REVIEW

Preoperative Anemia Treatment with Intravenous Iron Therapy in Patients Undergoing Abdominal Surgery: A Systematic Review

Tiffany Moon · Aaron Smith · Taylor Pak · Brian H. Park ·

Sascha S. Beutler · Travis Brown · Alan D. Kaye · Richard D. Urman

ABSTRACT

Introduction: Preoperative anemia is associated with increased morbidity, mortality, and healthcare costs. As a result of the increased incidence of chronic blood loss and iron deficiency anemia in abdominal surgery patients and its impact on patient outcomes, we systematically evaluated the quality of evidence for preoperative intravenous (IV) administration of iron to patients with anemia undergoing major abdominal surgery with the focus on clinical outcomes.

Methods: In this systematic review, PubMed, Cochrane, The Cumulative Index to Nursing and Allied Health Literature, Web Of Science, and Excerpta Medica Database databases were searched up to 2019 using specific keywords. Inclusion criteria were patients that were over 18 years of age, underwent abdominal surgery, and received an IV iron treatment in the preoperative setting.

Results: The nine studies included in the final systematic review do not provide consistent evidence of a reduced incidence of allogeneic blood transfusions with preoperative IV iron administration. However, IV iron administration did consistently cause a significant increase in hemoglobin levels relative to oral iron therapy or no iron.

Conclusion: Overall, these findings are consistent in that IV iron administration is highly effective at rapidly increasing hemoglobin levels in patients with iron deficiency anemia undergoing major abdominal surgery. Unfortunately, there is currently no evidence of reduced incidence of allogeneic blood transfusions or other enhanced outcomes.

Keywords: Abdominal surgery; Anemia; Hemoglobin; Iron; Preoperative

T. Moon · A. Smith · T. Pak
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

B. H. Park · S. S. Beutler · T. Brown · R. D. Urman (✉)
Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: rurman@bwh.harvard.edu

A. D. Kaye
Department of Anesthesiology, LSU Health Shreveport, Shreveport, LA, USA

R. D. Urman
Center for Surgery and Public Health, Harvard Medical School, Boston, MA, USA

Key Summary Points

The studies identified and evaluated in this review demonstrate a consistent, significant increase in hemoglobin levels in the intravenous iron group, but do not consistently report a significant reduction in the number of red blood cell transfusions intraoperatively.

Thus, we recommend that abdominal surgery patients be evaluated and treated for iron deficiency anemia prior to receiving surgery.

More studies are necessary to definitively determine the efficacy of IV iron administration in decreasing morbidity and mortality for abdominal surgery patients.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13580687.

INTRODUCTION

Preoperative anemia remains a common problem in patients scheduled to undergo major abdominal surgery [1]. Many patients with colorectal cancer or uterine disease have lesions that predispose them to acute or chronic blood loss. One review found anemia present in 40–50% of patients scheduled for gynecological or colorectal surgery [1]. Much of this anemia is likely iron deficiency anemia (IDA) due to the high incidence of chronic blood loss in these patients. This is supported by Third National Health and Nutrition Examination Survey (NHANES III) data showing that iron deficiency

is the cause of at least 20% of anemia in adults over 65 [2].

Preoperative anemia is associated with increased healthcare costs, morbidity, and mortality [3–10]. Unoptimized red blood cell mass in the preoperative setting is also associated with increased blood transfusions and greater morbidity and financial burden [8, 11, 12]. In patients with colorectal cancer, blood transfusions have been associated with increased infection rates, longer hospital stays, higher mortality, and a greater risk of cancer recurrence [13, 14]. One meta-analysis showed a dose-dependent correlation between the amount of blood transfused intraoperatively and the incidence of colorectal cancer recurrence [15].

Given these findings, the 2018 Frankfurt Consensus Conference statement strongly recommends early detection and management of anemia before major elective surgeries with the use of iron supplementation for patients with iron deficiency anemia [16]. Similarly, a prior consensus statement released by the British Society for Haemotology recommends intravenous (IV) administration of iron if IDA is diagnosed near the day of surgery; otherwise, oral iron therapy could be used [17]. However, there remains a lack of robust evidence for this intervention because of a limited number of randomized controlled trials (RCTs) and inadequately powered studies. Several systematic reviews evaluating preoperative IV iron therapy use have reported similar limitations, but these were not focused on patients receiving abdominal surgery [18–20].

Therefore, we performed a systematic review to evaluate the current evidence for clinical effectiveness of preoperative IV iron administration as a treatment for anemia in patients undergoing major abdominal surgery.

METHODS

Protocol Registration

The protocol for this systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) guidelines. We enlisted the assistance of a research librarian and statistician in developing the protocol at Countway Library of Medicine, Boston, Massachusetts. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO Application Number 160868). This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Eligibility Criteria

The original studies considered for this systematic review included patients that were over 18 years of age, underwent major abdominal surgery, and received an intravenous iron treatment in the preoperative setting. Duplicate and non-English studies were removed before analysis. Review articles, incomplete trials, published abstracts, letters to the editor, study protocols, and case reports were excluded from this systematic review. Studies evaluating the wrong setting intervention, population, study design, and outcome were also excluded. The study flow diagram and all exclusion criteria can be found in Fig. 1.

