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COMPARISON OF EFFICACY AND SAFETY OF INTRAVENOUS FERRIC CARBOXYMALTOSE VERSUS IRON SUCROSE IN THE TREATMENT OF IRON DEFICIENCY ANAEMIA OF PREGNANCY

Obstetrics & Gynaecology

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ABSTRACT

Background: Iron deficiency anaemia is the most common anaemia diagnosed during pregnancy. The objective of this study was to compare the efficacy and safety of intravenous FCM and intravenous iron sucrose during pregnancy for the treatment of iron deficiency anaemia.

Methods: This study was conducted in the Department of Obstetrics and Gynecology Sher-i-Kashmir institute of medical sciences , Soura , Srinagar Kashmir over a period of 1 year. 100 pregnant females with haemoglobin (Hb) in the range 7-9.9 g/dl between 28 to 36 week gestation, were selected randomly out of which 50 were administered FCM (Group A) and 50 were administered Iron Sucrose (Group B). Hb and serum ferritin were assessed 2 weeks and 4 weeks after treatment and side effects of each drug was studied.

Results: The rise in mean Hb level at 2 weeks and 4 weeks in FCM group was significantly higher as compared to Iron Sucrose group (1.09 versus 0.52 g/dl and 1.80 versus 1.09 g/dl, respectively). Similarly, the rise in mean serum ferritin level at 2 weeks and 4 weeks was more in FCM as compared to Iron Sucrose group (144.25 vs 95.84 mcg/L and 121.31 vs 84.46 mcg/L, respectively). The adverse reactions were observed in 30% of patients in FCM group and 48% patients in iron sucrose group.

Conclusions: Ferric carboxymaltose was found to be more safe and efficacious as compared to iron sucrose.

KEYWORDS

Anaemia, Ferric carboxymaltose, Haemoglobin, Iron sucrose, Serum ferritin

INTRODUCTION

Anaemia is the most common haematological abnormality diagnosed during pregnancy. It is a global public health problem . The prevalence of Iron deficiency anaemia (IDA) in pregnancy in India ranges from 23.6%-61.4%.1 Besides mortality it also causes increased perinatal mortality and morbidity but remains a major preventable cause of poor perinatal and maternal outcome.

As per WHO, anaemia during pregnancy is defined as haemoglobin concentration of less than 11 gm% and haematocrit less than 33%.2 The centre of disease control and prevention defined anaemia as less than 11gm/dl in first and third trimester and less than 10.5 gm/dl in second trimester.3 Progression from iron deficiency to IDA in pregnancy is common, due to the increased demand for iron during pregnancy (about 1000 mg), required to support maternal haemoglobin mass expansion as well as the growing fetus and placenta.4 Diet alone cannot supply such high amounts of iron, because of poor bioavailability.5 All this makes iron supplementation, a necessity in all pregnant women.

Oral iron is the preferred choice of administration for mild to moderate anaemia, but has limitations like gastrointestinal adverse effects ,long course of therapy, non compliance and even in compliant patients, limited intestinal absorption .Therefore fails to compensate for the iron needs.6 Also, oral therapy is not sufficient for treatment of moderate to severe anemia, especially in the late second and third trimester. Parenteral therapy promises a better response in these patients and can obviate the need for blood transfusions in the antenatal and postpartum period .7 The intramuscular iron formulation is available but complications like pain, skin discolouration, abscess formation, allergic reaction, fever, lymphadenopathy and rarely anaphylaxis limits its use. Iron sucrose is widely being used all over the world with a good safety profile in pregnancy.8 Main disadvantage of intravenous (IV) iron sucrose is that it cannot be administered in a higher dose because of the risk of toxicity associated, thus requiring frequent visits to the hospital which puts a heavy burden on the hospital resources.9 With the challenge of optimizing iron delivery, new intravenous complexes have been developed in the last few years.10 A very good example of this is Ferric carboxymaltose (FCM). Intravenous Ferric Carboxy maltose is a novel iron complex which consists of a ferric hydroxide core stabilized by a carbohydrate shell. Its properties like near neutral pH, physiological osmolarity and increased bioavailability permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid session (15-minute infusion) without the requirement of a test dose.11 It has a very low immunogenic potential and therefore not predisposed to anaphylactic reactions.

