Original Article

Comparative Biochemical Effects of Ferric Carboxymaltose and Iron Sucrose: Focus on Hypophosphatemia and Calcium Homeostasis

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ABSTRACT

Objective: To assess the frequency and severity of hypophosphatemia that arises after treatment with ferric carboxymaltose and consequent hypocalcaemia, compared with iron sucrose, to better understand their safety implications in clinical practice.

Study Design: Comparative study

Place and Duration of Study: This study was conducted at the Al-Diwaniyah Teaching Hospital Diwaniyah, Iraq from 1st October 2024 to 31st May 2025.

Methods: Thirty patients diagnosed with iron deficiency anemia were enrolled. Half received ferric carboxymaltose, while the remaining 15 were treated with iron sucrose. Biochemical evaluations (serum phosphate and calcium) levels were performed before treatment and repeated two weeks after the final infusion to assess potential alterations associated with each therapy.

Results: In ferric carboxymaltose group, a notable decrease in serum phosphate levels and a mild reduction in calcium concentrations were observed, whereas the iron sucrose group maintained stable mineral profiles. These changes suggest that ferric carboxymaltose exerts distinct effects on mineral metabolism, potentially mediated by its pharmacodynamic properties.

Conclusion: The differential impact of FCM and IS on phosphate and calcium homeostasis underscores the importance of individualizing intravenous iron therapy choices. For patients with pre-existing mineral imbalances or risks of hypophosphatemia, careful consideration of metabolic effects is essential to optimize safety and clinical outcomes.

Key Words: Ferric carboxymaltose, Iron deficiency anaemia, Iron sucrose, Hypophosphatemia

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INTRODUCTION

Iron deficiency anemia (IDA) signifies a late-stage consequence of iron depletion, in which diminished iron levels disrupt erythropoiesis, leading to anemia and the emergence of microcytic, hypochromic red blood cells.[1] Hematological and biochemical parameters are essential for the diagnosis of IDA. According to the World Health Organization, anemia is defined as an hemoglobin (Hb) level below 130 g/L in males and below 120 g/L in non-pregnant females.

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A comprehensive assessment of iron status typically includes serum ferritin, serum iron concentration, and transferrin saturation.[2]

Effective management of iron deficiency (ID) begins with identifying the underlying etiology and implementing strategies to restore systemic iron balance. In most clinical scenarios, oral iron supplementation serves as the first-line therapeutic approach, given its cost-effectiveness, broad accessibility, and well-established efficacy in replenishing iron stores.[3]

The clinical application of parenteral iron therapy dates back to the early 20th century, when colloidal ferric hydroxide-based formulations were first introduced. Despite their initial promise, these preparations were soon limited by significant toxicity, primarily due to the uncontrolled release of free iron into the circulation. This concern catalyzed the development of more stable intravenous (IV) iron complexes, characterized by an iron core enveloped within a carbohydrate shell, an innovation designed to modulate iron release and mitigate adverse reactions. By the 1990s, the emergence of iron gluconate and iron sucrose (IS)

marked a pivotal advancement in IV iron therapy. These formulations demonstrated improved safety profiles with lower rates of severe hypersensitivity.[4]

Iron sucrose represents one of the earliest IV iron formulations. It remains among the most extensively utilized parenteral iron therapies in clinical practice. The active pharmaceutical ingredient comprises a polynuclear iron(III) hydroxide core stabilized within a sucrose matrix.[5] Advancements in pharmaceutical technology have enabled the development of third-generation IV iron formulations designed to address the limitations of earlier therapies. These newer agents were specifically engineered to mitigate the toxicity associated with labile iron release and to overcome the dosing constraints inherent to traditional preparations such as iron sucrose. Among the most prominent third-generation IV iron compounds are ferric carboxymaltose (FCM), iron isomaltoside, and ferumoxytol. Each features a highly stable iron-carbohydrate complex that permits the administration of larger single doses over shorter infusion times, thereby enhancing both clinical efficiency and patient convenience.[4] IV iron sucrose necessitates multiple administrations to achieve therapeutic targets. In contrast, FCM is distinguished by its low immunogenic potential, thereby significantly reducing the risk of hypersensitivity and anaphylactic reactions. It permits the delivery of large single doses over brief infusion periods. A growing body of clinical evidence supports the safety and efficacy of FCM in the management of IDA, with studies consistently demonstrating substantial improvements in hemoglobin concentrations and iron indices following treatment.[6]

Since its FDA approval in 2013, the prescribing information for FCM has undergone multiple revisions, some of which have increasingly highlighted the concern regarding hypophosphatemia (HPP) as a notable adverse effect associated with FCM therapy.

