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ORIGINAL RESEARCH

Comparative effects of parenteral iron therapy in stable iron deficiency anemia with mild vs severe anemia

Tawfiq Almezeiny[1*]

ABSTRACT

Background: Iron deficiency anemia (IDA) is frequently identified in hemodynamically stable patients and may be managed variably, including potentially avoidable transfusion. Whether intravenous (IV) iron produces similar hemoglobin (Hb) responses across anemia severity remains unclear.

Methods: We conducted a retrospective observational study of adults (≥18 years old) with IDA who were hemodynamically stable, considered asymptomatic, and who electively received IV ferric carboxymaltose in the hospital IV unit from January 1, 2022, through the end of June 2022. IDA was defined as Hb ≤ 12 g/dl with baseline serum iron ≤75 µg/dl. We excluded patients with cardiac disease, renal disease, fainting episodes, pregnancy, missing results, or loss to follow-up. Patients were grouped by baseline Hb: Group 1 (Hb 5-9 g/dl) and Group 2 (Hb 9.1-12 g/dl). We compared baseline and 1-month follow-up Hb and serum iron and calculated the final augmentation magnitude of Hb (FAM) and serum iron augmentation (IA).

Results: The final cohort included 296 patients (Group 1, n = 52; Group 2, n = 244). Hb increased in most patients in both groups. Mean FAM was higher in Group 1 than in Group 2 (3.34 *vs.* 1.37 g/dl; $p < 0.05$). Mean IA was also higher in Group 1 than in Group 2 (204 *vs.* 137.8 µg/dl; $p < 0.05$). No major adverse events (AEs) occurred; 16 patients (6.5%) experienced mild AEs. No patient received a transfusion during follow-up.

Conclusion: IV iron therapy was effective and well tolerated across Hb strata, with significantly greater Hb augmentation among patients with more severe anemia.

Keywords: Anemia, iron deficiency, serum iron, iron therapy, transfusion.

Introduction

Iron deficiency is the most prevalent nutritional deficiency worldwide and a leading cause of anemia. Iron deficiency anemia (IDA) is frequently identified in adults and children presenting to the emergency department (ED). Many patients remain asymptomatic and undiagnosed for prolonged periods because hemoglobin (Hb) concentrations often decline gradually, allowing physiologic adaptation.

Clinicians often detect IDA incidentally through routine laboratory testing. Some patients develop mild exertional symptoms but do not seek medical care. Causes of IDA include reduced dietary iron intake or impaired absorption, increased iron requirements during adolescence and pregnancy, bariatric surgery, heavy menstrual bleeding, chronic gastrointestinal blood loss, polyps, and malignancy. Patients may report fatigue, dyspnea, palpitations, syncope, or headaches.

Management of IDA varies among ED physicians. Some hemodynamically stable patients are admitted and receive aggressive treatment, including potentially avoidable transfusions. In this study, we evaluated the impact of parenteral iron therapy in patients with moderate-to-severe anemia versus those with mild anemia over 4 weeks. This comparison has not been previously reported; therefore, whether iron therapy is

Correspondence to: Tawfiq Almezeiny
*Assistant Professor of Emergency Medicine and Critical Care at King Saud University, Faculty of Medicine, Riyadh, Saudi Arabia.
Email: talmezeiny@ksu.edu.sa; almezeiny@gmail.com
Full list of author information is available at the end of the article.
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similarly effective across the spectrum of anemia severity was unclear.

Subjects and Methods

We conducted a retrospective observational study of adults (≥18 years old) who electively received parenteral iron therapy in the hospital intravenous (IV) unit. We included adults diagnosed with IDA who were hemodynamically stable and considered asymptomatic by their primary care physician (PCP).

We enrolled 329 patients over a 6-month period, from January 1, 2022, through the end of June 2022 (Fig. 1). All patients had IDA with an Hb level ≤ 12 g/dl and a baseline serum iron level ≤ 75 µg/dl. We excluded 13 patients because of cardiac disease, renal disease, fainting episodes, or pregnancy. We excluded an additional 20 patients because of missing results or loss to follow-up. No patient received a blood transfusion during the 1-month study period. The final cohort included 296 patients.

