ARTICLE IN PRESS
JID: YTMRV [mNS;May 5, 2021;17:29]

Transfusion Medicine Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.elsevier.com/locate/tmrv

Review

Effectiveness of Iron Supplementation With or Without Erythropoiesis-Stimulating Agents on Red Blood Cell Utilization in Patients With Preoperative Anaemia Undergoing Elective Surgery: A Systematic Review and Meta-Analysis

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A R T I C L E I N F O

Article history:
Available online xxx

Keywords:
Systematic Review [Publication Type]
Elective Surgical Procedures
Anemia
Iron
Blood Transfusion
Hematinics
Hemoglobins
Preoperative Care

A B S T R A C T

Patient Blood Management (PBM) is an evidence-based, multidisciplinary, patient-centred approach to optimizing the care of patients who might need a blood transfusion. This systematic review aimed to collect the best available evidence on the effectiveness of preoperative iron supplementation with or without erythropoiesis-stimulating agents (ESAs) on red blood cell (RBC) utilization in all-cause anaemic patients scheduled for elective surgery. Five databases and two trial registries were screened. Primary outcomes were the number of patients and the number of RBC units transfused. Effect estimates were synthesized by conducting meta-analyses. GRADE (Grades of Recommendation, Assessment, Development and Evaluation) was used to assess the certainty of evidence. We identified 29 randomized controlled trials (RCTs) and 2 non-RCTs comparing the effectiveness of preoperative iron monotherapy, or iron + ESAs, to control (no treatment, usual care, placebo). We found that: (1) IV and/or oral iron monotherapy may not result in a reduced number of units transfused and IV iron may not reduce the number of patients transfused (low-certainty evidence); (2) uncertainty exists whether the administration route of iron therapy (IV vs oral) differentially affects RBC utilization (very low-certainty evidence); (3) IV ferric carboxymaltose monotherapy may not result in a different number of patients transfused compared to IV iron sucrose monotherapy (low-certainty evidence); (4) oral iron + ESAs probably results in a reduced number of patients transfused and number of units transfused (moderate-certainty evidence); (5) IV iron + ESAs may result in a reduced number of patients transfused (low-certainty evidence); (6) oral and/or IV iron + ESAs probably results in a reduced number of RBC units transfused in transfused patients (moderate-certainty evidence); (7) uncertainty exists about the effect of oral and/or IV iron + ESAs on the number of patients requiring transfusion of multiple units (very low-certainty evidence). Effect estimates of different haematological parameters and length of stay were synthesized as secondary outcomes. In conclusion, in patients with anaemia of any cause scheduled for elective surgery, the preoperative administration of iron monotherapy may not result in a reduced number of patients or units transfused (low-certainty evi-

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https://doi.org/10.1016/j.tmrv.2021.03.004

Please cite this article as: H. Van Remoortel, J. Laermans, B. Avau et al., Effectiveness of Iron Supplementation With or Without Erythropoiesis-Stimulating Agents on Red Blood Cell Utilization in Patients With Preoperative Anaemia Undergoing Elective Surgery:

dence). Iron supplementation in addition to ESAs probably results in a reduced RBC utilization (moderate-certainty evidence).

Introduction

Patient Blood Management (PBM) is "an evidence-based, multidisciplinary approach aimed at optimizing the care of patients who might need transfusion. PBM encompasses all aspects of patient evaluation and clinical management surrounding the transfusion decision-making process, including the application of appropriate indications, as well as minimization of blood loss and optimization of patient red cell mass. PBM can reduce the need for allogeneic blood transfusions and reduce health-care costs, while ensuring that blood components are available for the patients who need them. PBM puts the patient at the heart of decisions made around blood transfusion, promoting appropriate use of blood and blood components and the timely use of alternatives where available"[1,2].

Given that the mean prevalence of preoperative anaemia in patients scheduled for major surgery is around 35% [3], and untreated anaemia in patients who undergo surgical procedures is associated with increased postoperative morbidity and mortality as well as increased transfusion requirements [4], the appropriate management of preoperative anaemia is an important part of PBM.

Iron-deficiency anaemia is the most common type of preoperative anaemia and can be caused by an underlying disease, disorder or a nutritional deficit (eg, bleeding, diet, malabsorption, chronic inflammatory disease or cancer). [5] Therefore, the therapeutic use of iron supplements (which increases body iron stores and hemoglobin concentrations) with or without erythropoiesis-stimulating agents (ESAs, that stimulate the bone marrow to make red blood cells [RBCs]), is an elective treatment for preoperative anaemia and could avoid or reduce the need for a RBC transfusion in the perioperative period.

In 2018, the International Consensus Conference on PBM recommended "the use of iron supplementation to reduce RBC transfusion rate in adult preoperative patients with iron-deficient anaemia undergoing elective surgery" and recommended that "short-acting erythropoietins in addition to iron supplementation should be considered to reduce transfusion rates in adult preoperative patients with hemoglobin concentrations <13 g/dL undergoing major orthopedic surgery"[6]. The underlying scientific basis for these recommendations were 22 (non-)randomized controlled trials (RCTs) that studied the effectiveness of preoperative iron supplementation with or without ESAs, compared to placebo, standard of care or no treatment, in patients undergoing an elective surgery. In a follow-up project, three full systematic reviews were conducted to gather the best available scientific evidence on the effectiveness (review 1), safety (review 2) and cost-effectiveness (review 3) of iron and/or ESA therapy in adult patients with preoperative anaemia, regardless of its aetiology, undergoing elective surgery.

The aim of this systematic review (review 1) is to identify, synthesize and critically appraise the best available and most up-to-date evidence on the effectiveness of the preoperative administration of iron supplementation with or without ESAs in patients undergoing elective surgery. The conclusions from this review will inform researchers, medical personnel and patients and will serve as a direct scientific basis to formulate or update recommendations in this field.

