


# Ferric Carboxymaltose for Anemic Perioperative Populations: A Systematic Literature Review of Randomized Controlled Trials

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**Importance:** Perioperative anemia is a common comorbid condition associated with increased risk of morbidity and mortality in patients undergoing elective surgical procedures.

**Objective:** We conducted a systematic literature review (SLR) to determine the efficacy and safety of the use of intravenous ferric carboxymaltose (FCM) for the treatment of perioperative anemia in preoperative, intraoperative, and postoperative elective surgical care.

**Evidence Review:** Studies meeting inclusion criteria for the SLR reported on treatment efficacy in an adult study population randomly allocated to FCM for the treatment of perioperative anemia during the perioperative period. After screening, 10 of 181 identified studies from searches in MEDLINE and EMBASE databases were identified for inclusion in this review.

**Findings:** Preoperative treatment was reported in six studies, intraoperative treatment in one study, postoperative treatment in two studies, and both pre- and postoperative treatment in one study. Together, 1975 patients were studied, of whom 943 were randomized to FCM, of whom 914 received FCM treatment. The 10 studies reported elective surgical populations for colorectal, gastric, orthopedic, abdominal, urologic, plastic, neck, gynecologic, and otolaryngologic procedures. Given the clinical and methodological heterogeneity of the studies, the analyses were limited to qualitative assessments without meta-analyses. All 10 studies reported statistically greater changes in hemoglobin concentration, serum ferritin, and/or transferrin saturation with FCM treatment compared with comparators (placebo, oral iron, standard care, or a combination of these). Two studies reported statistically significant differences in transfusion rate and 2 studies reported significant differences in length of hospital stay between FCM and its comparator(s).

**Conclusions and Relevance:** This SLR adds to existing data that administration of FCM in preoperative and postoperative settings improves hematologic parameters. Several studies in the review supported the beneficial effects of FCM in reducing transfusion rate and length of stay. Larger, well-designed, longer-term studies may be needed to further establish the efficacy and safety of FCM in elective surgery patients with perioperative anemia.

**Keywords:** intravenous iron, hemoglobin, elective surgery, patient blood management, iron-deficiency anemia

## Plain Language Summary

Preoperative and postoperative anemia occur frequently in patients undergoing elective surgery.<sup>1</sup>

Perioperative anemia is associated with an increased risk of morbidity, mortality, and other adverse postoperative outcomes.<sup>1-4</sup>

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Iron deficiency is a common cause of anemia in surgical patients, affecting at least 10% of surgical patients during the preoperative period and at least 20% during the postoperative period.<sup>5,6</sup>

Blood transfusion is frequently administered as part of the standard of care for perioperative anemia<sup>7</sup> and may produce a temporary increase in hemoglobin levels<sup>8</sup> but is associated with poor outcomes.<sup>9</sup>

This systematic review evaluated the effectiveness and safety of ferric carboxymaltose in patients with perioperative anemia, with a focus on patients' health states during the preoperative and postoperative period.

The 10 identified studies included patient populations undergoing elective colorectal, gastric, orthopedic, abdominal, urologic, plastic, neck, gynecologic, and otolaryngologic procedures.

Comparators were placebo, oral iron, standard care, or a combination of these interventions.

Overall, this review found that ferric carboxymaltose significantly increased hemoglobin level, serum ferritin concentrations, and transferrin saturation in patients with perioperative anemia who were undergoing elective surgery.

## Introduction

Perioperative anemia is a common comorbid condition associated with increased risk of morbidity and mortality in patients undergoing elective surgical procedures. The most common etiology of perioperative anemia in adults is iron deficiency. Clinical signs and symptoms of iron-deficiency anemia (IDA) are protean and vary widely, and perioperative health outcomes associated with IDA include reduced physical function, prolonged postoperative recovery, increased length of hospital stay, and mortality.<sup>1-4,10</sup> Among orthopedic patients, the preoperative prevalence of anemia is estimated at 24% to 44%, and postoperative estimates are significantly higher.<sup>1</sup> Among patients with advanced colon cancer undergoing colectomy, the estimated prevalence of anemia is reported to be as high as 75.8%.<sup>11</sup>

In preoperative evaluation for IDA, diagnostic assessment and pre-surgical treatment varies. One recognized intervention is blood transfusion, with an estimated 6.6 million red blood cell (RBC) units administered annually to elective surgery patients in the United States.<sup>4</sup> To assess the use of an intravenous iron in anemic perioperative patient populations, a systematic literature review (SLR) was conducted and focused on the safety and efficacy of ferric carboxymaltose.

## Methods

### Study Design

The study protocol was designed and executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).<sup>12</sup> All review methods were conducted a priori according to the established protocol. Publication screening, selection, and assessments of bias were carried out by the authors, with consensus for reconciliation. Included studies were conducted in adults ( $\geq 18$  years of age) with anemia (if not IDA) who had been identified for elective surgery and randomly allocated to receive intravenous (IV) FCM or comparator(s). Inclusion also required study publication in peer-reviewed journals. Studies were excluded if the design was nonexperimental, if efficacy was not reported, or if the investigative treatment consisted of only IV FCM in combination with either erythropoietin or an erythropoiesis-stimulating agent; animal and pediatric studies were also excluded. Conference abstracts and grey literature were excluded.

### Literature Search

Comprehensive, computer-based literature searches for records were performed systematically using the MEDLINE (PubMed, US National Library of Medicine, National Institutes of Health) and EMBASE databases. The electronic search strategy was peer reviewed and developed with guidance from a university librarian at St. John's University College of Pharmacy and Health Sciences. Databases were searched from their inception to January 2021 for abbreviations and full-phrase versions of keywords and Medical Subject Headings combined with Boolean operators as outlined in the [Supplementary Data, Appendix 1](#). Two reviewers independently and in duplicate assessed titles and abstracts of identified records for trial eligibility, and a third reviewer resolved any discrepancies by discussion or adjudication until consensus was reached. Relevant records were further assessed by examining the full-text articles. A snowball method (using a key manuscript as a starting point and consulting the bibliography to find other relevant titles on the subject) was used to search the identified literature to additional studies. Data were extracted onto a standardized extraction form.

## Risk of Bias and Quality Assessment

Internal validity and risk of bias for each study meeting final inclusion criteria were assessed in duplicate by 2 independent reviewers using the Cochrane Risk of Bias Tool.<sup>13</sup> The key types of bias that were examined were selection, performance, detection, attrition, and reporting. The overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)<sup>14</sup> approach to determine the strength of the conclusions/recommendations from this review.

## Outcome Measures

The primary outcomes were the absolute or relative change from baseline in hemoglobin (Hb) concentration (g/dL), serum ferritin (ng/mL), and % transferrin saturation (TSAT). Primary outcomes that were reported in alternative units were converted for consistency across studies for ease of interpretability; conversions were quality controlled for accuracy. Secondary outcome measures were the proportion of patients who received a perioperative blood transfusion, the occurrence of adverse events, treatment-related adverse events, postoperative mortality, length of hospital stay, and any validated measure of quality of life (QOL).

## Results

### Study Selection

We identified 244 citations, 208 through database searching and 36 through other sources. The number was decreased to 181 after removing duplicates (Figure 1). The 181 citations were screened based on title and abstract, and 139 were excluded. After screening the full-text articles of the remaining 42 citations, 32 were excluded. Ultimately, 10 eligible studies were included in this systematic review.

### Study Characteristics

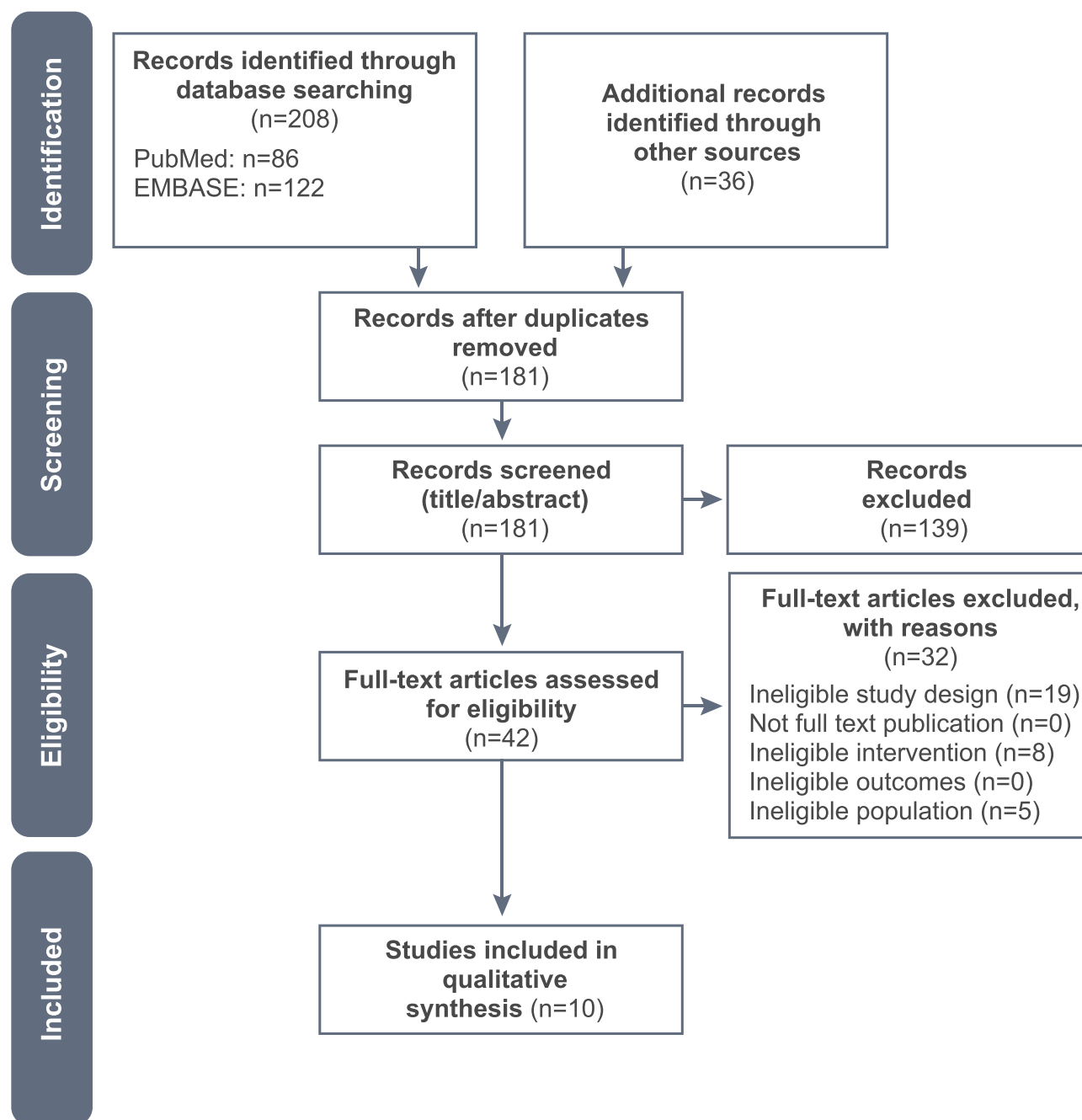
All 10 studies included in the systematic review were randomized clinical trials and were published between 2014 and 2020.<sup>7,15–23</sup> Five studies were conducted in Europe (United Kingdom,<sup>15,21,23</sup> Spain<sup>15,16</sup>), 2 studies in Oceania (Australia<sup>7,17</sup>), and 3 studies in Asia (South Korea<sup>19,20,22</sup>).

