Safety and Efficacy of Intravenous Ferric Carboxymaltose for Treatment of Iron Deficiency Anaemia in Pregnancy - An Intervention Study Done in a Tertiary Care Hospital of Pune

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ABSTRACT

BACKGROUND

Anaemia is one of the major public health problems in developing nations. Iron deficiency anaemia (IDA) is the commonest type of anaemia in pregnancy. Parenteral iron therapy is a recommended modality of treatment of IDA. Inj. Ferric Carboxymaltose (FCM) is a dextran free preparation which is safe, easy to deliver and better tolerated. A maximum of 1000 mg can be infused at a time. The present study was intended to assess the efficacy and safety of Inj. FCM in the treatment of iron deficiency anaemia in the second and third trimester.

METHODS

This prospective study was conducted at a tertiary care centre at Pune. Pregnant women with iron deficiency anaemia of moderate and severe grade were infused 1000 mg of Inj. FCM by longer infusion protocol. A total of 165 pregnant women were included in the study. The efficacy of Inj. FCM was monitored by the rise in the haemoglobin level at 03-, 06- and 08-weeks post infusion of FCM injection and serum Ferritin levels. The safety was assessed by analysing the adverse reactions.

RESULTS

No serious adverse reaction was recorded in any of the patients. The rise in haemoglobin (Hb) in second and third trimester of moderate and severe grade of anaemia was significant ($P < 0.001$). The target level of 10 g / dl was achieved in every patient. Only 03 patients received blood transfusion and that was for obstetric indications. No blood transfusion was because of anaemia per se. The rise in serum ferritin level was also statistically significant ($P < 0.001$).

CONCLUSIONS

Inj. FCM is an excellent modality to treat iron deficiency anaemia in pregnancy. It is safe and the rise of haemoglobin with correction of anaemia is satisfactory in a short span of time. In our country where only a handful of patients had regular antenatal check-up and non-compliancy and refractory anaemia is rampant, Inj. FCM is a big boon.

KEYWORDS

Iron Deficiency Anaemia, Inj. Ferric Carboxymaltose, Serum Ferritin, Blood Transfusion

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DOI: 10.18410/jebmh/2021/340

How to Cite This Article:
Vishal AK, Bhasin D, Dangwal VD, et al. Safety and efficacy of intravenous ferric carboxymaltose for treatment of iron deficiency anaemia in pregnancy - an intervention study done in a tertiary care hospital of Pune. J Evid Based Med Healthc 2021;8(22):1803-1807. DOI: 10.18410/jebmh/2021/340

Submission 01-09-2020,
Peer Review 10-09-2020,
Acceptance 09-04-2021,
Published 31-05-2021.

BACKGROUND

Anaemia is one of the major public health problems in the developing nations. More than 70 % of pregnant women in South-East Asia region (prevalence > 40 %) suffer from nutritional anaemia.[1] The WHO defines anaemia in pregnancy as haemoglobin levels below 11 g / dl. It is further graded as moderate (7.0 - 10.9 g / dl), severe (4 - 6.9 g / dl) and very severe (< 4.0 g / dl). The centre for disease control defines a haemoglobin level below 10.5 g / dl in second trimester as anaemia in pregnancy.[2] In a singleton gestation the maternal need for iron averages close to 1000 mg.[3] Iron deficiency anaemia (IDA) is the commonest type of anaemia in pregnancy and depending upon the socio-economic status, may be found in up to 50 to 90 % of all pregnancies.[4] The dietary deficiency of iron (Low bioavailability diets) is the primary cause of IDA.[5] The symptoms and signs are related to the severity of anaemia and may vary from weakness, light-headedness, headache, loss of appetite, dysphagia, skin and nail changes, to ankle swelling, dyspnoea on exertion and palpitation.[6] The blood picture shows a reduction in both haemoglobin and the packed cell volume. The ferrokinetic parameters show a reduction of Serum iron (< 60 mcg / dl), less transferrin saturation (< 20 %) and increased total iron binding capacity (TIBC). The peripheral blood smear is characteristically microcytic and hypochromic. The RBC show anisocytosis and polychromasia.[7] Serum Ferritin levels normally decrease during pregnancy. Levels less than 10 -15 ng / ml confirm IDA.[8,9]