Information Sources and Data Analysis

We searched several research databases, including PubMed, Cochrane, CLINAHL, WOS, and EMBASE, on September 20, 2019, for all publications through November 1, 2020. The search term list (see Appendix A in the supplementary
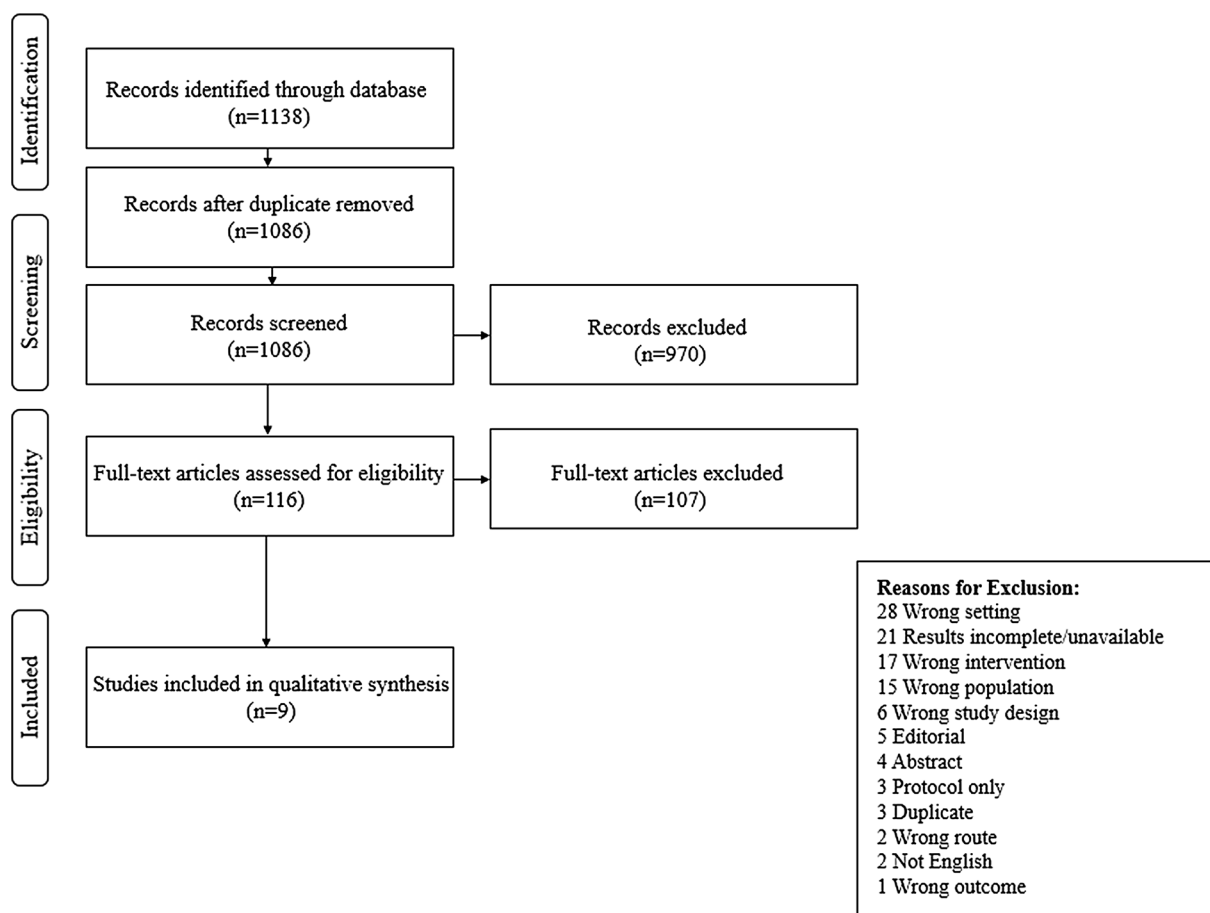

Fig. 1 Study flow diagram with exclusion criteria. Of the 1138 studies initially identified through the database search, only nine were eventually included in the qualitative analysis

material) included the following terms: "anemia", "hemoglobin", "hematocrit", "preoperative period", "preoperative care", "perioperative period", "perioperative care", "postoperative period", "postoperative care", "iron", "iron compounds", "hematinics", "treatment outcome", "outcome assessment", "outcome and process assessment", and "patient outcome assessment".

The studies were independently identified and subsequently reviewed by six authors in two different phases. The systematic review results were collected and processed using Covidence software (Melbourne, Australia) [20]. During the first phase, one author (BP) screened all titles and abstracts produced by the databases' search criteria to determine eligibility. A second author (TP) read the full text of each article that made it past the screening phase and independently decided if the publication should be included. After this, a third author (TM) evaluated the validity of reasons for the excluded articles. Disagreements were harmonized by consensus, and a final set of studies was chosen using the aforementioned methods. A qualitative analysis was performed in the second phase instead of a meta-analysis because of the high heterogeneity across the nine studies [21]. One reviewer extracted data (AS), and another (RU) verified the data. Extracted data included publication title, author(s), year of publication, location of publication design of the study, population characteristics, intervention given to the patient population, comparator(s), and outcome results (Table 1). We then performed another review of the publishded data, and another author (TB) re-queried the databases and, in consultation with the senior author (RU), added three more studies to the systematic review, following the aforementioned process.

Outcomes

The primary outcome examined in the included studies was change in serum Hb. The secondary areas of interest were transfusion rates, morbidity and mortality, and hospital length of stay (LOS).

Quality Assessment

The quality and risk of bias of the four randomized and two non-randomized studies were assessed with the Cochrane Risk Assessment tool and Newcastle–Ottawa Scale (NOS), respectively. The Cochrane Risk Assessment tool assesses bias in randomized studies by assigning a rank of "high," "low," or "clear" in five subcategories [22]. Subcategories include selection bias, which is evaluated on random sequence generation and allocation concealment; reporting bias, which is evaluated on selective reporting; performance bias, which is evaluated on blinding of participants and personnel; detection bias, which is evaluated on blinding of outcome assessment; attrition bias which is evaluated on incomplete outcome data; and other sources of bias. Study quality was defined as "good" if the study had no "high" ratings for risk of bias. Study quality was defined as "fair" if the study had 1–2 "high" ratings for bias. Study quality was defined as "poor" if the study had three or more "high" ratings.

