RESEARCH ARTICLE
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Efficacy, Safety, and Tolerability of Ferric Carboxymaltose and Iron Sucrose in Iron Deficiency Anemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Lokman H. Tanrıverdi [1], Ahmet Sarıcı[2]

[1]İnönü University Faculty of Medicine, Department of Medical Pharmacology, Malatya, Türkiye
[2]İnönü University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Malatya, Türkiye

Lokman Hekim Tanrıverdi, MD, PhD, İnönü University Faculty of Medicine, Department of Medical Pharmacology, Malatya, Türkiye
lokmanhekim.tanriverdi@inonu.edu.tr
0000-0003-4263-5234

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Abstract
Objective. To comprehensively compare the efficacy, safety, and tolerability of two commonly used intravenous iron preparations, ferric carboxymaltose (FCM) and iron sucrose (IS), in adult patients with iron-deficiency anemia (IDA).
Methods. A systematic literature search was conducted across PubMed, Ovid Medline, Web of Science, Scopus, and the Cochrane Library up to Jan 1, 2024, to identify randomized controlled trials directly comparing FCM and IS treatments in adult patients with IDA. Primary outcome was change in hemoglobin levels during folllow-up. Meta-analyses were conducted with inverse variance random effects models.
Results. Fourteen trials were included, with a total of 4757 patients. FCM resulted in a nonsignificant increase in hemoglobin levels (mean difference [MD] = 0.45 g/dL, 95% confidence interval [CI] = 0.08 to 0.83, p=0.02) and ferritin levels (MD = 37.32 ng/mL, 95% CI = 18.98 to 55.65, p<0.01) compared to IS. FCM was associated with a higher risk of hypersensitivity reactions compared to IS (RR: 2.97, 95% CI: 1.35–6.52, p<0.01) but showed no significant difference in severe adverse events (RR: 1.03, 95% CI: 0.88–1.21, p=0.70) and had a nonsignificant increased risk of hypophosphatemia (RR: 2.84, 95% CI: 0.89–9.06, p=0.08).
Conclusions. Ten studies showed some concerns of risk of bias, and four studies had a high risk of bias for the change in hemoglobin levels during follow-up. Lack of standardized definitions for hypersensitivity reactions and variability in dosing protocols and follow-up durations across studies may affect the generalizability of our safety findings.
Keywords: ferric carboxymaltose, iron sucrose, iron-deficient anemia, hypophosphatemia, hypersensitivity.

Introduction

Iron deficiency anemia (IDA) is a prevalent condition with significant health consequences, affecting various patient populations, including those with chronic diseases, heavy menstrual bleeding, and gastrointestinal disorders interval [1-4]. Intravenous (IV) iron therapy is often preferred in cases where rapid iron repletion is necessary or when oral iron formulations are ineffective or poorly tolerated [5,6]. Among IV iron therapies, ferric carboxymaltose (FCM) and iron sucrose (IS) are widely used. FCM allows for larger doses in fewer administrations compared to IS, making it more convenient for patients and healthcare providers [7-9]. FCM is a colloidal iron (III) hydroxide complexed with carboxymaltose, a carbohydrate polymer that facilitates controlled iron release. This allows for the replenishment of iron stores required for the synthesis of hemoglobin, myoglobin, and various enzyme systems involved in oxygen transport and cellular metabolism. Unlike dextran-based formulations, FCM enables iron uptake via the reticuloendothelial system without the release of free iron, thereby reducing the risk of oxidative stress. IS is also an iron (III) hydroxide complex with sucrose that undergoes dissociation within the reticuloendothelial system. The released iron contributes to increased serum iron concentrations and is subsequently incorporated into hemoglobin, restoring iron levels in iron-deficient patients [7-9].

Previous randomized controlled trials (RCTs) have examined the comparative efficacy and safety of FCM and IS, particularly in the treatment of anemia in various populations [10-16]. However, the using of FCM and IS in different patient populations and clinical contexts has shown varying efficacy and safety results [6,17,18]. In the REPAIR-IDA trial [15], which included 2,584 patients with IDA and chronic kidney disease (CKD), FCM showed a significantly greater increase in hemoglobin (Hb) levels compared to IS (1.13 g/dL vs. 0.92 g/dL; 95% CI, 0.13–0.28), with a higher proportion of patients in the FCM group achieving an Hb increase of ≥1.0 g/dL (48.6% vs. 41.0%). Importantly, no significant difference was observed between the two treatments regarding cardiovascular safety, including major adverse cardiac events, though FCM was associated with a higher incidence of transient hypertensive episodes .

In a study by Mahey et al. [19] involving 60 women with anemia due to abnormal uterine bleeding, FCM resulted in a more rapid increase in Hb levels at 6 weeks compared to IS ($p=0.005$), though no significant difference was observed at 12 weeks ($p=0.11$) . Similarly, Lee et al. demonstrated that FCM was as effective as IS in achieving Hb ≥10 g/dL in women with preoperative anemia due to menorrhagia, with a significantly shorter time to reach this target in the FCM group (7.7 days vs. 10.5 days) .

