A COMPARATIVE STUDY ON SAFETY, EFFICACY & COST EFFECTIVENESS OF FERRIC CARBOXYMALTOSE & IRON SUCRose IN DIALYSIS PATIENTS AT A TERTIARY CARE HOSPITAL

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ABSTRACT
The objective of our study was to evaluate the safety, efficacy and cost effectiveness of FCM, compared to IV iron sucrose in dialysis patients who have iron deficiency anemia. A prospective observational comparative study was carried out in 69 hemodialysis patients during the period of 6 months in a tertiary care hospital in Southern India. Our results showed that Ferric Carboxymaltose (FCM) was more efficacious, safer and cost effective compared to iron sucrose. Our study highlights on primary efficacy parameters - Hemoglobin(Hb), ferritin, serum iron and transferrin saturation (TSAT). In case of Hb, TSAT, serum iron FCM showed a decreased level of 69.25% ng/mL decrease whereas for iron sucrose only 53.81 ng/mL was observed. At least one drug-related treatment-emergent ADR occurred in 7 of 40 (17.3%) subjects in the FCM group and 13 of 29 (44.8%) subjects in the iron sucrose group. FCM has the advantage of allowing more iron to be administered in fewer infusions in patients with chronic kidney disease. FCM was superior to iron sucrose in replenishing the iron stores.

KEYWORDS: Ferric Carboxymaltose, Hemodialysis, Iron sucrose.

INTRODUCTION
According to World Health Organization (WHO) Global Burden of Disease Project, kidney diseases contribute about 850,000 deaths in every year of which Chronic Kidney Disease (CKD) is the 12th leading cause of death and 17th leading disability in the world. Approximately total burden of CKD is 800 per million in India.[1] The one who develop End Stage Renal Disease (ESRD) lose about 85 to 90 percent of kidney function and have a Glomerular Filtration Rate (GFR) of <15, should undergo dialysis or renal transplantation.[2] Certain conditions like anemia, hyperphosphatemia, hypoalbuminemia and hyperparathyroidism has been associated with CKD.[3] Among them, Iron Deficiency Anemia (IDA) is the most common complication of CKD.[4,5] When kidneys are damaged, they do not make enough erythropoietin resulting in the decreased production of Red Blood Cells (RBCs) causing anemia.[6] The reasons for iron deficiency in patients with ESRD includes less intake and reduced intestinal absorption of dietary iron, blood losses and/or increased iron requirements during therapy with Erythropoiesis Stimulating Agents (ESA).[1,4] In the dialysis patients, their treatment itself leads to iron loss.[8] Also continuous iron loss occurs due to blood withdrawal and gastrointestinal bleeding. For a Hemodialysis (HD) patient, an average of 1 to 2 g of iron will lose yearly. So, all dialysis patients receiving erythropoietin will develop IDA unless they are provided with IV iron preparations.[9] The symptoms of IDA include weakness, fatigue or lack of stamina, shortness of breath during exercise, headache, dizziness, pale skin, rapid heartbeat etc.[10]

Iron is considered as essential mineral found in every cell of the body.[11] The iron content in a normal adult ranges from 2-4 gm.[12] Even though it’s major role is in oxygen transportation and storage, it also play an important role in oxidative metabolism, synthesis and degradation of lipids, carbohydrates, Deoxyribo Nucleic Acid (DNA) & Riboxy Nucleic Acid (RNA) and also required for the Electron Transport Chain (ETC) in the mitochondria for Adenosine triphosphate (ATP) synthesis.[13] In 2012, Kidney Disease Improvement Global Outcome (KDIGO) clinical practice guidelines for anemia in CKD aimed to provide guidance on diagnosis, evaluation, management and treatment for all CKD patients are at risk of or with anemia. The serum ferritin is the gold standard method

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for evaluation of storage iron. The Transferrin Saturation (TSAT) is the most commonly used investigation for measuring the availability of iron to support erythropoiesis. For adult patients with anemia with /without iron or ESA therapy, KDIGO suggested IV iron if TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. [14]