We assigned patients to two groups based on baseline Hb level: Group 1 had moderate to severe anemia (Hb 5-9 g/dl), and Group 2 had mild anemia (Hb 9.1-12 g/dl). We recorded baseline and demographic characteristics for both groups. The PCP initiated treatment in the office setting.

Iron dosing and therapeutics

After confirming the diagnosis, the PCP calculated each patient's required iron dose. At our center, we used ferric carboxymaltose (FCM; Ferinject®). The concentration of FCM was 50 mg iron/ml in the injection/infusion solution. Our hospital followed a standard dosing calculation, which the inpatient pharmacist supervised and monitored according to institutional guidelines (Table 1). The total required dose depended on two factors: Hb level and patient body weight [1,2].

Staff diluted the calculated dose in 100-250 ml of normal saline and infused it over 30-60 minutes. During the infusion in the IV unit, an experienced nurse closely monitored each patient for potential adverse events (AEs). We recorded blood test results obtained at the initial visit (before iron therapy) and 1 month after therapy for every enrolled patient.

We performed statistical analyses and generated graphics using licensed Stata® 17 statistical software. We used the

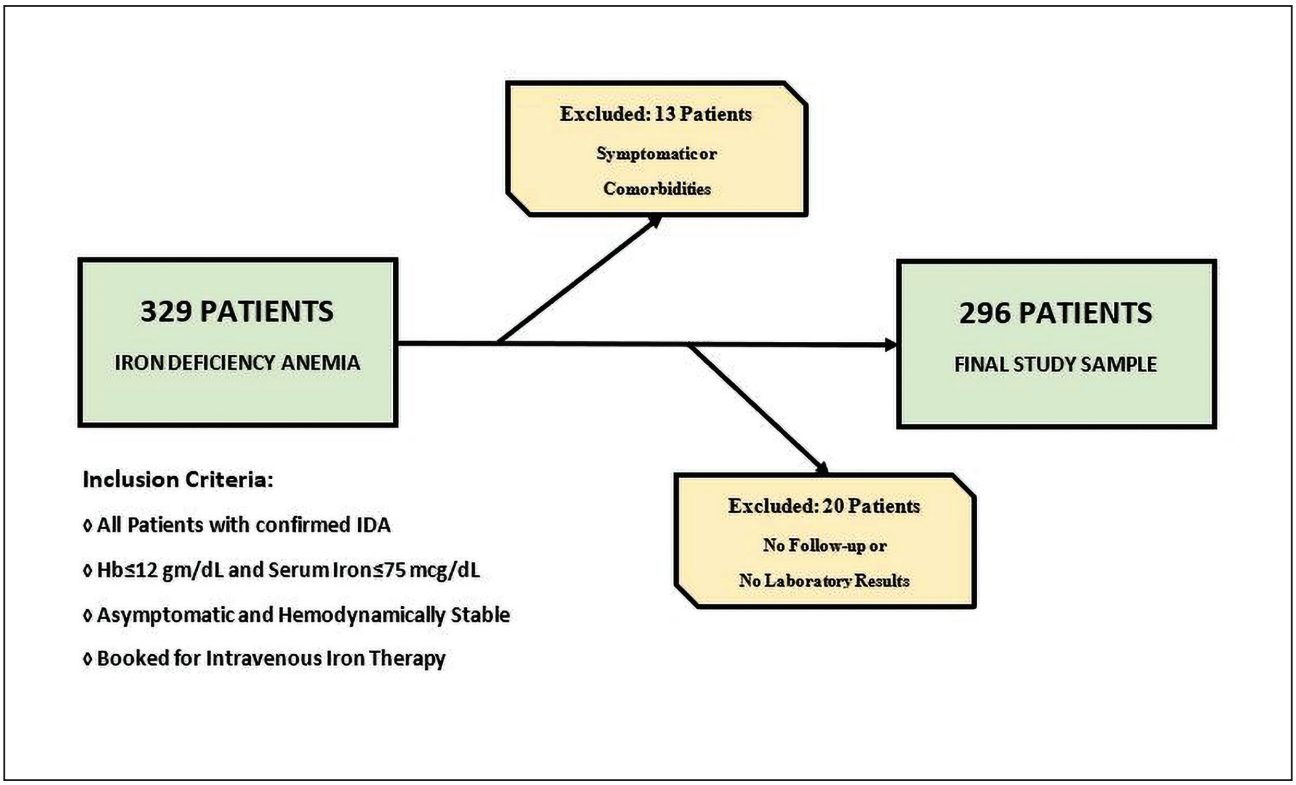

Figure 1. *Study flowchart. Abbreviations: Hb, hemoglobin; IDA, iron deficiency anemia; IV, intravenous.*

Table 1. *IV ferric carboxymaltose dosing protocol by Hb level and body weight.*

Hb level, g/dl	Body weight < 35 kg	Body weight 35-70 kg	Body weight > 70 kg
<10	500 mg	1,500 mg	2,000 mg
10-14	500 mg	1,000 mg	1,500 mg
≥14.1	500 mg	500 mg	500 mg

Abbreviation: Hb, hemoglobin.

Table 2. *Baseline characteristics and changes in Hb and serum iron after IV iron therapy, by baseline Hb group.*

Parameter	Group 1 (Hb 5-9 g/dl)	Group 2 (Hb 9.1-12 g/dl)	*p*-value*
Patients, *n* (%)	52 (17.5%)	244 (82.4%)	
Age, mean (SD), years	38.5 (12)	35.8 (10.8)	
19-76		14-86	
Sex ratio (men:women)	1:9	1:20	
Hb, baseline mean (SD), g/dl	8.06 (0.85)	11.2 (1.5)	
Hb, follow-up mean (SD), g/dl	11.5 (1.35)	12.2 (1.5)	
FAM, mean (SD), g/dl	3.34 (1.6)	1.37 (1.5)	<0.05
FAM, 95% CI, g/dl	2.7-4	1-1.6	
Serum iron, baseline mean (SD), µg/dl	5.8 (14.5)	10.3 (16.3)	
Serum iron, follow-up mean (SD), µg/dl	195.8 (145)	148 (138)	
204 (51)		137.8 (127.5)	<0.05
IA, 95% CI, µg/dl	83.4-325	106-170	

**p*-values compare Group 1 versus Group 2.

Abbreviations: CI, confidence interval; FAM, final augmentation magnitude of hemoglobin; Hb, hemoglobin; IA, serum iron augmentation.

