxy maltose, Haemoglobin, Iron deficiency anaemia, Iron isomaltoside, Iron sucrose, Serum Ferritin

INTRODUCTION

The prevalence of anaemia in India according to National Family Health Survey 5 (NFHS 5) is 57% among all women of age between 15-49 years. The prevalence of anaemia in Uttar Pradesh among women aged between 15-49 years is 50.4%.[1] In the human body, most of the iron is part of the erythrocyte haemoglobin, while the rest is mainly stored in macrophages and hepatocytes. Much of the body's iron stores are required to fuel erythropoiesis in order to ensure sufficient red blood cell production to transport oxygen to all tissues. Daily intake of iron is 10-20 mg/day of which only 10% (Fe++) is absorbed by enterocytes. Once inside the enterocyte, iron is either stored as ferritin or transported across the basolateral membrane into the blood, depending on the iron requirements of the body.

Ferritin is an important iron-protein complex which is found in almost all tissues, with highest levels seen in the liver and spleen. Small quantities are also found in blood, and this is proportionate to iron stores in the body. Studies

on healthy individuals have shown that serum ferritin reflect the iron stores in the body. It is therefore used in clinical practice as a marker to assess iron stores.[2]

Oral iron therapy is currently the treatment of choice for the majority of patients with IDA but it has demerits like poor absorption, poor compliance and gastro-intestinal side effects.[3] By contrast, parenteral iron compounds are first taken up by macrophages and then released into the bloodstream overcoming the effects of hepcidin so parenteral iron helps in restoring iron stores faster and more effectively than oral iron.

Iron sucrose

The iron sucrose molecule is a polymer consisting of two main molecules; sucrose and an iron (III) hydroxide. Following intravenous administration, it is dissociated into iron and sucrose by reticuloendothelial system and iron is transferred from the blood into pool of iron in the liver and bone marrow. It is then sequestered by Ferritin into a non-ionic form from which iron is easily available. No test dose is required. The dose of 100 mg is diluted with 100 ml of normal saline prior to infusion and to be infused over a period of at least 15 min (6mg/min). 200 mg/day given on alternate days until the required dose is infused not exceeding 600 mg per week. Supplied as 5 ml vial with 100 mg of elemental iron (20 mg/ml).

Ferric carboxymaltose

Parenteral iron complex consisting of colloidal ferric III hydroxide core stabilized by carbohydrate shell so there is controlled delivery of iron to cells of reticuloendothelial system and subsequent delivery to the iron binding proteins ferritin and transferrin. FCM has low immunogenic potential, dextran free product and not predisposed to anaphylactic reaction [4] It is administered by slow intravenous infusion with maximum dose of 1000 mg/week/dose diluted in 0.9% normal saline and infused over 15 minutes. Stored above 30°C.

Iron isomaltoside

The isomaltoside 1000 component of ferric derisomaltose consists of 3-5 glucose units with an average molecular weight of approximately 1000 Da.[5] Linear carbohydrates with a molecular weight of less than 1300 Da have been shown to not induce immune responses in vivo and potentially leads to generation of less oxidative stress and less immunological toxicity. It should be given through slow intravenous infusion with a maximum single dosage of 20 mg/kg actual body weight. A rapid infusion (doses up to 1,000 mg must be administered over more than 15 minutes and doses exceeding 1,000 mg must be administered over 30 minutes or more). The vials should be stored below 30°C.

METHODS

This was a cross sectional, randomized comparative study conducted June 2023 to Dec 2024 in Department of Obstetrics & Gynaecology, Hind Institute of Medical Science, Barabanki, Uttar Pradesh. Sample size was calculated by the following statistical method.

Total of 87 female patients of age group 18-50 years with haemoglobin level of <10 gm/dl and serum ferritin <100 ng/dl in Gynaecology OPD and IPD were included in the study. Women who are known case of anaemia other than iron deficiency anaemia like sickle cell anaemia, thalassemia, aplastic anaemia, anaemia of acute haemorrhage or anaemia of chronic disease and who have acute febrile illness and septicaemia were excluded. Detailed history was taken and women with recent (<3 months) history of upper GI bleed or with recent (1 month) administration of blood transfusion or intravenous iron infusion or erythropoietin were excluded from the study. Women with known history of hypersensitivity with intravenous iron preparations were excluded. They were assigned to 3 groups of Iron Sucrose (IS) group, Ferric Carboxymaltose (FCM) group and Iron Isomaltoside (IIM) group which included 29 women in each group with a ratio of 1:1:1. Baseline values of Haemoglobin and serum ferritin was noted on Day 1. Iron requirement was calculated by Ganzoni formula:

Iron deficiency (mg) = [target Hb (g/dl) – actual Hb (g/dl)] × body weight (kg) × 2.4 + stored iron (500 mg)

Vitals before the therapy were recorded and documented, after which the required dose of iron was given intravenously as per the protocol. Group A were administered IV iron sucrose as 200 mg in 100 ml 0.9% normal saline over 15-20 min on alternate days till required dose was completed. Patients in the FCM group were administered required dose by diluting in 100 ml 0.9% NS over 15 minutes (maximum dose of 1000mg in single sitting in patient with weight 35-70 kg.). Subsequent doses (if needed) were planned on day 7 and day 14 and doses were rounded off to the nearest 100 mg. Patients in the IIM group received the calculated dose diluted in sterile 0.9% NS. The dose of <1000mg was infused over 15-30 minutes and >1000 mg was given in 30-45 minutes. The maximum dose should not exceed 1500 mg per infusion.

Patients was monitored closely for any minor and major adverse changes during the therapy. Haemoglobin and serum ferritin was repeated at the end of 4 weeks. The observed values were compared and analysed.

Statistical analysis

The statistical analysis was done using SSP26 and advance excel. Qualitative variables were presented in numbers and percentage while quantitative were presented as mean and standard deviation. Chi Square test was used for test

significance for categorical variable whenever any expected cell will <5 then Fisher-Exact test was used and quantitative variable by T-Test and Anova was used for mean comparison and p value <0.05 was considered as statistically significant.

RESULTS

Estimation of rise in haemoglobin

The data is found to be statistically significant (p=0.000) which means all three parenteral iron preparations were efficient in increasing haemoglobin level on day 28.

Table 1: Mean age of patients according to groups.

Groups	N	Mean age	Std. deviation	Minimum	Maximum	p value
Sucrose	29	35.04	4.780	19	47	1.378, 0.258# (NS)
Isomaltoside	29	36.72	3.963	23	45	
FCM	29	34.66	4.228	26	48	
Total	87	34.15	4.351	19	48	

NS#: non significance

Table 2: Distribution of the patients according to parity.

Parity	Patients (n=87)	Percentage
P0	10	11.5
P1	19	21.8
P2	25	28.7
P3	18	20.7
P4 and above	15	17.2

Table 3: Demographic profile of the patients according to their socioeconomic status (as per Kuppuswany scale).

Socioeconomic status	Patients (n=87)	Percentage
Upper class	3	3.4
Upper middle class	12	13.7
Lower middle class	47	54
Upper lower class	20	22.9
Lower class	5	5.7

Comparison of rise of hemoglobin in all groups

The figures presents the haemoglobin (Hb) levels on the 1st day and 28th day after iron infusion among three groups: sucrose, isomaltoside, and FCM. A one-way ANOVA test was conducted to determine if there were statistically significant differences in Hb levels among the three groups. The results indicated an F-value of 5.065 and a p value of 0.03, demonstrating a significant difference in Hb levels on day 28 between at least two of the groups (p<0.05).

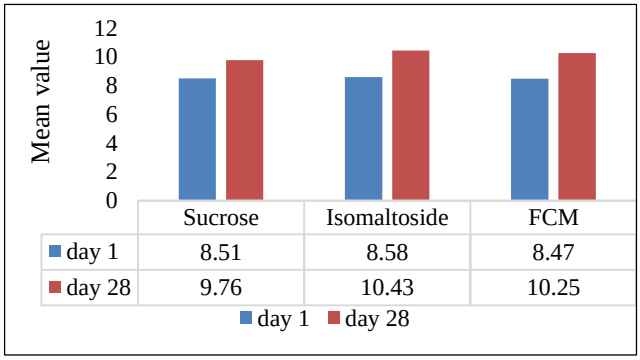

Figure 1: Comparison of rise in haemoglobin in three groups.

Comparison of rise in mean haemoglobin in 3 groups

Figure 2 shows rise in mean haemoglobin among three groups on day 1 and day 28 of therapy. The rise in haemoglobin was found to be statistically significant when compared between IS and FCM group (p=0.001) and between IS and IIM group (p=0.000). The rise in haemoglobin was statistically non-significant between IIM and FCM group (p=0.960).

