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Original Research Article

A comparative study of efficacy and safety of intravenous ferric carboxymaltose versus iron sucrose in the treatment of iron deficiency anaemia of pregnancy in a tertiary care hospital

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ABSTRACT

Background: Anaemia is a global public health problem. To optimize iron delivery in pregnancy, new intravenous complexes like Ferric carboxymaltose (FCM) have been developed in the few years. This study aims to compare the efficacy and safety of FCM vs the iron sucrose during pregnancy.
Methods: This study was conducted in the Department of Obstetrics and Gynaecology, Shri Maharaja Gulab Singh (S.M.G.S.) Hospital, Government Medical College Jammu, Jammu and 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

Pregnancy is a unique, exciting, and often joyous time in a woman's life as it highlights the woman's amazing creative and nurturing powers while providing a bridge to the future. The growing fetus depends entirely on its mother's healthy body for all needs. Consequently, pregnant women must take steps to remain as healthy and well-nourished as they possibly can, for their baby to remain healthy.[1] Anaemia is the commonest medical disorder during pregnancy with varied prevalence, aetiology and degree of severity in different populations.[2] It is a global public health problem and is responsible for 40% of maternal deaths in developing countries out of which it is responsible for 25% of direct maternal deaths. The prevalence of Iron deficiency anaemia (IDA) in pregnancy in India ranges from 23.6%-61.4%.[3] Besides mortality it also causes increased perinatal mortality and morbidity but remains a major preventable cause of unfavourable perinatal and maternal outcome.

World Health Organization (WHO) defines anaemia as haemoglobin (Hb) less than 11 g/dl during pregnancy. 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 route of administration for mild to moderate anaemia, but it has its own limitations like gastrointestinal adverse effects and long course of therapy. Noncompliance with a prescribed course of oral iron is thus common, and even in compliant patients, limited intestinal absorption fails to compensate for the iron needs.[6] Also oral iron is often not capable of replenishing severe iron deficits.

Parenteral iron therapy is effective alternative to oral iron. The intramuscular iron formulation is available but complications like pain, skin discolouration, abscess formation, allergic reaction, fever, lymphadenopathy and rarerly anaphylaxis limits its use. Iron sucrose is widely being used all over the world with a good safety profile in pregnancy.[7] 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.[8]

With the challenge of optimizing iron delivery, new intravenous complexes have been developed in the last few years.[9] 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.[10] 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 aim of the present study was to evaluate and compare the efficacy and safety of intravenous Ferric Carboxymaltose versus intravenous Iron Sucrose in the treatment of iron deficiency anaemia of pregnancy in terms of rise in haemoglobin (g/dl) and serum ferritin (mcg/L).

METHODS

This study was 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 2016 to October 2017 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 e**.**g. Thalassemia, Haemochromatosis, or any other iron storage disorder
- Multiple pregnancy
- Known history of hypersensitivity to any iron preparations
- Recent history of any significant bleeding/surgery (within three months prior to screening)
- Known case of hypothyroidism
- Serious medical condition or any uncontrolled systemic disease e.g. chronic renal disease, severe cardiovascular disease, chronic or acute hepatic disorder, tuberculosis etc.
- Known case of Hepatitis B/C infection or of acquired immune deficiency syndrome (HIV/AIDS)
- Evidence of any significant congenital anomaly on ultrasound.

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 like age, education, occupation, socio economic status was obtained. Patients were interviewed for their obstetrical and menstrual history. The baseline Hb and serum ferritin of both the groups were recorded. The total dose requirement for iron was calculated by the formula:

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

Target Hb has been taken as 11 g/dl as per WHO.

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.

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. Each recipient was kept under observation in the hospital for at least 4 hours for signs of any intolerance. All minor and major local and systemic side effects were documented. Delayed side effects of both the drugs were addressed and a protocol was followed to monitor them. 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 was made.

RESULTS

Majority of patients belonged to the age group 20-29 years. Mean gestation age, parity and mean body mass index of both the groups were comparable. Demographic and general characteristics of the study subjects have been summarized (Table 1).

Table 1: General characteristics of the study subjects.

Variable	Group A	Group B
Mean age (years)	26.02±3.59	24.9±3.57
Mean gestational age (weeks)	33.44±1.92	33.02±2.36
Primigravida	34%	40%
Mutligravida	66%	60%
Middle class	68%	66%
Rural residence	46%	48%
Urban residence	54%	52%
Mean BMI (kg/m^2)	23.47±2.41	22.90±2.48
Uneducated	16%	20%
Read and write	84%	80%
Unemployed	76%	78%

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 drug reactions (%)	30	48

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 patients 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 patients 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. (%)
Diarrhoea	2 (4.00)	5 (10.00)
Nausea	3 (6.00)	3 (6.00)
Constipation	3 (6.00)	3 (6.00)
Abdominal pain	0 (0.00)	3 (6.00)
Injection site reactions	1 (2.00)	3 (6.00)
Headache	2 (4.00)	2 (4.00)
Dysgeusia	0 (0.00)	2 (4.00)
Skin discoloration	1 (2.00)	2 (4.00)
Vomiting	2 (4.00)	1 (2.00)
Hypersensitivity	0 (0.00)	0 (0.00)
Hypertension	0 (0.00)	0 (0.00)
Hot flushing	1 (2.00)	0 (0.00)
Hypotension	0 (0.00)	0 (0.00)
Total	15 (30.00)	24 (48.00)

Mild adverse reactions were observed in 30% patients in Group A, while in Group B it was observed in 48% patients. No major side effect was noted making both the drugs safe in pregnancy (Table 5).

DISCUSSION

We as a nation have been battling against anaemia since many years. Iron is one of the most abundant minerals in nature and most life forms require it. Ironically, it is also the most common nutrient deficiency in the world leading to anemia, which has now become a serious global health concern. 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.[12] 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 search for an ideal parenteral iron preparation has led to the introduction of Ferric carboxymaltose. This study was conducted with the aim to compare the efficacy and safety of intravenous Ferric Carboxymaltose with Iron Sucrose in Iron deficiency anaemia of pregnancy. 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 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 Christoph et al, 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.[13-19]

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).[20] 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.[21]

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

Based on the observations of this study it is thus worthy to say that Ferric Carboxymaltose, because of its high efficacy and safety can revolutionize the management of Iron deficiency anaemia in pregnancy. Therefore, it must be used as a first line drug for its management to decrease the high incidence and the burden of the disease on our health set up.

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