Laso-Morales et al. [20] compared FCM and IS in 104 patients with postoperative anemia following colorectal cancer surgery. Both treatments led to comparable increases in Hb by postoperative day 30 (FCM: 2.5 g/dL vs. IS: 2.4 g/dL), but FCM was associated with a lower infection rate (9.8% vs. 37.2%, $p<0.05$) . In contrast, a study conducted in Japan on patients with IDA due to hypermenorrhea showed non-inferiority of FCM compared to saccharated ferric oxide, with a mean Hb increase of 3.90 g/dL in the FCM group and 4.05 g/dL in the control group (difference: -0.15 g/dL; 95% CI -0.35 to 0.04) .

A recent trial [21] conducted in China compared the efficacy of FCM and IS in 371 patients with IDA. The primary endpoint of achieving an Hb increase of ≥2 g/dL within 8 weeks was met by 99.4% of FCM-treated patients compared to 98.3% of IS-treated patients, confirming non-inferiority (difference: 1.12%; 95% CI -2.15 to 4.71) . Additionally, a higher proportion of FCM-treated patients achieved early Hb response at 2 weeks (85.2% vs. 73.2%; 95% CI 3.31 to 20.65), and FCM showed a greater increase in transferrin saturation (TSAT) and serum ferritin levels at all time points.

These findings highlight the variability in the efficacy and safety outcomes of FCM and IS across different patient populations and clinical scenarios. To date, there have been no systematic reviews comparing FCM and IS, in the managment of IDA regardless of etiology. Given the need for more conclusive evidence, we conducted a systematic review and meta-analysis of RCTs to compare the efficacy and safety of FCM and IS in the treatment of IDA.

MATERIALS AND METHODS

This systematic review was conducted following a predefined protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42022337858).

Eligibility Criteria

We identified RCTs evaluating the efficacy and safety of FCM versus IS in patients with IDA regardless of the etiology. We excluded studies that were not RCTs, including observational studies, case reports, case series, narrative reviews, editorials, commentaries, or expert opinions. Studies involving individuals under 18 years of age were also excluded. Additionally, we excluded studies that compared FCM) or IS with oral iron, placebo, or other intravenous iron formulations (e.g., ferric derisomaltose, ferric gluconate) without a direct comparison between FCM and IS. Studies that did not report at least one predefined outcome of interest or provided incomplete or unclear data that could not be extracted for meta-analysis or those not published in English were also excluded.

Search Strategy and Study Selection

A systematic search was performed in the Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), Ovid MEDLINE, PubMed, and Web of Science up to January 1, 2024. The search strategy was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. Additionally, the reference lists and citations of included studies from the past five years were screened for relevant articles. Only studies published in English were considered. Detailed search strategies are provided in the Supplementary File. References identified through the database searches were imported into EndNote v21.3 (Clarivate Analytics). After removing duplicates, full-text articles were retrieved if their abstracts were deemed eligible by at least one reviewer. Each full-text article was then independently assessed for final inclusion in this systematic review and meta-analysis, with any disagreements resolved through consensus.

Outcomes

The primary efficacy outcome was the change in hemoglobin (Hb) levels during follow-up, while the primary safety outcome was the risk of serious or severe adverse events. Secondary outcomes included a Hb increase of 2 g/dL during follow-up, achievement of 12 g/dL Hb levels during follow-up, change in serum ferritin levels from baseline, hypersensitivity reactions, risk of hypophosphatemia, and withdrawals due to adverse events.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. The extracted data included:

- Study characteristics: first author, year of publication, study design, etiology, sample size, intervention details (type of iron preparation (FCM or IS) with cumulative dose, primary outcome, and prespecified secondary outcomes in the protocol.
- Participant characteristics: number of patients, age, gender, race (white, black or African American, asian, other), ESA use, previous iron therapy, baseline Hb value (g/dL), baseline ferritin levels (ng/mL), baseline TSAT (%), baseline eGFR values (mL/min/1.73 m^2) for each arm in the included studies.

Data were double-checked for accuracy and consistency. In case of incomplete outcome data, we employed available-case analysis, and if a study reported results graphically, we extracted data using digital analysis tool [23].

Risk of Bias Assessment

Two reviewers (LHT, AVH) independently assessed the risk of bias (RoB) in the included RCTs using the Cochrane risk of bias tool RoB2.0 [24], with any disagreements resolved through discussion. The RoB2.0 tool evaluates five domains of bias: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. A study was considered at high RoB if at least one domain was rated as "high risk," and was deemed to have "some concerns" if at least one domain raised concerns without any domains rated as high RoB.

Statistical Analyses

Meta-analyses were primarily conducted using inverse variance random effects models; for rare outcomes (i.e., incidence <10%), the Mantel-Haenszel method was applied. Between-study variance (τ^2) was calculated using the Paule-Mandel method [25], with confidence intervals adjusted using the Hartung-Knapp method [26]. Dichotomous outcomes were presented as relative risks (RR) with 95% confidence intervals (CI), and continuous outcomes as mean differences (MD) with 95% CI. Between-study heterogeneity was assessed using Cochran's Q test and I^2 statistics (with values <30% indicating low heterogeneity, 30%-60% moderate, and >75% substantial heterogeneity) [27]. Publication bias was visually examined using funnel plots and statistical methods, including Egger's tests. Sensitivity analyses were conducted by sequentially excluding each study to assess the impact on pooled RR estimates.