2. Material and Methods

This systematic review was not prospectively registered but was carried out according to the pre-defined methodological standards of the Centre for Evidence-Based Practice[7]. We planned and reported the systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[8].

2.1. Eligibility Criteria

Studies were eligible for inclusion if they answered the following PICO question: "In elective surgery patients with preoperative anaemia regardless of its aetiology (population), is iron monotherapy or the combination of ESAs with iron therapy (interventions), compared to placebo, standard of care or no treatment (comparator) effective (1) to reduce blood product utilization; (2) to increase haematological parameters; and/or (3) to reduce the length of hospital/intensive-care unit (ICU) stay (outcomes)?" Full texts of potentially relevant articles were reviewed according to pre-defined inclusion and exclusion criteria (**Appendix A**)

2.2. Data Sources and Searches

A literature search was performed in 5 databases (MEDLINE (via the PubMed interface), Embase (via Embase.com), Web of Science, Transfusion Evidence Library, the Cochrane Library [both The Cochrane Database of Systematic Reviews and The Cochrane Central Register of Controlled Trials)] and 2 trial registries (WHO International Clinical Trials Registry Platform and ClinicalTrials.gov) for eligible studies from the time of inception of the database until November 6, 2020. We developed search strategies for each database consisting of index terms and free text terms (**Appendix B**). Additionally, for each included study, the reference list and the first 20 similar articles in PubMed were screened for other relevant publications.

2.3. Study Selection

Search yields were exported to a citation program (EndNote X7.5), duplicates were discarded, and the de-duplicated EndNote file was uploaded to the EPPI Reviewer Web software (Version 4.11.2.1)[9].

Two reviewers (HVR and JL) independently performed the title and abstract screening followed by the full text assessment according to the eligibility criteria (cfr. supra). Disagreements were resolved by discussion or by consulting a third reviewer (BA) and/or by consulting authors or trial investigators to request additional relevant information that was not available in the publication.

2.4. Extraction of Study Characteristics

Information concerning study design, population characteristics, intervention(s) vs comparison, co-interventions (ie, applied in both the intervention and comparison group), the RBC transfusion trigger, primary and secondary outcomes were extracted independently by two reviewers (HVR and JL). Authors were contacted via email (if available) in case information was missing.

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2.5. Data Synthesis

Primary and secondary outcome data were extracted for the following comparisons: IV and/or oral iron monotherapy vs placebo, standard of care or no treatment (comparison 1); IV iron monotherapy versus oral iron monotherapy (comparison 2); IV iron preparation versus another IV iron preparation (comparison 3); IV and/or oral iron + ESA therapy versus placebo, standard of care or no treatment (comparison 4). More details about data synthesis of effect measures can be found in **Appendix C**.

2.6. Grading of the Evidence

The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) was used to assess the certainty of the evidence [10]. The certainty of the evidence for each outcome was graded as 'high', 'moderate', 'low' or 'very low'. Experimental studies receive an initial grade of 'high' by default and may be downgraded based on pre-specified criteria (**Appendix D**).

The GRADEpro GDT (Guideline Development Tool) software was used to create summary of findings tables that depict the certainty of evidence and the magnitude of relative and absolute effects for each primary and secondary outcome. Summarized evidence conclusions were formulated according to the certainty of the evidence (discussed and confirmed with an external methodologist, GB), which was reflected in the wording of the statements[11,12]. Due to the lack of information concerning the minimal clinical important difference magnitude of the primary and secondary outcomes, the magnitude of these effect estimates was not determined.

3. Results

3.1. Description of Studies

3.1.1. Study Selection

The systematic literature search resulted in a total of 8221 citations (after duplicate removal) which were scrutinised by two reviewers independently. Fig. 1 represents the study selection process. We eventually included 32 peer-reviewed publications (29 RCTs [13–42] with 2 references describing the results of 1 trial [33,34] and 2 non-RCTs [43,44]), 2 study protocols [45,46] and 36 trial registrations [47–82] that investigated the effectiveness of preoperative administration of iron monotherapy or ESAs in addition to iron therapy.

3.1.2. Included studies

3.1.2.1. Iron monotherapy. Summarized characteristics of the 11 included studies can be found in Table 1. Five studies compared oral (ferrous sulphate or ferrous citrate) or IV iron (iron sucrose or ferric carboxymaltose) therapy to placebo, usual care or no iron treatment [19,21,30,41,44], five other studies compared IV iron therapy (ferric carboxymaltose, iron polymaltose, iron sucrose) to oral iron therapy (ferrous sulphate, iron protein succinylate) [14,23,25,26,32], and one study compared IV ferric carboxymaltose to IV iron sucrose therapy [29].In all 11 studies, iron administration was started preoperatively. Five studies investigated the effect of a single preoperative dose of IV iron. [14,19,25,41,63] The effect of multiple preoperative administrations of IV or oral iron was studied in 3 [23,26,32] and 2 studies [30,44], respectively. In one study, iron administration occurred both preoperatively and postoperatively (within 2 days after surgery)[21].

Elective surgery settings included colorectal cancer surgery in 4 studies [19,23,30,44], gynaecological surgery (ie, benign uterine diseases causing menorrhagia) in 2 studies [26,29], orthopaedic surgery (i.e. joint arthroplasty) in 2 studies [14,25], abdominal surgery in 2 studies [21,41], and cardiac surgery (i.e. coronary artery bypass and/or open valve surgery) in 1 study [32].

Preoperative anaemia was defined as <14.0 g/dL for men and <12.0 g/dL for women in 1 study [25], <13.5 g/dL for men and <12.5 g/dL for women in 1 study [19], <13.5 g/dL for men and <11.5 g/dL for women in 1 study [30], <13.0 g/dL for men and <12.0 g/dL for women in 4 studies [21,23,32,41], and <10.0 g/dL for all patients in 2 studies. [29,44] Two studies did not explicitly define anaemia, but were included because baseline Hb levels were <13 g/dL in all patients [14,26].