The design and patient flow of the included studies are summarized in Table 1. Studies investigated the use of FCM in the following surgical populations: cancer

(colorectal,<sup>18</sup> gastric<sup>19</sup>), cardiac,<sup>21</sup> menorrhagia,<sup>20</sup> orthopedic (hip arthroplasty,<sup>16,22</sup> total knee arthroplasty<sup>15,22</sup>), abdominal,<sup>17,23</sup> and a combination of orthopedic, abdominal, neck, gynecologic, urologic, plastic, and ear, nose, and throat (ENT).<sup>7</sup> Ferric carboxymaltose was administered preoperatively in 5 studies,<sup>16,18,20,21,23</sup> intraoperatively in 1 study,<sup>22</sup> postoperatively in 3 studies,<sup>7,15,19</sup> and perioperatively (both preoperatively and postoperatively) in 1 study.<sup>17</sup> With respect to blinding, 2 studies used a double-blind design,<sup>16,23</sup> 3 were single-blind,<sup>15,19,22</sup> and 5 were open-label.<sup>7,17,18,20,21</sup> Follow-up periods for patients varied, spanning from 2 weeks post-infusion,<sup>20</sup> 4 weeks postoperatively<sup>15,17,22</sup> to 2 to 6 months after hospital discharge.<sup>7,15,16,19,21,23</sup>

In total, 1975 study patients were randomized across the 10 studies, 943 (48%) of whom were randomized to receive IV FCM, and of these, 914 (97%) received their assigned treatment. Three studies compared IV FCM with oral ferrous sulfate (dose: 100 mg per day<sup>15</sup> to 200 mg twice daily<sup>15,21</sup>), 1 study compared IV FCM with IV iron sucrose (dose: 200 mg iron x 3/week),<sup>20</sup> and 2 studies compared IV FCM with standard of care (no intervention<sup>7</sup> or no treatment, continued observations, oral iron recommendations, and allogeneic blood transfusion [ABT]).<sup>17</sup> The comparator for 3 of the remaining 4 studies was IV saline placebo,<sup>19,22,23</sup> and the comparators for the other remaining study (triple-arm, parallel design) were 1 mL subcutaneous (SC) saline placebo with 250 mL of IV saline placebo and 40,000 IU/1 mL SC erythropoietin (EPO) with 1000 mg IV FCM diluted in 250 mL saline.<sup>16</sup> The dosages of IV FCM across studies varied in terms of total dose and dosage calculation as well as administration time, which spanned 6 to 30 minutes. In 3 studies, IV FCM was given in a single dose of 1000 mg;<sup>7,22,23</sup> in the 7 others, the dose was determined by the Ganzoni formula to correct the total iron deficit,<sup>15</sup> manufacturer recommendation (15 mg/kg),<sup>7,17</sup> weight cutoffs (<50 or ≥50 kg),<sup>19,20</sup> weight cutoffs in combination with inclusion Hb values,<sup>18,21</sup> or blood loss ( $5 \times 10^{-7}$  mcg/L) if blood loss was ≥100 mL.<sup>17</sup> For 8 of the 10 studies, the maximum single dose of IV FCM was 1000 mg;<sup>7,15–17,19,22,23</sup> Keeler et al and Padmanabhan et al allowed a maximum total dose of up to 2000 mg (2 doses of 1000 mg administered 7 days apart and when required).<sup>15,21</sup>

The hematologic inclusion criteria varied among the studies, with 5 requiring IDA with Hb limits (9–12 g/dL,<sup>16</sup> <11 g/dL [women] or <12 g/dL [men],<sup>18</sup> <12 g/dL [women] or <13 g/dL [men]<sup>21,23</sup> and ≥7–<10 g/dL<sup>19</sup>); 4 requiring IDA with specific hematologic profiles (serum



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the study selection process.

**Note:** Adapted from Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.<sup>37</sup>

ferritin <300 µg/L, transferrin saturation <25%, and Hb <12 g/dL [women] or <13 g/dL [men];<sup>17</sup> Hb 7–12 g/dL with serum ferritin ≤100 µg/L or TSAT ≤20%;<sup>7</sup> serum ferritin <300 µg/L and Hb <10 g/dL),<sup>20,22</sup> and 1 requiring anemia and/or IDA with a specific hematologic profile (Hb 8.5–12 g/dL, TSAT <20%, or both<sup>15</sup>).

Institution-specific medical care standards specifically relating to perioperative blood management (PBM) were explicitly stated in 3 of the 10 studies.<sup>15–17</sup> The first study used thromboprophylaxis with low-molecular-weight heparin and prophylaxis with proton pump inhibitors for upper gastrointestinal bleeding.<sup>16</sup> The second used

**Table 1** Design and Patient Flow of Included Studies

Study	Study Description				Design	Prespecified Blood Transfusion Criteria	Randomized N	Treated N	Withdrawn N
	Perioperative State (Surgery)	Study Group Assignment	Design	Prespecified Blood Transfusion Criteria					
Bisbe et al (2014) <sup>15</sup>	Postoperative (orthopedic)	<b>G1:</b> IV FCM 700–1000 mg single dose on postop day 1 <b>G2:</b> Oral ferrous sulfate 100 mg/d from postop day 7 to 30	Single-blinded	3. Hb <70 g/L=3 RBC transfusions independent of symptoms 4. Hb 71–89 g/L=2 RBC transfusions in presence of severe symptoms (HF with NYHA Class ≥III dyspnea, ACS, hemodynamic instability [hypotension, orthostatism], and/or acute or exacerbated chronic respiratory failure)	122 <b>G1:</b> 60 <b>G2:</b> 62	121 <b>G1:</b> 59 <b>G2:</b> 62	<b>G1:</b> 7 (LTFU) <b>G2:</b> 11 (LTFU)		
Bermabeu-Wittel et al (2016) <sup>16</sup>	Preoperative (orthopedic hip)	<b>G1:</b> EPO 40,000 IU/1 mL EPO SC + IV FCM 1000 mg (2500 mg vials diluted in 250 mL of saline) infused over 20 min <b>G2:</b> 1 mL placebo (saline) SC + IV FCM 1000 mg (2500 mg vials diluted in 250 mL of saline) infused over 20 min <b>G3:</b> 1 mL placebo (saline) SC + IV placebo (250 mL of saline) infused over 20 min	Double-blind	1. Hb <70 g/L=3 RBC transfusions independent of symptoms 2. Hb 71–89 g/L=2 RBC transfusions in presence of severe symptoms (HF with NYHA Class ≥III dyspnea, ACS, hemodynamic instability [hypotension, orthostatism], and/or acute or exacerbated chronic respiratory failure)	303 <b>G1:</b> 100 <b>G2:</b> 103 <b>G3:</b> 100	293 <b>G1:</b> 97 (hip surgery—osteosynthesis, n=66 [68%]; partial arthroplasty, n=27 [28%]; total arthroplasty, n=4 [4%]) <b>G2:</b> 101 (hip surgery—osteosynthesis, n=70 [69%]; partial arthroplasty, n=28 [28%]; total arthroplasty, n=3 [3%]) <b>G3:</b> 97 (hip surgery—osteosynthesis, n=60 [62%]; partial arthroplasty, n=33 [34%]; total arthroplasty, n=4 [4%])	<b>G1:</b> 14 (discontinued intervention, n=6 [not operated, n=3, iron sucrose administration in follow-up period, n=3]); excluded from per protocol analysis, <sup>a</sup> n=8 <b>G2:</b> 17 (discontinued intervention, n=6 [not operated, n=2, iron sucrose administration in follow-up period, n=4]); excluded from per protocol analysis, <sup>a</sup> n=11 <b>G3:</b> 11 (discontinued intervention, n=4 [not operated, n=3, iron sucrose administration in follow-up period, n=1]); excluded from per protocol analysis, n=7 <sup>a</sup>		
Froessler et al (2016) <sup>17</sup>	Perioperative (abdominal)	<b>G1:</b> Preop—IV FCM single 15 mg/kg injection (maximum: 1000 mg) administered over 15 min Postop—IV FCM 0.5 mg per recorded 1 mL blood loss if blood loss ≥100 mL, given within 2 days of surgery <b>G2:</b> Usual care consisting of no treatment, observation, oral iron recommendations, and ABT; prescription and administration of IV iron allowed	Open (masking not used)	Not reported	72 <b>G1:</b> 40 <b>G2:</b> 32	72 <b>G1:</b> 40 <b>G2:</b> 32	Not reported		

(Continued)

Table 1 (Continued).