The NOS is used as a tool to assess the quality of non-randomized studies using a scoring system that rates studies on the basis of selection, comparability, and outcome [23]. Study quality is defined as "good" if the study scored in the ranges of 3–4 for selection, 1–2 for comparability, and 2–3 for outcome. Study quality was defined as "fair" if the study scored 2 for selection, 1–2 for comparability, and 2–3 for outcome. Study quality was defined as "poor" if the score did not meet criteria for either "good" or "fair."

RESULTS

Literature Search

A total of 1138 articles were identified and screened. After removal of duplicates, case reports, animal studies, and conference abstracts, the remaining 116 full-text studies were assessed for eligibility. Of those, 107 were excluded and nine studies remained that met the criteria for this systematic review (Fig. 1).

Table 1 Study characteristics

First author (location, year)	Study design	Patient characteristics		N	Intervention	Comparator	Outcomes	
		Anemia definition	Surgery type		IV iron therapy (dose); duration		Primary	Secondary
Richards (UK, 2020)	Multicenter randomized double-blinded controlled	Hb < 13 g/dL in men or < 12 g/dL in women	Elective major open abdominal surgery	487	FMC (1000 mg × 1 dose); 10–42 days preop	Placebo	Composite risk of blood transfusion or death; number of transfusion episodes from randomization until 30 days postop	Total units RBCs or other blood component received at 30 days and 6 months postop, Hb change from randomization to surgery and 8 weeks and 6 months postop, ICU and total hospital LOS
Edwards (UK, 2009)	Single-center randomized blinded prospective cohort	Hb < 13.5 g/dl in men or < 12.5 g/dL in women	Elective resection for colorectal carcinoma	60	Iron sucrose (300 mg × 2 doses); 2 weeks before surgery	Placebo	Hb levels between recruitment and day of randomization	Transfusion rate, changes in serum iron markers, LOS, AEs
Keeler (UK, 2017)	Multicenter randomized open-label prospective cohort	Hb < 12 g/dL in men or < 11 g/dL in women	Elective surgery for non-metastatic colorectal carcinoma	116	FCM (1000 mg × 3 doses); 2 weeks preop	Ferrous sulfate (20 mg BID)	Differences in the mean volume of transfusions	Changes in Hb and hematinic profiles
Froessler (UK, 2018)	Single-center randomized non-blinded prospective cohort study	Hb < 13 g/dL in men or < 12 g/dL in women	Elective and urgent major abdominal surgery	72	FCM (1000 mg); preop and (0.5 mg/L blood lost); 2 days postop	No IV iron therapy	Incidence of transfusion	Hb levels, change in Hb between time points, LOS, morbidity, 30-day mortality, QoL score

Table 1 continued

First author (location, year)	Study design	Patient characteristics		N	Intervention	Comparator	Outcomes	
		Anemia definition	Surgery type		IV iron therapy (dose); duration		Primary	Secondary
Kim (South Korea, 2009)	Single-center randomized open-label controlled trial	Hb < 9 g/dL	Surgery for menorrhagia	76	Iron sucrose (dose according to Ganzoni's formula 3 times per week); 3 weeks preop	Oral iron succinylate therapy (80 mg) daily for 3 weeks	Recruitment and admission Hb	None
Laso-Morales (Spain, 2017)	Multicenter retrospective cohort	Hb < 13 g/dL	Elective resection for colorectal carcinoma	322	Iron sucrose or FCM (dose according to Ganzoni equation); 4–6 weeks preop	Oral iron therapy or no iron	RBC transfusion requirement	Postop infection rate, hospital LOS
Wilson (the Netherlands, 2018)	Single-center retrospective cohort	Hb < 12.9 g/dL in men or < 12 g/dL in women	Elective resection for colorectal carcinoma	318	FCM (1000–2000 mg); time from diagnosis to surgery	No IV iron therapy	Change in Hb	Percentage of patients who received a blood transfusion, AEs
Calleja (Spain, 2015)	Multicenter retrospective and prospective cohort	Hb < 13 g/dL in men or < 12 g/dL in women	Elective resection for colorectal carcinoma	266	FCM (1000 mg); 2–4 weeks before surgery	No IV iron therapy	Periop and 30-day postop transfusion requirements	LOS, postop complication, Hb and iron parameters, percentage of patients with normalized Hb

Table 1 continued

First author (location, year)	Study design	Patient characteristics		Surgery type	N	Intervention	Comparator	Outcomes	
		Anemia definition				IV iron therapy (dose); duration		Primary	Secondary
Kam (China, 2020)	Single-center prospective propensity-score matched cohort	Hb < 10 g/dL before transfusion or Hb < 12 g/dL after recent transfusion		Elective resection for colorectal carcinoma	100	Iron sucrose (500 mg) or iron isomaltoside (1000 mg); at least 2 weeks preop	No IV iron therapy	Change in Hb	Percentage of patients who received an RBC transfusion

AEs adverse events, *BID* twice a day, *FCM* ferric carboxymaltose, *Hb* hemoglobin, *ICU* intensive care unit, *IV* intravenous, *LOS* length of stay, *periop* perioperative, *preop* preoperative, *postop* postoperative, *QoL* quality of life, *RBC* red blood cell, *UK* United Kingdom

Study Characteristics

Study characteristics are summarized in Table 1. All of the studies in this systematic review included cohorts of patients undergoing abdominal surgery who had a preoperative diagnosis of anemia. A total of nine studies were included. The studies involved a total of 1817 patients. The studies did not all examine the same postoperative outcomes. Three of the studies were conducted in the UK, two in Spain, one in Australia, one in South Korea, one in the Netherlands, and one in China. The design of the studies included two randomized and blinded studies from Edwards et al. and Richards et al., three randomized non-blinded studies from Froessler et al., Keeler et al., and Kim et al., one non-randomized non-blinded study from Calleja et al., two retrospective cohort studies from Wilson et al. and Laso-Morales et al., and a prospective propensity-matched study from Kam et al. Six of the studies were limited to patients with planned colorectal cancer resection. In contrast, Froessler et al. and Richards et al. used patients from a broader category of major abdominal surgery. The study from Kim et al. was limited to patients scheduled for surgical treatment of menorrhagia.

