ORIGINAL RESEARCH

Comparitive study of the efficacy and safety of Iron isomaltoside versus Iron sucrose in Iron deficiency anaemia of pregnancy

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Received: 08 June, 2023 Accepted: 13 July, 2023

ABSTRACT

Background: Anaemia is the most common medical disorder during pregnancy.[1] About 36.5 % of pregnant women worldwide are anaemic. The prevalence of Iron deficiency anaemia in pregnancy in India ranges from 23.6%-61.4%. Therefore to handle this burden new iron formulations need to be evaluated, including parentral forms as many patients are noncompliant and intolerant to oral iron. **Materials & Methods:** a prospective, comparative, open-label, randomized, single center trial conducted in the post graduate department of Obstetrics and Gynaecology, S.M.G.S Hospital, GMC Jammu over a period of one year with the aims of comparing the efficacy , safety and tolerability of iron isomaltoside vs iron sucrose in pregnant females suffering from iron deficiency anaemia. 100 pregnant females between gestational age of 28- 36 weeks, Hb 7-9.9 g/dl, serum ferritin levels <30 mcg/l were selected and divided into 2 groups of 50 each after 1:1 randomisation and labelled as Group A - Iron isomaltoside group and Group B-Iron sucrose group. Haemoglobin levels (g/dl) and serum ferritin (mcg/L) were checked pretreatment and at 2 weeks and 4 weeks of treatment to compare the 2 groups. Side effects were also observed for and statistical analysis was done using appropriate tests. **Results:** Post treatment, at 2 weeks mean rise in Hb was 0.9 ± 0.3g/dl vs 0.3 ± 0.14 g/dl ($p<0.0001$) and at 4 weeks, 1.64 vs 1.03g/dl) ($p<0.0001$) in Group A & B. At two weeks post-treatment, mean total serum ferritin level was significantly higher in Group A as compared to that of Group B (157 vs 86 mcg/L ; $p<0.0001$).Similarly after four weeks post-treatment, mean total serum ferritin level was also significantly higher in Group A as compared to that of Group B (133.86 vs 83.6 mcg/L; $p<0.0001$). Adverse reactions were observed in 16% patients in each group. **Conclusion:** Iron Isomaltoside should be used as a first line treatment to bring about a revolution in the management of iron deficiency anaemia of pregnancy as it is safe and more efficacious than Iron sucrose

Key Words: Iron Isomaltoside, Iron sucrose

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INTRODUCTION

Anaemia is the most common medical disorder during pregnancy.[1] About 36.5 % of pregnant women worldwide are anaemic. The prevalence of Iron deficiency anaemia in pregnancy in India ranges from 23.6%-61.4%.[2] It is responsible for 40% of maternal deaths in developing countries and causes maternal complications like pre-eclampsia, intercurrent infections, preterm labour, heart failure, uterine inertia, post partum hemorrhage, cardiac failure, shock, puerperal sepsis, subinvolution of uterus, failing lactation, puerperal venous thrombosis, pulmonary embolism. It also causes adverse reproductive outcomes such as preterm delivery, low birth weight infants, IUGR, IUD, low apgar score, decreased iron stores for the baby, which may lead to impaired development, poor growth trajectory in infancy, childhood and adolescence.[3,4]

WHO defines anaemia in pregnant females as Hb <11g/dl and Haematocrit <33% and grades it as mild(Hb=10.0-10.9g/dl), moerate(Hb=7.0 - 9.9g/dl) and severe(Hb<7 g/dl). The gold standard to detect iron deficiency is serum ferritin value, serum concentration below 15 mcg/L indicates iron depletion in all stages of pregnancy.

FOGSI recommends administration of parenteral iron therapy to patients who are unable to tolerate oral iron, who are poorly or non compliant to oral iron and patients who need rapid restoration of iron stores.[5] Current intravenous iron formulations include ferric gluconate, iron sucrose, iron polymaltose, ferric carboxymaltose and iron isomaltoside. Iron Sucrose

and Iron Isomaltoside are dextran free intravenous iron alternatives.

Iron sucrose is widely used with a higher bioavailability and a good safety profile in pregnancy.[6] Its main disadvantage is that it cannot be administered in a higher dose because of the risk of toxicity , requires frequent visits to the hospital to complete dose and puts a heavy burden on the hospital.

