Original Article

TO EVALUATE THE SAFETY AND EFFICACY OF INJECTION FERRIC CARBOXYMALTOSE IN MANAGEMENT OF MODERATE AND SEVERE ANEMIA IN SECOND AND THIRD TRIMESTER PREGNANCY

Madhukar Shinde[1], Hemant Deshpande[1], Mariam Dilshad Shaikh[1], Shaikh Mohammed Yusuf Dilshad[2]

[1]Department of Obstetrics and Gynaecology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune 411018, India.
[2]Jawaharlal Nehru Medical College; Datta Meghe Institute of Medical Sciences, Sawangi, 442001, India.
Corresponding Author: Dr. Mariam Dilshad Shaikh
Email address: drmariamdilshad@gmail.com

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Abstract

Background: Ferric carboxymaltose (FCM) is a novel and effective drug in raising haemoglobin levels and in particular replenishing iron stores, however there is a limited knowledge about its safety and efficacy in Indian pregnant women. We performed this study to evaluate the safety and efficacy of injection FCM in management of moderate and severe anemia in 2nd and 3rd trimester pregnancy.

Methods: Prospective study conducted at Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune. 30 pregnant patients of moderate anaemia and 30 pregnant patients of severe anaemia with gestational age 20 weeks and above as determined by correlating last menstrual period (LMP) and clinical examination were included. Data was recorded before injection FCM transfusion, followed by two weeks and four weeks post transfusion. Adverse effects post infusion were carefully noted. Data was analysed by GraphPad Prism 8.0.2 software using the repeated measures ANOVA followed by post hoc turkey test wherever required. Statistically significant P-value = 0.05

Results: Data was recorded from 60 patients for safety and efficacy out of which 30 patents had severe and 30 had moderate anemia. Haemoglobin level increased significantly after two weeks (0.92g/dL p = <0.0001) and after four weeks (1.92g/dL p = <0.0001) post FCM injection as compared to Hb level before injection. Significant increase in Hb levels was also observed in severe and moderate anemia patients. Increase in Hb levels for severe anemia pateints after 2 weeks (0.96g/dL, p = <0.0001) and 4 weeks (1.96g/dL, p= <0.0001) post FCM injection and for moderate anemia patients 2 weeks (0.89g/dL, p= <0.0001) and 4 weeks (1.88g/dL, p= <0.0001) post FCM injection was observed as compared to Hb level before injection. Patients who received FCM injection in second trimester and third trimester showed significant increase in Hb levels. Second and third trimester patients showed increase in Hb level after 2 weeks (0.93g/dL, p = <0.0001 and 0.89g/dL, p = <0.0001 respectively) and after 4 weeks (1.98g/dL, p = <0.0001 and 1.81g/dL, p = <0.0001 respectively). Post transfusion reaction was observed in 16% of the patients with itching and rashes being the most common.

Conclusion: FCM can significantly increase Hb in a shorter amount of time in patients who have ante-partum iron deficiency anaemia, particularly in people who have severe anaemia. Because it is able to deliver a substantial iron dose in a relatively short period of time, FCM may be an effective treatment option for patients who need to replenish their iron stores in a more expedient manner.

Keywords: Anemia; ferric carboxymaltose; pregnancy; trimester.

Introduction

Anemia is the most prevalent public health issue worldwide, particularly in low-income and developing nations, with India having the highest prevalence [1].Anemia in pregnancy is mainly due to nutritional causes, usually iron deficiency affecting severely both mother and developing fetus[2].

Most women in India, already have low iron stores at the onset of pregnancy due to malnutrition, low socio-economic status, poor diet due to low income, multiparity, less gap in between pregnancies, adding to already increased Iron demand in pregnancy.

Pregnancy-related iron deficiency anaemia is indirectly linked to maternal mortality because it increases the risk of heart failure, postpartum haemorrhage, sepsis, and shock. Significant maternal, foetal, and neonatal morbidity are also linked to it [3]. Blood transfusions, cardiovascular issues, depression, weakness, and lethargy that impair physical and mental function are all more likely to occur, and lower immunity makes people more susceptible to infections. Additionally, it results in preterm birth [4], intrauterine growth restriction [5], foetal death, low birth weight, an increased risk of infections, low APGAR birth scores, and delayed neurocognitive development [6].

Oral iron is recommended as the first line treatment for iron deficiency anemia and also as prophylaxis to prevent iron deficiency in pregnancy.

However, gastrointestinal side effects coupled with poor compliance and poor tolerability leads to significant disadvantage of oral iron supplementation.

Intravenous (i.v.) iron solutions provide a higher and faster replenishment of iron stores than oral iron therapy without the gastrointestinal side effects that are associated with oral iron. The development of dextran-free parenteral iron formulations with improved safety profiles and rapid delivery periods has revolutionised the use of this approach for treating iron deficiency anaemia, and it needs to be considered the main therapy for moderate to severe IDA [7].