Definitions and Measures

The definition of anemia varied between studies. The 1968 World Health Organization (WHO) criteria of baseline Hb levels less than 13 g/dL for men, and less than 12 g/dL for women were used to define anemia in two of the studies [24, 25]. Four studies defined anemia below the WHO Hb levels [26–29]. The Hb inclusion criterion in Keeler et al. was 12 g/dL in men and 11 g/dL in women; Wilson et al. restricted Hb levels to less than 12.9 g/dL in men, Kim et al. only enrolled patients with Hb levels below 9.0 g/dL and established IDA, and Kam et al. recruited patients with Hb less than 10 g/dL before transfusion or less than 12 g/dL after recent transfusion. Two studies used definitions for anemia slightly higher than the WHO criteria: Edwards et al. defined anemia below 13.5 g/dL for men and 12.5 g/dL for

women, and Laso-Morales et al. defined anemia as less than 13 g/dL for both sexes.

Association of Iron Therapy and Hemoglobin Levels

Changes in Hb for each cohort in each study are summarized in Table 2. All nine of the reviewed studies assessed the effect of preoperative intravenous iron therapy on Hb levels. Edwards et al., Kim et al., Wilson et al., and Kam et al. used changes in Hb levels as their primary outcome, while Richards et al., Laso-Morales et al., Froessler et al., Keeler et al., and Calleja et al. made this a secondary outcome. Of the nine studies answering this question, four of the five RCTs and three of four non-randomized studies found a significant increase in average Hb levels in the IV iron arm of the study compared to the control group.

In contrast to the other studies, Edwards et al. found no significant change in mean Hb levels between groups for either the whole study population or the subgroup of patients with anemia [30]. The iron sucrose group's median Hb increased by 0.5 g/dL from enrollment to hospital admission, while the usual care cohort increased by 0.1 g/dL.

Froessler et al. found a significant increase in mean Hb from enrollment to hospital admission in the IV ferric carboxymaltose (FCM) group versus usual care. The FCM group increased by 0.8 g/dL, while the usual care group increased by 0.1 g/dL [25]. Keeler et al. and Kim et al. compared oral iron therapy to IV iron therapy and found a significant increase in the mean Hb from enrollment to hospital admission in their IV iron cohorts compared to the oral iron cohorts. In Keeler et al., the FCM group's Hb increased by 1.55 g/dL while the oral iron group's only increased by 0.50 g/dL [26]. In Kim et al., the iron sucrose-treated group's mean Hb increased by 3.0 g/dL, while the oral iron group only increased by 0.8 g/dL [28]. Laso-Morales et al. noted that, compared to patients on either oral iron therapy or no supplemental iron, patients with anemia on IV iron therapy presented with significantly lower baseline Hb (10.8 g/dL vs 12.0 g/dL) but similar Hb on the

day of surgery, immediately postoperatively, at discharge, and 30 days postoperatively, implying that IV iron therapy was more effective in treating preoperative anemia [31]. Calleja et al. found a significant increase in mean Hb levels from enrollment to hospital admission in the FCM group versus usual care. This significant advantage is still present 30 days after surgery [24]. The FCM cohort mean Hb increased by 1.5 g/dL from enrollment to hospital admission versus only 0.5 g/dL in the usual care group. At 30 days postoperatively, these differences were 3.1 g/dL and 1.9 g/dL, respectively. Richards et al. similarly found a statistically significant increase in Hb from randomization to the time of surgery (mean difference 4.7 g/L) and at 8 weeks postoperatively (mean difference 10.7 g/L) [32]. Wilson et al. also found a significant increase in mean Hb levels from enrollment to hospital admission in the FCM group (1.05 g/dL) compared to usual care (0.16 g/dL) [27].

Association of Iron Therapy and Transfusion Rates

Transfusion rates and volumes for each cohort in each study are summarized in Table 2. Eight of the nine studies evaluated transfusion rates as an outcome. Of the five RCTs, three studies evaluated transfusion rates as a primary outcome, one as a secondary outcome, and one not at all. All non-randomized studies measured transfusion rates, two as a primary outcome, and two as a secondary outcome. Of the eight studies answering this question, only one found a significant improvement in transfusion rates.

Edwards et al. did not find a significant reduction in transfusion rates with iron sucrose administration, even when limiting their analysis to a small anemic subgroup [30]. Overall, 14.7% of patients from the iron sucrose group required transfusion, while 19.2% of the control group patients required transfusion. Similarly, Froessler et al. did not find a significant reduction in transfusion rates. Only 12.5% of FCM patients received transfusion, while 31.3% of usual care patients were transfused. They did find a significant reduction in the median

Table 2 Results of included studies

Study	Transfusion rate (%)			Blood transfused per patient			Change in Hb (g/dL) from IDA diagnosis to admission			Length of stay (days)		
	Control	IV iron therapy	p	Control	IV iron therapy	p	Control	IV iron therapy	p	Control	IV iron therapy	p
Richards et al., 2020	28	29	NS	0.65 units	0.61 units	NS	–	–	< 0.05[a]	9	9	NS
Edwards et al., 2009	19.2	14.7	NS	2 units	0 units	NS	0.1	0.5	NS	–	–	–
Keeler et al., 2016	23	18	NS	0.632 mL	0.693 mL	NS	0.5	1.55	0.001	6	6	NS
Froessler et al., 2018	31.3	12.5	NS	3 units	2 units	0.016	0.1	0.8	0.01	9.7	7	0.026
Kim et al., 2009	–	–	–	–	–	–	0.8	3.9	< 0.0001	–	–	–
Laso-Morales et al., 2017	16	17	NS	0.3 units	0.4 units	NS	–	–	–	9	9	NS
Wilson et al., 2018	–	–	NS	–	–	–	0.16	1.05	< 0.0001	–	–	–
Calleja et al., 2015	38.7	9.9	< 0.001	0.8 units	0.2 units	< 0.0001	0.5	1.5	< 0.0001	10.9	8.4	< 0.001
Kam et al., 2020	21.1	48.4	0.006	0.55 units	1.42 units	0.076	0.6	1.9	< 0.001	8.5	9	NS