Since many decades' oral iron supplementation is the mainstay treatment of IDA. Daily oral supplementation with 30 - 60 mg of elemental iron with 400 mcg of folic acid is recommended.[10] However the oral iron is not preferred by many patients because the minor ailments of pregnancy such as nausea, vomiting, bloating of abdomen and constipation are aggravated leading to its disruption. Parenteral iron therapy is indicated in women having iron intolerance, poor response to oral therapy and in non-compliance.[11,12]

Parenteral iron has the advantage of eliminating the non-compliancy and saving critical time in case of non-responders. Parenteral iron therapy came into effect in early nineties as iron-carbohydrate complexes. The two most commonly used compounds were iron-dextran and iron-sorbitol. They were very effective in treating IDA resistant to oral therapy,[13,14] but less popular because of the anaphylaxis and adverse reactions. The development of dextran free parenteral iron was a mile stone in the treatment of IDA.[15] Ferric Carboxymaltose injection contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to release utilizable iron to the iron transport and storage proteins in the body (Ferritin and transferrin). It has got near neutral pH and increased bioavailability. A maximum dose of 1000 mg can be given in a single setup within 15 - 20 minutes. Animal data suggest that iron released from ferric Carboxymaltose can cross the placenta and affect the skeletal development of foetus. Therefore, treatment with FCM should be confined to second trimester and beyond when period of organogenesis is complete.

Objectives

1. To treat the iron deficiency anaemia in second and third trimester of pregnancy with Inj. ferric Carboxymaltose (FCM)
2. To determine the efficacy of parenteral ferric Carboxymaltose in treating the iron deficiency anaemia of pregnant women in second and third trimester.
3. To assess the safety profile of parenteral ferric carboxymaltose

METHODS

Study Design and Population

This interventional study was conducted in Military Hospital Kirkee, a tertiary care centre of Pune from January 2016 to September 2020. Ethical clearance was taken for the index study from institutional ethical committee. All pregnant patients during the above study period were screened for anaemia on OPD basis in their first visit. Antenatal cases found to be anaemic in screening were subjected to other tests - peripheral blood smear, RBC indices and Hb electrophoresis to rule out other causes of anaemia in pregnancy and only iron deficiency anaemia (IDA) patients were taken for the study.

Operational Definitions

A Hb value of less than 11 g / dl in pregnancy was taken as cut-off to diagnose anaemia in pregnancy. Haemoglobin values between 10.9 - 7 g / dl and 6.9 – 4 g / dl were taken as moderate and severe grade of anaemia respectively (WHO guidelines)

Inclusion and Exclusion Criteria

The inclusion criteria for the study were pregnant patients with anaemia because of iron deficiency of moderate or severe grade in second and early third trimester. Those with anaemia in pregnancy caused by Vitamin B12 and Folic acid deficiency, thalassemia and very severe type of iron deficiency anaemias (< 4.0 g / dl) were excluded from the study.

Sampling Method and Sample Size Calculation

The sampling method in the study was convenience or purposive sampling. The required sample size was determined based on the prevalence of anaemia. A single population proportion formula with the following assumptions: $Z\,1\alpha/2$= value for 80 % CI, Prevalence of anaemia – 40 %, Design effect (DEFF): 1, the sample size becomes 150. By adding 10 % of study subjects as non-responsive rate, the final sample size becomes 165 (Results from Openepi, Version 3, open source calculator- SSPropor).

Sampling Technique and Protocol

All women in the study group were infused 1000 mg of Inj. FCM IV in the first setting irrespective of their weight. Since

the drug is assigned as FDA category C, we infused Inj. FCM after getting anomaly scan for second trimester pregnant patients. Written informed consent was taken prior to infusion.