Iron sucrose is a substitute for intravenous iron that is dextran-free. IV Iron Sucrose includes an inadequate dose, repeated infusions, and poor patient compliance despite a good increase in Hb levels. With the introduction of ferric carboxymaltose (FCM), an i.v. iron formulation that can be used at high doses and allows for fast delivery, treating iron deficiency anaemia is becoming easier [8].

The first of the recently approved treatments for high-dose and speedy replenishment of depleted iron stores is FCM, a novel parenteral iron compound free of dextran. FCM is composed structurally of a ferric hydroxide core and a carbohydrate shell. [9] The design of the macromolecular ferric hydroxide carbohydrate complex allows for controlled iron delivery to the RES cells and further transport to transferrin and ferritin, the iron-binding proteins, with little likelihood of releasing significant amounts of ionic iron into the serum. [10]

Treatment with FCM should be restricted to the second and third trimesters in order to assess the benefits against any potential risks to the mother and foetus. In most trials, it was determined that FCM is more effective over oral iron for replacing body iron and for increasing Hb levels. It was also found to be significantly quicker and more effective than ferrous sulphate. The efficiency of FCM is also associated with significant cost-saving benefits for hospitals, medical staff, and patients (less frequent and shorter hospital visits) [8].

Efficacy and safety of ferric carboxymaltose in correcting iron-deficiency anemia has been reported in an extensive reviewed by Bailie GR (2010) [11]. It concurs with effectiveness and tolerability of Ferric carboxymaltose (FCM, Ferinject) in the treatment of iron-deficiency anemia (IDA). They further report the improvement in the levels of Hb, ferritin and transferrin. Similar other studies show that FCM is an effective and well-tolerated option in the treatment of IDA [12, 13, 14].

RESULTS

The mean age of the study population was 25.4 ± 17 years. Majority of the study population belonged to the age group of 19-25 years (53.3%) followed by 26-30 years (35.0%) and > 30 years (11.7%) (Table 1).

Table 1: Distribution of study population according to Age

Age (yrs)	Frequency	Percent
19-25 years	32	53.3%
26-30 years	21	35.0%
> 30 years	7	11.7%

The study population was distributed based on gravida. Among the population, 26 (43.3%) were gravida 1, 13 (21.7%) were gravida 2, 10 (16.7%) were gravida 3, 8 (13.3%) were gravida 4, 2 (3.3%) were gravida 5 and 1 (1.7%) were gravida 6 (Table 2).

Table 2: Distribution of study population according to gravida.

Gravida	Frequency	Percent
1	26	43.3%
2	13	21.7%
3	10	16.7%
4	8	13.3%
5	2	3.3%
6	1	1.7%

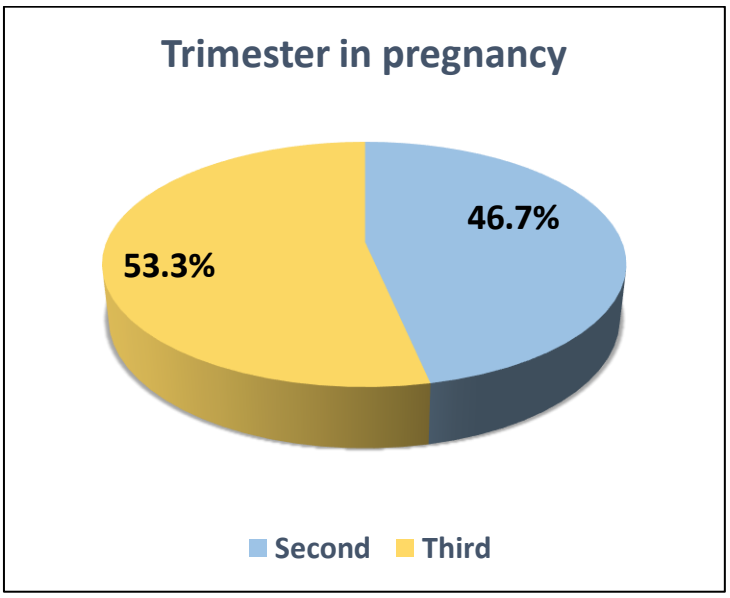
The study population was distributed based on whether the pregnancy was singleton or twin. It was found that 58 (96.7%) has singleton pregnancy and 2 (3.3%) subjects had twins.

Since our study focuses on analysing the safety and efficacy of FCM injection second and third trimester of pregnancy, the population under study had 46.7% subjects in their Second trimester and 53.3% in third trimester (Table 3, figure 1).