Iron isomaltoside is a new i.v. iron preparation, licensed since 2009 in the UK and Europe, approved by Drug Controller General of India (DCGI) in 2013 and by U.S. Food and Drug Administration (FDA) in 2020 for its use in IDA in adult population and in second and third trimester of pregnancy. Following I.V administration, iron isomaltoside is rapidly taken up by the cells of reticuloendothelial system followed by its breakdown to release free iron and isomaltoside.[7]It's only contraindications are known hypersensitivity to iron or any of its excipients, any iron overload or disturbance in utilization of iron and the first trimester of pregnancy.

MATERIALS AND METHODS

This study is a prospective, comparative, open-label, randomized, single center trial conducted in the post graduate department of Obstetrics and Gynaecology, S.M.G.S Hospital, GMC Jammu over a period of one year from November 2021- October 2022 after approval from the hospital ethics committee. With the aims of comparing the efficacy , safety and tolerability of iron isomaltoside vs iron sucrose in pregnant females suffering from iron deficiency anaemia.100 pregnant females attending OPD or admitted in hospital between gestational age of 28-36 weeks, Hb 7-9.9 g/dl, serum ferritin levels <30 mcg/l were selected and divided into 2 groups of 50 each after 1:1 randomisation and labelled as Group A - Iron isomaltoside group and Group B-Iron sucrose group.

Females with age <18 years , gestational age <28 weeks and >36 weeks, not willing to give informed consent, severe anaemia Hb<7 g/dl, allergic to IV iron compounds, thalassemia, Hemochromatosis, vitamin B12 deficiency, recent surgery or bleeding, Hepatitis B/C , AIDS and other medical or systemic disease were excluded from the study.

Detailed medical history taken, lab evaluation of Hb, CBC, peripheral smear, serum ferritin, serum iron and serum TIBC was done, prior deworming done and oral iron stopped 48 hours prior to theraphy and iron demand calculated using Ganzoni formula i.e Total iron dose (mg iron) = body weight(kg) x(target- actual Hb)(g/dl) x2.4 + iron for iron stores(mg iron)*

*Iron stores: body weight <35 kg = 15mg/kg body weight; body weight >35kg= 500 mg.

Iron sucrose was given by IV infusion according to deficit calculated, which was rounded up to the nearest multiple of 100. 200 mg of elemental iron diluted in 200 ml of normal saline 0.9% was the maximum dose given as slow IV infusion over a period of 30 minutes in this study and repeated on alternate days until the required dose was administered.

Iron isomaltoside was also given by IV infusion according to deficit calculated, which was rounded up to the nearest multiple of 100. Maximum single dose of 1000mg (10ml) diluted in 250 ml of sterile 0.9% normal saline was given over a period of 30 min, not exceeding 1000 mg/week or 15 mg of iron/kg body weight.

Before starting the infusion , vitals i.e. BP and pulse recorded ,emergency drugs and oxygen were made available. Repeat vitals after 10 minutes, 20 minutes and 1 hour of infusion were taken and foetal heart rate was assessed before and after the infusion. After infusion all the minor and major local and systemic side effects were looked for and documented. Haemoglobin levels (g/dl) and serum ferritin (mcg/L) were checked at 2 weeks and 4 weeks of treatment.

Data was analysed using Chi-square test/ Fischer's exact test, Mann Whitney U test, unpaired 't' test as per variables.

RESULTS

Mean age of Group A was 27.16 years and mean age group of Group B was 26.16 which was comparable (p=0.2). Mean gestation age of Group A was 31.86 and that of Group B was 32.86, the difference being comparable (p=0.06). 38% of patients in Group A and 44% of patients in Group B were primigravidae, while 62 % of patients in Group A and 56% of patients in Group B were multigravidae, both groups being statistically comparable (p=0.7). 86 % of patients from Group A and 90 % of patients in Group B were from middle class. Statistically, there was no significant difference (p=1.2).

