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Use of Intravenous Ferric Carboxymaltose: A Revolutionary Approach for Iron Deficiency Anaemia in Antenatal Women

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Introduction- Anaemia still has been prevailing as a significant global public health problem especially in low to middle economic countries, responsible for 40% of maternal deaths and out of which it accounts for 25% among direct cause. Besides maternal mortality it also causes increased perinatal morbidity and mortality although it is a major preventable cause of unfavourable perinatal and maternal outcome. There are various national programmes undertaken by Government of India catering to anaemia especially for pregnant population which has largely emphasised the oral iron supplementation but still the picture is gloomy and we have to go a long way. Prevalence of Iron deficiency anaemia (IDA) in pregnancy in India ranges from 23.6%-61.4%[1].

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Use of Intravenous Ferric Carboxymaltose: A Revolutionary Approach for Iron Deficiency Anaemia in Antenatal Women

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I. Introduction

Anaemia still has been prevailing as a significant global public health problem especially in low to middle economic countries, responsible for 40% of maternal deaths and out of which it accounts for 25% among direct cause. Besides maternal mortality it also causes increased perinatal morbidity and mortality although it is a major preventable cause of unfavourable perinatal and maternal outcome· There are various national programmes undertaken by Government of India catering to anaemia especially for pregnant population which has largely emphasised the oral iron supplementation but still the picture is gloomy and we have to go a long way. Prevalence of Iron deficiency anaemia (IDA) in pregnancy in India ranges from 23.6%-61.4%[1].

Different forms of oral iron preparations are available widely claiming the increased absorption rate with decreased side effect and have established to be a preferred route of administration for mild to moderate anaemia among pregnant population, but all has their own limitations like gastrointestinal side effects. Apart from oral preparation, parenteraliron sucrose therapy is an upcoming effective alternative but the main disadvantage of intravenous (IV) iron sucrose is that it cannot be administered at a higher dose because of the risk of toxicity, thus requiring frequent visits to the hospital[2]. Intravenous ferric carboxymaltose (FCM) have been developed recently; 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 [3]. It has a very low immunogenic potential and therefore not predisposed to anaphylactic reaction. Therefore, we undertook this study with the aim to compare the efficacy and tolerability of intravenous ferric carboxymaltose with oral iron therapy in pregnant population.

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II. Materials and Methods

This study was conducted in the department of obstetrics and gynaecology at Upper India Sugar Exchange Maternity Hospital, G.S.V.M. Medical College, Kanpur over a period from January 2019 to July 2020 after approval from ethical committee G.S.V.M Medical College Kanpur.

Study subjects: All antenatal patients, with hemoglobin range between 7-10.9 g/dl irrespective of parity.

Type of Study– Prospective interventional randomized clinical study.

Inclusion Criteria:

Patients willing to participate and follow up.

- Antenatal patients with a period of gestation 16-32 weeks.
- Haemoglobin level between 7-10.9 g/dl.
- Serum ferritin <30 mcg/L (Only for therapeutic group).
- Patients with known nutritional anaemia.

Exclusion Criteria:

- Pregnancy <16 weeks and after > 32 weeks period of gestation.
- Hemoglobin<7 gm/dl or >11 gm/dl.
- Intolerance to oral iron preparations
- Recent history of blood transfusion.
- History of any disease associated with iron overload disease like thalassemia, haemoglobinopathies like sickle cell anaemia.
- Multiple pregnancy.
- Hypersensitivity to iron preparations.
- History of antepartum haemorrhage.
- Known case of inflammatory bowel diseases.
- Serious medical condition like chronic kidney disease, severe cardiovascular diseases, hepatic diseases.
- Known case of hepatitis B, hepatitis C and HIV

III. Methodology

After written and informed consent of patients were enrolled in the study according to inclusion criteria. Sahli's method was used to know the baseline hemoglobin.

Total 235 pregnant women were included in the study, who were divided into 2 groups according to degree of anaemia.

1. Preventive Group (9 – 10.9g/dl)
2. Therapeutic Group (7 – 9g/dl)

Further these groups were divided into two subgroups IA, IB, IIA, IIB. Number of patients in these groups were [IA (n=60), IB(n=55), IIA(n=65), IIB(n=55)].

- Group I: Preventive Group

IA were treated with tablets of ferrous ascorbate once a day containing 100mg elemental iron as well as 5 mg of folic acid with tablet vitamin C 500 mg.

IB were treated with intravenous ferric corboxymaltose 1000 mg single dose.