Table 3: Distribution of study population according to trimester in pregnancy

Trimester in pregnancy	Frequency	Percent
Second	28	46.7%
Third	32	53.3%
Total	60	100.0%

Figure 1: Distribution of study population according to trimester in pregnancy

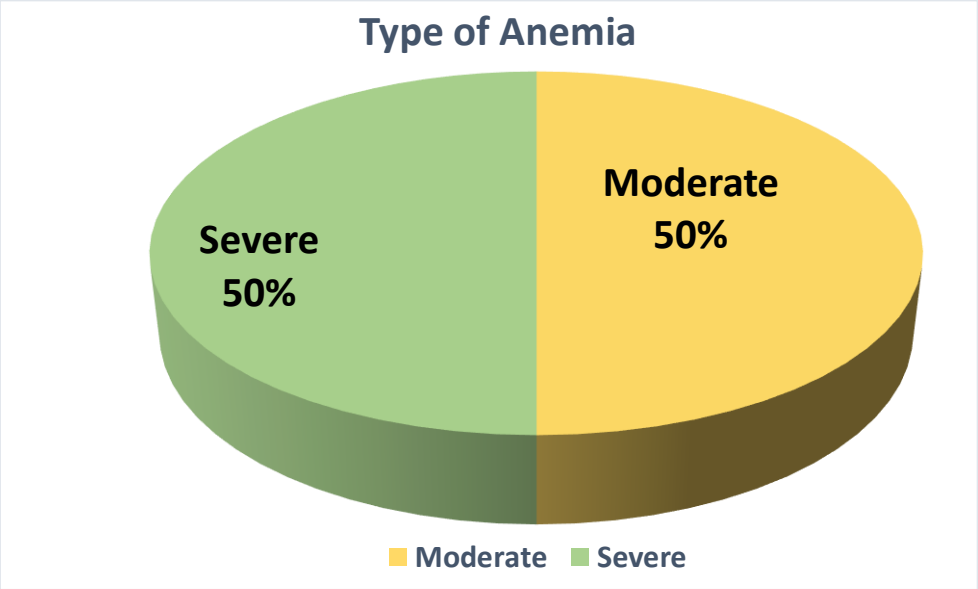


Our study population included subjects that had either severe or moderate anemia during pregnancy. Moderate and severe anemia was found in 50% of the population each (Table 4, figure 2).

Table 4: Distribution of study population according to type of anaemia

Type of Anemia	Frequency	Percent
Moderate	30	50%
Severe	30	50%
Total	60	100.0%

Figure 2: Distribution of study population according to type of anemia

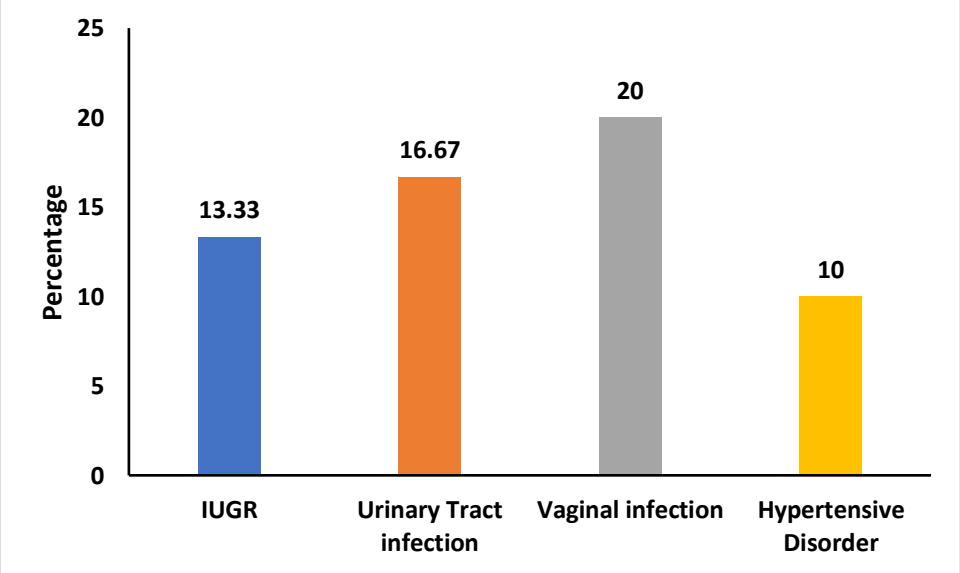


All patents were examined and investigated for pregnancy related IDA as a risk factor. Of the total population 36 (60%) subjects presented anemia as risk factor for vaginal infection (20%) followed by urinary tract infection (16.67%), IUGR (13.33), and hypertensive disorder (10%) (Table 5, Figure 3)

Table 5: Distribution of population with IDA associated comorbidity.