In 4 studies, it was unclear if the participants were iron-deficient (ie, no definition reported). [19,23,30,44] Three studies included iron-deficient patients only (ie, serum ferritin <30 µg/L in 2 studies [25,29], serum ferritin <30 µg/L and transferrin saturation <25% in 1 study [21]) whereas 3 other studies investigated a patient population of which a small minority was iron-deficient: 28–29% of the entire population in the first study [41] (serum ferritin <100 ng/mL and transferrin saturation <20%); 14–27% in the second study [32] (serum ferritin <22 µg/L); and 8% in the third study (serum ferritin <30 µg/L [14]). One additional study did not use a definition for iron-deficiency but referred to patients as having established iron-deficiency anaemia[26].

Co-interventions (ie, interventions administered identically to both the intervention and comparison group) were reported in 3 studies and consisted of neoadjuvant therapy [19], epidural anaesthesia [25], and a range of interventions (preoperative: Epoetin-α therapy; intraoperative: administration of tranexamic acid and ferric hydroxide sucrose, cell saver use; postoperative: administration of heparin, Epoetin-α (if Hb <15 g/dl) and ferric hydroxide sucrose)[14]. The RBC transfusion threshold applied was based on the Hb level (general threshold Hb <7–8 g/dL) and/or the clinical condition of the patient (eg, underlying chronic diseases). Information about co-interventions or RBC transfusion triggers was not reported in 8 studies [21,23,26,29,30, 32,41,44] and 5 studies [21,26,29,32,41], respectively.

3.1.2.2. Iron + ESA therapy. Summarized characteristics of the 20 included studies can be found in Table 2. The effectiveness of the following combined interventions was investigated: Epoetin-α or β + oral iron therapy in 8 studies [15,16,28,31,35,36,38,39], recombinant Human EPO (rHuEPO) + oral iron therapy in 5 studies [17,18,20,22,33,34], Epoetin-α + IV iron therapy in 3 studies [24,27,37], EPO + oral iron in 1 study [13] and rHuEPO + IV iron therapy in 3 studies[40,42,43].

In all studies, iron + ESA administration was started preoperatively. Half of the studies continued the administration postoperatively, ranging from 1 day until 14 days after surgery [13,15–18,20,22,24,27,33,34]. In all but 2 studies [39,40], multiple doses of ESAs were administered, with the initial dose around preoperative day 10–14 (range: preoperative day 28 to preoperative day 3).

Elective surgery settings included (major) orthopaedic surgery in 7 studies [13,16,20,31,36,38,42], colorectal cancer surgery in 6 studies [15,22,24,27,33,34,43], cardiac surgery in 3 studies [37,39,40], abdominal and/or gynaecological surgery in 3 studies [17,18,28] and major head and neck oncological surgery in 1 study[35].

Preoperative anaemia was defined according to the WHO definition in 3 studies (ie, Hb <13.0 g/dL for men and Hb <12.0 g/dL for women) [36,37,40], whereas 9 studies used another definition with Hb <13–13.5 g/dL as the most frequently used upper limit (in 6 studies [16,22,24,27,35,39]). Eight studies did not explicitly define anaemia, but were included because baseline Hb levels were <13 g/dL in all patients [13,15,17,18,20,31,38,42].

In only 6 studies, iron-deficiency was defined [20,22,24,28,31,37], whereas no information was available in

Table 1
Characteristics of the included studies investigating the effectiveness of iron monotherapy

Study	Design	Population (at baseline)			Intervention(s)	Comparison
Author, year, country		Type of elective surgery – demographics (age, gender)	Definition anaemia	Definition iron-deficiency		
Biboulet, 2018, France [14]	RCT	Orthopaedic surgery Intervention (IV iron + Epoetin-α): n=50, 84% women, median age 67 y (range: 60–75) Comparison (oral iron + Epoetin-α): n=50, 76% women, median age 71 y (range: 61–78)	None (patients were considered to be anaemic because baseline Hb levels were 10–12.9 g/dL)	Serum ferritin <30 µg/L (8% were iron-deficient)	Type: IV iron (ferric carboxymaltose - Ferinject) Dosis: 1000 mg Frequency: single dose preoperatively Time point: immediately after the anaesthetic consultation and baseline blood sampling Type: subcutaneous Epoetin-α (Eprex) Dosis: 40.000 IU Frequency: 3 doses preoperatively Time point: at 21 days, 14 d and 7 d before surgery	Type: oral iron (ferrous sulphate - Tardyferon) Dosis: 160 mg (per day) Frequency: twice daily Time point: starting the day after the anaesthetic consultation Type: subcutaneous Epoetin-α (Eprex) Dosis: 40.000 IU Frequency: 3 doses preoperatively Time point: at 21 d, 14 d and 7 d before surgery
Edwards, 2009, UK [19]	RCT	Colorectal cancer surgery Intervention (IV iron): n=34, 35% women, median age 67 y Comparison (Placebo): n=26, 35% women, median age 70 y *Only data from the anaemic patients were extracted (intervention (n=9) versus comparison (n=9))*	Hb <12.5 g/dL for women and <13.5 g/dL for men	None (% of iron-deficient patients not reported)	Type: IV iron (iron sucrose - Venofer) Dosis: 600 mg (2 infusions of 300 mg) Frequency: single dose preoperatively Time point: minimum 2 wk before surgery	Type: Placebo (0.9% saline) Frequency: single dose (2 infusions at least 24 h apart from each other) Time point: minimum 2 wk before surgery
Froessler, 2016, Australia [21]	RCT	Abdominal surgery (mixture of malignant and non-malignant) Intervention (IV iron): n=40, 52% women, mean age 64±15 y Comparison (usual care): n=32, 47% women, mean age 68±15 y	Hb <12.0 g/dL for women and <13.0 g/dL for men	Serum ferritin <300 µg/L, transferrin saturation <25% (all patients were iron-deficient)	Type: IV iron (ferric carboxymaltose) Dosis: - Preop: according to patient's body weight (15 mg/kg; at least 1000 mg) - Postop: 0.5 mg/mL blood loss Frequency: - Preoperative: single dose - Postoperative: single dose, only if blood loss >100 mL Time point: - Preoperative:15 minutes before surgery - Postoperative: within 2 post-operative days	Type: usual care (could consist of no treatment, continued observations, oral/IV iron, allogeneic RBC transfusion)
Keeler, 2017, UK [23]	RCT	Colorectal cancer surgery Intervention (IV iron): n=55, 36% women, median age 73.8 y (IQR: 67.4–78.6) Comparison (oral iron): n=61, 39% women, median age 74.7 y (IQR: 67.9–80.8)	Hb <12.0 g/dL for women and <13.0 g/dL for men	None (% of iron-deficient patients not reported)	Type: IV iron (ferric carboxymaltose - Ferinject) Dosis: according to the patient's Hb levels and body weight (maximum 1000 mg per week and 2000 mg during the trial) Frequency: 1 or 2 doses preoperatively Time point: - First dose: minimum 2 wk before surgery - Second dose: at least 7 d after first dose	Type: oral iron (ferrous sulphate) Dosis: 200 mg Frequency: twice daily Time point: 2 wk starting from initial recruitment visit

