International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Evaluation of Hypersensitivity Reactions to Ferric Carboxymaltose in Iron - Deficiency Anemia Patients: A Multicenter Randomized Trial

Dr. Poulami Gupta Banerjee[1], Dr. Manoj Mukhopadhyay[2], Prabhu Shanmugam[3], Kumari Lily[4], Dr. Utpalendu Banerjee[5]

West Bengal Chemical Industries Limited

Abstract: ***Iron deficiency anaemia is a widespread nutritional condition affecting physical and psychological well - being globally. While oral iron therapy is the standard treatment, its effectiveness can vary due to multiple factors. This has led to the emergence of intravenous iron therapies, such as Ferric Carboxymaltose (FCM), as an alternative for patients with inadequate responses to oral iron. Concerns regarding hypersensitivity reactions have arisen with intravenous iron, necessitating a detailed investigation. In this study, we evaluate the safety and efficacy of FCM compared to oral iron therapy in adult patients with iron deficiency anaemia and heart failure. Our research encompasses animal and human trials, with guinea pig tests revealing a 0% hypersensitivity rate for FCM. Additionally, a clinical trial involving 100 human subjects from various regions demonstrates no instances of hypersensitivity reactions. These findings suggest that FCM is a safe alternative for patients intolerant to oral iron formulations, with no evidence of hypersensitivity reactions. This study provides valuable insights into the utilization of FCM in managing iron deficiency anaemia, particularly in cases where oral iron is ineffective or not tolerated.***

Keywords: Iron deficiency anaemia, Ferric Carboxymaltose, intravenous iron therapy, hypersensitivity reactions, efficacy, safety profile

1. Introduction

Iron deficiency anaemia is a well - known form of nutritional anaemia globally. Iron deficiency anaemia can affect both physical as well as psychological functioning of human beings. Although, oral iron is considered as the first - line therapeutic regimen of iron deficiency anaemia, the absorption of oral iron might vary by several factors. This has led to the development of intravenous iron therapy, especially Ferric Carboxymaltose (FCM), which is a novel non - dextran form of intravenous iron approved for patients with iron deficiency anaemia and have insufficient response to oral iron therapy.1 To demonstrate the efficacy and safety profile of FCM in comparison to oral iron to the adult patients who have iron deficiency anaemia and heart failure, previousmulticentre, open label, randomized, single - dose, two - treatment, parallel arm bioequivalence study has been performed. Several trials have described the sustained improvement of patient outcomes in cases with heart failure as well[2]. However, the question arises regarding the safety profile of the drug Ferric Carboxymaltose, whether this is non - hypersensitive after its administration to human subjects or not.

Several iron infusion complexes are available to treat iron deficiency anaemia. Iron dextran is associated with elevated risks of potentially threatened anaphylactic reactions; whereas FCM if administered in a single dosage is comparatively safe.3 - [4]Hypersensitivity is recognized as an immunologically mediated allergic reaction occurring against substances, chemicals, cosmetics, or pharmaceutical products. In order to assess or evaluate toxic characteristics of a drug, it is important to determine its potential of triggering hypersensitivity reactions before - hand. Intravenous administration of iron may cause hypersensitivity reaction. Clinical research has shown that intravenous iron preparation though well - tolerated in patients still caused death in some cases. There are reports on anaphylactic shock and death related to FCM infusion as well.3It has been reported that the risk of hypersensitivity reactions associated with FCM is comparatively lower than iron dextran preparation due to non - dextran carbohydrate moiety of FCM.