Study	Study Description					Design	Prespecified Blood Transfusion Criteria	Randomized N	Treated N	Withdrawn N
	Perioperative State (Surgery)	Study Group Assignment	Design	Prespecified Blood Transfusion Criteria	Randomized N					
Khalafallah et al (2016) <sup>7</sup>	Postoperative (orthopedic, abdominal, ENT, plastic, gynecologic, urologic)	G1: IV FCM single 15 mg/kg injection (maximum: 1000 mg) over 15 min G2: No intervention (standard care)	Open-label	Not reported	201 G1: 103 G2: 98	201 G1: 97 G2: 94	G1: 6 (withdrawn from study, n=5; LTFU, n=1) G2: 4 (withdrawn from study, n=2; LTFU, n=2)			
Keeler et al (2017) <sup>18</sup>	Preoperative (oncological)	G1: IV FCM diluted in 250 mL 0.9% NS over 15 min; dose calculated using body weight and inclusion hemoglobin value. Maximum dose 1000 mg/wk and 2000 mg during trial; second dose ≥7 days after first, if needed G2: Oral ferrous sulphate 200 mg BID continued until surgery (patients advised to take without food and with liquid high in ascorbic acid to maximize enteric absorption)	Open-label	Not reported	116 G1: 55 G2: 61	116 G1: 55 G2: 61	G1: 4 (did not undergo surgical resection) G2: 2 (did not undergo surgical resection)			
Kim et al (2017) <sup>19</sup>	Preoperative (oncological)	G1: IV FCM 1–2 1000 mg injections for patients <50 kg or 500 mg injections for ≥50 kg over 6–15 min G2: IV saline placebo	Single-blinded	Per guidelines, Hb <7 g/dL	454 G1: 228 G2: 226	445 G1: 222 G2: 223	G1: 5 (did not complete study [LTFU, n=3; withdrew consent after treatment, n=1; physician withdrew patient for surgical complication, n=1]) G2: 10 (did not complete study [withdrew consent after treatment, n=6; LTFU, n=2; eligibility criteria violation recognized after treatment/received blood transfusion before treatment, n=2])			
Lee et al (2019) <sup>20</sup>	Preoperative (benign uterine diseases)	G1: IV FCM single dose administered over 15 min (maximum: 1000 mg); amount determined based on patient's body weight (<50 kg, 500 mg iron; ≥50 kg, 1000 mg iron). G2: IV IS single administration over 3 dosing visits per week (maximum: 600 mg iron/week in 200 mg iron doses. Dosage based on calculated iron deficit using the Ganzoni formula)	Open-label	Not reported	101 G1: 52 G2: 49	101 G1: 52 G2: 49	G1: 0 G2: 0			

Padmanabhan et al (2019) <sup>21</sup>	Preoperative (cardiac)	<b>G1:</b> IV FCM diluted in 250 mL of NS administered over 30 min (maximum: 1000 mg dose). A second dose was offered when required. Calculation of dosing regimen as follows: Hb > 100 and weight < 70 kg = 1000 mg; Hb > 100 and weight > 70 kg = 1500 mg; Hb 70–100 and weight < 70 kg = 1500 mg; Hb 70–100 and weight > 70 kg = 2000 mg <b>G2:</b> 200 mg ferrous sulphate PO BID	Open-label	Not reported	50 <b>G1:</b> 26 <b>G2:</b> 24	44 <b>G1:</b> 22 <b>G2:</b> 22	<b>G1:</b> 4 (LTFU) <b>G2:</b> 1 (LTFU)
Park et al (2019) <sup>22</sup>	Intraoperative (Unilateral TKA or THA)	<b>G1:</b> IV FCM 1000 mg diluted in 100 mL NS administered over 15 min. <b>G2:</b> IV 100 mL NS placebo	Single-blinded	Hb < 8 g/dL throughout entire perioperative period. If significant hemodynamic instability was observed despite adequate fluid administration or a requirement of an increasing amount of vasopressor was essential, allogenic transfusion of packed RBC was permitted with the Hb ≥ 8 g/dL. In case of transfusion, the subjects received one unit of packed RBC and the Hb level was followed to assess the further administration of additional packed RBC.	69 <b>G1:</b> 32 <b>G2:</b> 34	58 <b>G1:</b> 29 <b>G2:</b> 29	<b>G1:</b> 3 (withdrew consent, n=1, LTFU, n=2) <b>G2:</b> 5 (unnoticed cancer diagnosis, n=1; withdrew consent, n=1; LTFU, n=3)
Richards et al (2020) <sup>23</sup>	Preoperative (abdominal)	<b>G1:</b> IV FCM single dose 1000 mg in 100 mL NS administered over 15 min <b>G2:</b> IV 100 mL NS placebo	Double-blinded	Not reported	487 <b>G1:</b> 244 <b>G2:</b> 243	481 <b>G1:</b> 240 <b>G2:</b> 241	<b>G1:</b> 8 (not treated, n=4; withdrew consent, n=4) <b>G2:</b> 6 (not treated, n=2; withdrew consent, n=4)

**Note:** <sup>a</sup>Patients did not receive intervention, were not operated, or received iron sucrose administration in the follow-up period.

**Abbreviations:** ABT, allogeneic blood transfusion; ACS, acute coronary syndrome; BID, twice daily; EPO, erythropoietin; FCM, ferric carboxymaltose; G, treatment group; Hb, hemoglobin; HF, heart failure; IV, intravenous; IS, iron sucrose; LTFU, lost to follow-up; NS, normal saline; NYHA, New York Heart Association; PO, by mouth; RBC, red blood cell; SC, subcutaneous; TDD, total daily dose; TID, three times daily; THA, total hip arthroplasty; TKA, total knee arthroplasty.

a robust PBM protocol including preoperative treatment with iron, SC EPO, or both 1 month before surgery, discretionary tranexamic acid during and after surgery, and antithrombotic treatment with SC bempiparin (a low-molecular-weight heparin not approved in the United States); additionally, shed blood exceeding 400 mL was automatically reinfused via an autotransfusion device.<sup>15</sup> In the third study, patients in the usual care group received perioperative anemia management, which did not disallow prescription or administration of IV iron.<sup>17</sup> Five of the 10 studies prespecified blood transfusion thresholds; 3 specified Hb <7 g/dL,<sup>7,15–17,19</sup> and 1 of these set the number of RBC transfusions at 3.<sup>16</sup> Three of the 5 studies specified Hb <8 g/dL<sup>15,22</sup> or 7.1–8.9 g/dL in the presence of severe symptoms.<sup>16</sup>

## Study Populations

Baseline characteristics of patients are provided in [Table 2](#). Most of the study populations (9/10) had an average age of 60 years or older, and 9 of the 10 were generally evenly distributed with respect to age across treatment groups. The difference in age distribution between the FCM group and the comparator arm in the sixth study occurred by chance and was not explained by the authors. Eight studies had a greater percentage of women.<sup>7,15,16,19–22</sup> Mean weight was lowest among patients undergoing surgery for menorrhagia<sup>20</sup> and highest among those undergoing abdominal surgery.<sup>17</sup> The American Society of Anesthesiologists (ASA) physical status (grades ranged from I [defined as normal and healthy] to VI [declared brain-dead, organs to be donated]) varied by surgical population in the intervention group; 27–58% of patients undergoing abdominal surgery,<sup>17,23</sup> 45% undergoing colorectal cancer surgery,<sup>18</sup> and 20% undergoing orthopedic surgery had ASA Grade III (presence of severe systemic disease) or greater.<sup>15,24</sup> In each of the studies reporting baseline hematopoietic parameters, the patients met criteria for IDA (mean baseline Hb <11 g/dL, serum ferritin <300 ng/mL, and TSAT <25%).

## Risk of Bias Assessment

Overall, the studies were considered to have a high risk of bias, largely with regard to the blinding of patients and personnel and blinding of outcome assessments ([Figures 2 and 3](#)).

### Random Sequence Generation

Eight out of 10 studies were considered to have a low risk of bias for random sequence generation, as they clearly reported

appropriate randomization techniques.<sup>15,17–21,23,25</sup> However, the random sequence method using Excel in Khalafallah et al<sup>7</sup> was questionable and not described in Park et al,<sup>22</sup> making the risk of bias unclear.

### Allocation Concealment

Eight out of 10 studies were rated as having low risk of bias for allocation concealment.<sup>7,15,17,19,22,23,25</sup> The studies by Keeler et al<sup>18</sup> and Lee et al<sup>20</sup> did not adequately describe the concealment methods of treatment allocation by an independent unit; selection bias was thus deemed unclear in the risk of bias for allocation concealment.