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Table 1 (*continued*)

Study Author, year, country	Design	Population (at baseline) Type of elective surgery – demographics (age, gender)	Definition anaemia	Definition iron-deficiency	Intervention(s)	Comparison
Khalafallah, 2012, Australia [25]	RCT	Orthopaedic surgery 33 patients that completed the trial: 58% women, median age 68 y (range 45–91)	Hb <12.0 g/dL for women or <14.0 g/dL for men	Serum ferritin <30 µg/L (all patients were iron-deficient)	Type: IV iron (iron polymaltose - Ferrosig) Dosis: according to the patient's body weight at preadmission visit and entry Hb level according to the product guidelines Frequency: single dose Duration: 4 wk before surgery	Type: oral iron (ferrous sulphate) Dosis: 325 mg Frequency: daily Duration: 4 wk before surgery
Kim, 2009, South Korea [26]	RCT	Gynaecological surgery Intervention (IV iron): n=39, of which 9 dropped out. 30 remaining patients: mean age 42.0±7.4 y Comparison (oral iron): n=37, of which 11 dropped out. 26 remaining patients: mean age 42.3±8.0 y	refer to the patients as having “established iron-deficiency anaemia”, but do not provide a definition		Type: IV iron (iron sucrose - Venoferrum) Dosis: according to the patient's body weight and Hb levels (maximum 200 mg of elemental iron in each infusion) Frequency: every other day (3 times a week) Duration: start at 3 weeks before surgery	Type: oral iron (iron protein succinylate – Hemo-Q Soln) Dosis: 80 mg Frequency: daily Duration: start at 3 wk before surgery
Lee, 2019, South Korea [29]	RCT	Gynaecological surgery Intervention (IV iron – ferric carboxymaltose): n=52, mean age 44±5.7 y Comparison (IV iron – iron sucrose): n=49, mean age 43.4±5.0 y	Hb <10 g/dL	Serum ferritin <30 µg/L (all patients were iron-deficient)	Type: IV iron (ferric carboxymaltose - Ferinject) Dosis: according to the patient's body weight (<50kg: 500 mg iron; ≥50 kg: 1000mg) Frequency: single dose Time point: unclear (in relation to surgery)	Type: IV iron (iron sucrose - Venoferrum) Dosis: according to calculated iron deficit using the Ganzoni formula (maximum 600 mg per week in 200mg single administration sessions) Frequency: up to 3 dosing visits per week Time point: unclear (in relation to surgery)
Lidder, 2007, UK [30]	RCT	Colorectal cancer surgery Intervention (oral iron): n=24, 33% women, aged 47–89 y Comparison (usual care): n=25, 36% women, aged 57–80 y	Hb <11.5 g/dL for women and <13.5 g/dL for men	None (% of iron-deficient patients not reported)	Type: oral iron (ferrous sulphate) Dosis: 200 mg Frequency: daily (3 times) Time point: start at 2 wk before surgery	Type: usual care (not defined)
Okuyama, 2005, Japan [44]	Non-RCT	Colorectal cancer surgery Intervention (oral iron): n=32, 53% women, mean age 68.7±9.6 y Comparison (no iron): n=84, 50% women, mean age 66.7±11.2 y	Hb levels ≤10 g/dL	None (% of iron-deficient patients not reported)	Type: oral iron (ferrous citrate) Dosis: 200 mg Frequency: twice daily Time point: start at least 2 wk before surgery	Type: no iron treatment
Padmanabhan, 2019, UK [32]	RCT	Cardiac surgery Intervention (IV iron): n=22, 41% women, mean age 73±12 y Comparison (oral iron): n=22, 36% women, mean age 75±10 y	Hb <12.0 g/dL for women and <13.0 g/dL for men	Serum ferritin <22 µg/l (14% and 27% of patients in intervention and comparison, respectively)	Type: IV iron (ferric carboxymaltose - Ferinject) Dosis: according to patient's body weight and Hb levels (maximum 2000 mg) Frequency: 1–2 doses Time point: preoperative clinic visit (at least 3 wk before surgery)	Type: oral iron (ferrous sulphate) Dosis: 200 mg Frequency: twice daily
Richards, 2020, Australia [41]	RCT	Open abdominal surgery Intervention (IV iron): n=244, 51% women, median age 67 y (IQR 57–72) Comparison (placebo): n=243, 58% women, median age 65 y (IQR 50–72)	Hb <12.0 g/dL for women and <13.0 g/dL for men	Serum ferritin <100 ng/mL and transferrin saturation <20% (28% and 29% of patients in intervention and comparison, respectively)	Type: IV iron (ferric carboxymaltose - Ferinject) Dosis: 1000 mg Frequency: once Time point: a minimum of 10 days and a maximum of 42 d before surgery	Type: Placebo (100 mL normal saline) Frequency: once Time point: a minimum of 10 d and a maximum of 42 d before surgery