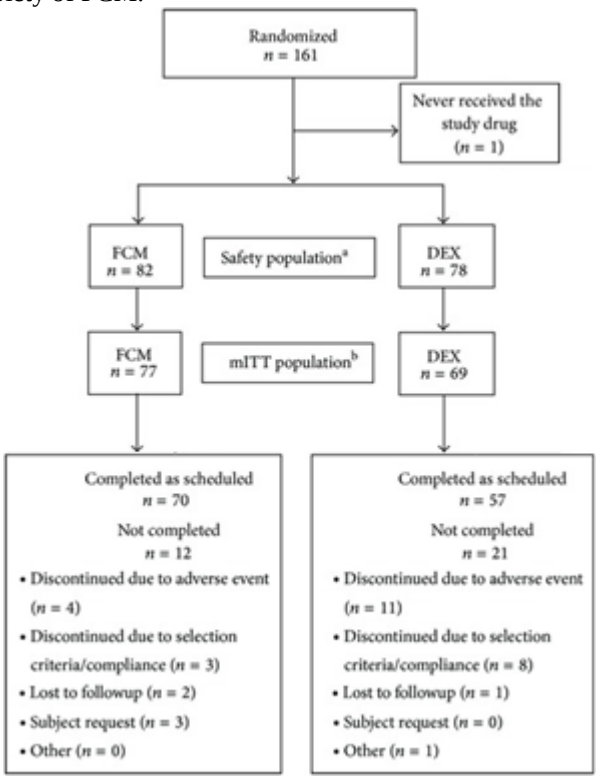


Figure 1: Comparative reports of Subjects treated with FCM versus DEX.4

The reports suggest that annual exposure of iron dextran has been decreased globally in between the years of 2008 and 2017, whereas, the annual exposure of FCM has been

increased over the same period and the cumulative global exposures of these two drugs are represented in the figure below. From 2008 to 2017 the global exposure of iron dextran has been decreased from 14.4 million to 9.7 million, while the global exposure of FCM has been increased from 0.6 million to 24.2 million (Fig.2). Also, the global reported rate of hypersensitivity reactions (anaphylactic shock) is much higher for iron dextran compared to FCM (Fig.3).5

The present study focuses on determination of efficacy and safety profile of FCM sponsored by Eskag Pharma Pvt. Ltd. To determine hypersensitivity potential of the drug Ferric Carboxymaltose sponsored by Eskag Pharma Pvt Ltd, animal tests have been done with guinea pigs. The evaluation of hypersensitivity reactions of Ferric Carboxymaltose injection, sponsored by Eskag Pharma Pvt. Ltd., was conducted at Bioscience Research Foundation in male and female guinea pigs using Magnusson and Kligman method following the rules of Drugs and Cosmetics - Schedule Y Guideline, 2019. None of the animals of the test group showed any sort of allergic reactions after application of Ferric Carboxymaltose injection. It proved the hypersensitivity activity rate of Ferric Carboxymaltose drug to be 0% and the drug has been classified as non - allergic under experimental conditions.

Group	Animal number	Sex	Gross Pathology Observation
G1 (Control)	1489	Male	External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1490		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1491		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1492		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1493		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1494		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1495	Female	External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1496		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1497		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1498		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1499		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1500		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized

Group	Animal number	Sex	Gross Pathology Observation
G2 (Test)	1501	Male	External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1502		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1503		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1504		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1505		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1506		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1507	Female	External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1508		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1509		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1510		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized

Group	Animal number	Sex	Gross Pathology Observation
G2 (Test)	1511	Female	External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1512		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
G3 (Positive control)	1513	Male	External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1514		External: Patchy erythema noticed over left flank area Internal: Nothing Abnormal Visualized
	1515		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1516		External: Patchy erythema noticed over left flank area Internal: Nothing Abnormal Visualized
	1517		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1518		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1519	Female	External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1520		External: Patchy erythema noticed over left flank area Internal: Nothing Abnormal Visualized
	1521		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1522		External: Patchy erythema noticed over left flank area Internal: Nothing Abnormal Visualized
	1523		External: Nothing Abnormal Visualized Internal: Nothing Abnormal Visualized
	1524		External: Patchy erythema noticed over left flank area Internal: Nothing Abnormal Visualized

Figure 4: Gross Pathology data of animals

Following this event, the present clinical trial is conducted by incorporating human subjects from four different regions in Kolkata and Howrah to identify whether Ferric Carboxymaltose drug is also non - hypersensitive to human subjects. A total of 100 population are included in the study from the regions of Behala, Basirhat, Howrah, and ID & BG. All of them are infused with diluted drug concentration to observe whether they develop any kind of analyphlactic shock, respiratory troubles, restlessness, or not. The pre - trial and post - trial physiological conditions of the human population are recorded.

2. Study Design

2.1. Overview

A multicenter, randomized trialis designed to assess hypersensitivity profile of intravenous FCM drug for the treatment of iron deficiency anaemia. In accordance with the instruction of the sponsor Eskag Pharma on the basis of their clinical experience, it has been recommended that the rate of iron infusion should be 50% at initiation, and the rate should not be increased until it is ascertained to be well - tolerated by the patient in 15 - 20 minutes. For the ease of recognition as well as appropriate management of hypersensitivity reactions to FCM formulation (sponsored by Eskag Pharma) the following diagnosis has been performed to the patients:

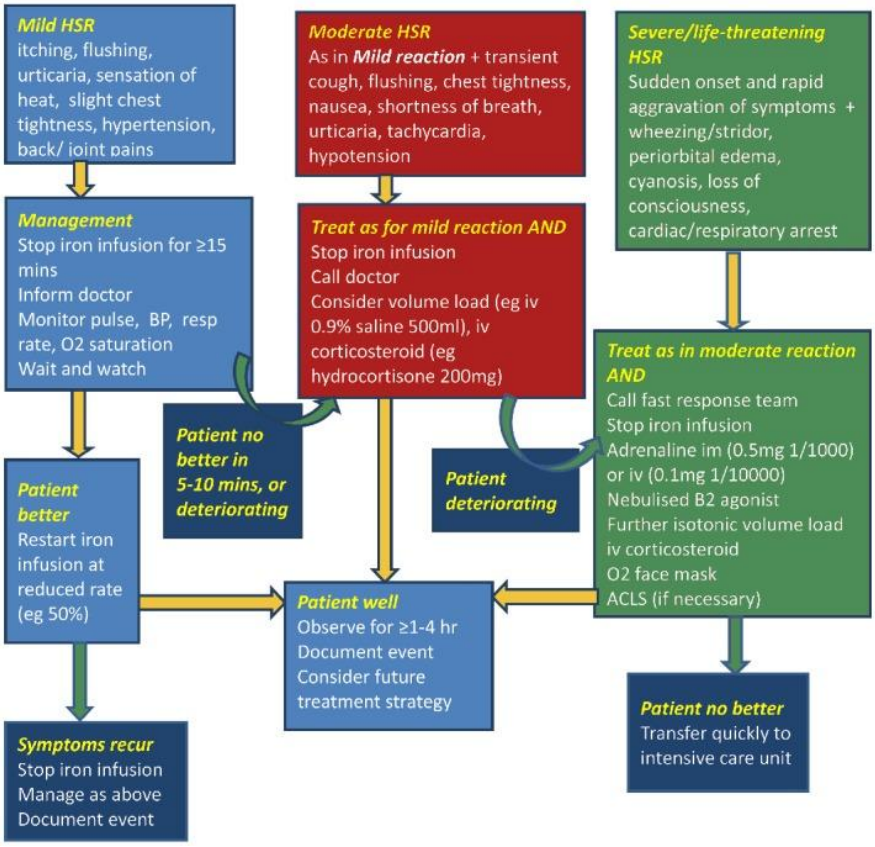


Figure 5: Gradation and management of hypersensitivity reaction

A total of 100 human subjects are included from four different centres of Basirhat (location 1), Behala (location 2), ID & BG (location 3), and Howrah (location 4). All patients received intravenous FCM in diluted form (100 ml Ns). The study is conducted for a period of ten months; it is initiated in June 2022 and ended in March 2023. Patient details including their names, haemoglobin levels, and batch numbersare recorded at the initiation of the study. Vitals are noted in form of pre - iron administration and post - iron administration details. Both pre - administration and post - administration vitals encompass oxygen saturation, blood pressure, body temperature, pulse rate, vision, taste, anaphylactic shock, respiratory problems, and restlessness of the patients. Importantly, the trial includes those with and without anaemia. Patients with known history of hypersensitivity, iron overload, intravenous iron therapy to any component of FCM were excluded from the study.

	DATE	TIME	PROCESS OF DOSAGE	AMOUNT OF FCM	Hb.	BATCH NO
Location 1	06.04.2022-21.05.2022	06:15 PM-12:00 AM	Diluted in 100 ml NS	4 ml	7-9.9	ITR-3204 A
Location 2	09:04:2022-16:10:2022	10:00 AM-12:00 AM	Diluted in 100 ml NS	4 ml	7-9.9	ITR-3304
Location 3	01:03:2023-25:03-2023	09:45 AM-12:00 AM	Diluted in 100 ml NS	4 ml	7-9.9	ITR-3204 B
Location 4	16:02:2023-22:03-2023	10:00 AM-12:00 AM	Diluted in 100 ml NS	4 ml	7-9.9	ITR-3203 A

Figure 6: Patient details of the trial

2.2. Treatment protocol and Follow - up

The study protocol has been conducted in 3 phases including screening, initial treatment, and follow - up. After obtaining informed consent from the patients the following clinical evaluations were performed to confirm study eligibility: SPO2 of >97%, blood pressure 70 - 80/120 - 140 mmHg, normal body temperature, pulse rate from 70 to 100 bpm, clear vision, normal taste, no anaphylactic shock, with or without respiratory problems, and with or without restlessness. If all these eligibility criteria were fulfilled, the qualified patients were considered for day 0 visit and be randomized.