	Frequency	Percentage
IUGR	8	13.33
Urinary Tract infection	10	16.67
Vaginal infection	12	20.00
Hypertensive Disorder	6	10.00

Figure 3: Distribution of population with IDA associated comorbidity

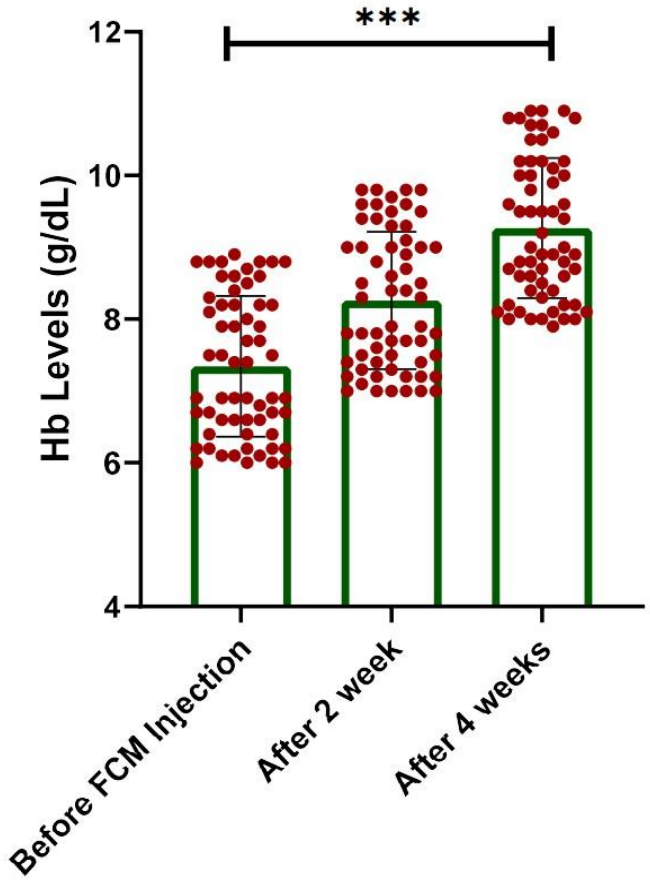


The mean Hb level was compared before giving Injection FCM (500mg), After 2 weeks of injection FCM and After 4 weeks of injection FCM. The mean Hb level increased significantly from Before giving Injection FCM to After 2 weeks of injection FCM to After 4 weeks of injection FCM. (Table 6, Figure 4)

Table 6: Distribution of study population according to Hb levels pre and post infusion

Hb level	**Mean**	**Std. Deviation**	**p-value**
Before giving Injection FCM	7.34	0.98	
After 2 weeks of injection FCM	8.26	0.96	
After 4 weeks of injection FCM	9.26	0.98	<0.0001

Figure 4: Hb levels pre and post FCM injection (*** P-value <0.0001).

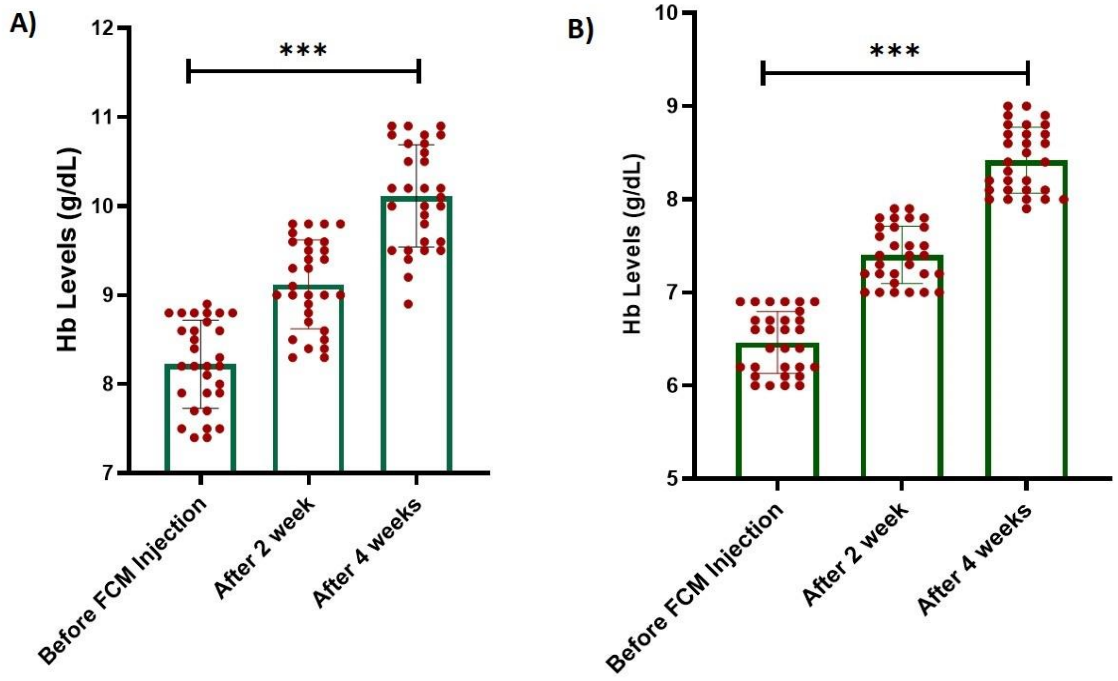


Among Moderate and Severe type of Anemia, the mean Hb level was compared between Before giving Injection FCM, after 2 weeks of injection FCM and After 4 weeks of FCM injection. The mean Hb level increased significantly from Before giving Injection FCM to After 2 weeks of injection FCM to After 4 weeks of injection FCM. (Table 7, Figure 5)