All analyses were performed using R, version 4.4.1 (www.r-project.org), with the meta and metafor packages. Statistical tests were two-sided, with a significance threshold of P <.05. A P for interaction <.1 was considered statistically significant for a given subgroup [28]. Subgroup analyses, based on the etiology of IDA and RoB for primary outcome, were conducted to explore potential sources of heterogeneity.

RESULTS

Study Selection

A total of 688 records were identified through database searches, including Cochrane CENTRAL, PubMed, Ovid MEDLINE, and Web of Science. After the removal of 292 duplicates, 396 records remained for screening. Of these, 331 were excluded based on titles and abstracts. Sixty-three full-text articles were assessed for eligibility, and 14 were excluded due to irrelevant interventions, 14 due to unsuitable study designs, 10 due to incorrect publication types, and 2 due to wrong population. After the screening, 14 randomized controlled trials (RCTs) involving a total of 4757 participants [11-16,19-21,29-33] were included in this meta-analysis (Figure 1).

Study Characteristics

Fourteen RCTs were included in this meta-analysis, comparing FCM and IS in various populations with IDA. The included studies are categorized based on the underlying causes of IDA. A detailed summary of study (Table 1) and patient characteristics (Table S1) of each included RCTs were provided.

In patients with gynecological disorders, three studies were identified. Mahey et al. (2015) compared FCM and IS in women with IDA due to abnormal uterine bleeding and found that FCM was more effective in raising hemoglobin levels with fewer adverse events [19]. Ikuta et al. (2018) examined Japanese women with hypermenorrhea-induced IDA, demonstrating the non-inferiority of FCM to IS in both efficacy and safety [11]. Lee et al. (2019) investigated patients with preoperative anemia due to menorrhagia, finding that FCM led to a faster and greater increase in hemoglobin levels compared to IS [31].

For patients with impaired iron absorption, three trials were included. Evstatiev et al. (2011) conducted the FERGIcor trial, focusing on IDA due to inflammatory bowel disease, and concluded that FCM was superior to placebo in improving hemoglobin [14]. Laso-Morales et al. (2022) compared single-dose FCM with multiple doses of IS in post-operative colorectal cancer patients, showing that FCM was more convenient and effective in correcting post-operative anemia [20]. Struppe et al. (2023) conducted a pilot study evaluating the impact of intravenous iron on bone turnover markers and serum phosphate levels, suggesting that FCM had a more favorable safety profile than IS [33].

In the group of patients with impaired renal function, three studies were identified. Onken et al. (2014) conducted the REPAIR-IDA trial, comparing FCM and IS in patients with IDA and impaired renal function, and found that FCM resulted in a quicker and more sustained increase in hemoglobin levels [15]. Roberts et al. (2016) evaluated the effects of intravenous iron on fibroblast growth factor 23 (FGF23) in hemodialysis patients, showing that FCM was associated with better outcomes than IS [29]. Bielesz et al. (2021) studied different iron dosing strategies in long-term hemodialysis patients, concluding that FCM was more effective and required fewer doses than IS [12].

In studies involving patients with mixed etiologies, Naqash et al. (2018) compared FCM and IS in women with IDA from various causes, concluding that FCM was more effective and had a better safety profile [13]. Jin et al. (2024) conducted a randomized trial in Chinese patients with mixed etiology IDA and found that FCM was non-inferior to IS, with the added benefit of fewer required doses [21].

For postpartum anemia, two studies were included. Rathod et al. (2015) investigated FCM in Indian women with postpartum anemia, showing significant improvement in hemoglobin levels with a single dose [16]. Similarly, Wajid et al. (2021) compared FCM and IS in women with postpartum anemia, concluding that FCM was more effective and safer than IS [32].

Lastly, in pregnancy-related IDA, Jose et al. (2019) compared FCM and IS in pregnant women and found that FCM provided superior outcomes in terms of hemoglobin improvement and safety profile [30].

Risk of Bias and Publication Bias

The Cochrane Risk of Bias 2 tool was used to assess the quality of the included studies. Ten studies were classified as having some concerns of risk of bias, and four studies were deemed to have a high RoB for change in hemoglobin levels during follow-up (Figure 2). All studies had some concerns of risk of bias in the domain of deviations from the intended interventions mostly because of the open-label study design.

To evaluate publication bias, a graphical funnel plot was used. Visual inspection of the plot revealed asymmetry, indicating the presence of publication bias but for two small and negative RCTs (Supplemental Fig 1.).