Although initially perceived as a mild, transient, and clinically insignificant adverse event, hypophosphatemia associated with FCM emerged as a more serious concern with increased utilization in routine clinical practice. Many cases presented with severe and symptomatic manifestations, occasionally persisting for several months. In some cases, affected individuals required hospital admission for therapeutic correction.[7] Hypophosphatemia induced by FCM often arises due to enhanced urinary phosphate loss. This effect is driven by an increasein circulating levels of the phosphaturic hormone fibroblast growth factor 23 (Fgf23), which begins within the first 24 hours post-infusion. Beyond its role as a phosphaturic hormone, FGF23 suppresses the renal conversion of 25-hydroxyvitamin D (25[OH]D) into its biologically active form. This dual action precipitates a mild decline in serum calcium concentrations. The ensuing hypocalcemia stimulates parathyroid hormone (PTH) secretion as a compensatory response; its inherent phosphaturic activity contributes to the persistence of hypophosphatemia, extending beyond the initial period of elevated Fgf23.[8]

Emerging research highlights a complex interplay between iron metabolism and phosphate homeostasis. In states of ID and inflammation, there is an upregulation of Fgf23 synthesis at both transcriptional and translational levels within bone tissue. However, this elevated Fgf23 expression typically does not result in hypophosphatemia, as it is counterbalanced by enhanced intracellular proteolytic cleavage of the hormone into inactive C-terminal and N-terminal fragments that do not exert phosphaturic effects. Although the underlying mechanism remains incompletely understood, it is postulated that FCM disrupts this regulatory balance, uncoupling Fgf23 production from its cleavage. Consequently, the excessive Fgf23 levels induced by ID lead to an accumulation of biologically active full-length Fgf23 following FCM administration, thereby precipitating hypophosphatemia.[9]

Phosphorus is a key to cellular functions, including structural stability, signaling, and energy metabolism. Its homeostasis is tightly regulated via dietary intake, hormonal control, and renal excretion. Normal adult serum phosphate levels range from 2.48-4.65 mg/dL.[10] Hypophosphatemia spans from mild to critical, defined by serum phosphate levels.[11] Phosphate levels commonly reach their lowest point around day 14 following infusion.[12,13]

METHODS

This prospective interventional study was carried out at Al-Diwaniyah Teaching Hospital in Diwaniyah Iraq from 1st October 2024 to 31st May 2025. Thirty patients with clinically confirmed iron deficiency anemia were recruited into the study, following thorough evaluation and eligibility screening performed by a consulting hematologist. Patients considered eligible for this study were adults aged between 18 and 65 years with a confirmed diagnosis of iron deficiency anaemia; they had not received any form of iron supplementation, oral or IV, for a minimum of one month before evaluation. Patients were excluded if they presented with acute bleeding-related anemia underlying renal impairment, active oncological disease, or current pregnancy or lactation. Furthermore, patients who received agents known to alter electrolyte balance, particularly serum calcium, phosphate, or vitamin D3 levels, such as denosumab. A total of 30 patients were enrolled, the first group of 15 patients were treated with a 500 mg single dose of ferric carboxymaltose while the second (control group) 15 patient received iron sucrose at a dose of 200 mg administered on alternate days, up to a cumulative total of 600 mg within one week.

A-Phosphate measurement: Serum phosphate was measured using a colorimetric method with the Mindray BA-88A analyzer. Phosphate reacts with ammonium molybdate under acidic conditions to form a complex absorbing at 340 nm, allowing accurate quantification.[14]

B-Calcium Measurement: Serum calcium was measured using the ARCHITECT c4000 analyzer via a colorimetric assay. Calcium ions formed a blue-purple complex with Arsenazo III dye, detected at 660 nm, with concentrations automatically computed by the system.[15]

C-Vitamin D3 Measurement: Vitamin D_3 levels were quantified using the ichroma™ II analyzer, following the manufacturer's protocols. The procedure involved sequential mixing of serum with releasing and detection buffers, followed by incubation at 35 °C. After placing the prepared strip into the analyzer, the system performed automated scanning and calculated serum 25(OH)D concentration in ng/mL within 12–15 minutes.

Statistical analysis of biochemical parameters was conducted using SPSS-26. A p-value below 0.05 was interpreted as indicating statistical significance

RESULTS

There were 28 (93.3%) females and only 2 (6.7%) males. The mean gender distribution, coded numerically, was identical in treatment groups, iron sucrose and ferric carboxymaltose (FCM) of 1.07±0.067, yielding a P-value of 1.000. The average age of participants in the iron sucrose group was 31.6±2.72 years, while the FCM group showed a mean age of 31.8±2.75 years (P=0.959). The values of phosphate and calcium before and after treatment with ferric carboxymaltose and iron sucrose are showed in Tables 1-4. The vitamin D3 level at baseline is showed in Table 5.