Table 7: Comparison of study population according to Hb levels in different types of anaemia pre and post FCM Injection

	Hb Levels						
	Before Injection		After 2 weeks		After 4 weeks		
Severity of Anemia	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	p-value
Moderate	8.23	0.49	9.12	0.50	10.11	0.57	<0.0001
Severe	6.46	0.33	7.42	0.31	8.42	0.35	<0.0001

Figure 5: Hb levels pre and post infusion in: A) Moderate anemia. B) Severe Anemia (*** P-value <0.0001)

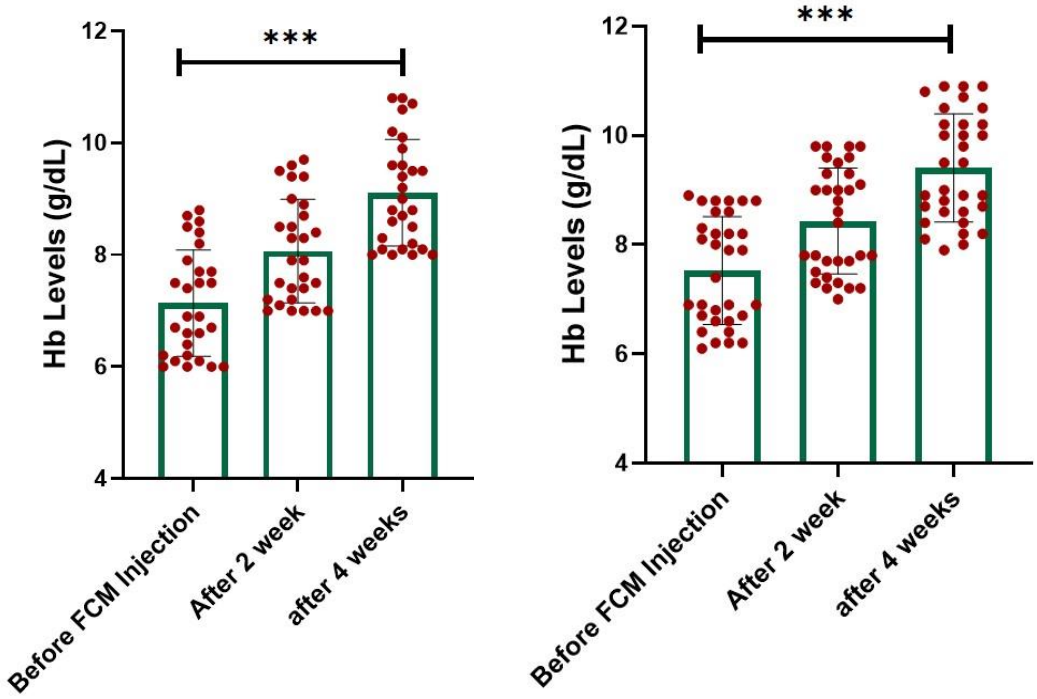


During the Second and Third Trimester, the mean Hb level was compared between Before giving Injection FCM, After 2 weeks of injection FCM and After 4 weeks of injection FCM. The mean Hb Levels increased significantly from before injection to after 2 weeks to after 4 weeks (Table 8, Figure 6).

Table 8: Comparison of study population according to Hb levels in second and third trimester of anaemia pre and post FCM Injection

	Hb Levels						
Trimester in pregnancy	Before Injection		After 2 weeks		After 4 weeks		P-Value
	Mean	Std. dev.	Mean	Std. dev.	Mean	Std. dev.	
2nd Trimester	7.13	0.95	8.06	0.93	9.11	0.95	<0.0001
3rd Trimester	7.84	0.99	8.73	0.97	9.65	0.99	<0.0001

Figure 6: Hb levels pre and post infusion in: A) Second trimester. B) Third trimester (*** P-value <0.0001)