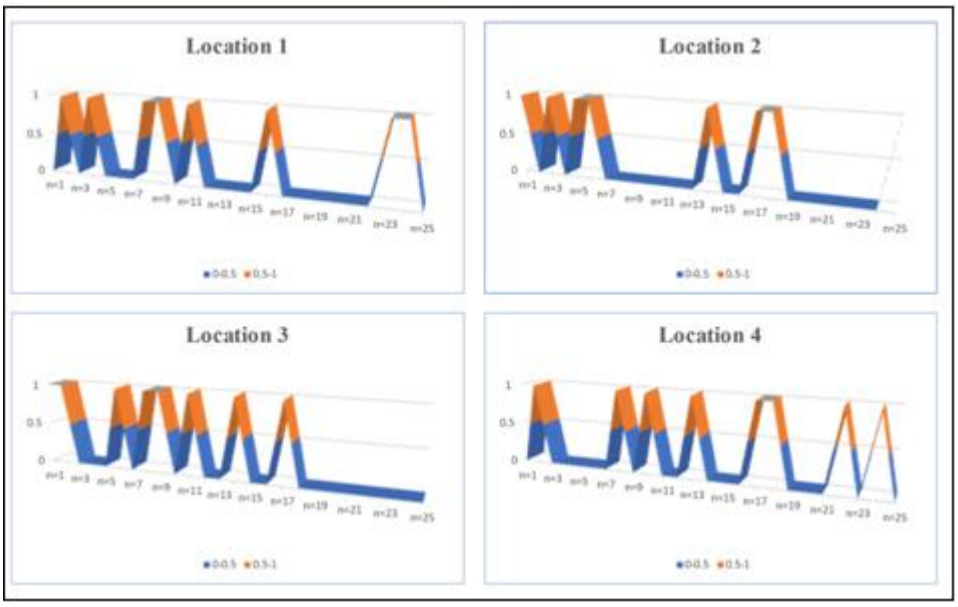
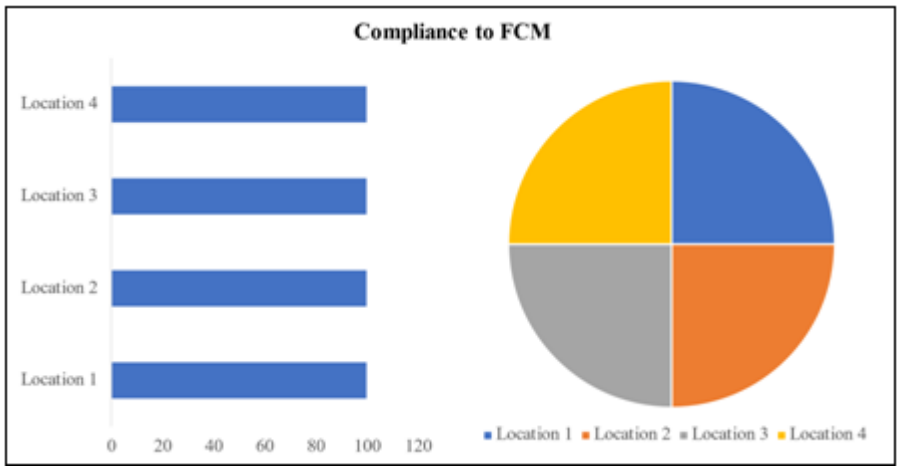


Figure 7: pre - iron administrations vitals of patients

2.3. Study End Points

Hypersensitivity reactions:

During the 10 - month period of the trial no single event of anaphylactic shock or hypersensitive reaction was observed to any of the patients. All patients had clear vision, normal taste, and no restlessness similar to the study initiation point. All of them had normal oxygen saturation, blood pressure, body temperature, and pulse rate. None of them suffered from any sort of respiratory problems. Even the participants who were previously reported with respiratory problems or restlessness, are found to be normal after infusion of Eskag - sponsored FCM injection. In addition, with ferric carboxymaltose, which has been formulated by Eskag Pharma, so far notrelated to possible iron deposition. Therefore, earlier clinical study performed with iron sucrose showed significant iron overload on liver parenchyma cell. In contrary to this, FCM is found not incorporated by liver parenchyma cell. These findings indicate that liver iron overload with FCM sponsored by Eskag is very unlikely. Chemical stability of ferric carboyxmaltose is higher compared to iron sucrose, but interestingly biostability order was reversed in human serum.