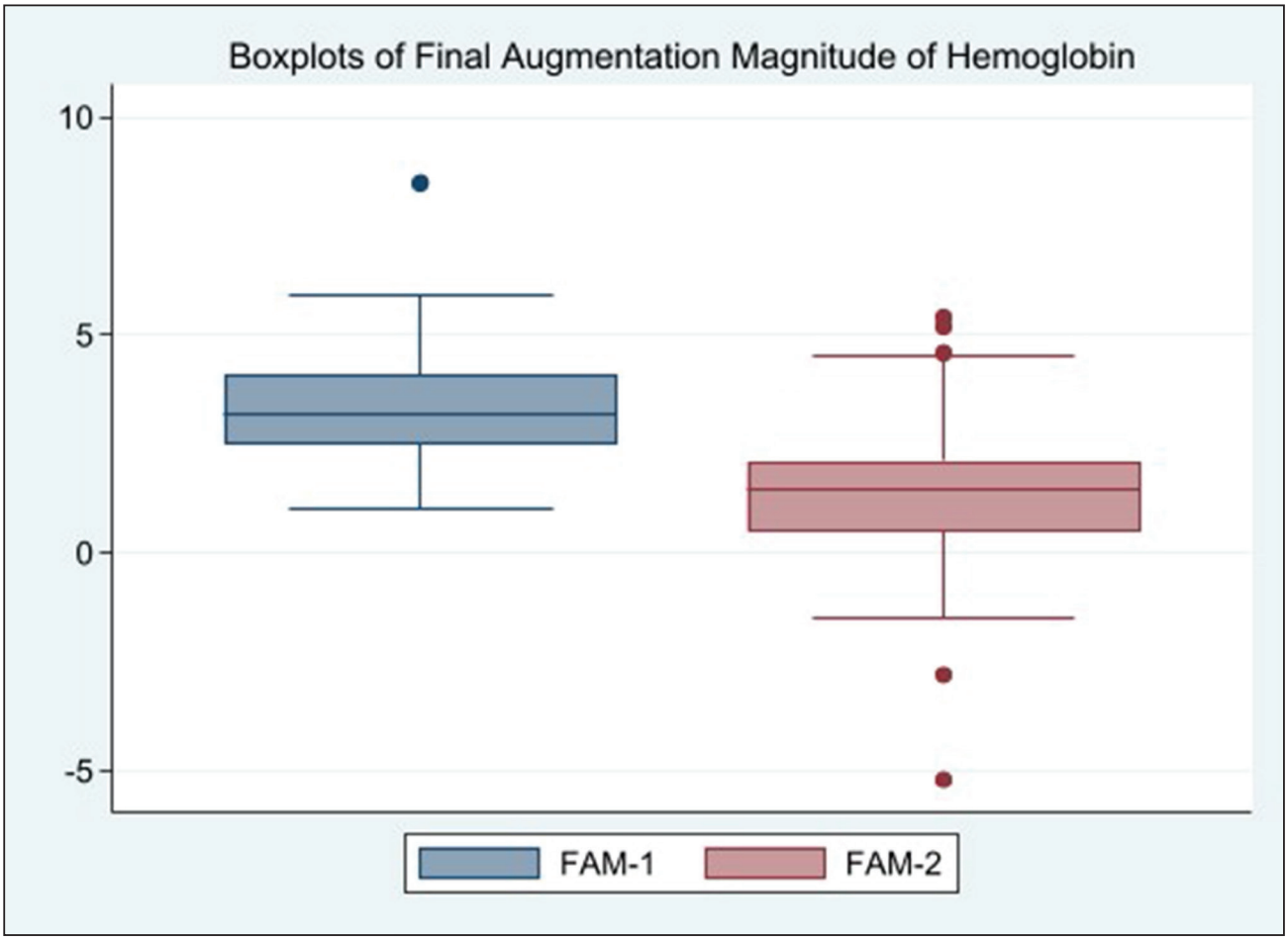

Figure 2. *Boxplot diagram of FAM in Group 1 and Group 2. Abbreviations: FAM, final augmentation magnitude of Hb.*

Student's *t*-test and Pearson's chi-squared test to assess statistical significance. We compared the two study groups using matched-pairs analysis.

Results

We enrolled 296 patients and assigned them to two groups based on baseline Hb level: Group 1 (Hb 5-9 g/dl; *n* = 52) and Group 2 (Hb 9.1-12 g/dl; *n* = 244). Baseline demographic and laboratory characteristics, as well as follow-up values, are presented in Table 2.

At the 1-month follow-up, Hb increased in most patients in both groups. The final augmentation magnitude of Hb (FAM) was greater in Group 1 than in Group 2, and both within-group changes were statistically significant ($p <$