### Blinding

Five of the 10 studies had an open-label design,<sup>7,17,18,20,21</sup> and 3 were patient-blinded only,<sup>15,19,22</sup> leading to a high risk of performance bias; the remaining studies had a double-blind design, which were assigned a low risk of bias.<sup>16,23</sup> Three studies had an unclear risk of detection bias; neither Keeler et al<sup>18</sup> nor Kim et al<sup>19</sup> clearly stated who performed the outcome assessments, and Bernabeu-Wittel et al<sup>16</sup> did not describe the study's blinding measures. Detection bias was low in Bisbe et al<sup>15</sup> and Richards et al<sup>23</sup> but was high in Froessler et al, Lee, Padmanabhan, and Park owing to a lack of description of outcome blinding measures in these open-label studies<sup>17,20–22</sup> and in Khalafallah et al owing to the recording of adverse events (AEs) by personnel who administered the study drug.<sup>7</sup>

### Incomplete Outcome Data

Risk of attrition bias was considered low in 3 studies, in Bernabeu-Wittel et al because losses to follow-up were disclosed and the attrition was reasonable and not expected to affect results,<sup>16</sup> in Froessler et al because the rationale was given for study termination<sup>17</sup> and Richards et al because attrition was described and accounted for in statistical analysis.<sup>23</sup> Risk of attrition bias was deemed unclear for 6 studies because no explanations were offered for withdrawal for either treatment group,<sup>7</sup> for the relevance of incomplete data sets available at the end of the study period,<sup>15,21,22</sup> for the impact of incomplete adherence—which was assessed in 1 study—to allocated treatment,<sup>18</sup> and for interpolation of missing data using linear regression analysis when the total sample size is very small.<sup>20</sup> The risk of attrition bias was high for Kim et al, in which a modified intention-to-treat analysis was used.<sup>19</sup>

**Table 2** Baseline Patient Characteristics of Included Studies

Author	Age, y, Mean ± SD	Sex, n (%)	Weight, kg, Mean ± SD	ASA Physical Status Classification, n (%)	Preoperative Hb, g/dL, Mean ± SD	Serum Iron, µg/dL, Mean ± SD	Preoperative Serum Ferritin, ng/mL, Mean ± SD	Preoperative TSAT, %, Mean ± SD
Bernabeu-Wittel (2016) <sup>16</sup>	G1: 84.6 ± 6.2 G2: 83.4 ± 6.4 G3: 82.3 ± 6.9	G1: 84 (81.5%) (F) G2: 87 (87.0%) (F) G3: 87 (87.0%) (F)	Not reported	G1: III (II–III) <sup>a</sup> G2: III (II–III) <sup>a</sup> G3: III (II–III) <sup>a</sup>	G1: 11.0 ± 0.8 G2: 11.0 ± 0.7 G3: 11.0 ± 0.7	Not reported	G1: 155 ± 170 G2: 137 ± 150 G3: 141 ± 130	Not reported
Keeler (2017) <sup>18</sup>	G1: Median (IQR): 73.8 (67.4–78.6) G2: Median (IQR): 74.7 (67.9–80.8)	G1: 35/20 (M:F) G2: 37/24 (M:F)	G1: Mean (95% CI): 79.0 (74.9, 83.2) G2: Mean (95% CI): 72.8 (68.7, 76.9)	G1: I–II, n=30; III–IV, n=25 G2: I–II, n=43; III–IV, n=18	G1: Recruitment: ~10.1; day of surgery: ~11.9 G2: Recruitment: ~10.4; day of surgery: ~11.0	Not reported	Not reported	Not reported
Kim (2017) <sup>19</sup>	G1: 60.9 ± 13.7 G2: 61.2 ± 12.6	G1: 125 (54.8%) (F) G2: 124 (54.9%) (F)	G1: 57.6 ± 9.7 G2: 58.1 ± 9.9	Not reported	G1: 11.6 ± 1.6 G2: 11.8 ± 1.6	G1: 24.6 ± 15.2 G2: 24.0 ± 11.1	G1: 115.9 ± 104.8 G2: 137.1 ± 123.9	G1: 10.8 ± 7.2 G2: 10.5 ± 5.4
Froessler (2016) <sup>17</sup>	G1: 64 ± 15 G2: 68 ± 15	G1: 19/21 (M:F) G2: 17/15 (M:F)	G1: 86 ± 27 G2: 88 ± 20	G1: II: 17 (42.5); III: 22 (55); IV: 1 (2.5) G2: II: 17 (53.1); III: 15 (46.9); IV: 0	G1: Randomization: 10.7 ± 1.3 (n=40); admission: 11.5 ± 1.3 (n=36) G2: Randomization: 10.6 ± 1.4 (n=32; P=0.76); admission: 10.7 ± 1.7 (n=29; P=0.12) Difference between randomization and admission: G1: 0.8 ± 0.8 (n=36) G2: 0.1 ± 1.3 (n=29; P=0.010)	Not reported	G1: Randomization, median (IQR): 19 (6–48) G2: Randomization, median (IQR): 37 (11–82)	G1: Randomization, median (IQR): 6 (3–10) G2: Randomization, median (IQR): 9 (7–15)
Bisbe (2014) <sup>15</sup>	G1: Mean (range): 72.7 (56–86) G2: Mean (range): 72.8 (40–86)	G1: 47 (78.3%) (F) G2: 50 (80.6%) (F)	G1: 79.6 ± 14.9 G2: 76.2 ± 11.9	G1: ≥III: 12 (20.0) G2: ≥III: 12 (19.4)	G1: 13.6 ± 0.9 G2: 13.6 ± 0.9	G1: 77 ± 22 G2: 74 ± 21	G1: 120 ± 111 G2: 164 ± 95	G1: 20.1 ± 6.6 G2: 20.4 ± 6.7

(Continued)

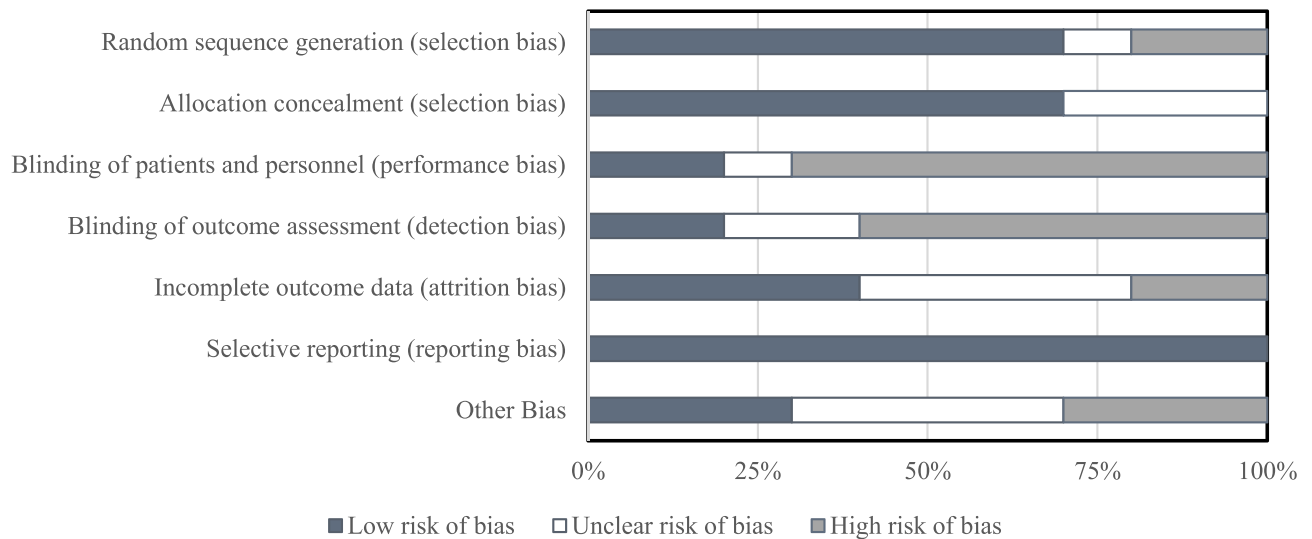
Table 2 (Continued).