Initially the first generation IV iron formulations like iron dextran have been used as an alternative to oral iron in the treatment of IDA but it resulted in severe immunological responses including fatal anaphylactic reactions. This paved way to the invention of second generation non-dextran preparations such as sodium ferric gluconate, which do not contain dextran or modified dextran, but they have significant dosage and administration rate limitation. They produced labile iron reactions at higher doses which may include hypotension, cramping, diarrhea or chest pain. [15] Iron sucrose, another iron preparation dissociates to iron and sucrose and the iron is transported as a complex with transferrin to target cells. [16] The iron in the precursor cell is incorporated into hemoglobin (Hb) as the cells mature into RBC. Recently a non-dextran parenteral iron preparation named Ferric Carboxymaltose (FCM), macromolecular ferric hydroxide carbohydrate complex has been introduced that can be rapidly administered in high doses. [15, 17] It allows controlled delivery of iron within the reticuloendothelial cells and subsequent delivery of the iron binding protein ferritin and transferrin, with minimal risk of release of large amounts of ionic iron in the serum. For the administration of typical 1000 mg course, 5 doses of iron sucrose and 1 dose of FCM is required. [18]

MATERIALS AND METHODS
A prospective observational comparative study conducted in the dialysis unit of GKNM Hospital, Coimbatore, Tamil Nadu from March 2015 to September 2015. All inpatients and outpatients who received FCM or iron sucrose during dialysis were included in our study. After getting proper consent from the patients, we collected data from 65 patients.

Ethical Consideration and Data Collection Method
The study protocol and informed consent form were approved by institutional ethics committee of GKNM Hospital, Coimbatore. During our study, we were in dialysis unit of GKNM Hospital and followed all the patients who met the inclusion criteria. Data was collected using a well-structured data collection form which includes patient’s demographics, medication history (including any allergy to drug and food), patient case history, laboratory parameters and medication chart. We reviewed the laboratory parameters regularly at each time when the patient visits the dialysis center. All the discrepancies observed have been documented appropriately in the data collection form designed for the study. Pharmaceutical care have been implemented by providing drug, disease or disorder, diet related information in person and also by leaflets, reminding patient for their next review. Adverse Drug Reactions (ADR) of FCM and iron sucrose were analyzed by Naranjo scale and reported.

The details on cost of the drugs (FCM and iron sucrose), cost of the supplies such as syringes, gauze, IV set, vasofix, supply management cost such as transport cost, storage facilities were collected from the pharmacy. The salary of pharmacists, clinical pharmacists, nurses, dialysis technicians, physicians were enquired and documented. The details of cost for laboratory services and treatment for ADR were collected from the patients. Statistical Analysis:

Statistical analysis was conducted by using paired student one sample t -test to compare the primary efficacy parameters. A P-value of <0.05 was considered to be significant. Using this value, percentages, means were calculated.

RESULTS AND DISCUSSION
Our study shows an analysis describing the outcomes of 69 patients in dialysis unit, who underwent IDA management by two iron supplements for 6 months in a tertiary care hospital at Southern India. Initially we analyzed 72 patients but 3 of them were excluded from the study, one undergone renal transplantation and the rest of them were transferred to distant dialysis center. Forty patients received FCM and 29 were iron sucrose. Male patients showed dominating as 45 in number while females were only 18 in number. After 6 months of follow up, 69 patients remained on treatment with no severe complaints and three were dropouts. Most of the patients had Diabetes Mellitus with hypertension in both the FCM and iron sucrose groups. Most of the dialysis patients in our study were graduated.

We evaluated the safety and efficacy of FCM and iron sucrose in each patient. Efficacy was evaluated by considering the primary and secondary parameters. Primary parameters include Hb values and iron profile (TSAT, ferritin and serum iron values). Secondary parameters include red blood cell indices (RBC, Hematocrit, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration and Red cell Distribution Width). Iron requirement was calculated based on the TSAT value. TSAT value is the ratio of serum iron and Total Iron Binding Capacity (TIBC), multiplied by 100. If TSAT is less than 25%, IV iron should be administered to the patient. All the patients in our study were well tolerated with the IV iron supplementation.