Mean BMI in both the groups was comparable (21.9 vs 22.18kg/m2 ; p=0.66). 70% of patients in Group A and 72% in patients B were vegetarian according to their dietary status. The relation between the two groups was statistically not significant (p=1.2). 48% of patients in Group A and 40 % of patients in Group B had a regular intake of iron capsules while 52% of patients in Group A and 60% of patients in Group B did not take their iron supplements regularly. Statistically, the difference was not significant (p=1.2). These above mentioned parameters have been described below in table no 1

Table no 1: Sociodemographic distribution in group A & B

S.N.O	PARAMETER	GROUP A (n=50)	GROUP B (n=50)	p Value
1	Mean age(years)	27.16±4.74	26.16±4.44	0.248
2	Mean Gestational age(weeks)	31.86±2.90	32.86±2.26	0.06

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3	Gravidity	Primi	19	22	0.7
		Multi	31	28	
4	Socioeconomic status	Lower middle	7	5	1.2
		middle	43	45	
5	Mean BMI		21.9±1.80	22.18±2.03	0.66
6	Dietary status	Veg	35(70%)	36(72%)	1.2
		Non veg	15(30%)	14(28%)	
7	Oral Iron intake	Regular	24(48%)	20(40%)	1.2
		Irregular	26(52%)	30(60%)	

Patients with haemoglobin level of moderate range (7-9.9 g/dl) were included in the study. Most patients in group A (82%) and in group B (84%) had their haemoglobin in the range of 8 to 9 g/dl. Mean values of pretreatment haemoglobin in both the groups were comparable statistically (p=0.52) as shown in Table no 2. Mean pre treatment serum ferritin of Group A was 17.58+_4.8 mcg/L and that of Group B was 17.79 +_4.09 mcg/L, the difference being statistically not significant (p=0.8). 66 % of patients in Group A and 70 % of patients in Group B had their pretreatment serum ferritin values less than 20 mcg/L

Table no 2: Hemoglobin values in group A& B

PRE-TREATMENT Hb(g/dl)	Group A No. (%) (n=50)	Group B No. (%)(n=50)
7-7.9	07(14)	06(12)
8-8.9	41(82)	42(84)
9-9.9	02(4)	02(4)
MEAN Hb(g/dl)	8.316+_0.3946	8.366+_0.376
p=0.52		

After 2 weeks of treatment rise in haemoglobin in Group B patients was from 0.5 to 1.99 g/dl only, while in Group A patients rise was significantly more from 1.0 to 2.99 g/dl, with the mean rise in Hb (at 2 weeks) of 0.9 +_0.32g/dl in Group A and of 0.3 +_0.14 g/dl in group B, this difference was highly statistically significant (p<0.0001). Similarly after 4 weeks of treatment rise in haemoglobin in Group B patients was from 0.5 to 1.99 g/dl only, while in Group A patients rise was significantly more from 1.0 to 2.99 g/dl, with the mean rise in Hb (at 4 weeks) of 1.64 +_0.3g/dl in Group A and of 1.03 +_0.27 g/dl in group B. Statistically, the rise was also highly significant (p<0.0001).

After 2 weeks of treatment rise in serum ferritin (mcg/L) in Group A were between100 to 199.99 mcg/L with a mean rise of 157±18.72 mcg/L, whereas in Group B rise was seen between 50 to 149.99 mcg/L with a mean rise of 86±16.7 mcg/L, the difference being statistically significant (p<0.0001). Similarly after 4 weeks of treatment rise in serum ferritin (mcg/L) in Group A were between100 to 199.99 mcg/L with a mean rise of 133.3±15.2 mcg/L, whereas in Group B rise was seen between 50 to 149.99 mcg/L with a mean rise of 83.6±17.4 mcg/L, the difference being statistically significant (p<0.0001). These findings have been mentioned in table no 3.

Table no 3: Pretreatment and post treatment indices in group A & B

VARIABLE (MEAN+_SD)	GROUP A	GROUP B
BASELINE HAEMOGLOBIN(g/dl)	8.316+_0.39	8.366+_0.376
HAEMOGLOBIN RISE (g/dl) AT 2 WEEKS	0.9+_0.32	0.3+_0.14
HAEMOGLOBIN RISE (g/dl) AT 4 WEEKS	1.64+_0.39	1.03+_0.27
BASELINE SERUM FERRITIN (mcg/L)	17.58+_4.88	17.79+_4.09
SERUM FERRITIN (mcg/L) AT 2 WEEKS	157+_18.72	86+_16.7
SERUM FERRITIN (mcg/L) AT 4 WEEKS	133.3+_15.2	83.6+_17.4
ADVERSE DRUG REACTIONS (%)	16	16