Infusion Protocol

Due to limited availability of safety data for its use in pregnancy a longer infusion protocol (2 - 3 hours) was followed. All patients were admitted and the infusion was planned in the morning hour. Maternal pulse and blood pressure and foetal heart rate were monitored before during and after infusion. An anaphylactic tray was prepared and kept ready at bedside of patient. Women were observed for one-hour post infusion before being discharged to home. Any adverse effect happened during infusion was recorded.

Post FCM Infusion Advice

A mandatory OPD visit was made at 03- and 06-weeks post Inj. FCM infusion and Hb was done on the same day. Subsequent visits were as per schedule. After 08 weeks of delivery, Hb and serum Ferritin levels were repeated.

Study Variables

Adverse Reactions

A total of 180 patients were enrolled in the study and were given Inj. FCM 1000 mg as per protocol. After infusion they were observed for any major or minor infusion adverse reactions. The adverse reactions are depicted in Table 2.

Rise in Hb and Ferritin Levels

The repeat Hb level and serum Ferritin was not done for many patients as they didn't report to the OPD on due time. Finally, we analysed the data of 165 patients.

The following parameters were analysed -

a) Pre and post Inj. FCM infusion haemoglobin level
b) Rise in haemoglobin level 03- and 06-weeks post Inj. FCM infusion and 08 weeks postpartum
c) Pre and post transfusion serum Ferritin (Baseline and 08 weeks postpartum)

The outcomes of successful treatment were defined as -

a) Raise in haemoglobin levels as measured at an interval of 03 & 06 weeks after the administration of ferric Carboxymaltose
b) Remission of anaemia in the study subjects
c) Any requirement of additional blood transfusion during the antenatal and postnatal periods
d) Rise in haemoglobin 08 weeks after the delivery
e) Any adverse reaction following the administration of parenteral ferric Carboxymaltose.

Statistical Analysis

All the data collected was analysed using statistical package for social sciences (SPSS) version 20. Mean with standard deviation were calculated for continuous variables and proportions for categorical variables. Paired t - test was used for comparisons of means for clinical parameters. A P - value of 0.05 was considered statistically significant.

RESULTS

A total of 165 patients received Inj. Ferric carboxy maltose (Inj. FCM) infusion for antenatal Iron deficiency anaemia. A total of 110 (67 %) were in second trimester and 55 (33 %) were in third trimester of pregnancy. Majority of patients were in parity 1, (75, 45 %), followed by parity zero, (52, 32 %), parity 2, (35, 21 %) and 03 patients (02 %) were parity 3. A total of 100 (61%) patients had moderate grade and 65 (39 %) had severe grade of anaemia (Table 1).

	Parameters	Freq N - 165	Percentage
Gravida status	Primigravida	28	17
	Second gravida	64	39
	Third gravida	60	36
	Fourth gravida and beyond	13	08
Parity	Zero	52	32
	One	75	45
	Two	35	21
	Three	03	02
Trimester	Second	110	67
	Third	55	33
Grade of anaemia	Moderate	100	61
	Severe	65	39
Mode of delivery	Vaginal	118	72
	LSCS	47	28

Table 1. Demographic Information of Women Enrolled in the Study

No Adverse Reaction	155
Burning / Tingling sensation	04
Gastrointestinal (Nausea, vomiting, Diarrhoea)	03
Nervous system disorders (Headache, dizziness)	01
Pruritus	01
Local site Irritation	01
Total	**165**