- Group II: Therapeutic Group:

IIA were treated with ferrous ascorbate 200mg elemental iron twice a day containing folic acid with tablet vitamin C 500mg.

IIB were treated with intravenous ferric carboxymaltose according to the calculated dose.

Iron Dose calculation: The total dose required for Hb restoration and repletion of iron stores was calculated by following Ganzoni formulae.

Total Iron deficit (mg) = Body weight in Kg x (target hemoglobin – actual hemoglobin) gm/dl x 2.4 + 1000 mg for iron storage

Ferric Carboxymaltose was administered only by I.V. drip infusion – maximum single dose of 500-1000 mg (20 ml) diluted in 100 ml sterile 0.9% NaCl solution over 15 minutes not more than once a week.

The patients were asked to follow up after 1 week, 3 weeks, 6 weeks and then till delivery.

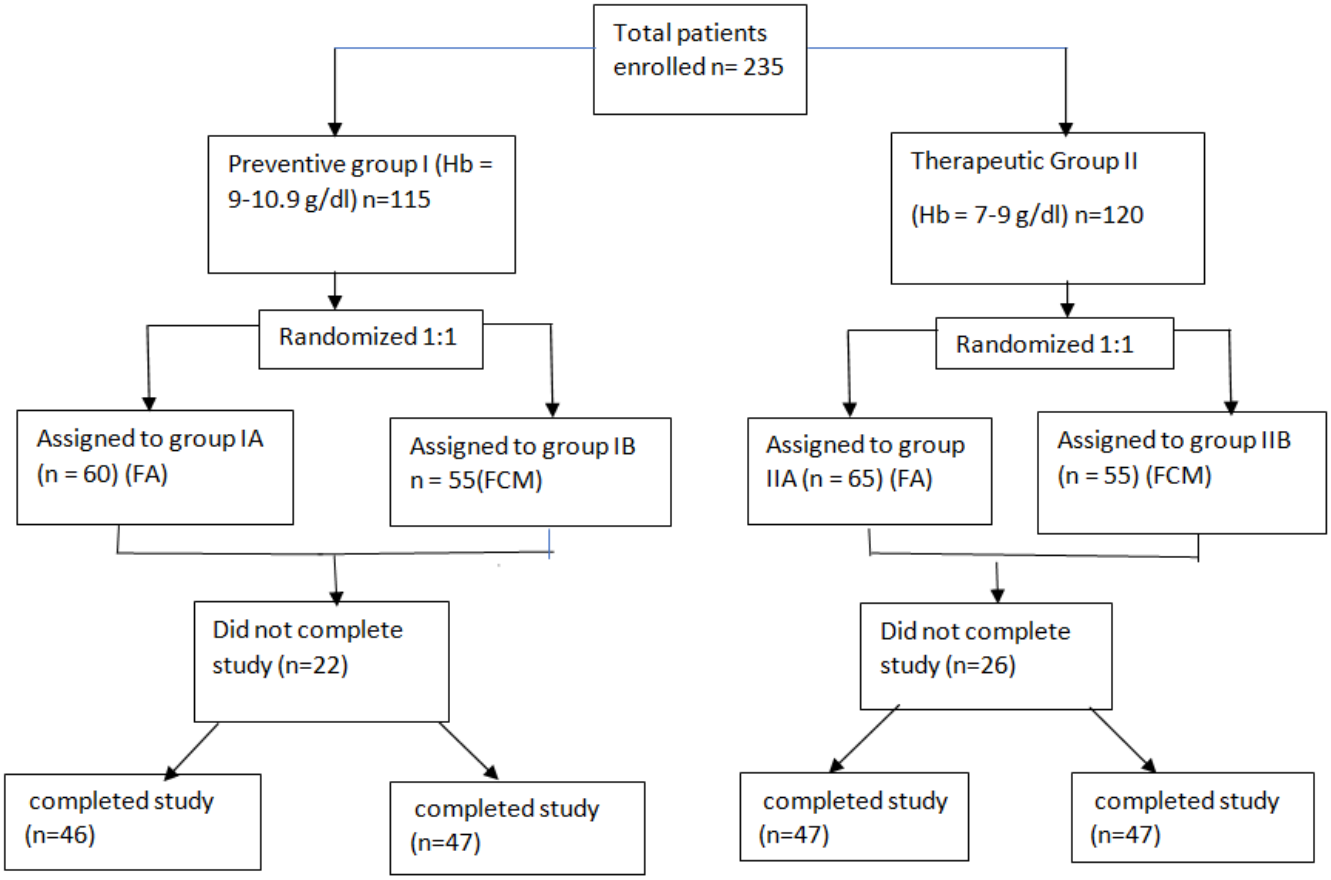
1. Day 0: The blood samples were taken for the following investigations (Hb, MCV, MCH, MCHC and serum ferritin level, peripheral blood picture, reticulocyte count) before starting medication to know the baseline values.
2. 1 weeks: to assess the reticulocyte count.
3. 3 weeks: to assess the Hb, MCV, MCH, MCHC levels.
4. 6 weeks: to assess the Hb, MCV, MCH, MCHC & Serum ferritin levels.
5. Followed till delivery: to assess maternal & fetal outcome.