In our study, there were slight significant alterations in mean Hb, ferritin, TSAT and serum iron between FCM and iron sucrose. The mean of all patients of each month (M1 to M6) was calculated and student t-one sample test was performed by using SPSS software. The t values, p values, upper and lower limits were found by keeping the confidence interval as 95%. All patients in our study
received ESA concurrently with IV iron supplementation. In case of Hb, values of 6 months were taken while for the iron indices values of 3 months were only taken since it was performed only in a few patients. In FCM patients, the study drug was administered at a loading dose of 200 mg in 4 consecutive dialysis, followed by dose of 200 mg FCM monthly in the proceeding months. In iron sucrose group, patients received the loading dose of 200 mg in consecutive four dialysis, followed by weekly 200mg. For IV FCM, the mean Hb increased steadily from baseline while iron sucrose showed only smaller increase comparatively in the similar time course. Baseline values of primary efficacy parameters of both iron sucrose and FCM were calculated by taking the average values of the first month. FCM showed a mean increase in Hb values of 5.267 g/dL from the baseline (5.123 g/dL) whereas in iron sucrose, 3.30 g/dL of Hb level was only increased from the baseline (2.814 g/dL) (Figure 1). Adrian et al reported that after receiving FCM, the majority of the patients achieved a clinically relevant increase in Hb levels of ≥ 1.0 g/dL. [19]

In the FCM group, the serum ferritin declined about 89.6 ng/mL from the baseline (158.85 ng/mL) with a P value of 0.024. In iron sucrose patients, the ferritin values were decreased from the baseline 89.582 ng/mL to 35.77 ng/L with statistically significant values (P value= 0.05) (Figure 2). Sedighi et al demonstrated that serum ferritin was reduced even after IV iron treatment. [20] Similarly a mean increase of 20.02 µg/dL was observed in serum iron concentration from the baseline value (39.76 ng/mL) in FCM group (P value=0.014). However in iron sucrose, the mean increase was 16.4 µg/dL from the baseline (11.37µg/dL) and was statistically significant (P value = 0.05) (Figure 3). Finally, the mean TSAT level also increased more significantly in the FCM subjects with an increase from 21.53% baseline to 24.73% compared to iron sucrose patients with 1.781% increase from the baseline value (11.57%) (Figure: 4). The secondary efficacy parameters were significantly greater in the FCM group showing increase from baseline in mean Hct, MCH, MCHC and RDW compared to iron sucrose. While comparing the efficacy parameters of both groups, FCM was found to be more efficacious than iron sucrose.

Safety parameters were analyzed by examining drug interactions and ADRs. Both FCM and iron sucrose groups were well tolerated and no serious ADRs were found. About 7 patients in FCM group and 13 patients in iron sucrose experienced mild to moderate ADRs. We monitored blood pressure, pulse rate and heart rate in all patients before, during and after the administration of both the drugs. At least one drug-related treatment-emergent ADR occurred in 7 of 40 (17.3%) subjects in the FCM group and 13 of 29 (44.8%) in the iron sucrose group. The most common ADRs were nausea (28.5% in the FCM group versus 15.38 % in iron sucrose), vomiting (14.2% versus 7.69%), hypertension (28.5% versus 7.69%), hypotension (14.2% versus 23.0%) and hypersensitivity reactions (14.2% versus 7.69%). ADRs like constipation, headache, dizziness, rashes and taste disturbances was also observed in iron sucrose group, each with 7.69%. Most commonly occurred ADR in FCM was hypertension. In one patient hypertension was resolved spontaneously after or near the end of the infusion.

One patient was advised to stop FCM infusion due to hypertension. After half hour, the patient’s vital signs...
became stable and the infusion was restarted with proper monitoring. Onken et al also observed that hypertensive events were more common in the FCM group than iron sucrose and was transiently resolved within 30 minutes of infusion. Hypotension associated with iron sucrose was corrected by giving 100ml of 0.9% w/v of normal saline. Nausea & vomiting was treated by giving an antiemetic drug, 2 mg/ml ONDANSETRON subcutaneously. Hypersensitivity reaction has been solved by 100mg of HYDROCORTISONE. The symptoms resolved within 1 hour and 1.5 hours in FCM and iron sucrose patients respectively. Likewise, rashes were also developed after 5 hours of infusion with iron sucrose group, for which an antihistamine DIPHENHYDRAMINE was administered orally and improved symptomatically within 2 days. Headache was treated with analgesics.