Only mild side effects were noted after the administration of the drugs. None of the patients presented with more than one side effect. However, 8 out of 50 patients in each group had adverse reactions ,therefore not statistically significant (p=0.6). No serious anaphylactic reactions or any other serious side effects were noted after the infusions in either group. The different side effects seen in the patients are mentioned below in Table no 4

Table no 4: Side effects in group A & B

ADVERSE DRUG REACTION	GROUP A NO(%) (n=50)	GROUP B NO(%)(n=50)	P value
Nausea	2(4%)	2(4%)	
Hypersensitivity reaction	1(2%)	1(2%)	
Vomitting	2(4%)	1(2%)	

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Injection site reactions(pain, swelling, irritation)	1(2%)	2(4%)	0.6
Headache	1(2%)	2(4%)	
Hot flushing	1(2%)	0(0%)	
Total	8(16%)	8(16%)	

DISCUSSION

In the present study, the mean age group of Group A was 27.16 ±4.74 and mean age group of Group B was 26.16±4.44, which was comparable (p=0.24) **.** Wesstrom J et al., (2020) conducted a similar study in maternity ward of Falu Hospital where the mean age of the patients was 29.2 years for the patients receiving Iron Isomaltoside and 29.1 for the patients receiving Iron Sucrose.[8] Mean age of the patients included in the study conducted by Holm C et al., (2019) was 32 years for Iron Isomaltoside group and 33 years for oral Iron group.[9]

In the present study, mean gestational age of Group A was 31.86+_2.90, while that of Group B was 32.86+_2.26, the difference being comparable (p=0.06). In the study conducted by Wesstrom J et al.,(2020), pregnant females from the beginning of the second trimester until a few days before delivery were identified.[8]

Most of the patients in our study were primigravida, belonged to middle class and had normal body weight in both the groups. 80 % of patients in Group A and 76% of patients in Group B ranging had BMI between 20.1-24.9 kg/m^2 This may be seen because of the high incidence of anaemia in adolescent girls of Indian setup, when iron stores are already deficient then they manifest as anaemia in their pregnancy.

Majority of the patients in our study were Vegetarian (about 70%) showing that dietary deficiency is one of the major cause of anaemia in our setup. Also the compliance of the patients in oral intake of the iron was poor with regular intake of iron seen in only 48% of patients in Group A and in Group B it was 40% .

Overall in our study we observed that mean rise in hemoglobin and ferritin either at end of 2 weeks or 4 weeks , was more after administration of Iron Isomaltoside in comparison to iron sucrose. At two weeks post-treatment, mean rise in Hb was 0.9 ± 0.3g/dl in Group A and 0.3 ± 0.14 g/dl in Group B. At four weeks post-treatment also, total rise in mean haemoglobin level were 1.64 vs 1.03g/dl in the two groups. the rise being highly significant statistically. At two weeks post-treatment, mean total serum ferritin level was 157 vs 86 mcg/L and at 4 weeks post treatment it was 133.86 vs 83.6 mcg/L in Group A as compared to Group B. Statistically, the rise was highly significant.

The results of our study are consistent with the study conducted by Derman R et al(2018), wherein for all the biochemical efficacy parameters, faster and/or greater improvements were found with iron isomaltoside.[10] IIM was more effective than iron sucrose in achieving a rapid improvement in Hb. Also analysis showed statistically significantly higher change from baseline in serum ferritin concentration in the iron isomaltoside group compared to the iron sucrose group at all time points.

In the study conducted by Auerbach M et al(2019), the increase in Hb concentration from baseline to weeks one and two was statistically significantly greater for IIM compared with IS.[11] The increase in serum ferritin from baseline to weeks one and two was statistically significant greater for IIM compared with IS.

However due to limited studies available on the topic at present, detailed evaluation of the efficacy and safety of Ironisomaltoside in Iron deficiency anaemia of pregnancy is needed.

CONCLUSION

Iron isomaltoside appears as an interesting option to apply high dose of iron in a single sitting, over a shorter time period, without much safety concerns. These properties make it superior to Iron Sucrose in terms of efficacy and safety. Its only side effect is its high cost which is very well compensated when the number of visits or days of admission in the hospital, patient comfort and convenience and institutional resource utilization are taken into account. It is thus recommended that Iron Isomaltoside should be used as a first line treatment to bring about a revolution in the management of iron deficiency anaemia of pregnancy to decrease the burden of the disease on our health setup. It is for us to rise to the challenge to conquer this malaise.

CONFLICTS OF INTEREST

None

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