Table 2. Adverse Events

	Trimester	Hb (Min)	Hb (Max)	Mean Hb	SD	95% CI
Second - Moderate	a) Base line Hb	7.0	9.8	8.52	0.84	8.30 - 8.73
	b) 03 weeks post FCM infusion	8.6	12.0	10.34	1.08	10.06 – 10.61
	c) 06 weeks Post FCM infusion	9.8	14.3	12.27	1.10	11.99 – 12.55
	d) 08 weeks post-partum	10.6	14.4	12.37	1.01	12.11 – 12.62
Second - Severe	a) Base line Hb	5.0	6.9	6.04	0.57	5.89 – 6.20
	b) 03 weeks post FCM infusion	7.1	9.1	8.16	0.59	8.00 – 8.33
	c) 06 weeks Post FCM infusion	9.2	11.2	9.94	0.44	9.81 – 10.06
	d) 08 weeks post-partum	9.6	11.4	10.34	0.34	10.24 – 10.43
Third - Moderate	a) Base line Hb	7.1	9.8	8.5	0.77	8.26 – 8.74
	b) 03 weeks post FCM infusion	8.9	12.4	10.46	0.81	10.21 – 10.71
	c) 06 weeks Post FCM infusion	10.4	13.6	12.12	0.87	11.85 - 12.38
	d) 08 weeks post-partum	10.5	14.3	12.66	0.85	12.39 – 12.92
Third - Severe	a) Base line Hb	5.2	6.9	6.07	0.51	5.81 – 6.33
	b) 03 weeks post FCM infusion	7.0	8.4	7.89	0.46	7.65 – 8.12
	c) 06 weeks Post FCM infusion	8.6	10.3	9.65	0.53	9.39 – 9.92
	d) 08 weeks post-partum	9.4	10.5	10.22	0.31	10.06 – 10.38

Table 3. Haemoglobin Level before and after Inj. FCM Infusion

	Trimester	Rise in HB (Min)	Rise in HB (Max)	Mean Rise in HB	SD	95 % CI	P Value
Second - Moderate	a) Base line Hb and 03 weeks post FCM infusion	1.2	2.4	1.82	0.32	1.74 - 1.90	< 0.001
	b) Base line Hb and 06 weeks post FCM infusion	2.6	4.8	3.76	0.49	3.63 - 3.88	< 0.001
	c) Base line Hb and 08 weeks post-partum	2.1	4.9	3.85	0.69	3.67 – 4.02	< 0.001
Second - severe	a) Base line Hb and 03 weeks post FCM infusion	0.8	2.7	2.12	0.38	2.02 - 2.23	< 0.001
	b) Base line Hb and 06 weeks post FCM infusion	2.7	5.0	3.89	0.39	3.79 – 4.00	< 0.001
	c) Base line Hb and 08 weeks post-partum	3.5	5.3	4.29	0.43	4.17 – 4.41	< 0.001
Third - Moderate	a) Base line Hb and 03 weeks post FCM infusion	1.3	2.9	1.96	0.33	1.86 – 2.06	< 0.001
	b) Base line Hb and 06 weeks post FCM infusion	2.8	4.5	3.62	0.38	3.50 – 3.73	< 0.001
	c) Base line Hb and 08 weeks post-partum	3.3	5.3	4.16	0.46	4.02 – 4.30	< 0.001
Third - Severe	a) Base line Hb and 03 weeks post FCM infusion	1.3	2.6	1.81	0.35	1.64 – 1.99	< 0.001
	b) Base line Hb and 06 weeks post FCM infusion	3.2	4.3	3.58	0.38	3.39 – 3.77	< 0.001
	c) Base line Hb and 08 weeks post-partum	3.6	5.2	4.15	0.50	3.90 – 4.40	< 0.001

Table 4. Rise in Haemoglobin Level during and after Pregnancy, Post FCM Infusion

SN	Trimester	Min	Max	Mean	SD	95 % CI	P Value
Second trimester - Moderate	a) Serum Ferritin level - Pre infusion	8	65	27.98	12.09	24.93 – 31.04	< 0.001
	b) Serum Ferritin level - Post Infusion	15	144	74.69	32.45	66.48 – 82.90	
Second trimester - Severe	a) Serum Ferritin level - Pre infusion	4	14	7.38	2.21	6.77 – 7.99	< 0.001
	b) Serum Ferritin level - Post Infusion	15	67	35.36	10.59	32.43 – 38.29	
Third trimester - Moderate	a) Serum Ferritin level - Pre infusion	8	54	23.05	9.32	20.16 – 25.94	< 0.001
	b) Serum Ferritin level - Post Infusion	45	165	106.83	30.25	97.45 – 116.2	
Third trimester –Severe	a) Serum Ferritin level - Pre infusion	4	9	5.73	1.53	4.96 – 6.51	< 0.001
	b) Serum Ferritin level - Post Infusion	23	42	31.67	5.63	28.82 – 34.51	