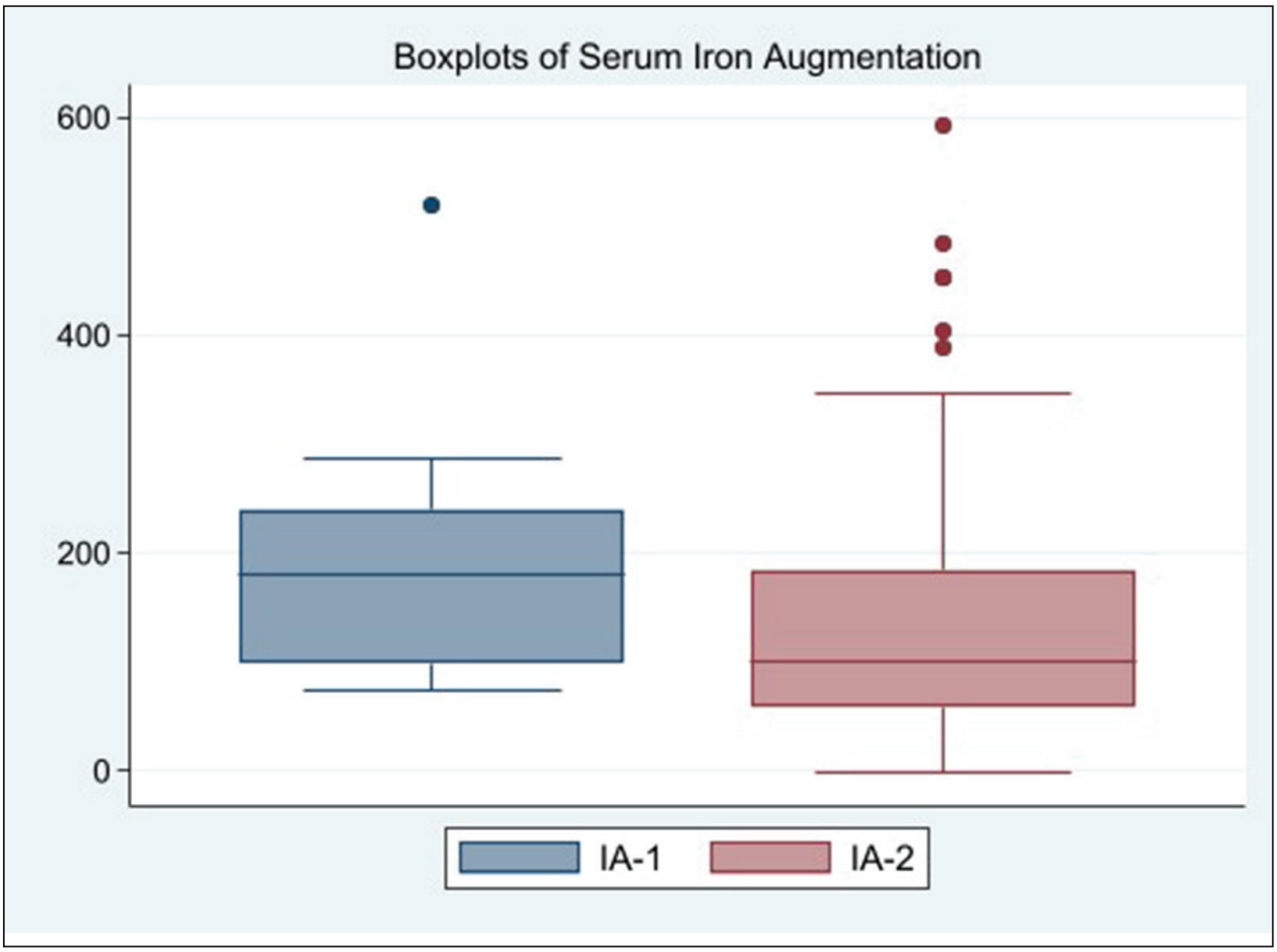

Figure 3. *Boxplot diagram of serum IA in Group 1 and Group 2. Abbreviation: IA, serum iron augmentation.*

0.05; Fig. 2). Serum iron levels also increased in both groups. IA was higher in Group 1 than in Group 2, and both within-group changes were statistically significant ($p < 0.05$; Fig. 3).

No major AEs, including anaphylaxis or severe hypotension, were reported. Sixteen patients (6.5%) experienced mild AEs, including mild erythema at the injection site, tachycardia, or hot flushes; all were managed with observation and symptomatic treatment and were discharged safely. Most patients (168 [56%]) were aged 30-45 years. Thirty-three patients had a history of bariatric surgery or intervention (5 in Group 1 and 28 in Group 2), including bands, gastric balloons, sleeve gastrectomy, or Roux-en-Y gastric bypass.