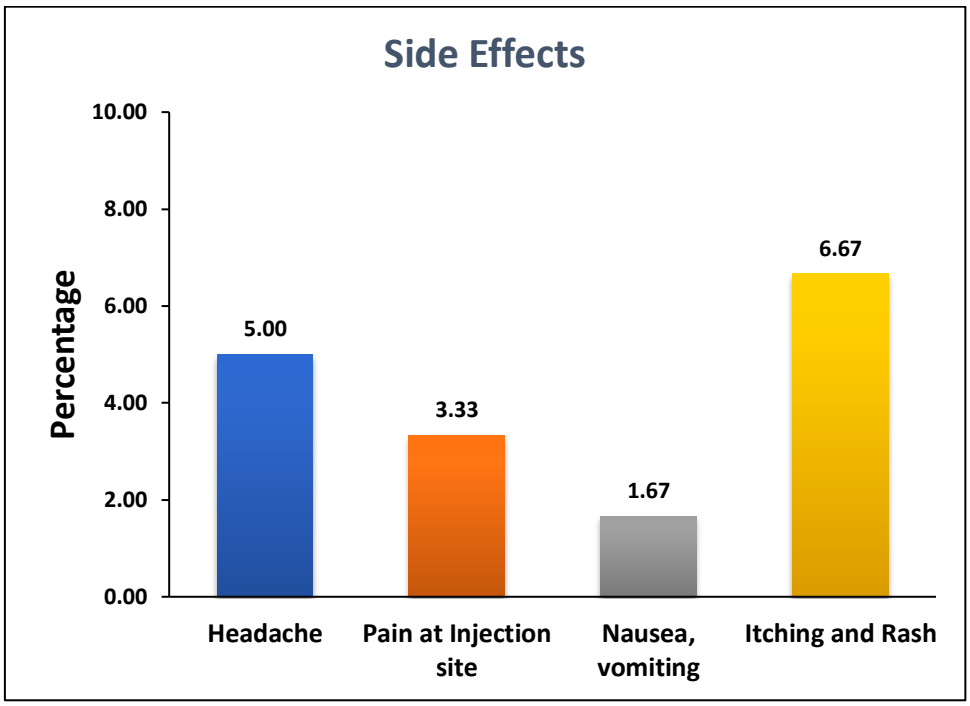


Post Transfusion reaction was reported among 10 (16%) patients. The most common was itching and rash (6.67%) followed by headache (5%), pain at injection site (3.33%) and nausea and vomiting (1.67%) (Table 9, figure 7)

Table 9: Distribution of study population according to adverse effects

Side Effect	Frequency	Percentage
Headache	3	5.00
Pain at Injection site	2	3.33
Nausea, vomiting	1	1.67
Itching and Rash	4	6.67

Figure 7: Side effects post transfusion



Discussion:

The results of the current study add to the growing body of data that FCM is both effective and safe in treating anaemia, particularly among pregnant women in India.

Risk Factors:

In our study 36 (60%) anemic subjects had vaginal infection (20%) followed by urinary tract infection (16.67%), IUGR (13.33), and hypertensive disorder (10%). Our study is in concurrence with other studies that have shown association of anemia with IUGR [5], bacterial vaginosis [15], gestational hypertension [16], UTI [17, 18].

Hb level:

In present investigation, the mean Hb level increased significantly from before giving Injection FCM to After 2 weeks of injection FCM followed by After 4 weeks of injection FCM. During the Second and Third Trimester, the mean Hb Levels increased significantly from before injection to after 2 weeks to after 4 weeks. *Bhat et al*. [19] reported that pregnant women reported increase of 2.37±0.51 g/dl in Hb level after receiving FCM. *Mishra et al*. [20] found that after three weeks of follow-up, the mean haemoglobin levels had grown by 2.37 gm percent; these results were statistically significant.

At 1 week after receiving FCM, Pandya et al., 2017 show that there was a statistically significant increase in Hb levels compared to those at the beginning of the trial (2.03 gm/dl) [21]. The findings of several other randomised, controlled studies in postpartum patients employing FCM as a treatment arm lend substantial credence to the conclusions drawn from our own research. A randomised, comparative study was conducted by Van Wyck et al., 2007 to compare the rise in mean haemoglobin level that occurred after receiving IV FCM with a mean of the total dose being 1.4 gm (n = 174) to the rise in mean haemoglobin level that occurred after receiving Ferrous sulphate 325mg three times a day (n = 178). Patients who were given IV FCM saw a significant increase in their haemoglobin levels earlier that was larger than or equal to 2.0 gm/dl (7 days in comparison to 14 days with the orally administered iron) [22].

In present study, among subjects with Moderate and Severe Anemia, the mean Hb Levels increased significantly after 2 weeks and after 4 weeks post FCM injection. It concurs with the study carried out by Gupte et al., 2021 where they show a significant increase in Hb level in severe anemia patients as early as 20 days post FCM administration. The FCM injection dosage varied in the range 500 mg to 2000 mg based on iron demand, with 1057 mg being the mean dosage [23].

Another study by Froessler et al., 2014 reported that the haemoglobin levels were significantly higher (p 0.001) at first post-infusion time point (three weeks) in comparison to pre infusion Hb levels across the severity groups. At the second post infusion visit, the haemoglobin levels of women with ID who also had mild or severe anaemia were significantly higher than the first visit post infusion (p 0.01). The average rise in haemoglobin concentration after infusion between three and six weeks was 6.8 (1.2) g/L in women who had mild anaemia, but the increase in moderate anaemia group was 14.2 (4.1) g/L. At the conclusion of the sixth week following the infusion, all of the women's haemoglobin concentrations were higher than the appropriate level suggested for women in pregnancy (110 g/L), with exception of the ID severe anaemia group [14].