Author	Age, y, Mean ± SD	Sex, n (%)	Weight, kg, Mean ± SD	ASA Physical Status Classification, n (%)	Preoperative Hb, g/dL, Mean ± SD	Serum Iron, µg/dL, Mean ± SD	Preoperative Serum Ferritin, ng/mL, Mean ± SD	Preoperative TSAT, %, Mean ± SD
Khalafallah (2016) <sup>7</sup>	G1: Median (IQR): 65 (55–73) G2: Median (IQR): 67 (60–76)	G1: 65 (63%) (F) G2: 50 (51%) (F)	G1: Median (IQR): 82 (70–91) G2: Median (IQR): 81 (69–88)	Not reported	G1: Median (IQR), postop day 1: 10.9 (9.9–12.0) G2: Median (IQR), postop day 1: 10.6 (9.6–11.7)	G1: Preop: 81.6 ± 15.6; postop, day 1: 33.5 ± 21.2; period effect; † mean difference (95% CI): –48.0 (–54.8 to –41.9) [P<0.0001] G2: Preop: 81.0 ± 21.2; postop, day 1: 33.5 ± 25.1; period effect; † mean difference (95% CI): –47.4 (–53.9 to –41.0) [P<0.0001]	G1: Postop, day 1, median (IQR): 170 (108–284) G2: Postop, day 1, median (IQR): 243 (134–471)	G1: Postop day 1, median (IQR): 10 (7–15) G2: Postop day 1, median (IQR): 11 (9–15)
Lee (2019) <sup>20</sup>	G1: 44.0 ± 5.7 G2: 43.4 ± 5.0	G1: 52 (100%) (F) G2: 49 (100%) (F)	G1: 56.2 ± 6.7 G2: 57.6 ± 9.1	Not reported	G1: 8.4 ± 1.4 G2: 8.4 ± 1.1	Not reported	G1: 58 ± 57 G2: 57 ± 39	G1: 6.1 ± 7.3 G2: 4.8 ± 5.9
Padmanabhan (2019) <sup>21</sup>	G1: 73 ± 12 G2: 75 ± 10	G1: 9 (41%) (F) G2: 8 (36%) (F)	G1: 78.9 ± 18.2 G2: 80.5 ± 13.1	Not reported	G1: 11.9 ± 0.89 G2: 113.9 ± 1.11	Not reported	G1: median (IQR) 62.8 (26.2–86.4) G2: median (IQR) 49.7 (19.7–88.8)	Not reported
Parf <sup>22</sup> (2019)	G1: 65.1 ± 10.2 G2: 62.0 ± 9.5	G1: 19 (65.5%) (F) G2: 21 (72.4%) (F)	G1: 64.2 ± 9.8 G2: 67.1 ± 11.8	G1: ≥III: 0 G2: ≥III: 0	G1: 12.5 ± 1.3 G2: 13.4 ± 1.1	G1: 92.4 ± 37.0 G2: 101.0 ± 46.5	G1: 90.6 ± 82.5 G2: 87.0 ± 105.2	G1: 29.4 ± 16.3 G2: 33.2 ± 17.2
Richards (2020) <sup>23</sup>	G1: Mean (range): 66 (57–72) G2: Mean (range): 65 (50–72)	G1: 125 (51%) (F) G2: 142 (58%) (F)	Not reported	G1: ≥III: 57 (23.4) G2: ≥III: 66 (27.2)	G1: 11.1 ± 1.2 G2: 11.1 ± 1.2	Not reported	All Groups: <100 – 57%	All Groups: <20 – 76%

Notes: \*Ns were not specified; †Estimated in the standard care group (G2) using repeated measures mixed effects linear regression with time from operation as a random factor, adjusted for sex. Outcomes were compared with preoperative sample concentrations; postoperative samples were taken on the first day after the operation.  
Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; G, treatment group (as defined in Table 1 in Intervention Groups and Regimen row); IQR, interquartile range; SD, standard deviation; TSAT, transferrin saturation.

	Bernabeu-Wittel et al (2016)	Keeler et al (2017)	Kim et al (2017)	Froessler et al (2016)	Bisbe et al (2014)	Khalafallah et al (2016)	Lee et al (2019)	Padmanabhan et al (2019)	Park et al (2019)	Richards et al (2020)
Random sequence generation	+	+	+	-	+	-	+	+	?	+
Allocation concealment	+	?	?	+	+	+	?	+	+	+
Blinding of patients and personnel	+	-	-	-	-	?	-	-	-	+
Blinding of outcome assessment	?	?	-	-	+	-	-	-	-	+
Incomplete outcome data	+	-	+	+	-	?	?	?	?	+
Selective reporting	+	+	+	+	+	+	+	+	+	+
Other Bias	+	?	?	?	?	+	-	-	-	+

**Figure 2** Risk of bias summary: authors' judgment about risk of bias for each item for each of the 6 included studies. The symbol "+" indicates low risk of bias, "?" indicates unclear risk of bias, and "-" indicates high risk of bias.



**Figure 3** Risk of bias: authors' judgment about risk of bias presented as percentages across all 6 included studies.

### Selective Reporting

In Keeler et al, the treatment effects for secondary endpoints of serum ferritin and TSAT were not reported and reported outcomes, including postoperative length of hospital stay and 90-day mortality rates, were not prespecified,<sup>18</sup> suggesting a high risk of reporting bias. For the other 9 included studies, all planned outcomes were reported.

### Other Potential Sources of Bias

One of the 6 studies had a robust institution-specific patient blood management program in place that may have influenced outcome assessments.<sup>15</sup> In 1 study, IV iron was not considered part of usual care at the time of study commencement, but was nonetheless not prohibited.<sup>17</sup> A differential number of patients experiencing protocol deviations was noted in the study groups of

1 study.<sup>18</sup> Kim et al elected to examine a binary primary outcome measure instead of a continuous outcome measure, which may have skewed response.<sup>19</sup> Subjects in the Lee et al study who were assigned to iron sucrose returned to the study site for three dosing visits, whereas those assigned to FCM only had one visit, which may have skewed the results in favor of IS.<sup>20</sup> A large portion of patients in the Padmanabhan et al study did not return to receive their second dose of FCM, which may have skewed the results against IV iron.<sup>21</sup> Lastly, the Park et al study was significantly underpowered for the primary outcomes selected resulting in potential high risk of bias.<sup>22</sup>

## Outcomes

All studies included reported absolute or relative change from baseline Hb concentrations. Change from baseline Hb concentration ranged from 1.3 g/dL<sup>21</sup> to 4.7 g/dL<sup>23</sup> among patients receiving preoperative FCM (including in the perioperative study) and 1.7 g/dL<sup>15</sup> to 3.2 g/dL<sup>7</sup> among those receiving postoperative FCM (Table 3). Six of the 10 studies<sup>15,20,21,23</sup> reported this outcome to be statistically significant versus comparators.<sup>7,16–19,22</sup> A key outcome measure was change from baseline in iron stores; findings showed that preoperative FCM administration resulted in an increase in serum ferritin concentrations of 229 µg/L (vs 19 µg/L at baseline)<sup>17</sup> to 558 µg/L (levels at randomization not reported)<sup>18</sup> and a 15%<sup>17</sup> to 35%<sup>19</sup> increase in TSAT. Postoperative administration resulted in a 114<sup>7</sup> to 571 µg/L<sup>15</sup> increase in serum ferritin concentration and 7.2%<sup>15</sup> to 20%<sup>17</sup> increase in TSAT. Both Bernabeu-Wittel et al<sup>16</sup> and Lee et al<sup>20</sup> did not report change from baseline TSAT.

A secondary efficacy outcome measure was proportion of patients who received perioperative ABT (Table 4). Two<sup>7,17</sup> of the 10 studies found statistically significantly lower rates of ABT in patients receiving FCM versus comparators in the perioperative surgical settings (absolute difference: 18.75%)<sup>17</sup> and postoperative (absolute difference: 4%).<sup>7</sup> The highest proportion of FCM-treated patients who received an ABT was 51.5% (53/103) in Bernabeu-Wittel et al, compared with 52% (52/100) in the FCM plus EPO group and 54% (54/100) in the placebo group;<sup>16</sup> in Khalafallah et al, 1% (1/103) of patients receiving FCM versus 5% (5/98) receiving standard of care received an ABT.<sup>7</sup>

Outcome measures included the proportion of patients who experienced AEs, postoperative mortality rate, and

hospital length of stay (Table 4). The proportion of patients with AEs was 6.8% (15/222) in the FCM group and 0.4% (1/223) in the placebo group in the study by Kim et al.<sup>19</sup> Bisbe et al reported AEs in 33% (20/60) of patients in the FCM group and 32% (20/62) in the ferrous glycine sulfate comparator group ( $P=NS$ );<sup>15</sup> this included all AEs reported during hospitalization (ie, before initiation of iron replacement therapy) and AEs related to surgical complications from initiation to 30 days postoperatively.<sup>15</sup> Five percent of patients experienced AEs in the FCM group compared to 2% in the placebo group (risk ratio 2.20, 95% CI 0.78–6.24).<sup>23</sup> Zero AEs among treatment groups were reported in both Lee et al<sup>20</sup> and Park et al.<sup>22</sup> Postoperative mortality was reported in 6 of the 10 included studies and ranged from 1% (2/237)<sup>23</sup> to 11.7% (12/103) among patients receiving FCM<sup>16</sup> compared with 0<sup>17,20,21</sup> to 10% (10/100) receiving placebo.<sup>16</sup> The deaths were not attributed to study drug in the 5 studies; 3 studies did not discuss the possibility of a relationship between the deaths and study drug.<sup>17,18,23</sup> 1 study stated that the single death was due to unrelated causes,<sup>21</sup> and 1 study stated that the causes of death were similar among the 3 treatment groups (IV FCM, IV FCM in combination with EPO, and placebo).<sup>16</sup>

The length of hospital stay ranged from 6<sup>17,18</sup> to 10.7 days<sup>19</sup> with FCM versus 6<sup>18</sup> to 11.6 days<sup>7</sup> with comparators (Table 5). Two of the 8 studies reported statistically significant differences in transfusion rate<sup>7,17</sup> and 2 studies reported significant differences in length of hospital stay between FCM and its comparators; the absolute difference in hospital stay was 3 days in Froessler et al<sup>17</sup> and 2.8 days in Khalafallah et al.<sup>7</sup> The variations in discharge criteria at the different institutions may have contributed to the differences in lengths of stay.