Despite the high incidence and burden of disease associated with anaemia, there is paucity of good quality trials concerning the use of FCM in pregnancy.11 The present study was conducted to evaluate the efficacy and safety of intravenous Ferric Carboxymaltose versus intravenous Iron Sucrose in the treatment of iron deficiency anaemia of pregnancy.

METHODS

This study was conducted in the post graduate Department of Obstetrics and Gynaecology, Sher-i-Kashmir institute of medical sciences , soura ,Srinagar. over a period of one year from November 2017 to November 2018 after approval from the hospital ethical committee. 100 pregnant females who met the inclusion criteria were considered for this study.

Inclusion criteria

- Gestational age 28-36 weeks
- Haemoglobin level between 7-9.9 g/dl (moderate anaemia)
- Serum ferritin <30 mcg/L.

Exclusion criteria

- Pregnancy < 28 weeks period of gestation.
- Prior history of blood transfusion or anticipated need for blood transfusion during the study
- History of any disease associated with iron overload
- Multiple pregnancy
- Known history of hypersensitivity to any iron preparations
- Recent history of any significant bleeding/surgery (within three months prior to screening)
- hypothyroidism
- Serious medical condition or any uncontrolled systemic
- Known case of Hepatitis B/C infection or of acquired immune deficiency syndrome (HIV/AIDS)
- Evidence of any significant congenital anomaly on ultrasound

Iron requirement was calculated according to Ganzoni's formula.13

2.4 × Body weight in kg × (Target Hb - Actual Hb in g/dl) + iron storage depot (1000 mg).

Target Hb was taken as 11 g/dl as per WHO. Based on their calculated dose, one group of 50 patients were given IV Ferric Carboxymaltose (Group A) and the other group of 50 patients were given IV Iron Sucrose (Group B).

Demographic data was obtained ,patients were interviewed about their medical , surgical ,obstetrics and menstrual histories .The baseline Hb

and serum ferritin of both the groups were recorded. For Iron Sucrose 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 , was not exceed 600 mg per week. For Ferric Carboxymaltose maximum single dose of 1000 mg (20 ml) diluted in 250 ml sterile 0.9% normal saline was given over a period of 15 minutes. Subsequent doses (if needed) were given on day 7 and day 14

Each recipient was kept under observation in the hospital for at least 6 hours for signs of any reaction. All minor and major side effects were documented . Outcome was assessed by measuring the rise in haemoglobin (g/dl) and serum ferritin (mcg/L) at 2 weeks and 4 weeks of treatment and studying the side effects of each drug and a comparison of the efficacy and safety between the two groups.

RESULTS

According to inclusion and exclusion criteria, 100 pregnant women were selected, written consent was taken and were randomized into two groups of 50 each.

Table1 shows the demographic characteristics of the study groups, which were comparable in the two groups.

Epidemiological data	Group A	Group B
Age (years)	27.02±3.59	25.9±3.57
Economic class		
Class 4	05	07
Class 5	45	43
Weight(kg)	58.3 ± 4.8	57.4±5.8
BMI	21.5±1.5	20.5±1.8
Mean gestational age (weeks)	32.44±1.92	32.02±2.36
Primigravida	30%	40%
Mutligravida	70%	60%
Rural residence	45%	48%
Urban residence	55%	52%
literacy	84%	80%
illiterate	16%	20%

Mean Hb in patients of Group A was 8.49±0.57 g/dl and that of Group B was 8.48±0.64 g/dl both the groups being statistically comparable (p = 0.93)

Table 2: Comparison of two groups according to the results obtained.