If anaemia is found late in pregnancy and compliance is expected to be low, the recommendations recommend that parenteral iron therapy, which may include FCM, be evaluated as a possible first-line treatment option.

Complications:

In our study, minor side effect was reported among 10 (16.6%) subjects. Our study is in concurrence with the study by Froessler et al., 2014. They have reported that 11% women experienced mild adverse events, while only 3.5% of the study population reported experiencing more than one adverse reaction. The most prevalent adverse being local irritation or skin soreness at infusion site, which occurred in 3% of women, whereas each of the other adverse events was detected in less than three percent of women. There was a statistically significant difference in the frequency of adverse events among severity groups ($p = 0.029$).

Mishra et al., 2018 reported that Sixteen of the women experienced local symptoms such as itching and irritation at the local site, while the remaining 19 of the women reported systemic effects such as giddiness, headache, and nausea [20].

Nausea, headache, dizziness, increased blood pressure, and responses at the injection site are some of the adverse medication reactions that frequently occur in patients who receive ferric carboxymaltose. Pandya et al., 2017 found that intravenous administration of FCM was safe and well tolerated; only four patients, or 0.7% of the total, experienced side effects such as nausea, shivering, palpitations, itching, or dyspnea. There were no reports of any adverse events that were considered significant [21]. Studies conducted by Rathod et al., 2015 and Damineni et al., 2016 came to the same conclusion: FCM was extremely well tolerated, with a rate of adverse events that was less than one percent [8].

In terms of the drug's tolerance and safety profile, the clinical studies with FCM investigated 5799 patients who were exposed to FCM. The majority of drug-related adverse effects were thought to be temporary and ranged from mild to moderate in intensity. Because of the lack of serious adverse effects, treatment was not permanently stopped in any patients. These investigations came to the conclusion that FCM has a clinically manageable safety profile and is well tolerated provided the appropriate dose, correct timing of infusion, and monitoring are used [24].

Conclusion

This prospective observational study demonstrates that 500mg of FCM administered intravenously is successful in the treatment of IDA in Indian pregnant women. In situations where resources are scarce, IV FCM is crucial in the treatment of IDA during pregnancy. When it comes to increasing Hb concentration and reconstituting iron

stores, FCM is superior and faster. Large doses could be administered over a brief period, which was very cost-effective for the patient and less demanding on hospital staff and resources.

It was found to significantly increase Hb in a shorter amount of time in patients who had ante-partum iron deficiency anaemia, particularly in people who had severe anaemia. Because it is able to deliver a substantial iron dose in a relatively short period of time, FCM may be an effective treatment option for patients who need to replenish their iron stores in a more expedient manner. The findings of our study provide evidence that IV FCM is both safe and effective in treating patients diagnosed with iron deficiency anemia in 2nd and 3rd trimester pregnancy in real-world clinical environment