Table 5. Serum Ferritin Levels during Pregnancy and Post FCM Infusion

Only mild adverse reactions were seen in (10, 6) patients (Table 2). Rise in Haemoglobin level during and after pregnancy, post FCM infusion was statistically significant (P < 0.001), (Table 4). Rise in Serum Ferritin levels post Inj. FCM infusion was statistically significant (P < 0.001) (Table 5).

DISCUSSION

In this interventional study, conducted in a tertiary care centre of Pune, all patients who received Inj. FCM infusion had no serious adverse effects. Minor side effects occurred in 10 patients out of which 02 developed intra infusion and 08 developed post one hour of transfusion. In the patients who developed minor reaction, infusion was stopped and restarted after half an hour of administration of Inj. Hydrocortisone 100 mg IV. All other post infusion minor side effects were self-limiting.

No foetal heart abnormalities were seen in any of the patients. None of them were kept overnight for observation. None of the patients reported any delayed adverse reaction in subsequent visits. In our study a total of 110 patients of second trimester had iron deficiency anaemia. The minimum Hb in moderate and severe grade of anaemia was 7.0 and 5.0 g / dl respectively. They were diagnosed to be anaemic in the initial visits and started on oral haematinics but the Hb level failed to rise despite the oral supplementation and dietary changes. The serum Ferritin levels were 8.0 and 4.0 ng / dl. A total of 55 patients in third trimester received Inj. FCM. The minimum haemoglobin in moderate and severe grade of anaemia was 7.1 g / dl and 5.2 g / dl respectively. Patients particularly of severe grade anaemia complained of weakness and easy fatigability, which was more pronounced in third trimester; however, none of them were clinically decompensated as cardiac output was not substantively decreased until the Hb level fell below 7 g / dl or haematocrit of 20 volume percent.

After 1000 mg of Inj. FCM infusion, the increase in haemoglobin was dramatic. In second trimester moderate grade of anaemia, the maximum rise was 4.8 g / dl and the Hb reached up to 14 g / dl with concurrent rise in serum Ferritin value. In second trimester severe grade of anaemia, the maximum increase in Hb was 5.0 g / dl from the base line and the maximum value was 11.2 g / dl. The rise of Hb in severe degree of anaemia in third trimester was less pronounced. The maximum Hb was 10.3 g / dl and minimum was 8.6 g / dl after 06 weeks post infusion. The rise in Hb after 03 and 06 weeks of infusion was statistically significant (P < 0.001). In third trimester, moderate degree of anaemia the rise in Hb was significant with a minimum increase of 2.8 g / dl and maximum increase of 4.5 g / dl and P value < 0.001.

The target level of Hb of more than 10 g / dl was achieved in every patient including third trimester patients having severe grade of anaemia. This was significant as this rise in Hb could have never been achieved by diet and oral supplementation alone in this short span of time. The symptoms of anaemia also improved significantly with lesser degree of weakness and feeling of well-being was reported by almost all.

Similar results were noted by multiple studies and the adverse events as shown in Table 2, were similar to other studies.[12,13,14,15] In clinical obstetrics, blood transfusion practices are common particularly in post-partum haemorrhage (PPH)

The risk of PPH and blood transfusion is increased when the pre delivery Hb is less than 8 g / dl. At this level of Hb any amount of increased bleeding jeopardizes the maternal health thus requiring blood transfusion. Despite its enormous clinical utility, blood transfusion has multiple risks and should be ideally avoided. It is associated with bacterial and viral disease transmission, ABO-incompatible blood transfusion, acute haemolytic allergic reaction, non-haemolytic transfusion reaction and transfusion related acute lung injury. Inj. FCM is a good alternative to blood transfusion if anaemia is detected early in pregnancy. It is safe and the rise of Hb with correction of anaemia is satisfactory in a short span of time. With the increase in Hb level, majority of women tolerate the blood loss occurring

during delivery well, thus decreasing the incidence of blood transfusions.