Variable (Mean±SD)	Group A	Group B
Baseline haemoglobin (g/dl)	8.49±0.57	8.48±0.64
Haemoglobin (g/dl) at 2 weeks	9.58±0.48	9.01±0.60
Haemoglobin (g/dl) rise at 2 weeks	1.09±0.37	0.53±0.17
Haemoglobin (g/dl) at 4 weeks	10.29±0.48	9.57±0.61
Haemoglobin (g/dl) rise at 4 weeks	1.80±0.51	1.09±0.13
Baseline serum ferritin(mcg/l)	14.5±6.29	16.03±5.95
Serum ferritin (mcg/l) at 2 weeks	158.73±16.02	111.87±12.86
Serum ferritin (mcg/l) rise at 2 weeks	144.25±15.89	95.84±12.25
Serum ferritin (mcg/l) at 4 weeks	135.79±15.14	100.49±10.43
Serum ferritin (mcg/l) rise at 4 weeks	121.31±14.96	84.46±10.26
Adverse reactions	31%	49%

At two weeks post-treatment, mean total Hb level was significantly higher in Group A as compared to that of Group B (9.58 versus 9.01 g/dl; p<0.0001). Mean rise in Hb was 1.09±0.37g/dl in Group A and 0.53±0.17 g/dl in Group B. Thus, statistically the difference was highly significant (p <0.0001) (Table 2).

At four weeks post-treatment also, mean total Hb level was significantly higher in Group A as compared to that of Group B (10.29 vs 9.57 g/dl; p<0.0001). At 4 weeks post treatment, in Group B patients rise in haemoglobin was from 0.5 to 1.99 g/dl only, while in Group A patient's rise was significantly more from 1.0 to 3.49 g/dl (Table 3). Total rise in mean haemoglobin level was more in Group A as compared to Group B (1.80 vs 1.09 g/dl), the rise being highly significant statistically (p<0.0001) (Table 2).

Table 3: Post-treatment rise in haemoglobin (g/dl) at 4 weeks.

Rise in Hb (g/dl)	Group A No. (%)	Group B No. (%)
0.5- 0.99	00 (0)	05 (10.00)
1.0-1.49	16 (32.00)	44 (88.00)
1.5-1.99	17 (34.00)	01 (02.00)
2.0-2.49	09 (18.00)	00 (0)
2.5-2.99	07 (14.00)	00 (0)
3.0-3.49	01 (02.00)	00 (0)
Total	50 (100.00)	50 (100.00)

Mean serum ferritin of Group A was 14.5±6.29 mcg/L and that of Group B was 16.03±5.95 mcg/L, the difference being statistically insignificant (p = 0.21). At two weeks post-treatment, mean total serum ferritin level was significantly higher in Group A as compared to that of Group B (158.73 versus 111.87 mcg/L; p<0.0001). Total rise in mean serum ferritin level at 2 weeks was more in Group A as compared to that of Group B (144.25 vs 95.84 mcg/L). Statistically, the rise was highly significant (p<0.0001) (Table 2).

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

Rise in S.ferritin (mcg/l)	Group A No. (%)	Group B No. (%)
50-99.99	04 (08.00)	45 (90.00)
100-149.99	44 (88.00)	05 (10.00)
150-199.99	02 (04.00)	00 (0)
Total	50 (100.00)	50 (100.00)

After four weeks post-treatment, mean total serum ferritin level was also significantly higher in Group A as compared to that of Group B (135.79 vs 100.49 mcg/L; p<0.0001) with the mean rise being 121.31 mcg/L in Group A as compared to 84.46 mcg/L in Group B. Statistically, the rise was highly significant (p<0.0001) (Table 2). In Group B patients rise of serum ferritin was from 50 to 149.99 mcg/L at 4 weeks post treatment, while in Group A patient's rise was significantly more from 50 to 199.99 mcg/L (Table 4).

Table 5: Adverse drug reactions post treatment.