Discussion

Anemia is commonly identified during hospital-based screening, and approximately 50% of cases are attributed to iron deficiency [3]. IDA is a hypochromic, microcytic anemia characterized by a Hb level ≤12 g/dl in association with a low serum iron level (≤75 µg/dl) and/or a serum ferritin level ≤ 20 ng/ml. Additional iron studies include total iron-binding capacity, transferrin, transferrin saturation, soluble transferrin receptor, free erythrocyte protoporphyrin, reticulocyte Hb content, and bone marrow iron staining. These tests are not routinely obtained but may be performed selectively at hematology/oncology centers when clinically indicated. In our study, most PCPs relied on serum iron or ferritin measurements. Low ferritin is diagnostic of iron deficiency; however, because ferritin is an acute-phase reactant, levels may be falsely normal or elevated during concurrent inflammation [1]. We, therefore, used serum iron to reduce potential misclassification that could arise from inflammation-related ferritin elevation.

Iron deficiency may be detected incidentally or in association with anemia at diagnosis. In this study, we focused on hemodynamically stable, asymptomatic patients with confirmed IDA who were referred by their PCPs to the IV unit for parenteral iron therapy.

This cohort included 296 patients, of whom 95% were women. This sex distribution is consistent with prior reports and reflects the higher prevalence of anemia among women, particularly during the reproductive years [4]. All patients in this study were asymptomatic and received IV iron electively.

To our knowledge, this is the first study to evaluate whether parenteral iron therapy produces comparable Hb augmentation in patients with mild versus more severe anemia. We observed a greater augmentation response in Group 1 (Hb 5-9 g/dl) than in Group 2 (Hb 9.1-12 g/dl). The mean FAM was 3.34 g/dl in Group 1 compared

with 1.37 g/dl in Group 2, representing an approximately three-fold difference. This between-group difference was statistically significant and warrants further investigation. Prior studies of parenteral iron therapy have not specifically reported differential augmentation by baseline Hb strata in this manner.

These findings support greater attention to identification and treatment of IDA in the ED, including consideration of iron studies and timely iron replacement for appropriate, hemodynamically stable patients. When anemia is identified in the ED, clinicians should consider additional evaluation and ensure structured follow-up for diagnostic clarification and definitive management, even when the patient is stable for discharge.

Despite the frequency of IDA, few studies have examined IDA management in the ED [4], and clinical guidance remains limited for hemodynamically stable, asymptomatic patients in whom IDA is detected during ED evaluation. Importantly, red blood cell (RBC) transfusion is often used despite the absence of hemodynamic instability. One in four patients with asymptomatic IDA receive an unnecessary RBC transfusion at some point [5]. The American Association of Blood Banks recommends avoiding RBC transfusion for iron deficiency in the absence of hemodynamic instability [6]. Motta et al. [7] evaluated IV iron therapy for IDA in the ED using a proposed management algorithm and reported that oral or IV iron was effective and safe, with fewer RBC transfusions and fewer hospital admissions. In that study, 22 of 71 patients received RBC transfusions in the ED or during hospitalization. In contrast, we excluded patients who received RBC transfusions during the study period to assess the Hb and serum iron response to iron therapy independent of transfusion effects.

Although patients with IDA may be asymptomatic, they can also present with a broad range of manifestations, including impaired memory, difficulty learning, short attention span, muscle fatigue, headache, lethargy, and occasional tachycardia [4]. Palpitations and exertional dyspnea are also common. Spradbrow et al. [4] described IDA in the ED setting; 19 of 171 patients (11%) received RBC transfusion in the ED, including some asymptomatic patients with very low Hb who received both iron therapy and RBC transfusion. In that study, one patient received IV iron, and 11 patients were started on oral iron supplementation. Because RBC transfusion may be avoidable in hemodynamically stable patients with IDA, clinicians should prioritize a structured follow-up plan and appropriate iron replacement as a more durable approach than a temporary transfusion strategy that may expose patients to risk without clear benefit [8]. Transfusion-associated risks include infection, transfusion-related acute lung injury, and transfusion-related immune modulation [9].