During each follow up visit, they were subjected to general examination and obstetrical examination. The patients were explained to record and observe the adverse effects and instructed to report immediately if serious adverse drug reaction occurs. Any adverse event like metallic taste, nausea, vomiting, dyspepsia, diarrhoea and constipation were recorded on the case record form in every follow up. Compliance was checked by verbal enquiry and verified by asking blackening of stools and staining of tongue.

IV. Statistical Analysis

Statistical analysis was done to analyse the difference in all the hematological parameters among the groups using percentages and chi-square test for categorical variables.

Flowchart Representing the No. of Patients Enrolled During Study



V. Results

Majority of patients had mean age of 27.59±3.08 years in all groups. Mean age of gestation was 21.65±3.83 week, 47.33% were primigravida and 53.71% were multigravida, 56.42% belonged to rural, 17% were illiterate and 18.76% had primary level of education in our study. All groups were comparable in terms of sociodemographic and general characteristics of study populations.

Table 1: Comparison of Two Subgroups among Preventive Group

Variables	IA(Mean±SD)	IB(Mean±SD))	p-value
Baseline hemoglobin(g/dl)	9.59±0.51	9.68±0.53	<0.0001
Hemoglobin at 34-37 wk	12.20±0.45	12.70±0.58	<0.0001
Hemoglobin(g/dl) rise at 34-37wk	2.71±0.39	3.06±0.53	<0.0001
Baseline serum ferritin	39.01±9.0	42.42±12.06	<0.0001
Serum ferritin rise at 6 weeks	17.30±5.89	85.17±15.86	<0.0001

Mean reticulocyte count in patients of group IA was 1.10±0.30and of group IB was 1.04±0.22 after 1week post treatment, which was significantly higher in latter group (1.40 versus 1.80 g/dl; p<0.0001). Mean rise in Hb was 2.71±0.39 g/dl in group IA and 3.06±0.53g/dl in group IB. Thus, statistically the difference was highly significant (p<0.0001) (Table 1)

Table 2: Comparison of Two Subgroups among Therapeutic Groups.

Variable	IA(Mean±SD)	IIB(Mean±SD)	P-VALUE
Baseline hemoglobin	8.22±0.52	7.97±0.59	<0.0001
Hb (rise at 3 week)	0.89±0.36	2.24±0.58	<0.0001
Hb (rise at 6 week)	2.06±0.53	3.79±0.68	<0.0001
Baseline serum ferritin	20.09±4.22	18.17±4.27	<0.0001
Ferritn (rise at 6 week)	19.64±8.10	87.94±14.14	<0.0001

Mean reticulocyte count of group IIA was 0.96±0.28% and that's of group IIB was 0.87±0.21% which was comparable before the intervention. At 1week post treatment, rise was higher in group IIB as compared to group IIA. Mean rise in reticulocyte count was 0.31±0.17 % in group IIA and 0.99±0.28 % in group IIB which was statistically highly significant (p<0.0001).

It was found that the mean rise in Hb and serum ferritin were higher in ferric carboxymaltose group as compare to ferrous ascorbate which was statistically highly significant (p<0.0001).

Table 3: Comparison of Other Parameters among Therapeutic Groups

Variables	IIA(Mean±SD)	IIB(Mean±SD)	P-VALUE
Baseline MCV	75.17±3.76	75.70±4.57	<0.0001
MCV (rise at 6 week)	7.62±2.62	11.60±2.89	<0.0001
Baseline MCH	26.34±1.54	26.22±1.54	<0.0001
MCH (rise at 6 weeks)	3.68±1.83	7.25±2.04	<0.0001
Baseline MCHC	28.39±1.97	28.37±2.07	<0.0001
MCHC (rise at 6 weeks)	3.99±1.53	6.73±1.45	<0.0001

Mean rise in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) was higher in ferric carboxymaltose group (IIB) as compared to oral ferrous ascorbate group (IIA) which was significant (TABLE 3).