Hb, haemoglobin; IQR, Interquartile range; IV, intravenous; RCT, Randomized Controlled Trial

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Table 2
Characteristics of the included studies investigating the effectiveness of iron + ESA therapy

Study	Design	Population (at baseline)			Intervention – ESA therapy	Intervention – iron therapy	Comparison
Author, year, country		Type of elective surgery – demographics (age, gender)	Definition anaemia	Definition iron-deficiency			
Bailey, 1993, Canada [13]	RCT	Orthopaedic surgery (hip) Intervention (EPO + oral iron): n=77 Comparison (placebo + oral iron): n=78	Not reported, for this review, we only extracted data on subgroups of patients with baseline Hb levels <11.5 and 11.5-12.4 g/dL	Patients with iron-deficiency were excluded	Type: subcutaneous (EPO) Dosis: 300 IU/kg Frequency: daily Time points: from 10 d before surgery until 3 d after surgery	Type: oral (ferrous sulphate) Dosis: 300 mg Frequency: daily Time points: from preoperative d 21 until discharge	Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as *Intervention – iron therapy*
Braga, 1997, Italy [43]	Non-RCT	Gastric or colorectal cancer surgery Intervention (rHuEPO): n=10, 60% women, mean age 61.6±9.3 y Comparison (standard of care): n=10, 60% women, mean age 61.6±9.3 y	Hb 8-11 g/dL	None	Type: subcutaneous (rHuEPO; Eprex) Dosis: 500 IU/kg in total (300,100 and 100 IU/kg) Frequency: 3 doses Time points: preoperative day 12, 8 and 4	Type: IV (iron saccharate) Dosis: 200 mg Frequency: 3 doses Time points: preoperative day 12, 8 and 4 (immediately after each rHuEPO dose)	No treatment
Cao, 2020, China [42]	RCT	Orthopaedic surgery (knee) Intervention (EPO + IV iron): n=35, 83% women, 67.7±8.4 y Comparison (IV iron): n=32, 87% women, 69.0±6.4 years	None	None	Type: subcutaneous (rHuEPO) Dosis: 10 000IU (150 IU/kg) Frequency: daily Time points: from preoperative day 3 until postoperative day 4	Type: IV (iron sucrose) Dosis: 200 mg Frequency: daily Time points: preoperative day 3, 2 and 1	IV iron: same modalities as *Intervention – iron therapy*
Christodoulakis, 2005, Greece [15]	RCT	Colorectal cancer surgery Intervention 1 (Epoetin-α 150 IU/kg + oral iron): n=69, 49% women, median age 72 y (range 43–91) Intervention 2 (Epoetin-α 300 IU/kg + oral iron): n=67, 55% women, median age 71 y (range 36–92) Comparison (standard of care): n=68, 59% women, median age 70 y (range 44–89)	Authors refer to the patients as “anaemic”, but do not provide a definition (baseline Hb levels (>9 and <12 g/dl))	None	Type: subcutaneous (Epoetin-α) Dosis: - Intervention 1: 150 IU/kg - Intervention 2: 300 IU/kg Frequency: daily Time points: from preoperative d 10 until postoperative d 1	Type: oral (elementary iron supplements) Dosis: 200 mg Frequency: daily Time points: preoperative d 10 until postoperative d 1	Oral iron: same modalities as *Intervention – iron therapy*
De Andrade 1996, USA [16]	RCT	Orthopaedic surgery (knee or hip) 3 strata of patients: Stratum 1 (Hb ≤10 g/dL, n=2);Stratum 2 (Hb >10 to ≤13 g/dL, n=96); tratum 3 (Hb >13 g/dL, n=218). Intervention 1 (Epoetin-α 100 IU/kg + oral iron): n=101, 58% women, mean age 65.98±13.44 y Intervention 2 (Epoetin-α 300 IU/kg + oral iron): n=112, 66% women, mean age 65.84±12.7 y Comparison (placebo + oral iron): n=103, 61% women, mean age 67.75±11.12 y As this review specifically concerns patients with preoperative anaemia, only outcomes analysed in the stratum 2 patients (too few patients in stratum 1 for analysis) were extracted.	Hb <9g/dL, data included from the stratum 2 patients because of their entry Hb levels (>10 and ≤13 g/dL).	None	Type: subcutaneous (Epoetin-α) Dosis: - Intervention 1: 100 IU/kg - Intervention 2: 300 IU/kg Frequency: daily Time points: from 10 d before surgery until postoperative d 4	Type: oral (elementary iron supplements) Dosis: ≥150 mg Frequency: daily Time points: from the first day of study medication until hospital discharge	Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as *Intervention – iron therapy*

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Table 2 (*continued*)