Table 4: Estimation of rise in haemoglobin among 3 groups on day 1 and day 28.

Groups	Day	N	Mean Hb	Std deviation	t, P* value
Sucrose	Day1	29	8.51	0.586	-17.990 0.000 (S)
	Day 28	29	9.76	0.667	
Isomaltoside	Day 1	29	8.58	0.858	-16.002 0.000 (S)
	Day 28	29	10.43	0.854	
FCM	Day 1	29	8.47	0.853	-21.647 0.000 (S)
	Day 28	29	10.25	0.716	

S: significance

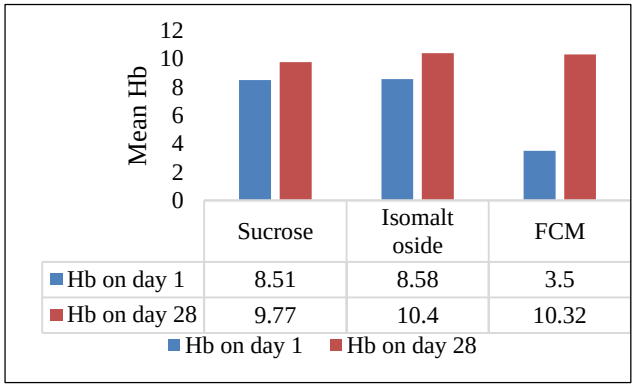

Figure 2: Comparison of change in Hb level with different groups.

Estimation of rise in serum ferritin

The data is found to be statistically significant (p=0.000) which means all three parenteral iron preparations were efficient in rising serum ferritin on day 28.

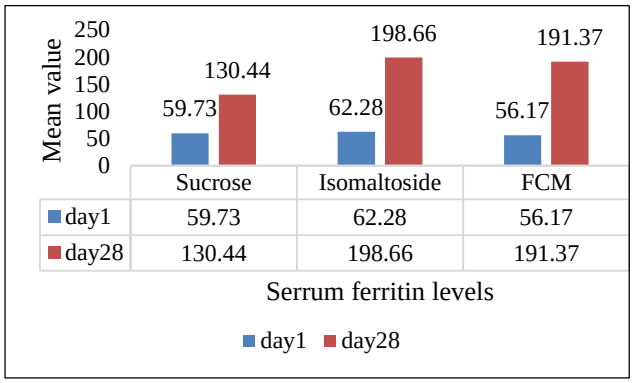

Figure 3: Comparison of serum ferritin level on day 1 and day 28 between the groups.

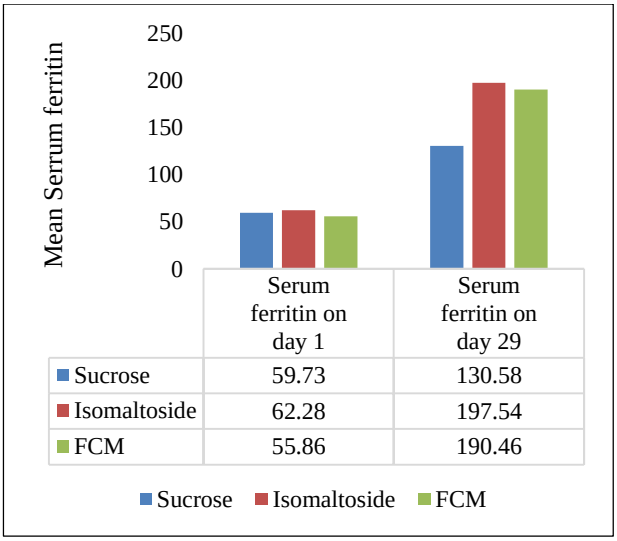

Figure 4: Comparison of rise in mean value of serum ferritin in 3 groups.

Comparison of rise of ferritin in all groups

The differences using post hoc tests to compare each pair of groups individually, revealed significant differences in serum ferritin levels between sucrose vs. isomaltoside (p = 0.000) and sucrose vs. FCM (p = 0.000), but not between isomaltoside and FCM (p = 0.905). Overall, isomaltoside and FCM resulted in higher serum ferritin levels compared to sucrose on day 28.

Adverse reactions in various groups

Though the adverse reactions were seen more commonly in group I but it was not found to be statistically significant.

Table 5: Types of adverse reaction in IS, IIM and FCM groups.