Table No. 1: Value of phosphate and calcium before treatment with ferric carboxymaltose and iron sucrose

	Groups	Mean	SE mean	P value
Phosphate level before treatment	Iron sucrose	4.053	0.2438	0.349
	Ferric carboxymaltose	4.220	0.1295	
Calcium level before treatment	Iron sucrose	8.753	0.1121	0.342
	Ferric carboxymaltose	8.892	0.1141	

Table No. 2: Value of phosphate and calcium before and after 2week of treatment with ferric carboxymaltose

	Mean	SE mean	P. value
Phosphate level before treatment	4.220	0.1295	0.045
phosphate level after 2 weeks	3.887	0.1142	
Calcium level before treatment	8.892	0.1141	0.042
Calcium level after 2 weeks	8.633	0.1720	

Table No. 3: Value of phosphate and calcium before and after 2 weeks of treatment with iron sucrose

	Mean	SE mean	P. value
Phosphate level before treatment	4.053	0.2438	0.238
phosphate level after 2 weeks	3.987	0.2362	
Calcium level before treatment	8.753	0.1121	0.329
Calcium level after 2 weeks	8.640	0.14266	

Table No. 4: Value of phosphate and calcium after treatment with ferric carboxymaltose and iron sucrose

	Groups	Mean	SE mean	P value
Phosphate level after 2 weeks	Iron sucrose	3.987	0.2362	0.706
	Ferric carboxymaltose	3.887	0.1142	
Calcium level after 2 weeks	Iron sucrose	8.640	0.1466	0.977
	Ferric carboxymaltose	8.633	0.1720	

Table No. 5: Value of vitamin D3 at baseline

	Groups	Mean	SE mean	P value
Baseline vitamin D3	Iron sucrose	13.206	1.7392	0.682
	Ferric carboxymaltose	14.106	1.3027	

DISCUSSION

Before treatment, baseline characteristics were statistically comparable across both groups (p>0.05), supporting the assumption of group equivalence. This comparability is essential for attributing any post-intervention differences to the treatment effects rather than pre-existing disparities. Baseline levels of active vitamin D3 were comparable between the two treatment groups, with no statistically significant difference

observed (p=0.682). This suggests that both groups entered the intervention phase with similar vitamin D status, minimizing its potential role as a confounding factor.

Regarding phosphate levels, treatment with FCM led to a statistically significant reduction post-intervention (p=0.045). This aligns with the established association between FCM and hypophosphatemia, a phenomenon primarily attributed to its influence on FGF23, which enhances renal phosphate excretion. The observed findings like those reported in multiple clinical studies, reinforce the consistency of this safety signal.[7,16,17]

Notably, while serum phosphate levels declined significantly following treatment, none of the participants in this study developed either biochemical or clinically evident hypophosphatemia. This suggests that despite the statistical significance, the reduction did not translate into a measurable clinical impact within the study. The modest reduction in serum calcium levels observed post-treatment with FCM (p=0.042), although remaining within the physiological range, may signal adaptive shifts in mineral metabolism. This response could reflect compensatory mechanisms triggered by phosphate alterations or nuanced changes in vitamin D homeostasis. As outlined in the comprehensive review by Schaefer et al[8], hypophosphatemia can precipitate mild hypocalcemia, primarily through FGF23-driven suppression of 1,25-dihydroxyvitamin D synthesis. This, in turn, impairs intestinal calcium absorption and may contribute to secondary hyperparathyroidism. Although phosphate disturbances were the primary focus of the systematic review by Schaefer et al[18], the analysis also sheds light on key implications for calcium homeostasis. In particular, the review underscores the potential for hypocalcemia, emerging as a downstream effect of disrupted phosphate metabolism.

In the iron sucrose (IS) group, changes in serum phosphate and calcium levels did not reach statistical significance (P>0.05), indicating a relatively neutral impact of IS on mineral metabolism within the studied timeframe. This contrasts with the metabolic alterations observed following ferric carboxymaltose (FCM) administration. Notably, Blazevic et al[19] have highlighted that while mild hypocalcemia may occasionally occur with IS, such events are typically transient and lack clinical relevance. Moreover, IS is consistently associated with a substantially lower incidence of hypophosphatemia compared to FCM.

Following treatment, FCM was associated with a statistically significant reduction in serum phosphate levels, alongside a mild decline in calcium concentrations. However, when directly compared with the iron sucrose group, these changes did not translate into a statistically significant intergroup difference, suggesting comparable impacts on mineral parameters across both treatment modalities.

CONCLUSION

Phosphate levels decreased and calcium levels showed a mild reduction in the FCM group, whereas no such changes were observed with IS. These findings highlight the distinct metabolic effects of FCM, particularly its influence on phosphate and calcium regulation. Such considerations are important when selecting intravenous iron therapies, especially for patients with pre-existing mineral imbalances.

Author's Contribution:

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