All studies reported mean values with the exception of Richards et al. and Kam et al., who reported median values for length of stay

Hb hemoglobin, *IDA* iron deficiency anemia, *NS* non-significant, *–* not reported, *CI* confidence interval

[a] Mean Hb values for control and IV iron groups not reported; however, mean difference on day of surgery was noted to be 0.47 g/dL between groups with CI 0.27–0.68

number of red blood cell (RBC) units transfused in the FCM group with a median of 2 units transfused in the FCM group and 3 units in the usual care group [25]. Keeler et al. also found no significant difference in the number of patients transfused or volume transfused over the course of the study [26]. In absolute terms, the FCM group received more units of blood on average (0.698 vs 0.632), while fewer patients were transfused (18% vs 23%). Wilson et al. did not find any statistically significant differences in postoperative transfusion rates between their two cohorts after multivariate analysis with a 46% reduction in postoperative transfusion rates in the IV iron cohort [27]. Laso-Morales et al. also found no significant difference in the number of patients who required RBC transfusion between patients with anemia on IV iron therapy and those on standard care (16% vs 17%) [31]. Richards et al. also similarly found that between the placebo and IV iron groups, mean units of transfused blood were not statistically different from randomization to 30 days postoperatively (0.65 vs 0.61 units) and 6 months postoperatively (0.94 vs 0.75 units) [32]. Similarly, Kam et al. found that significantly fewer patients in the IV iron group required transfusions than in the non-IV iron group (8 vs 30) [29].

The outlier was in the study by Calleja et al., which found that the perioperative and 30-day postoperative percentages of patients transfused and RBC units transfused were significantly reduced in their FCM cohort [24]. Only 9.9% of patients in the FCM group required transfusion, while 38.7% of patients in the usual care cohort required transfusion. Mean units transfused decreased from 0.8 to 0.2. These reductions were found to be independent of the surgical approach (laparoscopic versus open).

Association of Iron Therapy and LOS

Patient LOS for each cohort in each study are summarized in Table 2. Four studies measured patient LOS as an outcome. Froessler et al. and Calleja et al. showed a significant reduction in the LOS in FCM-treated patients versus the usual care cohort, which was 2.5 days and

4 days, respectively. In contrast, Keeler et al., Richards et al., and Laso-Morales et al. reported that the LOS was equivalent between the IV iron groups and the controls.

Quality of Included Studies and Risk for Bias

The grading schemes for the randomized and non-randomized studies are specified in Tables 3 and 4, respectively. All nine studies were classified as good owing to a low risk of bias in blinding, randomization, and other sources of bias for the RCTs and the good comparability of cohorts and appropriate statistical analysis in the non-randomized studies.

DISCUSSION

Our goal in this systematic review was to determine if preoperative IV iron therapy for patients with anemia undergoing abdominal surgery could improve clinical outcomes. Most studies reviewed demonstrate a rapid improvement in serum Hb with the administration of IV iron therapy, as evidenced by mean pre- and post-treatment mean Hb change. However, these studies did not provide consistent evidence of a reduced transfusion rate with preoperative IV iron administration. Thus, while we recommend the preoperative treatment of anemia with oral iron supplementation when possible, there is currently insufficient clinical evidence to justify IV iron administration as a standard treatment for all patients with anemia scheduled for major abdominal surgery.

The best evidence for reduction in transfusion frequency comes from Calleja et al., which showed significant reductions in transfusion rates, and Froessler et al., which showed a significant decrease in units transfused [24, 25]. This is in contrast to the other studies examining this outcome that showed no significant changes. In contrast to the mixed transfusion results, eight out of nine studies showed that IV iron therapy caused a significant increase in preoperative Hb relative to oral iron therapy or usual care. As Hb level is a key predictor for blood transfusion, it stands to reason that an

intervention that reliably increases Hb should also reduce the need for transfusions if large enough cohorts are examined.

There are several potential reasons for the heterogeneity between the studies. Edwards et al. had a good experimental design but was very much an outlier in study goals compared to the other five studies. This study included very few subjects with anemia and had a less stringent definition of anemia than WHO guidelines. This is reflected in the relatively high average ferritin levels (100.5 ng/mL) in the patients with anemia receiving IV iron therapy [30]. The amount of iron administered was also the lowest in this study at 600 mg total. Together, these factors limit our ability to make conclusions about the preoperative treatment of anemia as so few patients with anemia were treated in this study. Froessler et al. had a similar design to Edwards et al. but required included patients to have IDA and administered a much higher dose of IV iron therapy. This may explain why they found a significant improvement in Hb, units transfused, and LOS in their IV iron arm [25].

Keeler et al. was similar to Froessler et al. in study design and compared oral iron therapy to IV iron therapy but administered the lowest dose of IV iron therapy [26]. This reduced dose and the administration of oral iron therapy to the control group may have contributed to the lack of a significant reduction in transfusion rate or LOS in this study.

Kim et al. also compared oral iron therapy to IV iron therapy but included only patients with known IDA and administered one of the largest overall doses of IV iron therapy. This is likely why their study showed the largest increase in Hb concentrations with IV iron administration. However, they did not report transfusion rates [28].