Table 4: Comparison of Side Effects of FCM & Ferrous Ascorbate

	Ferrous ascorbate (IA+IIA)		Ferric carboxymaltose (IB+IIB)		P-VALUE
	n = 93	%	n = 94	%	
Gastrointestinal symptoms	45	48.38	1	1.06	<0.05
Hypersensitivity	00	00	00	00	-
Headache	00	00	1	1.06	-
Heartburn	2	2.15	00	00	-
Palpitations	00	00	1	1.06	
Total	47	50.6	3	2.7	-

Mild side effects were observed in 2.7% patients in FCM groups, while it was observed that 50.6% of patients in oral ferrous ascorbate group had significant side effects. No major adverse effects were noted making both the iron preparations safe in pregnancy (Table 4).

VI. Discussion

Iron deficiency anaemia is one of the most important causes of maternal and neonatal morbidity and mortality in developing world, so it should be corrected in all pregnant women to decrease its adverse related outcome. The aim of our study was to compare the efficacy, safety, tolerability and feto-maternal outcome of intravenous ferric carboxymaltose with oral ferrous ascorbate in pregnant women having mild to moderate iron deficiency anaemia. In our study, we found that for both preventive and therapeutic groups mean rise in haemoglobin at 6weeks post treatment was significantly higher in intravenous FCM group as compared to oral iron. *Bhargava and Maheshwari et al*[4], *Deeba et al* [5] studied that rise in haemoglobin was higher in intravenous group as compared to oral iron group. *Myers et al*[6] studied that ferric carboxymaltose group had the meanrise in hemoglobin was higher as compared to iron dextran after 6 weeks. *Onken et al* [7] study in antenatal patients, showed significant rise in mean hemoglobin in intravenous ferric carboxymaltose group as compared to oral iron.

In our study, there was a significant rise in serum ferritin levels after 6 weeks in preventive and therapeutic groups which was higher in intravenous FCM as compared to oral ferrous ascorbate which was highly significant. *Deeba et al* studied showed similar results as rise in serum ferritin after 6 weeks in ferrous ascorbate and *Mishra V et al* [8] found that mean serum ferritin risehigher in ferric carboxymaltose group.

Mean rise in MCV, MCH, MCHC in therapeutic group at 6 weekswere higher in intravenous FCM as compare to oral ferrous ascorbate groups and was highly significant. *Ambily J et al* [9] results were comparable with our study.

Fetomaternal outcomes were found better in intravenous FCM as compared to oral ferrous ascorbate but was not significant. Needs of blood transfusion and postpartum haemorrhage reduced in FCM group. *Anouk pel etal*[10] had done retrospective study and concluded that ferric carboxymaltose had slight less complications rate.

Gastrointestinal complications were more in oral ferrous ascorbate and which was nil in intravenous ferric carboxymaltose. There were no anaphylactic reactions reported with doses of intravenous ferric carboxymaltose. Side effects with oral ferrous ascorbate

were more as compared to intravenous ferric carboxymaltose. *Iftikar et al* [11] *and Onken et al* [12] proved that ferric carboxymaltose was well tolerated and showed better compliance than oral iron. *Froessler et al*[13] also reported minimal side effects with intravenous ferric carboxymaltose.

VII. Conclusion

We deduced that all haematological parameters (Hb, reticulocyte count, mean rise in hemoglobin at 3 and 6 weeks and serum ferritin level) were significantly increased in intravenousferric carboxymaltose group as compared to oral iron group. Although various oral iron preparations are mainstay of treatment of anaemia in pregnancy claiming higher absorption as well as bioavailability, but in current scenario, injection ferric carboxymaltose seems superior to oral iron therapy as a definite treatment of iron deficiency anaemia in pregnancy in both second and third trimester of pregnancy.

Based on the observations of our study it is thus worthy to say that Ferric carboxymaltose, due to its high efficacy, tolerability and safety profile can revolutionize the management of iron deficiency anaemia in pregnancy. Therefore, it must be used as a first line drug for decreasing the high incidence and burden of the iron deficiency especially in our health set up. Therapy contributing to be the maternal morbidity and mortality as well in cutting down the economic burden on the health system of our country.

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