Primary Outcome Results

In the overall analysis of 12 RCTs [11-13,15,16,19-21,29,30,32,33] involving 4734 participants, FCM resulted in a significant increase in Hb levels during follow-up compared to IS (mean difference [MD] = 0.45 g/dL, 95% confidence interval [CI] = 0.08 to 0.83, I^2=97%, p = 0.02) (Figure 3). The clinical importance of this finding suggests that FCM may offer modest benefits over IS in raising Hb levels across a broad population of IDA patients.

Subgroup Analysis Results

When stratified by etiology of anemia, FCM demonstrated a statistically significant improvement in Hb levels specifically in patients with postpartum anemia [16,32] (MD = 1.04 g/dL, 95% CI = 0.75 to 1.33, p < 0.01) but opposite to hemodialysis patients [12,29] (MD = -0.24 g/dL, 95% CI = -0.53 to 0.04, p < 0.01) when compared to IS (Supplemental Fig 2.). In another perspective, when classifying studies based on impaired iron absorption (MD = 0.17 g/dL, 95% CI = -0.34 to 0.69) [14,20,33], impaired renal function (MD = -0.09 g/dL, 95% CI = -0.46 to 0.28) [12,15,29], gynecological disorders (MD = 0.26 g/dL, 95% CI = -0.62 to 1.14) [11,19,31], postpartum anemia (MD = 1.04 g/dL, 95% CI = 0.75 to 1.33) [16,32], and mixed etiology (MD = 1.10 g/dL, 95% CI = -0.36 to 2.56) [13,21], there is a significant difference among subgroups in favor of postpartum anemia for FCM (Supplemental Fig 3.).

Secondary Efficacy Outcomes

The proportion of patients achieving an increase of ≥2 g/dL in Hb (3 RCTs, 1078 patients) [14,21,29] was comparable in the FCM group (RR = 1.06, 95% CI = 0.93 to 1.20, p = 0.38) than IS (Supplemental Fig 4.). FCM also showed nonsignificant superiority in achieving normal Hb levels during follow-up (RR = 1.77, 95% CI = 0.98 to 3.20, p = 0.06) [14,16,20,32] (Supplemental Fig 5).

Ferritin levels during follow-up were significantly improved in the FCM group compared to the IS group (MD = 37.32 ng/mL, 95% CI = 18.98 to 55.65, p < 0.01) [13,16,19,21,33] (Supplemental Fig 6).

Safety Outcomes

The pooled risk for serious or severe AEs was comparable between FCM and IS groups (RR = 1.03, 95% CI = 0.88 to 1.21, p = 0.70) [11-16,19,21,29-32] (Figure 4A). This finding suggests that both FCM and IS have acceptable safety profiles, with no clinically meaningful differences in serious AEs. FCM was associated with a significantly higher incidence of hypersensitivity reactions compared to IS (RR = 2.97, 95% CI = 1.35 to 6.52, p < 0.01) [11-16,19-21,29-32] (Figure 4B). The occurrence of hypophosphatemia was more frequent in the FCM group, although the difference did not reach statistical significance (RR = 2.84, 95% CI = 0.89 to 9.06, p = 0.08) [11,14-16,21,30] (Figure 4C). Similarly, pooled analysis of any AEs did not differ significantly between FCM and IS (RR = 0.89, 95% CI = 0.63 to 1.27, p = 0.53) [11-16,19,21,30] (Supplemental Fig. 7). No significant difference in withdrawal rates due to adverse events was observed between the two groups (RR = 1.53, 95% CI = 0.60 to 3.89, p = 0.37) [11,12,14,19-21,30,31] (Supplemental Fig. 8) (Table 2).

Discussion

Our meta-analysis demonstrated that FCM provides a potential advantage over IS in improving Hb and ferritin levels among patients with IDA. Notably, FCM showed a statistically significant improvement in Hb levels compared to IS, especially in patients with postpartum anemia. This analysis adds to the existing body of evidence by highlighting the differential impacts of FCM and IS across various subpopulations, underscoring FCM's enhanced efficacy in achieving target Hb levels swiftly. Although FCM is associated with a significantly increased risk of hypersensitivity reactions, and nonsignificant increase of hypophosphatemia and serious or severe AEs regardless of etiology of IDA, our findings suggest monitoring patients receiving both agents.

IDA represents a significant global health concern due to its widespread prevalence and profound impact on individual health and socio-economic development. According to the 2021 Global Burden of Disease (GBD) study [34], the global prevalence of anemia was 24.3%, equating to approximately 1.92 billion cases. Although this marks a decrease from 28.2% in 1990 [35], the absolute number of cases has grown due to population expansion. IDA remains the leading cause of anemia worldwide, constituting 66.2% of total cases, particularly affecting women of reproductive age and children under five. The primary etiologies of IDA include dietary iron deficiency, chronic inflammatory diseases, and conditions affecting iron absorption, such as gastrointestinal disorders and chronic kidney disease [3]. The widespread burden of IDA and its profound effects on quality of life, cognitive function, and physical performance underscore the importance of timely and effective iron repletion, particularly in populations with high physiological demands or significant iron losses [5].