Calleja et al. had a large experimental group, and the control group in this study was also receiving oral iron supplementation [24]. Unfortunately, interpretation of the results from Calleja et al. was limited by the fact that the control cohort is a retrospective cohort and the FCM cohort is a prospective cohort, separated from one another in time. Appropriate efforts were made to match the two cohorts, but

the chronological differences between the cohorts and lack of multivariate analysis limited the comparability between groups. This chronological effect was likely responsible for the increased rate of laparoscopic surgery in the more recent FCM cohort. These issues may explain why Calleja et al. observed such a large effect from FCM treatment on the transfusion rate. This may also explain why different lengths of stay were observed between the study arms. However, intraoperative blood loss was equal between groups, if not marginally higher in the FCM cohort. When the two surgical approaches were analyzed separately, the reduced need for transfusions is maintained. Thus, changes in surgical approach were less likely to be responsible for the findings of Calleja et al.

Wilson et al. utilized a fully retrospective study design with cohort assignment dependent upon provider preference [27]. As such, patients receiving IV iron therapy in this study were more likely to have more severe anemia, comorbidities, laparoscopic surgery, male gender, and to have been treated after the institution of a new patient blood management protocol that recommended increased usage of IV iron therapy. These factors make it challenging to make any definitive conclusions about their results, although they use an appropriate statistical approach to analyze it.

A high frequency of transfusion in the usual care group is a commonality in studies demonstrating a significant reduction in transfusion rate. Both Calleja et al. and Froessler et al. reported blood transfusion rates higher than 30% in control cohorts, while Edwards et al. and Keeler et al. report rates lower than 25%. This may indicate that preoperative IDA screening and IV iron treatment may be most effective for centers and surgeries that have especially high rates of transfusion.

Overall, these studies are consistent with IV iron therapy being highly efficacious for increasing levels of Hb in patients with IDA. Two of the studies also compared oral iron therapy to IV iron therapy. Both showed that IV iron therapy was significantly more efficacious at raising Hb than oral iron therapy, even in experimental circumstances where oral iron

Table 3 Cochrane risk of bias tool for randomized studies

Bias	Support for judgment	Author's judgment
Richards et al. (UK, 2020)		
Random sequence generation	Quote: "Randomisation was done by trained staff members using a secure web-based service through the Clinical Trials Unit at the London School of Hygiene & Tropical Medicine. The web-based service was provided by an independent research support organization"	Low risk
Allocation concealment	Quote: "Randomisation was 1:1 with allocation concealment that used minimisation, considering baseline haemoglobin (< 100 vs ≥ 100 g/L), age (< 70 vs ≥ 70 years), centre, and operation type (major, major plus, complex major)"	Low risk
Blinding of participants and personnel	Quote: "Because the intravenous iron was a dark-brown solution that is easily distinguishable from the saline placebo, dedicated unblinded study personnel were responsible for the preparation and administration of the study drug but had no other involvement in the trial. To ensure blinding of participants, their skin was swabbed with iodine, and the study treatment was shielded from vision (light protection bags) and infused through black tubing. Other clinical and research staff were blinded to the treatment allocated"	Low risk
Blinding of outcome assessment	Comment: No blinding of coprimary outcome assessment (composite endpoint of blood transfusion or death and the number of blood transfusion episodes). These objective outcomes are unlikely to change under unblinded conditions	Low risk
Incomplete outcome data	Comment: 3 patients withdrew from the study between randomization and surgery. Between surgery and follow-up visits (8 week and 6 month), 5 patients withdrew and 5 were lost to follow-up. Also, between surgery and follow-up visits, 22 deaths occurred, 3 of which had missing information needed for intention to treat analysis for coprimary endpoints	Unclear risk
Selective reporting	Comment: None identified	Unclear risk
Other bias	Comment: None identified	Unclear risk
Quality		Good
Edwards et al. (UK, 2009)		
Random sequence generation	Quote: "Computer-generated randomization sequence"	Low risk
Allocation concealment	Quote: "Sealed in sequentially numbered opaque envelopes"	Low risk
Blinding of participants and personnel	Quote: "Concealed from the patient by using an opaque sheath to cover the drug giving set"	Low risk
Blinding of outcome assessment	Quote: "Chief investigator and clinicians involved remained blinded to the treatment group for the duration of the trial"	Low risk
Incomplete outcome data	Quote: "One patient from each group failed to attend for the second infusion"	Low risk

Table 3 continued

Bias	Support for judgment	Author's judgment
Selective reporting	Comment: None identified	Unclear risk
Other bias	Comment: None identified	Unclear risk
Quality		Good
Keeler et al. (UK, 2017)		
Random sequence generation	Quote: "Recruited patients were randomized in a 1:1 fashion via a web-based system using variable block allocation"	Low risk
Allocation concealment	Quote: "The system was designed, set up and run by a unit independent of the study"	Low risk
Blinding of participants and personnel	Comment: Open label study but lack of blinding unlikely to influence objective outcomes	Low risk
Blinding of outcome assessment	Comment: No blinding unlikely to influence perioperative changes in hemoglobin, ferritin, transferrin saturation, and blood transfusion	Low risk
Incomplete outcome data	Quote: "Four patients had their operation cancelled on the day of surgery… one patient died during induction of anesthesia, and the operation was abandoned at initial laparotomy in one patient as inoperable disease was found" Comment: No incomplete outcome data was reported	Low risk
Selective reporting	Comment: None identified	Unclear risk
Other bias	Comment None identified	Unclear risk
Quality		Good
Froessler et al. (UK, 2009)		
Random sequence generation	Quote: "Computer-generated number sequence"	Low risk
Allocation concealment	Quote: "Allocation was conducted by telephone"	Low risk
Blinding of participants and personnel	Quote: "Surgeon performing the operation was informed of patient participation in the study but group allocation was not revealed"	Low risk
Blinding of outcome assessment	Comment: No blinding but objective measurement of transfusion incidence and hemoglobin unlikely to be influenced	Low risk
Incomplete outcome data	Quote: "The study was terminated early due to higher than expected rates of poor outcome in the usual care group"	Low risk
Selective reporting	Comment: None identified	Unclear risk
Other bias	Comment: None identified	Unclear risk
Quality		Good