Study Author, year, country	Design	Population (at baseline) Type of elective surgery – demographics (age, gender)	Definition anaemia	Definition iron-deficiency	Intervention – ESA therapy	Intervention – iron therapy	Comparison
Dousias, 2003, Greece [17]	RCT	Abdominal gynaecological cancer surgery Intervention (rHuEPO + oral iron): n=23, mean age 48±4 years Comparison (saline + oral iron): n=27, mean age 49±5 y	Authors refer to the patients as "mildly anaemic", but do not provide a definition (baseline Hb levels (≥9 and <12 g/dL)	None	Type: subcutaneous (rHuEPO) Dosis: 600 IU/mL Frequency: 3 doses Time points: preoperative d 14, 7 and the morning before the operation	Type: oral Dosis: 200 mg Frequency: daily Time points: preoperative d 14 to postoperative d14	Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as *Intervention – iron therapy*
Dousias, 2005, Greece [18]	RCT	Abdominal gynaecological cancer surgery Intervention (rHuEPO + oral iron): n=20, mean age 48.6±7.6 y Comparison (placebo + oral iron): n=18, mean age 46.9±7.1 y	None	None	Type: subcutaneous (rHuEPO) Dosis: 200 IU/kg Frequency: daily Time points: from preoperative d 10 to postoperative d 5	Type: oral Dosis: 200 mg Frequency: daily Time points: from preoperative d 10 to postoperative d 5	Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as *Intervention – iron therapy*
Faris, 1996, USA [20]	RCT	Orthopaedic surgery Intervention 1 (rHuEPO 100 IU/kg + oral iron): n=71 Intervention 2 (rHuEPO 300 IU/kg + oral iron): n=60 Comparison (placebo + oral iron): n=69 As our PICO specifically concerns patients with preoperative anaemia, only outcomes analysed in the subgroup analysis on patients with pre-treatment Hb levels >10 and ≤13 g/dL were extracted.	None	Ferritin <20 μg/L or total iron-binding capacity > 360 μg/dL (64.5 μmol/l) and oxygen saturation < 0.160	Type: subcutaneous (rHuEPO) Dosis: - Intervention 1: 100 IU/kg - Intervention 2: 300 IU/kg Frequency: daily Time points: from preoperative d 10 to postoperative d 4	Type: oral (ferrous sulphate) Dosis: 325 mg Frequency: daily (3 times) Time points: from preoperative d 10 to postoperative d 4	Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as *Intervention – iron therapy*
Heiss, 1996, Germany [22]	RCT	Colorectal cancer surgery Intervention (rHuEPO + oral iron): n=17, 59% women (3 of the 20 randomized patients dropped out), median age 66 y (range 42–80) Comparison (placebo + oral iron): n=10, 80% women, median age 61 y (range 42–74)	Hb 9-13 g/dL	Transferrin saturation ≤ 15%	Type: subcutaneous (rHuEPO) Dosis: 150 IU/kg Frequency: every 2 d Time points: from preoperative d 10 to postoperative d 2	Type: oral (ferrous sulphate) Dosis: 200 mg Frequency: daily Time points: each preoperative day	Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as *Intervention – iron therapy*

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Table 2 (*continued*)

Study	Design	Population (at baseline)			Intervention – ESA therapy	Intervention – iron therapy	Comparison
Author, year, country		Type of elective surgery – demographics (age, gender)	Definition anaemia	Definition iron-deficiency			
Kettelhack, 1998, Germany [24]	RCT	Colorectal cancer surgery Intervention (Epoetin-β + IV iron and additional oral iron in case of iron-deficiency): n=48, 56% women, median age 71 y (range 53–57) Comparison (placebo): n=54, 59% women, median age 67 y (range 37–91)	Hb 8.5-13.5 g/dL (= moderate anaemia)	Transferrin saturation <20%	Type: subcutaneous (Epoetin-β) Dosis: 20.000 IU Frequency: daily Time points: from a minimum of 5 (maximum 10) preoperative d until postoperative d 4	Type: IV iron (iron sulphate) Dosis: 40 mg Frequency: single dose Time points: postoperative d 1 Additional oral iron supplementation during the study in case of iron-deficiency (87% of patients; treatment modalities not specified)	Placebo: same modalities as *Intervention – ESA therapy* + Additional oral iron supplementation during the study in case of iron-deficiency (80% of patients; treatment modalities not specified)
Kosmadakis, 2003, Greece [27]	RCT	Gastrointestinal cancer surgery Intervention (Epoetin-α + IV iron): n=31, 52% women, mean age 67.1±2.1 y Comparison (placebo + IV iron): n=32, 41% women, mean age 66.4±2 y	Hb 8.5-13 g/dL (= moderate anaemia)	None	Type: subcutaneous (Epoetin-α) Dosis: 300 IU/kg Frequency: daily Time points: from preoperative d 7 until postoperative d 7	Type: IV iron (Venofer) Dosis: 100 mg Frequency: daily Time points: from preoperative d 7 until postoperative d 7	Placebo: same modalities as *Intervention – ESA therapy* + IV iron: same modalities as *Intervention – iron therapy*
Larson, 2001, Sweden [28]	RCT	Abdominal gynaecological cancer surgery Intervention (Epoetin-β + oral iron): n=15, mean age 46±1 y Comparison (oral iron): n=16, mean age 44±1 years	Hb <12 g/dL	Mean serum ferritin below the lower reference value and transferrin saturation <15 %	Type: subcutaneous (Epoetin-β; NeoRecormon) Dosis: 5.000 IU Frequency: twice per week Time points: 4 preoperative weeks	Type: oral (iron succinate) Dosis: 200 mg Frequency: twice daily Time points: 4 preoperative weeks	Oral iron: same modalities as *Intervention – iron therapy*
Olijhoek, 2001, The Netherlands [31]	RCT	Orthopaedic surgery Intervention 1 (Epoetin-α + IV iron): n=29, 93% women, mean age 64.9±14.7 y Intervention 2 (Epoetin-α + oral iron): n=29, 90% women, mean age 65.4±13.7 y Comparison 1 (placebo + IV iron): n=25, 88% women, mean age 65.8±13.3 y Comparison 2 (placebo + oral iron): n=27, 89% women, mean age 66.9±12.1 y	None	Serum total iron-binding capacity (TIBC) ratio <15 % and serum ferritin level <50 ng/mL	Type: subcutaneous (Epoetin-α) Dosis: 600 IU/kg Frequency: 2 doses Time points: preoperative d 14 and 7	Intervention 1: Type: IV (iron saccharate) Dosis: 200 mg Frequency: 2 doses Time points: preoperative d 14 and 7 Intervention 2: Type: oral Dosis: 200 mg Frequency: daily Duration: 2 preoperative weeks	Control 1: Placebo: same modalities as *Intervention – ESA therapy* + IV iron: same modalities as intervention 1 in *Intervention – iron therapy* Control 2: Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as intervention 2 in *Intervention – iron therapy*