Parenteral iron therapy, such as FCM and IS, is a critical option when oral iron formulations are ineffective, poorly tolerated, or contraindicated, such as in patients with severe IDA, malabsorption syndromes, chronic kidney disease, or those who cannot adhere to oral regimens due to gastrointestinal side effects [7,36]. FCM offers a practical advantage in delivering higher doses in a single administration, allowing for rapid repletion and improved patient compliance [37]. However, FCM's association with hypersensitivity reactions and hypophosphatemia necessitates careful monitoring [38]. IS, while requiring multiple administrations to achieve adequate iron levels, may be preferable in patients with a higher sensitivity to infusion reactions [39]. Thus, the choice of IV iron therapy should be tailored to individual patient needs, considering efficacy, safety profiles, and logistical considerations.

Increasing Hb levels in patients with IDA is of paramount importance across diverse subpopulations and etiologies [36,40]. In patients with CKD, there is a consensus that the correction of Hb levels with intravenous iron therapy has been linked to improved outcomes in terms of reduced hospitalizations and enhanced quality of life [41]. Additionally, in the obstetric population, correcting Hb in pregnant and postpartum women addresses not only maternal anemia but also reduces the risks associated with postpartum hemorrhage and supports optimal fetal development [42]. Achieving target Hb levels thus has significant implications, serving to mitigate the morbidity associated with anemia and, ultimately, enhance patient-centered outcomes across these varied clinical contexts.

The safety profile of parenteral iron agents, particularly FCM and IS, is a crucial consideration in clinical practice, as it impacts adherence, tolerability, and preference in managing IDA. In accordance with our results, FCM has a favorable safety profile with a lower incidence of adverse events compared to IS, as observed in meta-analyses among obstetric and gynecologic populations [10]. FCM's ability to deliver a high dose in a single administration session not only enhances patient adherence by reducing the need for multiple infusions but also aligns well with clinical settings that prioritize efficiency. However, FCM is associated with treatment-emergent hypophosphatemia, especially in cases requiring repeated dosing, which mandates careful monitoring. IS was known to require multiple doses for full iron replenishment in IDA patients, but it carried a higher risk of severe hypersensitivity reactions when comparing to a carbohydrate polymer containing agents [43]. Both agents rarely lead to true anaphylaxis, with most reactions being mild infusion-related responses. The robust safety and tolerability of these agents, combined with their low rates of treatment discontinuation due to adverse events, underscore their suitability and reliability in clinical practice for a range of IDA etiologies.

Shin et al. reported the safety of ferric carboxymaltose and iron sucrose, which are widely used in obstetric and gynecological iron deficiency anemia patients, in their systematic review. The incidence of adverse events was

reported to be lower in the FCM group than in the IS group (P = 0.003). No serious adverse events were reported in either group [10].
In a systematic review and meta-analysis reported by Bharadwaj et al., fewer side effects were observed in the FCM group compared to the IS group. 26% fewer side effects were reported in the FCM group compared to the IS group (p = 0.001) [44].
Srimathi et al. reported a meta-analysis of pregnant women aged 15-49 years with IDA who were given FCM and IS. A total of 18 studies were included. Fewer side effects were reported in the FCM group compared to the IS group (p=0.003) [45].
In the prospective study conducted by James et al. on 120 pregnant IDA patients, the number of patients given FCM and IS was 60 each. Mild side effects were reported to occur in 7.5% of the patients included in the study [46].
Hardy et al. examined the frequency of hypophosphatemia in their retrospective study of the data of patients who received FCM or IS. 52 patients were included in the IS group and 78 patients were included in the FCM group. The phosphate level measured before treatment in the IS group was 1.08 ± 0.23 mmol/L and was reported not to have changed significantly after IS administration (1.00 ± 0.29 mmol/L; p = 0.37). Hypophosphatemia was reported in 22% of the patients after IS infusion, with phosphate levels falling below 0.80 mmol/L (all were within the normal range before injection). The mean phosphate level before treatment in the FCM group was 1.08 ± 0.18 mmol/L and decreased to 0.82 ± 0.29 mmol/L after iron administration (p < 0.0001). After FCM application, 13% of patients had a phosphate level of < 0.32 mmol/L and 51% had a phosphate level of < 0.80 mmol/L [47].
It is also important to note that published RCTs lack standardized definitions for hypersensitivity reactions. For instance, Ikuta et al. [11] used MedDRA definitions -provides a standardized set of terms for hypersensitivity reactions, categorized into five groups, which aids clinicians and researchers in estimating the risk for the general population- whereas Lee et al. [31] used The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0) to report adverse event and safety data but both reported just a few of safety outcomes but none of hypersensitivity related AEs. Therefore, our safety parameters, including severe adverse events and hypersensitivity reactions, should be interpreted with caution. This uncertainty and heterogeneity in reporting AEs should be considered by guideline developers and policy makers, as this study provides the most comprehensive and first-of-its-kind data on this subject.
Our meta-analysis has several strengths, including the large number of patients analyzed across multiple clinical settings and the inclusion of both short-term and long-term efficacy outcomes. However, it is important to acknowledge certain limitations. First, not all trials reported data on key safety outcomes, such as hypophosphatemia or standardized definitons for serious or severe AEs or hypersensitivity, which may limit the generalizability of our findings regarding adverse events. Second, while we included a broad range of patient populations, the heterogeneity in dosing protocols, follow-up durations, etiologies across the included studies may have influenced the observed treatment effects.
Conclusions: This systematic review and meta-analysis provide a potential advantage of FCM over IS in improving hemoglobin and ferritin levels, particularly among patients with gynecological disorders underlying iron deficiency anemia. While both iron preparations demonstrated comparable efficacy in the general population, the findings underscore the importance of considering the specific etiology of anemia when choosing between these treatments.