Table 3 continued

Bias	Support for judgment	Author's judgment
Kim et al. (South Korea, 2009)		
Random sequence generation	Quote: "Computer-generated randomization tables"	Low risk
Allocation concealment	Quote: "Group allocation was determined by one of the authors who was not involved in patient care"	Low risk
Blinding of participants and personnel	Comment: Open label study but lack of blinding unlikely to influence objective outcomes	Low risk
Blinding of outcome assessment	Comment: No blinding but objective outcome of change in hemoglobin level unlikely to be influenced	Low risk
Incomplete outcome data	Comment: None identified	Unclear risk
Selective reporting	Quote: "Participants who had $\geq$ 80% compliance were included in the analysis for efficacy"	Low risk
Other bias	Comment: None identified	Unclear risk
Quality		Good

therapy compliance would be expected to be higher than normal. However, this effect on serum Hb does not consistently lead to a significantly reduced frequency of transfusions in these studies. Thus, more research is necessary to definitively determine whether IV iron therapy reduces the need for transfusions in major abdominal surgery.

Recent reviews and meta-analyses of the efficacy of IV iron administration in patients with anemia have been performed looking at orthopedic surgery patients, cardiac surgery patients, and surgical patients generally. In their meta-analysis, Shin et al. found that there was insufficient evidence for benefit from perioperative IV iron administration on transfusion rates or recovery in major orthopedic surgery, similar to our findings [33]. Hogan et al. performed a systematic review looking at this question for cardiac surgery and also found a lack of evidence for improved outcomes with IV iron administration as a result of a lack of studies examining that question [34]. In a

Cochrane meta-analysis, Ng et al. examined the efficacy of IV iron therapy in surgical patients with anemia and found that while IV iron therapy did cause a significant increase in Hb and ferritin, there was no significant decrease in transfusion rates [35]. They also reported that the evidence for a significant improvement in Hb was weak. Another recent meta-analysis from Peters et al. also evaluated IV iron administration in all surgical patients, with similar findings to Ng et al. [36]. Thus, the results we report here are similar to prior meta-analyses and systematic reviews looking at similar questions.

Strengths and Limitations

Our systematic review has several strengths. We performed a comprehensive search with broad search terms, enlisted methodology expertise, and did not limit the search to elective surgeries or by time frame. We included all experimental

Table 4 Newcastle–Ottawa Scale for non-randomized studies

	Author's judgment	Support for judgment	Score
Laso-Morales et al. (Spain, 2017)			
Selection			
Representativeness of the exposed cohort	Truly representative of patients with iron deficiency anemia undergoing resection for colorectal cancer	Non-elective procedures, non-anemic cases, and patients who had already received RBC transfusions were excluded	1
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	Both exposed and non-exposed cohorts drawn from two Spanish centers from January 2012 to December 2013	1
Ascertainment of exposure	Secure record	Clinical characteristics and laboratory data collected from medical record	1
Demonstration that outcome of interest was not present at start of study	Yes	Primary outcome was relative RBC transfusion rate (%) and RBC transfusion index (units/patient)	1
			4
Comparability			
Comparability of cohorts on the basis of the design or analysis	Study controls for differences in blood transfusion criteria	The following transfusion protocol was uniformly applied across participating centers: a restrictive transfusion trigger of Hb < 8 g/dL unless "active cardiac disease or symptoms of acute anemia" in which a less restrictive transfusion trigger, Hb < 9 g/dL, was used	1
			1
Outcome			
Assessment of outcome	Record linkage	Clinical characteristics and laboratory data were collected from medical records	1
Was follow-up long enough for outcomes to occur?	Yes	Follow-up extended to 30 days post-surgery	1
Adequacy of follow-up of cohorts	Yes	Complete follow-up with all subjects accounted for	1
			3

Table 4 continued

	Author's judgment	Support for judgment	Score
Overall quality			Good
Wilson et al. (the Netherlands, 2006)			
Selection			
Representativeness of the exposed cohort	Yes, truly representative of patients with anemia undergoing resection for colorectal cancer	Only patients who had surgery in the emergency setting and those with missing data with respect to baseline Hb levels and blood transfusions were excluded	1
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	Both exposed and non-exposed cohorts drawn from the Reiner De Graaf Hospital from January 1, 2010 to July 1, 2016	1
Ascertainment of exposure	Secure record	Hb values manually obtained from medical records	1
Demonstration that outcome of interest was not present at start of study	Yes	Primary outcome was relative change in allogenic blood transfusion requirements between exposed and non-exposed cohorts	1
			4
Comparability			
Comparability of cohorts on the basis of the design or analysis	Study controls for differences in blood transfusion criteria	Performed multivariate analysis to control for differences in the severity of the anemia and condition of the patient	1
			1
Outcome			
Assessment of outcome	Independent blind assessment	Clinical and pathologic data collected by the Dutch Surgical Colorectal Audit, a disease-specific national audit. The data set is based on evidenced-based guidelines and is crosschecked on a yearly basis with data from the Netherlands Cancer Registry	1
Was follow-up long enough for outcomes to occur?	Yes	Follow-up extended to 30 days post-surgery	1