In our study only 03 patients required blood transfusion. In our country where only a handful of patients have regular antenatal check-ups, non-compliancy to oral iron therapy and also refractory anaemia being rampant; Inj. FCM is a big boost in improving maternal health.

CONCLUSIONS

Inj. Ferric Carboxymaltose infusion is an excellent modality to treat moderate and severe grade of iron deficiency anaemia in second and third trimester of pregnancy. A single dose of 1000 mg is sufficient enough to correct the anaemia. It is safe having very negligible side effects. It is easy to administer and noncompliance can be reduced by infusion in a single sitting on OPD basis. Inj. FCM infusion is an effective modality in cases of non-compliant patients to oral iron therapy and in cases of refractory anaemia. There is also a significant drop in blood transfusion rates.

Limitations

Patients were advised to restart oral iron after 01 week of Inj. FCM infusion. However only 12 % of the patients continued oral iron throughout pregnancy (100 mg / day) and the remaining discontinued it either because of iron intolerance or non-compliance.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] WHO. The global prevalence of anaemia in 2011. Geneva: World Health Organization 2015.
[2] Centers for Disease Control and Prevention. CDC criteria for anaemia in children and childbearing-aged women. MMWR Morb Mortal Wkly Rep 1989;38(22):400-404.
[3] Gautam CS, Saha L, Sekhri K, et al. Iron deficiency in pregnancy and the rationality of iron supplements prescribed during pregnancy. Medscape J Med 2008;10(12):283.
[4] Sharma JB, Shankar M. Anaemia in pregnancy. JIMSA 2010;23(4):253-260.
[5] Indian Council of Medical Research. Evaluation of the national nutritional anaemia prophylaxis programme. New Delhi: Indian Council of Medical Research 1989.
[6] Romslo I, Haram K, Sagen V, et al. iron requirement in normal pregnancy as assessed by serum Ferritin, serum transferrin saturation and erythrocyte protoporphyrin determinations. Br J Obstet Gynaecol 1983;90(2):101-107.
[7] Harthoorn-Lasthuizen EJ, Lindemans J, Langenhuijsen MM. Erythrocyte zinc protoporphyrin testing in pregnancy. Acta Obstet Gynecol Scand 2000;79(8):660-666.
[8] American College of Obstetricians and Gynaecologists. ACOG practice bulletin No. 95: anaemia in pregnancy. Obstet Gynecol 2008;112(1):201-207.
[9] WHO. Guideline: daily iron and folic acid supplementation in pregnant women. Geneva: World Health Organisation 2012.
[10] Sharma JB, Jain S, Mallika V, et al. A prospective, partially randomized study of pregnancy outcomes and hematological responses to oral and intramuscular iron treatment in moderately anaemic pregnant women. Am J Clin Nutr 2004;79(1):116-122.
[11] Singh K, Fong YF, Kuperan P. A comparison between intravenous iron polymaltose complex and oral ferrous fumarate in the treatment of iron deficiency anaemia in pregnancy. Eur J Haematol 1998;60(2):119-124.
[12] Singh K, Fong YF. Intravenous iron polymaltose complex for treatment of iron deficiency anaemia in pregnancy resistant to oral therapy. Eur J Haematolol 2000;64(4):272-274.
[13] Christoph P, Schuller C, Studer H, et al. Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose. J Perinat Med 2012;40(5):469-474.
[14] Friedrisch JR, Cancado RD. Intravenous ferric carboxymaltose for the treatment of iron deficiency anaemia. Rev Bras Hematol Hemother 2015;37(6):400-405.
[15] Christoph P, Schuller C, Studer H, et al. Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose. J Perinat Med 2012;40(5):469-474.