FCM INFUSED PATIENTS DETAILS - HOWRAH UNIT

PATIENT DETAILS								PRE IRON ADMINISTRATION VITALS								POST IRON ADMINISTRATION VITALS (AFTER 4Hrs)								
SL. NO.	DATE	TIME	PROCESS OF DOSAGE	AMOUNT OF FCM	PATIENT'S NAME	Hb.	BATCH NO	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	REMARKS
6	16-02-2023	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	ASTO MONDAL	7.5	ITR-3203A	99%	150/80	98° F	88	CLEAR	NORMAL	NO	YES	YES	99%	140/80	98° F	80	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
1	17-02-2023	10:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	JAYDUL SAHA	8.5	ITR-3203A	98%	130/70	99° F	85	CLEAR	NORMAL	NO	YES	YES	99%	190/90	99° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
12	17-02-2023	10:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	GOPAL GUPTA	9	ITR-3203A	98%	130/70	99° F	80	CLEAR	NORMAL	NO	NO	NO	99%	140/80	99° F	80	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
9	18-02-2023	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	MADAN PRASAD SHAH	8.9	ITR-3203A	99%	120/70	99° F	77	CLEAR	NORMAL	NO	NO	NO	99%	190/90	99° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
7	18-02-2023	06:15:00 PM	DIALUTED IN 100 ml Ns	4 ml	PROTIMA KOLEY	9.9	ITR-3203A	98%	130/70	98° F	78	CLEAR	NORMAL	NO	NO	NO	99%	160/80	98° F	85	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
17	20-02-2023	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	MITHU RAY	7	ITR-3203A	99%	130/70	98° F	77	CLEAR	NORMAL	NO	YES	YES	99%	190/90	98° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
20	21-02-2023	06:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	TARUN DAS	8.5	ITR-3203A	97%	130/70	99° F	80	CLEAR	NORMAL	NO	NO	NO	99%	140/80	98° F	85	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED

FCM INFUSED PATIENTS DETAILS - ID & BG UNIT

PATIENT DETAILS								PRE IRON ADMINISTRATION VITALS								POST IRON ADMINISTRATION VITALS (AFTER 4Hrs)								
SL. NO.	DATE	TIME	PROCESS OF DOSAGE	AMOUNT OF FCM	PATIENT'S NAME	Hb.	BATCH NO	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	REMARKS
1	01-02-2023	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	BHOLA MAHATO	9.5	ITR-3204B	99%	120/70	99° F	77	CLEAR	NORMAL	NO	NO	NO	99%	190/90	99° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
2	02-02-2023	09:45:00 AM	DIALUTED IN 100 ml Ns	4 ml	RUPESH KR. ROY	8.7	ITR-3204B	99%	140/80	98° F	77	CLEAR	NORMAL	NO	YES	YES	99%	160/80	98° F	90	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
3	02-02-2023	12:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	RAJA BASU	7.8	ITR-3204B	97%	120/70	98° F	78	CLEAR	NORMAL	NO	NO	NO	99%	140/80	98° F	80	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
4	03-02-2023	12:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	SHIB SANKAR MALAKAR	7.5	ITR-3204B	99%	140/80	99° F	99	CLEAR	NORMAL	NO	NO	NO	99%	150/90	98° F	80	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
5	04-02-2023	06:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	SANDHYA MONDAL	8.6	ITR-3204B	99%	130/80	98° F	80	CLEAR	NORMAL	NO	NO	NO	99%	140/70	98° F	85	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
6	05-02-2023	06:15:00 PM	DIALUTED IN 100 ml Ns	4 ml	MILAN BISWAS	9.7	ITR-3204B	98%	130/70	98° F	78	CLEAR	NORMAL	NO	NO	NO	99%	160/80	98° F	85	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
7	05-02-2023	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	NITISH KR. MONDAL	8.5	ITR-3204B	98%	120/70	98° F	72	CLEAR	NORMAL	NO	NO	NO	99%	140/80	99° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED

FCM INFUSED PATIENTS DETAILS - BEHALA UNIT

PATIENT DETAILS								PRE IRON ADMINISTRATION VITALS								POST IRON ADMINISTRATION VITALS (AFTER 4Hrs)								
SL. NO.	DATE	TIME	PROCESS OF DOSAGE	AMOUNT OF FCM	PATIENT'S NAME	Hb.	BATCH NO	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	REMARKS
1	04-06-2022	10:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	SK SAMIM AKTAR	7	ITR-3304	98 %	130 /70	99° F	85	CLEAR	NORMAL	NO	YES	YES	99 %	190 /90	99° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
2	07-06-2022	10:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	REHANA BIBI	7.5	ITR-3304	99 %	120 /70	99° F	72	CLEAR	NORMAL	NO	NO	NO	99 %	140 /80	98° F	88	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
3	07-06-2022	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	SAMBHUNATH DHARA	8.5	ITR-3304	99 %	140 /80	99° F	77	CLEAR	NORMAL	NO	YES	YES	99 %	140 /80	98° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
4	08-06-2022	06:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	BASUDEB TUNG	7.4	ITR-3304	99 %	130 /80	99° F	88	CLEAR	NORMAL	NO	NO	NO	99 %	160 /80	99° F	90	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
5	08-06-2022	09:45:00 AM	DIALUTED IN 100 ml Ns	4 ml	JHARNA DAS	8.7	ITR-3304	99 %	140 /80	98° F	77	CLEAR	NORMAL	NO	YES	YES	99 %	160 /80	98° F	90	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
6	08-06-2022	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	JYOTSNA DUTTA	8	ITR-3304	99 %	150 /80	98° F	88	CLEAR	NORMAL	NO	YES	YES	99 %	140 /80	98° F	80	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
7	08-06-2022	06:15:00 PM	DIALUTED IN 100 ml Ns	4 ml	RAJA DHANUK	9.7	ITR-3304	98 %	130 /70	98° F	78	CLEAR	NORMAL	NO	NO	NO	99 %	160 /80	98° F	85	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED

FCM INFUSED PATIENTS DETAILS - BASIRHAT UNIT

PATIENT DETAILS								PRE IRON ADMINISTRATION VITALS								POST IRON ADMINISTRATION VITALS (AFTER 4Hrs)								
SL. NO.	DATE	TIME	PROCESS OF DOSAGE	AMOUNT OF FCM	PATIENT'S NAME	Hb.	BATCH NO	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	SPO2	BP	TEMP.	PULSE RATE	VISION	TASTE	ANAPHYLACTIC SHCOK	RESPIRATORY PROBLEMS	RESTLESSNESS	REMARKS
1	06-04-2022	06:15:00 PM	DIALUTED IN 100 ml Ns	4 ml	KALIPADA SARKAR	9.7	ITR-3204A	98 %	130 /70	98° F	78	CLEAR	NORMAL	NO	NO	NO	99 %	160 /80	98° F	85	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
2	06-04-2022	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	GOPAL SARDAR	9.2	ITR-3204A	99 %	130 /70	98° F	77	CLEAR	NORMAL	NO	YES	YES	99 %	190 /90	98° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
3	06-04-2022	06:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	TILAK KR SARKAR	9.1	ITR-3204A	97 %	130 /70	99° F	80	CLEAR	NORMAL	NO	NO	NO	99 %	140 /80	98° F	85	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
4	07-04-2022	10:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	HASANUR JAMAL MOLLA	8	ITR-3204A	98 %	130 /70	98° F	72	CLEAR	NORMAL	NO	YES	YES	99 %	140 /80	98° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
5	09-04-2022	10:00:00 AM	DIALUTED IN 100 ml Ns	4 ml	BIDYUT DEY	7.5	ITR-3204A	99 %	120 /70	99° F	72	CLEAR	NORMAL	NO	NO	NO	99 %	140 /80	98° F	88	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
6	09-04-2022	02:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	ARIF BILLA	9.5	ITR-3204A	99 %	120 /70	99° F	77	CLEAR	NORMAL	NO	NO	NO	99 %	190 /90	99° F	79	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED
7	09-04-2022	10:00:00 PM	DIALUTED IN 100 ml Ns	4 ml	MARJINA BIBI	8.3	ITR-3204A	98 %	150 /80	98° F	77	CLEAR	NORMAL	NO	NO	NO	99 %	140 /80	99° F	80	CLEAR	NORMAL	NO	NO	NO	NO PROBLEMS OCCURRED

Figure 6: Compliance to FCM with respect to anaphylactic shock

Efficacy:

Ferric Carboxymaltose (FCM) and Iron Sucrose are both intravenous iron formulations used to treat iron deficiency anemia.6Ferric Carboxymaltose (FCM) and Iron Sucrose are both intravenous iron formulations used to treat iron deficiency anemia. Here's a comparison of their characteristics:

1) Chemical Composition:
   - Ferric Carboxymaltose: It is a complex of ferric iron and a carbohydrate called carboxymaltose.7
   - Iron Sucrose: It is a complex of ferric iron and sucrose.7
2) Indications:
   - Ferric Carboxymaltose: Used for the treatment of iron deficiency anemia in various conditions, such as in patients with inflammatory bowel disease, chronic kidney disease, and during pregnancy when oral iron is not tolerated or ineffective.8
   - Iron Sucrose: Also indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease, especially those on hemodialysis.
3) Administration:
   - Ferric Carboxymaltose: Usually administered as a single high - dose infusion, which allows for larger doses to be given at once, reducing the need for multiple administrations.
   - Iron Sucrose: Typically administered in smaller doses over multiple sessions due to the risk of adverse reactions with larger doses.
4) Efficacy: Both ferric carboxymaltose and iron sucrose have been shown to effectively increase hemoglobin levels and replenish iron stores in patients with iron

deficiency anemia. They have demonstrated similar efficacy in clinical trials.