Table 4 continued

	Author's judgment	Support for judgment	Score
Adequacy of follow-up of cohorts	Yes	Data set collected by the Dutch Surgical Colorectal Audit includes information on patient, tumor, treatment, and 30-day and in-hospital outcome characteristics of all patients undergoing a resection for primary colorectal carcinoma in the Netherlands	1
			3
Overall quality			Good
Calleja et al. (Spain, 2015)			
Selection			
Representativeness of the exposed cohort	Yes, somewhat representative of colon cancer patients with anemia	Inclusion criteria limited to patients "diagnosed with colon adenocarcinoma located at least 15 cm above anal margin"	1
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	Although exposed cohort was drawn prospectively and the non-exposed cohort retrospectively, both cohorts were drawn from the same participant centers. To avoid selection bias, the retrospective cohort was obtained in a sequential manner independently of outcomes	1
Ascertainment of exposure	Secure record	Collected from surgical intervention 2011 registries	1
Demonstration that outcome of interest was not present at start of study	Yes	Primary outcome was relative reduction in allogenic blood transfusion requirements between exposed and non-exposed cohorts	1
			4

Table 4 continued

	Author's judgment	Support for judgment	Score
Comparability			
Comparability of cohorts on the basis of the design or analysis	Study controls for differences in blood transfusion criteria	Standardized blood transfusion protocol of being "always performed in patients with hemoglobin levels under 7 g/dL, under physician criteria between 7 and 9 g/dL, and not recommended over 9 g/dL." Defined iron deficiency anemia using WHO criteria of Hb level < 13 g/dL in men and < 12 g/dL in women	1
			1
Outcome			
Assessment of outcome	Record linkage	Outcomes collected from surgical intervention 2011 registries	1
Was follow-up long enough for outcomes to occur?	Yes	Follow-up extended to 30 days post-surgery in the exposed cohort. 30-day time frame supported by a previous study which "found evidence for improved hemoglobin concentrations and reduced transfusions" in the 30-day post-surgery period in patients with gastrointestinal cancer and with anemia treated with FCM	1
Adequacy of follow-up of cohorts	No statement		0
			2
Overall quality			Good
Kam et al. (China, 2020)			
Selection			
Representativeness of the exposed cohort	Yes, somewhat representative of patients undergoing resection for colorectal adenocarcinoma with iron deficiency anemia	Patients were excluded if tumor histology was not consistent with adenocarcinoma or if anemia was not due to iron deficiency	1

△ Adis

Table 4 continued

	Author's judgment	Support for judgment	Score
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	Data for non-exposed cohort was collected retrospectively from a database of all patients treated in Hospital Authority hospitals in Hong Kong, which includes Queen Elizabeth Hospital, where the exposed cohort's data was obtained	1
Ascertainment of exposure	Secure record	Data collected prospectively from surgical records	1
Demonstration that outcome of interest was not present at start of study	Yes	Primary outcome was mean Hb change after use of preoperative IV iron therapy. At baseline preoperatively, there was no statistical difference between mean Hb in the exposed and non-exposed cohorts	1
			4
Comparability			
Comparability of cohorts on the basis of the design or analysis	Study used 2:1 propensity score matching to control for first Hb level, age, sex, transfusion of RBC prior to IV iron therapy, use of oral iron supplement, and tumor location	After matching there were no statistical differences between median age, sex, premorbid status, medical comorbidities, use of antiplatelet or anticoagulant medication, RBC transfusions, or percentage taking oral iron therapy prior to surgery	1
			1
Outcome			
Assessment of outcome	Record linkage	Outcomes prospectively collected from medical records as patients underwent elective operations	1
Was follow-up long enough for outcomes to occur?	Yes	For the outcome of interest, mean Hb change from the time of initial IV iron administration (at least 2 weeks prior to surgery) and admission for surgery, there was adequate follow-up	1

Table 4 continued

	Author's judgment	Support for judgment	Score
Adequacy of follow-up of cohorts	Complete follow-up—all subjects accounted for	After propensity score matching, 38 patients where included in the IV iron group and 62 patients in the historic (non-IV iron) cohort, all of whom were followed through duration of the study	1
			3
Overall quality			Good

Hb hemoglobin, *IV* intravenous, *RBC* red blood cell

designs to avoid selection bias. We assessed quality using the Cochrane risk of bias tool and the Newcastle–Ottawa Scale assessment of study quality.

Our systematic review is the most recent and comprehensive on this topic but was limited to only nine articles, including five good-quality RCTs and four good-quality non-randomized studies. One of our systematic review's main limitations is the lack of publications investigating iron therapy as a preoperative intervention for major abdominal surgery. We acknowledge the surgical heterogeneity inherent in the broad category of major abdominal surgery. However, most studies presented in this systematic review involve patients undergoing bowel resection for colorectal cancer, and the additional studies are of good quality. We felt that excluding studies that did not specifically include patients with colorectal cancer would detract from an already sparse body of literature. In all, we were only able to identify nine good-quality studies that met our inclusion and exclusion criteria; nevertheless, strong conclusions could not be drawn from these studies given the heterogeneity both in surgical populations and in specific outcomes data. Individual studies may not have given high enough doses of the treatment or have been inadequately powered to identify significant differences between groups.

There are several studies that discuss the safety of IV iron treatment that were excluded from this systematic review since they did not meet our inclusion criteria [37–40].

CONCLUSIONS

There is a paucity of RCTs evaluating the merits of IV iron supplementation in patients with anemia undergoing major abdominal surgery. The studies identified and evaluated in this systematic review demonstrate a consistent, significant increase in hemoglobin levels in the intravenous iron group but do not consistently report a significant reduction in the number of transfusions intraoperatively. More studies are necessary to definitively determine the efficacy of IV iron therapy in decreasing morbidity and mortality for patients. Thus, we recommend that patients be evaluated and treated for IDA before receiving abdominal surgery. There is currently insufficient evidence of improved outcomes to support the administration of IV iron therapy in all cases of IDA. However, when patients are diagnosed with significant IDA close to their day of surgery, IV iron therapy appears to be far more efficacious at resolving anemia than oral iron therapy and would be a reasonable intervention.

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