CRediT author statement:
Ahmet Sarıcı: Conceptualization, Visualization, Investigation, Writing- Original draft preparation, Writing- Reviewing and Editing.
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Figure Legends

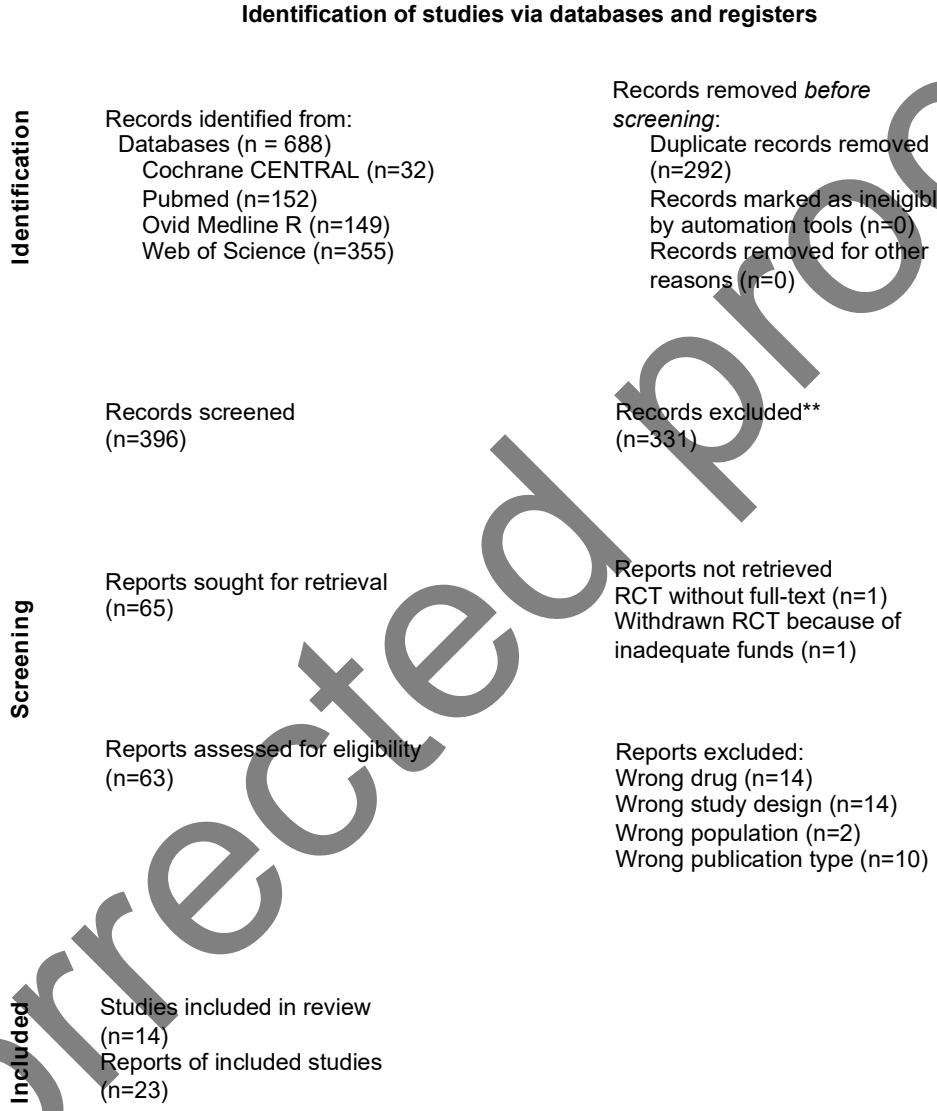

Figure 1. PRISMA flow diagram of eligible studies

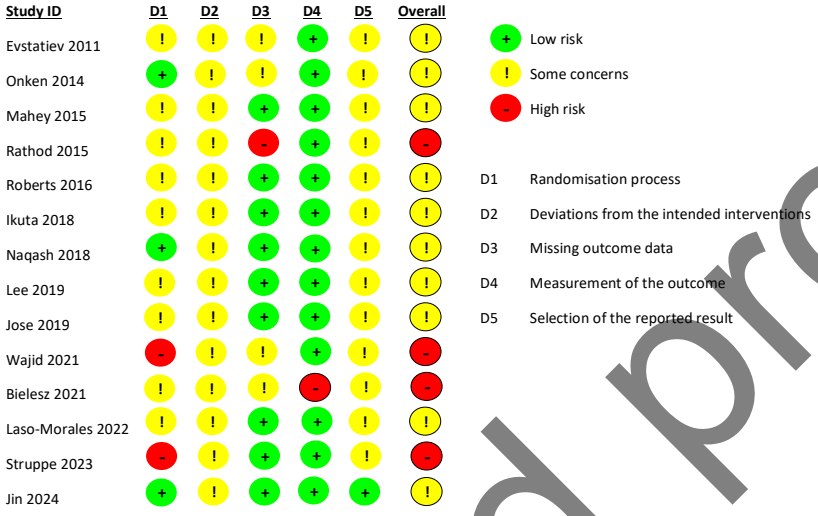

Figure 2. Risk of bias assessment of the included RCTs in terms of change in hemoglobin levels during follow-up.

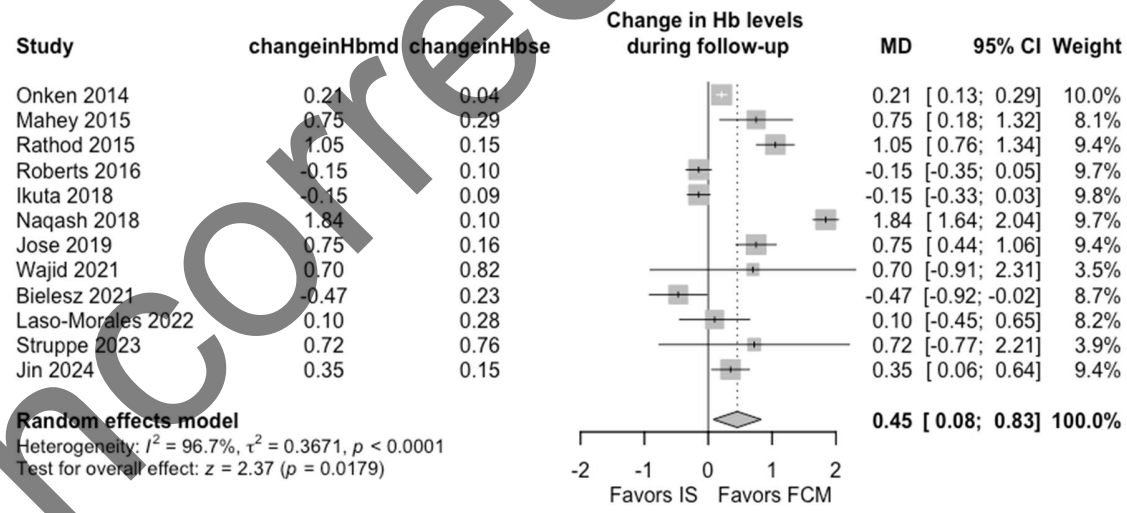

Figure 3. Forest plot of change in hemoglobin levels during follow-up.