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Table 2 (*continued*)

Study	Design	Population (at baseline)			Intervention – ESA therapy	Intervention – iron therapy	Comparison
Author, year, country		Type of elective surgery – demographics (age, gender)	Definition anaemia	Definition iron-deficiency			
Qvist, 1999/2000, Denmark [33, 34]	RCT	Colorectal cancer surgery Intervention 1 (rHuEPO + oral iron): n=38, 68% women, mean age 69 y (range 48–86), pre-entry median Hb 7.9 mmol/L (range 5.3–8.5) Comparison (placebo + oral iron): n=43, 53% women, mean age 69 years (range 40–85), pre-entry median Hb 7.6 mmol/L (range 5.1–8.5)	Hb 5-8.5 mmol/L	None	Type: subcutaneous (rHuEPO) Dosis: 300 IU/kg Frequency: 1 dosis Time points: preoperative d 4 AND Type: EPO Dosis: 150 IU/kg Frequency: daily Time points: from preoperative day until postoperative d 3	Type: oral Dosis: 200 mg Frequency: daily Time points: from preoperative d 4 to preoperative d 1	Placebo: subcutaneously on a daily basis from preoperative d 4 to postoperative d 3 + Oral iron: same modalities as *Intervention – iron therapy*
Scott, 2002, USA [35]	RCT	Major head and neck oncologic surgery Intervention (Epoetin-α + oral iron): n=29, 45% women, mean age 68±11 y Comparison (placebo + oral iron): n=29, 38% women, mean age 62±11 y	Hb ≥10 and ≤13.5 g/dL	None	Type: subcutaneous (Epoetin-α) Dosis: 600 IU/kg Frequency: 3 doses Time points: - between preoperative d 19 and 10 - between preoperative d 12 and 6 - on the day of surgery	Type: oral (ferrous sulphate) Dosis: 150 mg Frequency: twice daily Time points: from the time of administration of the first dose of Epoetin-α until the day of surgery	Placebo: same modalities as *Intervention – ESA therapy* + Oral iron: same modalities as *Intervention – iron therapy*
So-Osman, 2014, The Netherlands [36]	RCT	Orthopaedic surgery Intervention (Epoetin-α or -β + oral iron): n=125, 90% women, 71±12 y Comparison (no treatment): n=138, 51% women, 71±12 y	Hb<13 g/dL for men and <12g/dL for women	None	Type: subcutaneous (Epoetin-α or -β) Dosis: 40.000 IU Frequency: 4 doses (one/week) Time points: one per week in the 3 preoperative weeks and one on the day of surgery	Type: oral (ferrofumerate) Dosis: 200 mg Frequency: thrice daily Duration: 3 preoperative weeks	No treatment

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Table 2 (*continued*)

Study	Design	Population (at baseline)			Intervention – ESA therapy	Intervention – iron therapy	Comparison
Author, year, country		Type of elective surgery – demographics (age, gender)	Definition anaemia	Definition iron-deficiency			
Urena, 2017, Canada [37]	RCT	Cardiac surgery Intervention (Epoetin-α + IV iron): n=48, 54% women, mean age 81±7 y Comparison (placebo): n=52, 48% women, mean age 81±7 years	Hb<13 g/dL for men and <12g/dL for women	Ferritin <30 µg/L	Type: subcutaneous (Darbepoetin-α; Aranesp) Dosis: 0.75 µg/kg Frequency: 2 doses Time points: preoperative day 10 (±4) and 1 (±1)	Type: IV (iron sucrose – Venofer) Dosis: 200 mg Frequency: 2 doses Time points: preoperative day 10 (±4) and 1 (±1)	Placebo (0.9% saline): same modalities as *Intervention – ESA therapy*
Weber, 2005, The Netherlands [38]	RCT	Orthopaedic surgery Intervention (Epoetin-α + oral iron): n=467, 89.9% women, mean age 67±11 y Comparison (standard of care): n=237, 89.5% women, mean age 66.7±10.8 y As our PICO specifically concerns patients who only receive allogeneic transfusion, and not autologous transfusion, only outcomes analysed in patients receiving allogeneic transfusions only were extracted.	None	None	Type: subcutaneous (Epoetin-α; Aranesp®/Erypro®) Dosis: 40.000 IU Frequency: 4 doses (one/week) Time points: one per week in the 3 preoperative weeks and one on the day of surgery	Type: oral Dosis: not specified Frequency: daily Time points: 3 preoperative weeks	Standard of care
Weltert, 2015, Italy [39]	RCT	Cardiac surgery Intervention (Epoetin-α + oral iron): n=300, 25% women, median age 75 y (range: 47–96) Comparison (Oral iron) n=300, 27% women, median age 74 y (range: 40–90) For the outcome of number of patients transfused, the authors provided data on the purely anaemic patients (baseline Hb levels <13 g/dl). Hence, 100% is anaemic (% of iron-deficient patients not reported).	Hb <13 g/dL	None	Type: subcutaneous (Epoetin-α; Eprex) Dosis: 80.000 IU Frequency: single dose Time points: preoperative day 2	Type: oral (Ferrolin) Dosis: 15 mL (equivalent to 40mg elemental iron) Frequency: daily Duration: from the day of admission	Oral iron: same modalities as *Intervention – iron therapy*
Yoo, 2011, South Korea [40]	RCT	Cardiac surgery Intervention (rHuEPO + IV iron): n=37, 65% women, mean age 56±12 y Comparison (standard of care): n=37, 62% women, mean age 59±12 y	Hb<13 g/dL for men and <12g/dL for women	Patients with iron deficiency anaemia were excluded from the study	Type: IV (rHuEPO; Epocain) Dosis: 500 IU/kg Frequency: single dose Time points: 16–24 h before surgery	Type: IV (iron sucrose – Venofer) Dosis: 200 mg Frequency: 1 dosis Time points: 16–24 h before surgery	Placebo (saline): same modalities as *Intervention – ESA therapy*