Adverse drug reactions	Group A no. (%)	Group B no. (%)
Injection site reactions	1 (2.00)	3 (6.00)
Itching and rash	3(6.00)	2(4.00)
Headache	2 (4.00)	2 (4.00)
dysgeusia	0(0.00)	2(4.00)
Abdominal pain	0 (0.00)	3 (6.00)
Diarrhoea	2 (4.00)	5 (10.00)
Nausea	3 (6.00)	3 (6.00)
Vomiting	2 (4.00)	1 (2.00)
Constipation	3 (6.00)	3 (6.00)
Skin discoloration	1(2.00)	2(4.00)
hypersensitivity	0(0.00)	0(0.00)
hypertension	0(0.00)	0(0.00)
hypotension	0(0.00)	0(0.00)
Hot flushing	1(2.00)	0(0.00)
Total	15(30.00)	24(48.00)

Mild side effects were observed in 30% patients , in group A, while in group B it was observed in 48% patients .no major side effects was noted making both the drugs safe in pregnancy(table5)

Hospital stay in days	Group A	Group B
Mean ± sd	10.16±1.095	3.12± 0.39

DISCUSSION

Nutritional anemia in pregnancy is a major public health problem especially in India and most common is iron deficiency anaenia .It is alarming to know that the prevalence of anaemia in India is as high as 62% and it is projected that India has the utmost prevalence among the South Asian countries.14 Anaemia in pregnancy is associated with unfavorable consequences both for the mother and the fetus and is a major cause of maternal and perinatal mortality and morbidity. The detection of anaemia in pregnancy and its effective management is available, affordable and possible.

The present study compared two intravenous preparations for the correction of iron deficiency anaemia in pregnany.fcm was found non inferior to iron sucrose in correction of anaemia and it led to significantly higher and rapid Hb rise as compared to iron sucrose group and with significantly less number of visits.. There was a statistically significant rise in Hb in FCM group as compared to that of Iron Sucrose (1.80 vs 1.09 g/dl). Serum ferritin also was significantly higher in the FCM group (121.31 vs 84.46 mcg/L) with comparatively

lesser side effects (30% vs 48%), all of them being mild in nature. The first study on the use of FCM for treatment of IDA in pregnancy was published by Christoph P et al.15. The study concluded comparable safety and tolerability of FCM to ISC and that FCM offers the advantage of a much higher iron dosage at a time reducing the need for repeated applications and increasing patients' comfort. The results of the present study with regard to efficacy and safety of FCM in comparison with Iron Sucrose have been consistent with the other studies conducted by, Patel J et al, Garg R et al,Metgud MC et al, Boughton S et al, Joshi SD et al and Maheshwari B et al.16-21

Ferric Carboxymaltose is a novel iron complex which consists of a ferric hydroxide core stabilized by a carbohydrate shell. It has a very low immunogenic potential and therefore not predisposed to anaphylactic reactions. It is a macromolecule complex with a molecular weight of 150 Kilo Daltons with a very high stability and half-life (16 hours).22 On administering it allows for controlled delivery of iron within the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins ferritin and transferrin, with minimal risk of release of large amounts of ionic iron in the serum thus allows rapid administration of high doses of iron in a single sitting without much safety concerns.23

Ferric carboxymaltose thus seems superior to Iron sucrose for definitive treatment of anaemia in pregnancy. The only limiting factor is its high cost but this is very well compensated when the number of visits/ days of admission in hospital is taken into account. Also reduced frequency of venous access reduces the risk of infection

CONCLUSION

From our study we conclude that , ferric carboxymaltose is safe and efficient in treatment of iron deficiency anaemia in pregnancy as compared to iron sucrose with lesser adverse effects and better patient compliance. As the hospital stay is less in patients receiving ferric carboxymaltose , it increases patient's compliance and decreases bed occupancy and burden on health facility. Therefore, it must be used as a first line drug for its management.

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