Validated measures of QOL included the Short Form Health Survey (SF-36 and SF-12) in 5 studies,<sup>7,16,17,20,21</sup> the EuroQol 5-dimension quality of life scale (EQ-5D) in 3 studies,<sup>15,21,23</sup> the Barthel Index questionnaires in 1 study,<sup>15</sup> the Multidimensional Fatigue Inventory (MFI),<sup>23</sup> and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire and the QLQ Gastric Cancer Module (QLQ-STO22) in 1 study.<sup>19</sup> There were no statistically significant differences between IV FCM and comparators in QOL (overall score, change in score, or treatment effect) in any of these 7 studies.<sup>7,15–17,19,21,23</sup> Bisbe et al reported no significant differences between IV FCM and the comparator (ferrous

**Table 3** Primary Outcome Measures: Change from Baseline in Hb, Serum Ferritin, and TSAT

Study	Surgery	Surgical Setting	Change from Baseline Hb (g/dL)			Change from Baseline Serum Ferritin (µg/L), Mean (SD)			Change from Baseline TSAT (%), Mean (SD)		
			Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Bisbe et al (2014) <sup>15</sup>	Orthopedic	Postop	1.7 (1.2) <sup>a</sup>	1.3 (1.0) <sup>a</sup>	—	571 (229) <sup>a</sup>	60 (88) <sup>a</sup>	—	7.2 (−5.2) <sup>a</sup>	0.7 (−5) <sup>a</sup>	—
Bernabeu-Wittel et al (2016) <sup>16</sup>	Hip fracture	Preop	1.38 (0.72) <sup>b</sup>	1.53 (0.56) <sup>b</sup>	0.88 (0.43) <sup>b</sup>	317 (140) <sup>b</sup>	288 (110) <sup>b</sup>	−4 (−10) <sup>b</sup>	—	—	—
Froessler et al (2016) <sup>17</sup>	Abdominal	Periop	1.9 (1.4) <sup>c</sup>	0.9 (1.4) <sup>c</sup>	—	229 (131–498) <sup>d</sup>	62 (24–146) <sup>d</sup>	—	15 (13–16) <sup>d</sup>	5 (0–3) <sup>d</sup>	—
Khalafallah (2016) <sup>7</sup>	Orthopedic, abdominal, ENT, plastic, gynecologic, urologic	Postop	3.2 (0.16) <sup>e</sup>	2.81 (0.18) <sup>e</sup>	—	114 (73.2) <sup>e</sup>	−133 (−41.1) <sup>e</sup>	—	20 (1.1) <sup>e</sup>	13.3 (1.4) <sup>e</sup>	—
Keeler et al (2017) <sup>18</sup>	Colorectal cancer	Preop	1.55 (0.93–2.58) <sup>f</sup>	0.50 (−0.13–1.33) <sup>f</sup>	—	558 (330–1085) <sup>f</sup>	27.5 (17–51.5) <sup>f</sup>	—	19 (16–29) <sup>f</sup>	9 (5–14) <sup>f</sup>	—
Kim et al (2017) <sup>19</sup>	Gastrectomy (cancer)	Preop	3.3 <sup>g</sup>	1.6 <sup>g</sup>	—	233.3 <sup>h</sup>	53.4 <sup>h</sup>	—	35.0 <sup>h</sup>	19.3 <sup>h</sup>	—
Lee et al (2019) <sup>20</sup>	Benign uterine diseases	Preop	2.2 (0.3)	1.9 (0.2)	—	—	—	—	—	—	—
Padmanabhan et al (2019) <sup>21</sup>	Cardiac	Preop	1.3 (0.9) <sup>i</sup>	4.4 (0.9) <sup>i</sup>	—	313 [228, 496] <sup>j</sup>	5.5 [−1.4, 19.4] <sup>j</sup>	—	— <sup>k</sup>	— <sup>k</sup>	—
Park et al (2019) <sup>22</sup>	Unilateral TKA or THA	Intraop	0.3 (1.00) <sup>l</sup>	−0.8 (0.78) <sup>l</sup>	—	1157.5 (412.3) <sup>m</sup>	83.8 (52.5) <sup>m</sup>	—	8.7 (10.4) <sup>m</sup>	−19.5 (−5.2) <sup>m</sup>	—
Richards et al (2020) <sup>23</sup>	Open abdominal surgery	Preop	4.7 (2.7–6.8) <sup>n</sup> ; 10.7 (8–13.8) <sup>o</sup> ; 7.3 (3.6–11.1) <sup>p</sup>	—	—	—	—	—	—	—	—

**Notes:** Treatment groups are defined in Table 1 in Intervention Groups and Regimen row; <sup>a</sup>Values are increase in mean (SD) from postoperative day 4 to postoperative day 30; <sup>b</sup>Values are increase in mean (SD) from baseline to 60 days postdischarge (change in SD from baseline to 60 days postdischarge); <sup>c</sup>Values are increase in mean (SD) from discharge to postoperative week 4; <sup>d</sup>Values are increase in median (first quartile–third quartile) from randomization to postoperative week 4; <sup>e</sup>Values are increase in mean (SD) from postoperative day 1 to postoperative week 12; <sup>f</sup>Values are increase in median (first quartile–third quartile) from baseline to day of surgery; <sup>g</sup>Values are increase in median from baseline to postoperative week 12; <sup>h</sup>Values are increase in mean (SD) between enrollment and surgical admission; <sup>i</sup>Values are increase in mean (interquartile range) between enrollment and surgical admission; <sup>j</sup>Statistical difference reported in favor of FCM (P=0.001); no data provided; <sup>k</sup>Values are increase in mean (SD) from baseline to postoperative day 30; <sup>l</sup>Values are increase in median (interquartile range) from baseline to postoperative day 5; <sup>m</sup>Values are increase in mean (95% CI) from baseline to 6 months following intervention; <sup>n</sup>Values are increase in mean (95% CI) from baseline to 6 months following intervention; <sup>o</sup>Values are increase in mean (95% CI) from baseline to 8 weeks following intervention; <sup>p</sup>Values are increase in mean (95% CI) from baseline to 8 weeks following intervention.

**Abbreviations:** ENT, ear, nose, and throat; FCM, ferric carboxymaltose; Hb, hemoglobin; THA, total hip arthroplasty; TKA, total knee arthroplasty; TSAT, transferrin saturation.

**Table 4** Secondary Outcome Measures: ABT, AEs, and Mortality

Study	Surgery	Surgical Setting	Proportion of Patients Receiving an ABT, n/N (%)			Proportion of Patients Experiencing AEs, n/N (%)			Postoperative Mortality, n/N (%)		
			Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Bisbe (2014) <sup>15</sup>	Orthopedic	Postop	3/59 (5.1)	2/62 (3.2)	—	20/59 (33.9)	20/62 (32.3)	—	—	—	—
Bernabeu-Wittel (2016) <sup>16</sup>	Hip fracture	Preop	53/103 (51.5)	52/100 (52.0)	54/100 (54)	—	—	—	12/103 (11.7)	12/100 (12.0)	10/100 (10.0)
Froessler (2016) <sup>17</sup>	Abdominal	Periop	5/40 (12.5)	10/32 (31.3)	—	—	—	—	1/40 (2.5)	0/32 (0)	—
Khalafallah (2016) <sup>7</sup>	Orthopedic, abdominal, ENT, plastic, gynecologic, urologic	Postop	1/103 (0.1)	5/98 (5.1)	—	—	—	—	—	—	—
Keeler (2017) <sup>18</sup>	Colorectal cancer	Preop	6/55 (10.9)	6/61 (9.8)	—	—	—	—	5/55 (9.1)	4/61 (6.6)	—
Kim (2017) <sup>19</sup>	Gastrectomy (cancer)	Preop	3/218 (1.4)	4/219 (1.8)	—	15/222 (6.8)	1/223 (0.4)	—	—	—	—
Lee et al (2019) <sup>20</sup>	Benign uterine diseases	Preop	0/52	0/49	—	0/52	0/49	—	0/52	0/49	—
Padmanabhan et al (2019) <sup>21</sup>	Cardiac	Preop	16/20 (80)	12/20 (60)	—	0/20	3/20	—	1/20 (5) (unrelated causes)	0/29	—
Park et al (2019) <sup>22</sup>	Unilateral TKA or THA	Intraop	2/29 (6.9)	4/29 (12.8)	—	0/29	—	—	—	—	—
Richards et al (2020) <sup>23</sup>	Open abdominal surgery	Preop	68/237 (29)	67/237 (28)	—	11/237 (5)	5/237 (2)	—	12/238 (5)	10/236 (4)	—

**Note:** Treatment groups are defined in Table 1.

**Abbreviations:** ABT, allogenic blood transfusion; AE, adverse event; ENT, ear, nose, and throat; FCM, ferric carboxymaltose; IV, intravenous; THA, total hip arthroplasty; TKA, total knee arthroplasty.