In practice, ED clinicians may not routinely evaluate iron deficiency when laboratory results suggest hypochromic microcytic anemia (eg, mean corpuscular volume < 70 fl), and patients may instead be referred to a PCP for outpatient evaluation [10]. This gap may be particularly consequential in older adults: only 38% of elderly patients with stable, asymptomatic anemia undergo additional ED testing for iron deficiency, despite IDA being the most common cause of anemia in this population [11].

Limitations

There are several important limitations to this study. The retrospective, observational design limits causal inference and increases the risk of selection bias, as treatment decisions and referral to the IV unit were determined by PCPs rather than a standardized protocol. This was a single-center study of patients electively treated in an IV unit, which may limit generalizability to other settings, including ED-initiated treatment pathways and institutions using different referral patterns or dosing practices. The cohort was overwhelmingly composed of women (95%), limiting the applicability of the findings to men and potentially reflecting sex-specific referral or treatment patterns.

The follow-up period was limited to 1 month; therefore, we could not assess the durability of the Hb and serum iron responses, the recurrence of iron deficiency, or longer-term clinical outcomes. We defined IDA using Hb and serum iron criteria and relied on serum iron rather than incorporating a standardized panel of iron indices (eg, serum ferritin, transferrin saturation, or inflammatory markers). Because serum iron can fluctuate with recent intake, diurnal variation, and intercurrent illness, misclassification of iron status remains possible despite the rationale for avoiding ferritin-related bias during inflammation. The study did not account for important contributors to treatment response and anemia etiology, such as ongoing blood loss (eg, menstrual or gastrointestinal), dietary factors, adherence to any concurrent oral iron supplementation, inflammatory conditions, or evaluation for alternative causes of microcytic anemia (eg, hemoglobinopathies), all of which could confound observed augmentation.

The analysis focused on laboratory changes (FAM and IA) rather than patient-centered outcomes such as symptom improvement, functional status, quality of life, return visits, admissions, or subsequent transfusion requirements. AE ascertainment was limited to events observed during infusion and the immediate monitoring period; delayed reactions and events occurring after discharge may have been undercaptured. Finally, because dosing was based on an institutional protocol and body weight and Hb strata, residual variability in actual administered dose, infusion timing, and interval to follow-up laboratory testing may have introduced additional measurement variability.

Conclusions

Our findings indicate that IV iron therapy is effective and safe for hemodynamically stable patients with IDA across the spectrum of Hb levels, from mild to severe. The magnitude of Hb augmentation was significantly greater (approximately threefold) among patients with more severe anemia.

RBC transfusion remains an important therapeutic option for patients with moderate-to-severe anemia. However, when patients decline transfusion for personal

reasons, clinicians should consider alternative strategies, particularly when patients are hemodynamically stable and have mild-to-moderate symptoms. Clinicians should clearly discuss the potential benefits and risks of each therapeutic option with patients before initiating treatment.

List of abbreviations

AE	Adverse event
ED	Emergency department
FAM	Final augmentation magnitude of hemoglobin
FCM	Ferric carboxymaltose
Hb	Hemoglobin
IA	Serum iron augmentation
IDA	Iron deficiency anemia
IV	Intravenous
PCP	Primary care physician
RBC	Red blood cell

Conflict of interests

The authors declare no conflicts of interest.

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Consent for participation

Not applicable.

Consent for publication

All authors consent to the publication of this manuscript.

Ethical approval

The hospital review board waived ethical approval because this study was a retrospective medical chart review with no patient contact.

Author details

Tawfiq Almezeiny[1]

1. Assistant Professor of Emergency Medicine and Critical Care, College of Medicine, King Saud University, Riyadh, Saudi Arabia

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