We evaluated the biochemistry parameters and include electrolytes, phosphate, LFTs, PTH and bicarbonates. While assessing phosphorous levels, 34 patients were excluded who were on phosphate binder SEVLAMER. Out of the total 35 patients, 19 took FCM and 16 were iron sucrose. A non-significant decrease in phosphorous level (remained in the normal levels) were observed in 13 patients of FCM group but none in iron sucrose group. Hypophosphatemia were observed in the FCM group which was transient and not associated with the development of a serious ADR. One proposed explanation states that FCM transiently increases the levels of intact form of fibroblast growth factor 23a, leading to temporary reductions in plasma phosphate levels. Quinibi et al in his thesis conveys that a transient hypophosphatemia observed in the FCM group was not associated with any clinically relevant ADR. We suggested that monitoring serum phosphate levels may be beneficial in FCM patients, who were predisposed to phosphate homeostasis deregulation such as hyperparathyroidism or hypovitaminosis D. Two patients showed a slight non-significant variation in the LFT of FCM group and was not associated with significant changes in bilirubin levels. Iftikhar et al concluded that there was a mean increase in ALT and AST values from baseline to final value in the FCM group but remained within the respective normal changes. It might be due to the ADRs of FCM. A patient received 200mg FCM accidently for 3 consecutive dialysis showed elevated serum ferritin level and was advised to discontinue FCM for next two months. The patient was safe and no clinical changes were observed. IV iron sucrose was halted in one patient due to infection. Infection and inflammation alter iron homeostasis through immune-mediated mechanisms and restricts the supply of readily available iron. Our study showed no drug interactions.

Cost effectiveness analysis was carried out in all patients. For each hospital visits, a patient needs an IV set, gauze and vasofix for dialysis. The only extra expenses are the syringes to administer the drug into the dialysis tube. Both FCM and iron sucrose requires same number of hospital visits for dialysis. Iron sucrose needs to be administered four times per month while FCM, once in a month only, which emphasizes the use of FCM. So the total cost of disposable varied in each group. The management of ADR reflects the expenses for the treatment including headache, vomiting, hypotension etc. Monitoring costs includes the time spent by the healthcare professionals in providing pharmaceutical care to the patient. The patients are under complete medical observation during the infusion. Test dose is needed for iron sucrose to check hypersensitivity reactions. Iron sucrose needs to administer by diluting with 100 ml 0.9% w/v, normal saline, needs 1 hour for its administration while FCM was directly administered as IV push, which reduces the time loss. It produces considerable benefit including less disruption to their personal life. Productivity cost reflects missed days of work due to treatment of the patient as well as the caregiver who accompanies him. Productivity loss of iron sucrose exceeds FCM since the iron sucrose requires additional time for infusion. These factors will have a beneficial financial impact on patients and potentially to the wider community. Dillon et al concluded that the higher drug price of FCM may well be offset by savings in staff time and bed space (especially compared with iron sucrose) with greater efficacy. Health services and staffs also gain potential benefits from the newer iron therapies. More efficient use of the health services with reduced treatment, waiting time will all lead to save both nursing and medical time. It is cost effective for the patient and reduces burden for doctors and healthcare professionals by saving their time.

CONCLUSION

Our study aimed to find the best among IV iron supplements, FCM and iron sucrose in terms of efficacy, safety and cost effectiveness. FCM has shown the advantage of allowing more iron to be administered in fewer infusions in patients with CKD. It showed greater efficacy and produced significantly greater and sustained increase in Hb in a shorter period of time comparatively. FCM was superior to iron sucrose in replenishing the iron stores measured by ferritin, and in increasing TSAT, serum iron -indicators of iron available for erythropoesis. FCM shown better tolerability compared to iron sucrose with a lower incidence of ADRs. It was associated with transient, asymptomatic hypophosphatemia but managed automatically. Also FCM produced potential cost savings compared to iron sucrose, as iron sucrose required multiple outpatient visits and repeated IV access for patients to meet the standard therapeutic regimen.

LIMITATIONS OF OUR STUDY

Our study also underwent difficulty in defining relationship between exposure and outcome due to shorter period of time. The low sample size of our study results in fewer data. Usually the efficacy parameters like ferritin, TSAT and serum iron is evaluated once in 3
months but was neglected by some subjects due to financial problems. Short term follow-up limited us to describe the long-term safety of FCM and iron sucrose.

**FUTURE RECOMMENDATIONS**

We recommend using FCM for the treatment of IDA associated with CKD. Even though FCM showed a transient hypophosphatemia and non-significant LFT changes, it produced better tolerability. So we suggested monitoring the phosphorous levels and LFT while administering FCM. We recommend further studies to be carried out on long-term safety of FCM and iron sucrose as well as on the aspects of molecular weight.

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