References

1. Chaparro, C. M., & Suchdev, P. S. (2019). Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. *Annals of the New York Academy of Sciences*, *1450*(1), 15–31. https://doi.org/10.1111/nyas.14092
2. Friedman, A. J., Chen, Z., Ford, P., Johnson, C. A., Lopez, A. M., Shander, A., Waters, J. H., & van Wyck, D. (2012). Iron deficiency anemia in women across the life span. *Journal of women's health (2002)*, *21*(12), 1282–1289. https://doi.org/10.1089/jwh.2012.3713
3. Smith, C., Teng, F., Branch, E., Chu, S., & Joseph, K. S. (2019). Maternal and Perinatal Morbidity and Mortality Associated With Anemia in Pregnancy. *Obstetrics and gynecology*, *134*(6), 1234–1244. https://doi.org/10.1097/AOG.0000000000003557
4. Rahmati, S., Azami, M., Badfar, G., Parizad, N., & Sayehmiri, K. (2020). The relationship between maternal anemia during pregnancy with preterm birth: a systematic review and meta-analysis. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 33(15), 2679–2689. https://doi.org/10.1080/14767058.2018.1555811
5. Rondó, P. H., & Tomkins, A. M. (1999). Maternal iron status and intrauterine growth retardation. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *93*(4), 423–426. https://doi.org/10.1016/s0035-9203(99)90144-x
6. Abu-Ouf, N. M., & Jan, M. M. (2015). The impact of maternal iron deficiency and iron deficiency anemia on child's health. *Saudi medical journal*, *36*(2), 146–149. https://doi.org/10.15537/smj.2015.2.10289
7. Jimenez, K., Kulnigg-Dabsch, S., & Gasche, C. (2015). Management of Iron Deficiency Anemia. *Gastroenterology & hepatology*, *11*(4), 241–250.
8. Rathod, S., Samal, S. K., Mahapatra, P. C., & Samal, S. (2015). Ferric carboxymaltose: A revolution in the treatment of postpartum anemia in Indian women. *International journal of applied & basic medical research*, *5*(1), 25–30. https://doi.org/10.4103/2229-516X.149230
9. Cançado, R. D., & Muñoz, M. (2011). Intravenous iron therapy: how far have we come? *Revista brasileira de hematologia e hemoterapia*, *33*(6), 461–469. https://doi.org/10.5581/1516-8484.20110123
10. Lyseng-Williamson, K. A., & Keating, G. M. (2009). Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs*, *69*(6), 739–756. https://doi.org/10.2165/00003495-200969060-00007
11. Bailie G. R. (2010). Efficacy and safety of ferric carboxymaltose in correcting iron-deficiency anemia: a review of randomized controlled trials across different indications. *Arzneimittel-Forschung*, *60*(6a), 386–398. https://doi.org/10.1055/s-0031-1296303
12. Wani, S., Noushad, M., & Ashiq, S. (2019). REGAIN STUDY: Retrospective Study to Assess the Effectiveness, Tolerability, and Safety of Ferric Carboxymaltose in the Management of Iron Deficiency Anemia in Pregnant Women. *Anemia*, *2019*, 4640635. https://doi.org/10.1155/2019/4640635
13. Kant, S., Haldar, P., Malhotra, S., Kaur, R., Rath, R., & Jacob, O. M. (2020). Intravenous ferric carboxymaltose rapidly increases haemoglobin and serum ferritin among pregnant females with moderate-to-severe anaemia: A single-arm, open-label trial. *The National medical journal of India*, *33*(6), 324–328. https://doi.org/10.4103/0970-258X.321145
14. Froessler, B., Collingwood, J., Hodyl, N. A., & Dekker, G. (2014). Intravenous ferric carboxymaltose for anaemia in pregnancy. *BMC pregnancy and childbirth*, *14*, 115. https://doi.org/10.1186/1471-2393-14-115
15. Verstraelen, H., Delanghe, J., Roelens, K., Blot, S., Claeys, G., & Temmerman, M. (2005). Subclinical iron deficiency is a strong predictor of bacterial vaginosis in early pregnancy. BMC infectious diseases, 5, 55. https://doi.org/10.1186/1471-2334-5-55
16. An, H., Chen, H., Li, Z., Zhang, L., Zhang, Y., Liu, J., Ye, R., & Li, N. (2022). Association of Gestational Hypertension with Anemia under 5 Years Old: Two Large Longitudinal Chinese Birth Cohorts. Nutrients, 14(8), 1621. https://doi.org/10.3390/nu14081621
17. Bembalagi S and Sojitra MP. Study of relationship between anemia and urinary tract infection in pregnant women. Al Ameen J Med Sci 2018; 11(1):71-75.
18. Ru, Y., Pressman, E. K., Cooper, E. M., Guillet, R., Katzman, P. J., Kent, T. R., Bacak, S. J., & O'Brien, K. O. (2016). Iron deficiency and anemia are prevalent in women with multiple gestations. *The American journal of clinical nutrition*, *104*(4), 1052–1060. https://doi.org/10.3945/ajcn.115.126284
19. Bhat V, Kiran B, Deshmukh G, Kulkarni K, Rodge A. Efficacy and safety of ferric carboxymaltose in Indian pregnant women with iron deficiency anemia. Int J Reprod Contracept Obstet Gynecol 2021;10:4402-6.
20. Mishra, V., Roy, P., Gandhi, K., Choudhary, S., Aggarwal, R., & Sokabaj, S. (2018). Safety and Efficacy of Intravenous Ferric Carboxy Maltose in Iron Deficiency Anaemia During Post-partum Period. *Journal of Nepal Health Research Council*, *15*(3), 208–211. https://doi.org/10.3126/jnhrc.v15i3.18841
21. Pandya M, Patil P, Naik S, Ingole S, Jain R, Ferric Carboxymaltose Injection in Postpartum Iron Deficiency Anemia: Results from the prescription-event monitoring study. Indian J Obstet Gynecol Res 2017;4(1):92-95
22. Van Wyck, D. B., Martens, M. G., Seid, M. H., Baker, J. B., & Mangione, A. (2007). Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. *Obstetrics and gynecology*, *110*(2 Pt 1), 267–278.

23. Gupte, S. A., Venkataraman, G., Shah, A. S., Mudholkar, A. S., & Jangam, S. M. (2021). Clinical effects and safety of ferric carboxymaltose in pregnancy: An Indian real-life experience. *The journal of obstetrics and gynaecology research*, *47*(10), 3464–3470.

24. Lyseng-Williamson, K. A., & Keating, G. M. (2009). Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs*, *69*(6), 739–756.