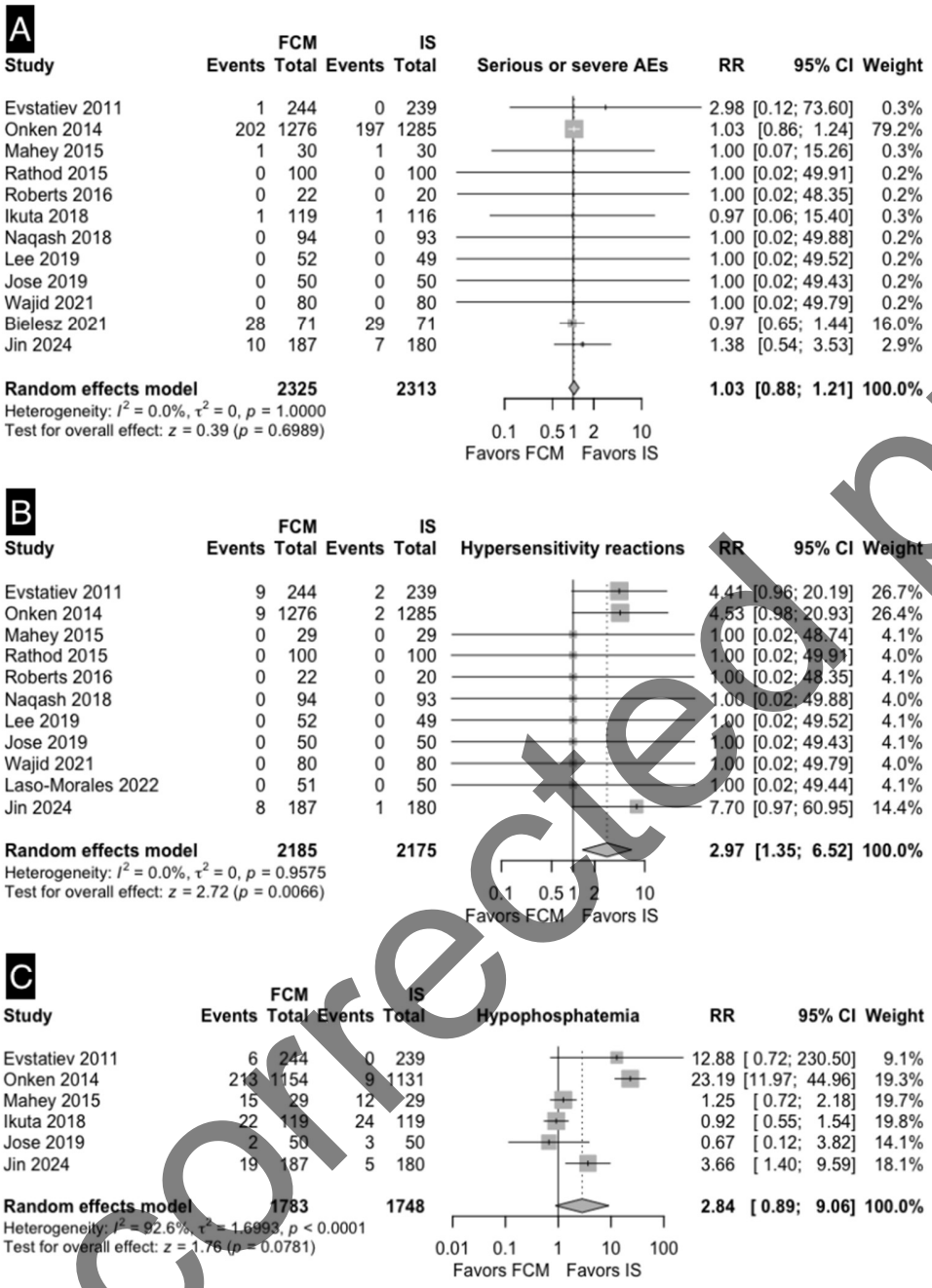

Figure 4. Forest plot of risk of serious or severe adverse events (A), hypersensitivity reactions (B), and hypophosphatemia (C).

Table 1. Study characteristics of the included trials

Reference	Study design	Population	Sample size	Intervention, Cumulative dose+SD (mg)	Comparator, Cumulative dose+SD (mg)	Primary outcome
Estatiev 2011 [14]	Multicenter, open-label RCT	IBD-associated IDA	485	FCM, 1377+381	IS, 1160+316	Hemoglobin response rate at week 1
Onken 2014 [15]	Multicenter, open-label RCT	NDD-CKD-associated IDA	2584	FCM, 1464+158	IS, 963+138	Noninferiority in the change from baseline to highest hemoglobin level at Day 56
Mahey 2015 [19]	Open-label RCT	Uterine bleeding-associated IDA	60	FCM, N/A	IS, N/A	Rise in hemoglobin levels above baseline
Rathod 2015 [16]	Double-blinded RCT	Postpartum-associated IDA	300	FCM, N/A	IS, N/A	Changes in hemoglobin and serum ferritin levels at 2 and 6 weeks post-treatment
Roberts 2016 [29]	RCT	HD-CKD-associated IDA	42	FCM, 200	IS, 200	Change in fibroblast growth factor 2 (FGF23) levels from pre-infusion to Day 2 post-infusion
Ikuta 2018 [11]	Multicenter, open-label RCT	Hypermenorrhea-associated IDA	294	FCM, 1349+N/A	IS, 1357+N/A	Mean change in hemoglobin from baseline to highest observed level