5) Safety Profile:
   - Ferric Carboxymaltose: Generally well - tolerated, but like any iron infusion, it may cause some side effects, such as headache, dizziness, nausea, or local reactions at the injection site. Serious allergic reactions are rare but possible.8
   - Iron Sucrose: Generally considered safe, but it may also cause side effects like nausea, vomiting, diarrhea, and injection site reactions. Anaphylactic reactions are possible but uncommon.
6) Dosage and Frequency:
   - Ferric Carboxymaltose: Due to its high - dose infusion, it can be given in larger amounts less frequently compared to iron sucrose.
   - Iron Sucrose: Given in smaller doses over multiple sessions due to the risk of adverse reactions with higher doses.
7) Cost: The cost of these medications may vary depending on the region, healthcare system, and other factors. In some cases, one formulation may be more cost - effective than the other.

Ferric Carboxymaltose (FCM) Group:
- Total iron deficit was calculated for each patient before starting the treatment.
- FCM was administered intravenously using the product of Eskag Pharma.
- The maximum dose per sitting was 1000 mg of FCM.
- The FCM dose was diluted in 200 ml of 0.9% normal saline and infused over 30 minutes. The longer infusion protocol of 30 minutes was used due to limited safety data for its use in pregnancy, which deviates from the manufacturer's recommended 15 - minute infusion.
- Subsequent doses (if needed) were planned on day 7 and day 14, and the doses were rounded off to the nearest 100 mg.

Iron Sucrose (ISC) Group:
- Patients in the ISC group were administered intravenous iron sucrose using the product "InjOrofer S" from Emcure Pharmaceuticals Ltd., Pune, India.
- The initial dose of ISC was 300 mg.
- ISC was administered in 200 ml of normal saline over 15 - 20 minutes.
- The treatment was given twice weekly until the required dosage was completed, with the maximum not to exceed 600 mg per week.

Safety Monitoring:
- The general condition of the patient, blood pressure, and pulse rate were noted before the infusion.
- During the infusion, blood pressure and pulse rate were monitored every five minutes.
- Fetal heart rate monitoring was performed both before and after the infusion to ensure the safety of the fetus during treatment.

The results showed that the mean rise in hemoglobin at 12 weeks was significantly higher in the FCM group compared to the ISC group. Specifically:

FCM Group: The mean increase in hemoglobin was 29 g/L (grams per liter) after 12 weeks of treatment.
ISC Group: The mean increase in hemoglobin was 22 g/L after 12 weeks of treatment.

The p - value, which is a statistical measure, was reported to be less than 0.001. This indicates that the difference in hemoglobin increase between the FCM and ISC groups was statistically significant.

In summary, the study suggests that treatment with ferric carboxymaltose resulted in a greater increase in hemoglobin levels compared to iron sucrose treatment after 12 weeks of therapy in the studied population. This difference in efficacy may have clinical implications when choosing between these two intravenous iron formulations for the management of iron deficiency anemia in pregnant patients or other populations. However, it's essential to consider other factors, such as safety, tolerability, and individual patient characteristics, when making treatment decisions. Always consult with a healthcare professional for personalized medical advice.

1) Baseline Hb levels:
- FCM group (n = 50): Baseline hemoglobin levels were 85.7 g/L with a standard deviation of ± 8.9 g/L.
- ISC group (n = 50): Baseline hemoglobin levels were 86.7 g/L with a standard deviation of ± 8.6 g/L.

The difference in baseline hemoglobin levels between the two groups was not statistically significant (p value not mentioned). The confidence interval (CI) for the difference ranged from - 4.49 to 2.49 g/L.

2) Endline Hb levels (after 12 weeks):
- FCM group (n = 50): Hemoglobin levels at the end of 12 weeks were 115.3 g/L with a standard deviation of ± 4.6 g/L.
- ISC group (n = 50): Hemoglobin levels at the end of 12 weeks were 108.8 g/L with a standard deviation of ± 4.4 g/L.