Adverse reaction	Groups								Chi-square, p value
	Sucrose		Isomaltoside		FCM		Total		
	Count	%	Count	%	Count	%	Count	%	
Yes	6	21.4	3	10.3	3	10.3	12	14.0	1.780, 0.467* [NS]
No	23	78.6	26	89.7	26	89.7	74	86.0	
Total	29	100.0	29	100.0	29	100.0	86	100.0	

DISCUSSION

As per WHO, Iron Deficiency Anaemia (IDA) is the most common nutritional deficiency in the world, with 30% of the population being affected with this condition.[6] Due to limitations of older parenteral iron preparation, search of novel drug resulted in iron sucrose and latest is ferric carboxy maltose and iron isomaltoside. Blood transfusions are usually reserved for most severe cases and life-threatening situations.

Increase in haemoglobin

The study found a significant increase in haemoglobin levels with all three parenteral iron preparations (p=0.000), consistent with previous researches.

At 4 weeks, mean Hb levels were 9.77±0.692 (IS) and 10.32±0.668 (FCM) (p=0.009). Other studies, such as those by Sharma et al, also showed FCM's superiority over IS with statistically significant improvements.[9,8] In the

present study, the overall increase in mean Hb at the end of 4 weeks was 1.21 g/dl in IS group and 1.79 g/dl in IIM group (p=0.000) which was statistically significant. Derman et al showed increase in Hb 2.83 g/dL in the iron isomaltoside group and 2.34 g/dL in the iron sucrose group (p=0.000) after the treatment of iron deficiency anaemia with intravenous Iron sucrose and IIM respectively.[10] When compared the rise of mean Hb in IIM and FCM, showed rise in Hb of 1.79 g/dL in the IIM group (p=0.000) and 1.75 g/dL in the FCM group (p=0.000) found to be statistically non-significant (p=0.960) as found in a similar study conducted in 2023 by Harikrishnan et al found mean increase of haemoglobin was 3.1g/dL and 3.64 g/dL of Hb in IIM and FCM group respectively (p =0.32).[11] They concluded that the safety and efficacy comparison trial showed no statistically significant difference between the two parenteral preparations.

Increase in ferritin

The increase in serum ferritin was statistically significant in all three parenteral iron preparations (p=0.000).

In this study, the mean rise in serum ferritin at 4 weeks was 72.13±23.484 in the IS group, 134.77±35.946 in the IIM group, and 131.08±32.337 in the FCM group. Ferritin levels increased significantly in the IS group (59.729±22.29 to 130.58±38.02) and FCM group (55.862±22.41 to 190.46±41.96), with p=0.000. These findings align with studies by Basha et al, Naqash et al, and Derman et al, showing statistically significant rises in ferritin levels with FCM and IIM compared to IS.[8,10,12] In the IIM group, ferritin rose from 62.27±21.31 to 197.54±45.733, consistent with prior research (p=0.000). The rise in serum ferritin compared between IIM and FCM group was statistically non-significant (p=0.818) in our study which was consistent with similar study conducted by Harikrishnan et al, with p value of 0.76.[11]

Adverse reactions

In this study, adverse reactions occurred in 21.4% (IS) and 10.3% (IIM and FCM) groups, with chills (50%) and headache (41.7%) being the most common. These findings align with previous studies by Derman et al, Joshi et al, and Kennedy et al, which reported higher adverse effects in IS compared to FCM and IIM.[10,13,14] Notably, no serious hypersensitivity reactions were observed in this study.

This study has few limitations. The limited sample size limits the generalisability of data. Additionally, its single centre nature might limit variety of clinical presentations and patient demographics, potentially impacting study's external validity. The limited 4 weeks follow up period may not have been long enough to record long term or potential complications that could arise beyond this timeframe.

CONCLUSION

This study concludes that, the rise in Hb and ferritin was statistically significant in all three groups after intravenous iron infusion, However, the improvement was higher in iron isomaltoside and ferric carboxy maltose group compared to iron sucrose group. Administration of high dose of ferric carboxy maltose (max 1000 mg) and iron isomaltoside (max 1500mg) in single visit reduces the number of infusions, pricks and costs compared to iron sucrose. The ability to deliver a high dose of iron within a short duration of time without any serious adverse effects makes ferric carboxy maltose and iron isomaltoside superior for patients requiring quicker replenishment of iron stores. Our study further strengthens the clinical trial findings of good safety and efficacy of ferric carboxy maltose and iron isomaltoside in patients with iron deficiency anaemia in real-world clinical practice.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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