**Table 5** Secondary Endpoint Outcomes: Hospital Length of Stay and QOL

Study	Surgery	Surgical Setting	Length of Hospital Stay, d			Instrument	Validated QOL Measure		
			Group 1	Group 2	Group 3		Group 1	Group 2	Group 3
Bisbe (2014) <sup>15</sup>	Orthopedic	Postop	7.9 (1.7) <sup>a</sup>	7.6 (0.9) <sup>a</sup>	—	EQ-5D Barthel questionnaire	Total EQ-5D increase: 0.6 (0.9) <sup>b</sup> Barthel increase: 92.6 (6.2) <sup>b</sup>	Total EQ-5D increase: 0.6 (0.17) <sup>b</sup> Barthel increase: 93.0 (8) <sup>b</sup>	—
Bernabeu-Wittel (2016) <sup>16</sup>	Hip fracture	Preop	7 (5–10) <sup>c</sup>	8 (6–11) <sup>c</sup>	8 (6–10) <sup>c</sup>	SF-36v2	Physical decrease: 4.4 (1.4) <sup>d</sup> Mental decrease: 2.7 (20) <sup>d</sup>	Physical decrease: 7.4 (11) <sup>d</sup> Mental decrease: 1.2 (13) <sup>d</sup>	Physical: 4.5 (15) <sup>d</sup> Mental: –2 (20) <sup>d</sup>
Froessler (2016) <sup>17</sup>	Abdominal surgery	Periop	6 (1, 19) <sup>e</sup>	9 (1, 23) <sup>e</sup>	—	SF-36	SF-26 decrease (pre-post): 8 (18) <sup>f</sup>	Decrease (preop to postop): 6 (17) <sup>f</sup>	—
Khalafallah (2016) <sup>17</sup>	Orthopedic, abdominal, ENT, plastic, gynecologic, urologic	Postop	7.8 (10.3) <sup>a</sup>	11.6 (15.6) <sup>a</sup>	—	SF-36	SF-36 increase: 13.4 <sup>g</sup> Physical increase: 13.4 <sup>g</sup> Mental increase: 13.3 <sup>g</sup>	SF-36 increase: 9.1 <sup>g</sup> Physical increase: 7.9 <sup>g</sup> Mental increase: 9.9 <sup>g</sup>	—
Keeler (2017) <sup>18</sup>	Colorectal cancer	Preop	6 (5–10) <sup>c</sup>	6 (4–9) <sup>c</sup>	—	—	—	—	—
Kim (2017) <sup>19</sup>	Gastroctomy (cancer)	Preop	10.7 (7.9) <sup>a</sup>	10.9 (13.8) <sup>a</sup>	—	EORTC QLQ-C30v3 QLQ-STO22	Fatigue (week 3): 30.0 (26.8, 33.1) <sup>h</sup> Dyspnea (week 12): 9.5 (7.2, 11.8) <sup>h</sup>	Fatigue (week 3): 34.6 (31.3, 37.9) <sup>h</sup> Dyspnea (week 12) 14.2 (11.3, 17.1) <sup>h</sup>	—
Lee et al (2019) <sup>20</sup>	Benign uterine diseases	Preop	—	—	—	SF-12	PCS (visit 3 vs visit 1): 3.7 ± 10.0 MCS (visit 3 vs visit 1): 4.5 ± 8.0	PCS (visit 3 vs visit 1): 2.3 ± 8.0 MCS (visit 3 vs visit 1): 1.6 ± 6.5	—
Padmanabhan et al (2019) <sup>21</sup>	Cardiac	Preop	7 (6–12) <sup>c</sup>	9 (6–14) <sup>c</sup>	—	EQ-5D SF-36	—	—	—
Park et al (2019) <sup>22</sup>	Unilateral TKA or THA	Intraop	—	—	—	—	—	—	—
Richards et al (2020) <sup>23</sup>	Open abdominal surgery	Preop	9 (7–14) <sup>c</sup>	9 (5–14) <sup>c</sup>	—	EQ-5D-5L MFI	EQ-5D-5L Utility score: 10-day: 0.80 (0.20); 8-week: 0.79 (0.20); 6-month: 0.82 (0.22) EQ-5D-5L Health score: 10-day: 70.6 (20.5); 8-week: 70.7 (19.4); 6-month: 75.0 (18.4) MFI: 10-day: 53.2 (18.4); 8-week: 52.9 (17.1); 6-month: 48.8 (18.9)	EQ-5D-5L Utility score: 10-day: 0.81 (0.21); 8-week: 0.77 (0.21); 6-month: 0.82 (0.21) EQ-5D-5L Health score: 10-day: 73.8 (19.6); 8-week: 71.1 (19.5); 6-month: 76.2 (19.2) MFI: 10-day: 50.5 (18.9); 8-week: 53.9 (17.7); 6-month: 47.4 (19.1)	—

**Notes:** Treatment groups are defined in Table 1; <sup>a</sup>Values are mean (standard deviation); <sup>b</sup>Values are the mean (standard deviation) increase from before surgery to postoperative day 30; <sup>c</sup>Values are median (first quartile–third quartile); <sup>d</sup>Values are mean (standard deviation) decrease from baseline to 60 days postdischarge; <sup>e</sup>Values are median (minimum, maximum); <sup>f</sup>Values are mean (standard deviation) increase from presurgery/intervention to postoperative week 4; <sup>g</sup>Values are the increase from postoperative day 1 to postoperative week 12; <sup>h</sup>Values are mean (95% confidence interval).

**Abbreviations:** ED-5Q, EuroQol 5-dimension quality of life scale; EORTC, European Organization for Research and Treatment of Cancer; FCM, ferric carboxymaltose; IV, intravenous; MCS, mental health composite scores; MFI, Multidimensional Fatigue Inventory; PCS, physical health composite scores; QLQ-C30v3, Quality of Life Questionnaire-Core 30 version 3; QLQ-STO22, Quality of Life Questionnaire-Stomach; QOL, quality of life; SF-12, Short Form-12 Health Survey; SF-36, 36-Item Short Form Survey; THA, total hip arthroplasty; TKA, total knee arthroplasty.

glycine sulfate) in total EQ-5D and Barthel scores.<sup>15</sup> However, among patients with preoperative iron deficiency (serum ferritin <100 ng/mL), the IV FCM group had significantly better (ie, lower) mean  $\pm$  SD EQ-5D subscores than the comparator group for “usual activities” ( $1.9 \pm 0.3$  vs  $2.1 \pm 0.3$ ;  $P=0.026$ ) and “anxiety or depression” ( $1.3 [0.6]$  vs  $1.6 [0.7]$ ;  $P=0.074$ ) at the end of the study.<sup>15</sup> In addition, among patients with severe postoperative anemia (Hb <10.0 g/dL), the FCM group had significantly better scores for “usual activities” than the comparator group at the end of the study ( $1.9$  vs  $2.3$  [SD not reported];  $P=0.04$ ).<sup>15</sup>

## Overall Quality of Evidence

The GRADE criteria were applied to rate the quality of evidence for all specified outcomes in this review ([Supplementary Data, Appendix 2](#)). Evidence quality was downgraded for risk of bias, inconsistency, indirectness, and imprecision. Across both primary and secondary endpoints, the overall quality of evidence was determined to be very low ([Table 6](#)). Publication bias was not detected. The rationale for these judgments are outlined in the [Supplementary Data, Appendix 3](#).

## Discussion

This SLR supports the use of FCM as treatment for adult patients with IDA in the preoperative and postoperative health states. In both the preoperative and postoperative elective surgery settings, IDA is a modifiable risk factor for elective surgical management.<sup>26,27</sup> The 10 studies identified for inclusion in this SLR consistently reported change from baseline improvement in the three primary outcome measures: hemoglobin, ferritin, and TSAT.<sup>7,15–19</sup> For these studies, there was less consistency for the association of FCM as treatment for perioperative IDA with each of the five secondary outcomes: ABT, adverse events, postoperative mortality, hospital length of stay, and QoL measures (see [Tables 4 and 5](#)).

Current guidelines from the Australian National Health and Medical Research Council<sup>29</sup> and the United Kingdom National Institute for Health and Care Excellence<sup>30</sup> recommend consideration of alternatives to blood transfusions for patients undergoing surgery and advise restrictive hemoglobin thresholds (<7.0 g/dL) for blood transfusions. In this SLR, three of the postoperative surgery studies reported either significantly fewer total ABT events<sup>17</sup> or a significantly smaller proportion of patients receiving ABT<sup>7,19</sup> with FCM

than with the comparator. In the six preoperative surgery studies, the percentage of patients receiving ABT was not significantly different between assigned groups.<sup>16,18–21,23</sup> In one preoperative surgery study, FCM was associated with reduced hospital readmission for post-surgical complications.<sup>23</sup> Nonetheless, additional studies will be needed to fully assess the association of perioperative IV iron repletion, averted ABT, and associated ABT complications.<sup>28,32</sup> Adverse events during hospitalization were recorded in three studies;<sup>15,21,23</sup> as either estimated blood loss,<sup>21</sup> number of blood transfusions,<sup>23</sup> or gastrointestinal AEs.<sup>21,33</sup> Post-operative mortality rates varied across the studies and was lowest in the study of benign uterine surgery and highest in the study of hip fractures.<sup>16,20</sup> Length of hospital stay and measures of QoL also varied across studies ([Table 5](#)). Advanced age, as well as multiple comorbidities may have played a role in the lack of significance between FCM and comparators in these studies.<sup>7</sup>

While all 10 studies were randomized controlled trials, clinical and methodological heterogeneity was evident across the studies ([Table 1](#)), along with variation in the design elements (eg, type of blinding, duration of follow-up, timing of preoperative and postoperative assessments, comparator used, dosage, treatment schedule). All of these factors are important considerations when evaluating the utility of the exposure for the reported primary and secondary outcomes. A meta-analysis was not deemed feasible for this SLR, given the heterogeneity across the studies. Nonetheless, our findings are consistent with two prior quantitative syntheses of IV iron repletion in surgical patients which reported the efficacy of FCM associated with postoperative hemoglobin in elective surgeries.<sup>34,36</sup> Additionally, for this SLR we conducted a thorough systematic qualitative assessment, which permitted a quality of evidence GRADE assessment ([Table 6](#)) for each of the primary and secondary outcomes. Although the overall quality of evidence scores were very low, future SLRs with GRADE assessments and consensus guideline considerations will likely benefit from assessment of iron repletion for elective surgeries partitioned as preoperative versus postoperative interventions. Together, the totality of data from these studies support the beneficial effect of FCM for hematological parameters in elective surgery, while continuing to inform on the role of iron repletion in perioperative patient management.<sup>31</sup>