The difference in hemoglobin levels between the two groups at the end of 12 weeks was statistically significant (p value not mentioned). The confidence interval (CI) for the difference ranged from 4.7 to 8.29 g/L.

3) Change in Hb levels from baseline to 12 weeks:
- FCM group (n = 50): The mean change in hemoglobin levels from baseline to 12 weeks was an increase of 29.6 g/L with a standard deviation of ± 8.2 g/L.
- ISC group (n = 50): The mean change in hemoglobin levels from baseline to 12 weeks was an increase of 22.1 g/L with a standard deviation of ± 8.2 g/L.

The difference in the change in hemoglobin levels between the two groups was statistically significant (p value not mentioned). The confidence interval (CI) for the difference ranged from - 4.24 to - 10.76 g/L.

In summary, the study shows that after 12 weeks of treatment, the ferric carboxymaltose (FCM) group had a significantly greater increase in hemoglobin levels compared to the iron sucrose (ISC) group. The difference in the change

in hemoglobin levels between the two groups was approximately 7.5 g/L in favor of the FCM group.

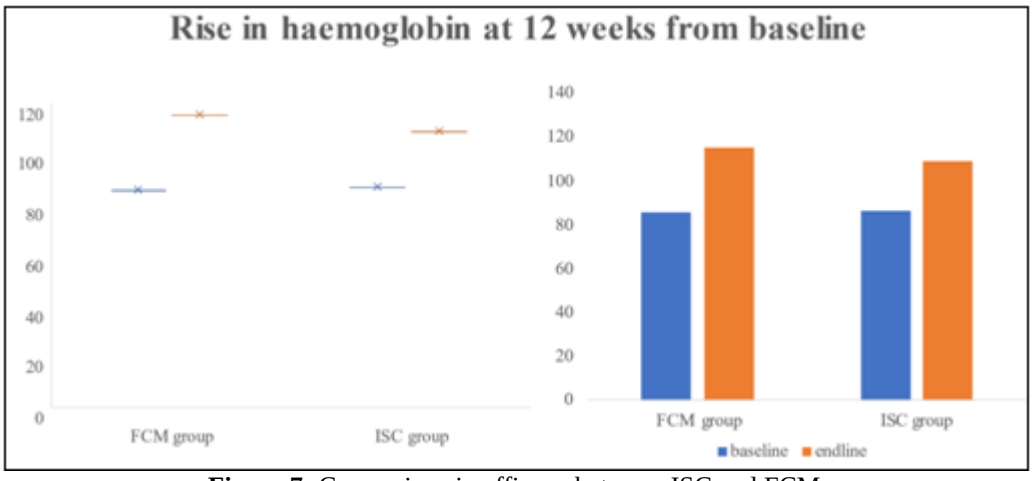


Figure 7: Comparison in efficacy between ISC and FCM

3. Discussion

Intravenous iron is increasingly used for patients with iron deficiency anaemia. When oral iron becomes poorly tolerated or are ineffective, the infusion of iron particles is recommended. However, acute allergic reactions are frequently observed with iron infusion in patients with iron deficiency anaemia. The report published by the European Medicines Agency (EMA) in 2013 revealed that adverse drug reactions were evident with all intravenous iron drugs available in Europe at that time. The 2 - year investigative study expressed that the iron formulations of sodium ferric gluconate, iron (III) - hydroxide dextran complex, iron sucrose, iron (III) isomaltoside 1000, and ferric carboxymaltose were associated with adverse hypersensitive reactions to the patients. The EMA stated that hypersensitivity reactions can occur to anyone given intravenous iron; thus, it is essential to check the preparation of the infusion as per the governance of the manufacturer or sponsor. In the present study, as per the instruction of the sponsor Eskag Pharma on the basis of their clinical experience, it has been recommended that the rate of iron infusion should be 50% at initiation, and the rate should not be increased until it is ascertained to be well - tolerated by the patient in 15 - 20 minutes. While there is a large number of reports on life - threatening hypersensitivity reactions of iron infusions, the present trial report reflecting not a single event of allergic reactions to any of the patients remains noteworthy. Complement activation - associated pseudo - allergy induced by iron nanoparticles is possibly a more common pathogenetic mechanism with acute reactions to the formulations of intravenous iron compared to immunological IgE - mediated responses. In this background, the Eskag Pharma sponsored FCM infusion formulation seems to be safe for the patients with iron deficiency anaemia without any threats of hypersensitive reactions. The present study recommends the utilisation of Eskag - sponsored Ferric Carboxymaltose infusion to the patients who have iron deficiency anaemia and are intolerant to oral iron formulations.

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