Naqash 2018 [13]	RCT	Mixed etiology	200	FCM, N/A	IS, N/A	Achievement of target hemoglobin a ferritin levels
Lee 2019 [31]	Multicenter, open-label RCT	Hypermenorrhea-associated IDA	101	FCM, 923.1+207.3	IS, 939.6+352.3	Proportion of patients achieving hemoglobin levels ≥10 g/dL within 2 weeks after the first administration
Jose 2019 [30]	Open-label RCT	Pregnancy-associated IDA	100	FCM, 1739.6+105.5	IS, 1730.4+121.9	Improvement in hemoglobin and ferritin levels
Wajid 2021 [32]	RCT	Postpartum-associated IDA	160	FCM, N/A	IS, N/A	Recovery of normal hemoglobin leve by day 21
Bielesz 2021 [12]	Open-label RCT	HD-CKD-associated IDA	142	FCM, N/A	IS, N/A	Change in hemoglobin at week 40 fr baseline

Table 2. Safety of FCM compared with IS in anemia patients.

Outcomes	Number of studies	FCM		IS		Pooled Effect Size RR (95%CI)	P value	I-square (%)
		Number of events	Total number of patients	Number of events	Total number of patients			
Serious or severe AEs	12	243	2325	235	2313	1.03 (0.88; 1.21)	0.6989	0
Hypersensitivity reactions	11	26	2185	5	2175	2.97 (1.35; 6.52)	0.0066	0
Hypophosphatemia	6	277	1783	53	1748	2.84 (0.89; 9.06)	0.0781	92.6
Any AEs	9	470	2169	443	2167	0.89 (0.63; 1.27)	0.53	47
Withdrawal rate	8	11	804	6	788	1.53 (0.60; 3.89)	0.37	0