**Table 6** Quality of Evidence (GRADE) Assessment

Outcome	Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other Considerations	Quality of Evidence
<b>Absolute or relative change in hemoglobin concentration</b>								
Rationale	10/10	8/10 RCTs inadequately blinded outcome assessments; 8/10 RCTs inadequately blinded participants and personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Positive effect demonstrated in 10/10 RCTs. Both clinical and methodologic heterogeneity are high. Therefore, some inconsistency exists.	Secondary endpoint in 6/10 studies (primary in 4/10) and therefore may not be powered appropriately. The intervention was given preop. in 7/10 studies, postop. in 3/10, and intraop. in 1/10. Difficult to make direct comparisons because of difference in comparators and populations.	1 study terminated early; no CIs reported for 6/10 studies; wide CI/IQR for 5/10 studies. Insufficient sample sizes (<400 total) in 8/10 studies.	Undetected	There are potentially many subgroups in this analysis (eg, type of surgery, severity of condition, age) that may have affected findings that cannot be considered because of small sample sizes.	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect. There generally appears to be a consistent effect with low risk of AEs. Most articles report positive outlook on use in future similar patient populations. Patients appear neutral to positive.
<b>Absolute or relative change in iron stores (serum ferritin)</b>								
Rationale	8/10 (Not Lee or Richards)	7/8 RCTs inadequately blinded outcome assessments; 7/8 RCTs inadequately blinded participants and personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Positive effect demonstrated in 8/8 RCTs. Both clinical and methodologic heterogeneity are high. Direction appears consistent but variation appears large and therefore inconsistent.	Secondary endpoint in 6/8 studies (primary in 1 study) and therefore not sufficiently powered. Difficult to make direct comparisons because of differences in comparators and populations.	1 study terminated early; no CI reported for 4/8; wide CI/IQR range for 4/4 studies. Insufficient sample sizes (<400 total) in 8/8 studies.	Undetected	Selective reporting in 2/8 studies (TSAT/ferritin endpoint not prespecified).	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

(Continued)

Table 6 (Continued).

Outcome	Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other Considerations	Quality of Evidence
<b>Absolute or relative change in iron stores (TSAT)</b>								
Rationale	6/10 (Not Lee, Bernabeu-Wittlil, Padmanabhan, or Richards)	5/6 RCTs inadequately blinded outcome assessments; 6/6 RCTs inadequately blinded participants and personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results	Positive effect demonstrated in 6/6 RCTs. Both clinical and methodologic heterogeneity are high. Direction appears consistent but variation appears large and therefore inconsistent.	Secondary endpoint in 5/6 studies (primary in 1 study) and therefore not sufficiently powered. Difficult to make direct comparisons because of difference in comparators and populations	1 study terminated early; no confidence interval reported for 3/6; wide CI/IQR for 3/3 studies. Insufficient sample sizes in each study (<400 total).	Undetected	Selective reporting in 2/6 studies (TSAT/ferritin endpoint not prespecified).	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.
<b>Proportion of participants who received a perioperative ABT</b>								
Rationale	10/10	5/10 RCTs inadequately blinded outcome assessments; 7/10 RCTs inadequately blinded participants; 6/10 inadequately blinded personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Positive effect reported in 2/10 studies (no difference in 8/10 studies). Consistency in findings may be an artifact of the disease severity/age/complexity of the surgery. Large variations in degree to which outcome is affected.	Primary endpoint in 4/10; percentage of blood transfusions secondary endpoint in 3/10; number of transfused blood units primary endpoint (1/10); reported as an absolute number in 8/10. Difference in populations and intervention schedules may have influenced outcome.	1 study terminated early; no CI reported for 6/10; wide CI/IQR for 3/6. Uncertain if there was a large enough sample size despite a large enough number of events to calculate a precise effect estimate. Several studies had only 1 participant with the outcome of interest.	Undetected	N/A	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect. The studies in this review looked at populations who had a large range of bleed/transfusion risk perioperatively. Need to assess ABT risk and adequately power the studies to detect sufficient number of events. Event may be too rare in some cases.

<b>Proportion of participants who experienced adverse events</b>								
Rationale	6/10 (Not Bermabeu-Wittel, Froessler, Khalafallah, Keeler)	5/6 RCTs inadequately blinded outcome assessments; 5/6 RCTs inadequately blinded participants and personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	No SAE (4/6); no significant difference in safety reported for 4/6 studies.	Prespecified secondary endpoint (3/6). Safety was not assessed similarly within or between. Studies also had different comparators.	I study terminated early. Not clear how safety was assessed.	Undetected	N/A	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect. Lack of evidence, high inconsistency in reporting, high indirectness, and high imprecision.
<b>Postoperative mortality</b>								
Rationale	Directly reported in 6/10 studies; indirectly in 4/10 as apparently no deaths occurred during follow-up.	8/10 RCTs inadequately blinded outcome assessments; 8/10 RCTs inadequately blinded participants and personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Results were not consistent; may be an artifact of severity of disease in population under study.	Not a surrogate outcome; prespecified secondary endpoint (2/6); primary endpoint composite (1/6) all-cause (2/6); 30-day (1/6). Death is dichotomous; however, the assumption in 4/10 studies is that no one had died.	Insufficient number of events to make a conclusion. Not a primary outcome in 9/10 studies, so likely underpowered to observe the true effect.	Undetected	N/A	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

(Continued)

Table 6 (Continued).

Outcome	Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other Considerations	Quality of Evidence
<b>Length of hospital stay</b>								
Rationale	8/10 (Not Lee or Parks)	4/10 RCTs inadequately blinded outcome assessments; 5/8 RCTs inadequately blinded participants and personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Both clinical and methodologic heterogeneity are high. Heterogeneity among healthcare systems may also have influenced this outcome. Inconsistent results.	Not a surrogate outcome; prespecified secondary endpoint in 4/10 studies.	Wide CIs present in most studies.	Undetected	N/A	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.
<b>Any validated measure of quality of life</b>								
Rationale	7/10 (Not Padmanabhan, Keeler, or Parks)	6/7 RCTs inadequately blinded outcome assessments; 5/7 RCTs inadequately blinded participants and personnel. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Both clinical and methodologic heterogeneity are high. Results reported inconsistently owing to different instruments. No difference of effect is consistent.	Surrogate marker; outcome not assessed similarly within and among studies, yielding very indirect comparisons.	Wide CIs present in most studies. Extreme imprecision present. Concentrated on certain subgroups in some studies.	Undetected.	Selective reporting was present for this outcome in a few studies.	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

Abbreviations: AE, adverse event; CI, confidence interval; IQR, interquartile range; RCT, randomized clinical trial; SAE, serious adverse event; TSA†, transferrin saturation.

## Limitations

Several methodologic limitations in this systematic review are noteworthy. Physicians were not blinded in 5 studies (4 open-label<sup>7,18,20,21</sup> and 1 patient-blinded<sup>19</sup>). In 3 other studies, the physician was blinded to treatment allocation, but the comparators used in those studies (eg, oral iron<sup>15</sup> or usual care consisting of no treatment, oral iron recommendation, and transfusion<sup>17,22</sup>) might allow the physician to distinguish which patients were assigned to receive IV FCM vs the comparator in others. Overall, the risks of performance and biases were high or uncertain, highlighting the need for more effective blinding of patients and study personnel involved in the administration of study drug or outcome assessments. Blinding in some studies may not be feasible, despite the impact of blinding on the measurement of study outcomes. For example, a difference in route of administration between treatment arms, ethical considerations (possibility of exposing study patients to risks when blinding with placebo), or logistical hurdles (eg, limited economic support or authorization to use or access appropriate placebos and masking procedures) may be challenging in independent investigator-initiated studies.<sup>7,35</sup>

Other limitations of study heterogeneity may limit generalizability of the findings resulting from differing thresholds of Hb level, inclusion criteria, baseline clinical characteristics (eg, Hb, serum iron, serum ferritin, TSAT, ASA classification), IV FCM dosing and timing of administration, Hb thresholds for intervention (IV iron and transfusion). Heterogeneity or absence of reporting of secondary outcomes such as duration of follow-up, differences in criteria for hospital discharge (which would affect length of stay and may explain differences observed between the studies), and QOL instrument used (SF-36,<sup>7,16</sup> EQ-5D and Barthel questionnaire,<sup>15</sup> and EORTC QLQ-C30 and QLQ-STO22<sup>19</sup>) did not allow for a more in-depth review. Bias assessments in this review were qualitative, and meta-analysis was not feasible.

## Conclusion

The preoperative correction of anemia and other hematological parameters with IV FCM appears to be a viable intervention to mitigate known risks associated with post-surgical anemia and consequent events such as the need for transfusion.<sup>36</sup> Postoperative patients with IDA, in whom oral iron is contra-indicated who are not able to tolerate oral iron or achieve a satisfactory response to oral

iron may also benefit from FCM administration.<sup>7,28</sup> The benefits of IV iron suggested by this SLR support the recommendations of guidelines that incorporate the use of IV iron in patients undergoing elective surgery.

## Abbreviations

ABT, allogeneic blood transfusion; AE, adverse event; ASA, American Society of Anesthesiologists; ENT, ear, nose, and throat; EORTC-QLQ-C30, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EPO, erythropoietin; EQ-5D, EuroQol 5-dimension quality of life scale; FCM, ferric carboxymaltose; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; Hb, hemoglobin; IDA, iron-deficiency anemia; IV, intravenous; NHMRC, National Health and Medical Research Council; NICE, National Institute for Health and Care Excellence; NS, not significant; PBM, perioperative blood management; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QLQ-STO22, Quality of Life Questionnaire-Gastric Cancer Module; QOL, quality of life; RBC, red blood cell; SC, subcutaneous; SD, standard deviation; SLR, systematic literature review; TSAT, transferrin saturation.

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## Author Contributions

JJJ, LMM, NB, MS: Main contribution to the study concepts and study design as well as supervision and revision of the manuscript.

JJJ, MS, LMM: Main contribution to the data acquisition, analysis, and interpretation.

JJJ and LMM: Main contribution to manuscript preparation.

NB: Main contribution to statistical support.

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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