ESA, erythropoiesis-stimulating agent; RCT, Randomized Controlled Trial; Hb, Haemoglobin; IV, intravenous; RBC, Red Blood Cell; rHuEPO, recombinant human erythropoietin

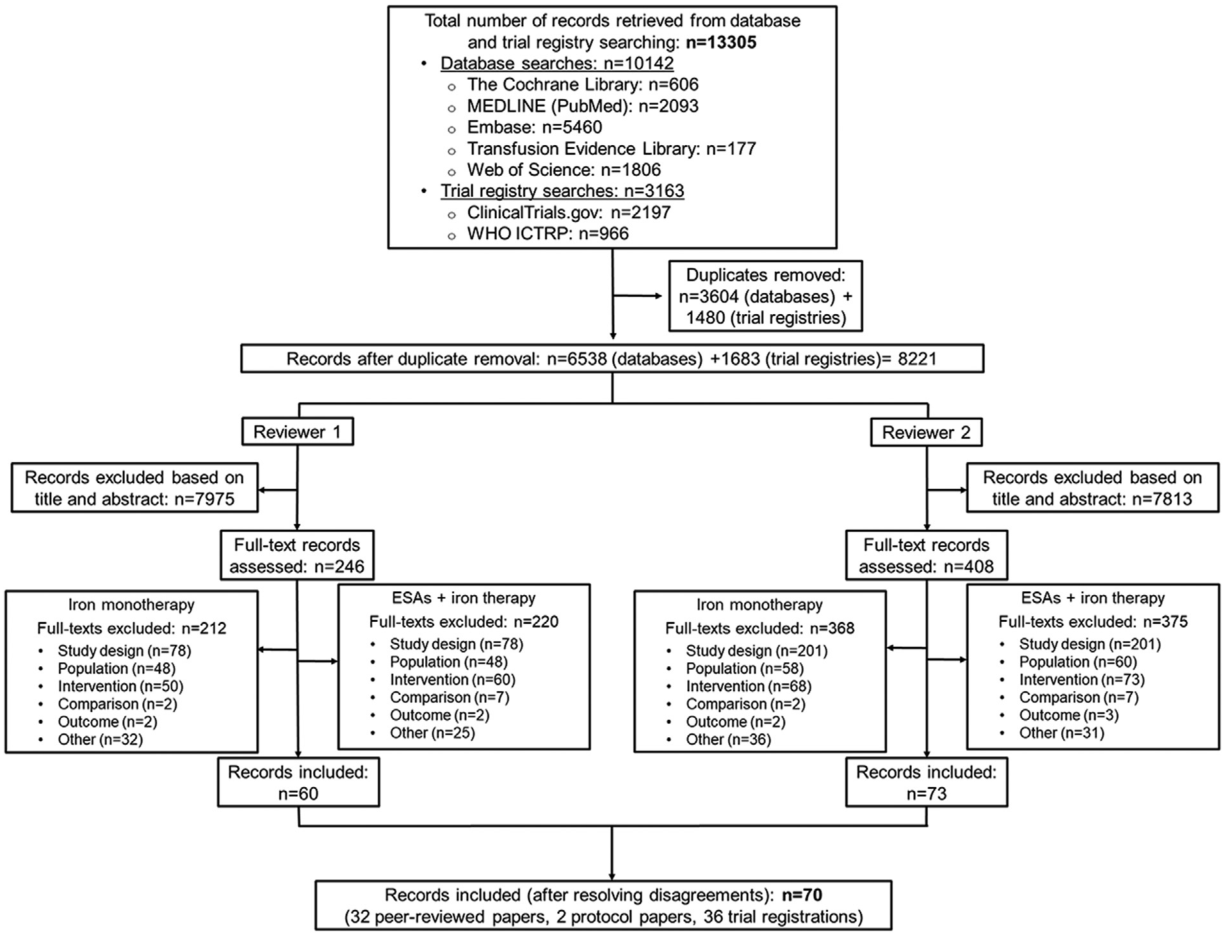

Fig. 1. Study identification and selection process of the systematic review.

12 studies [15–18,27,33–36,38,39,42,43] and 2 studies excluded patients with iron-deficiency [13,40].

Intra- and post-operative co-interventions (ie, interventions administered to both the intervention and comparison group) were reported in 12 studies: blood salvaging techniques or haemodilution in 6 studies [16,20,37,39,40,42], anti-thrombotic prophylaxis in 5 studies [16,18,36,37,42], folic acid in 2 studies [15,22], protamine sulphate in 1 study [37], tranexamic acid in 2 studies [40,42], and crystalloid and colloid infusion in 1 study[40]. The RBC transfusion trigger applied perioperatively was based on Hb levels (general threshold Hb <7–9 g/dL) and/or blood loss (eg, >15% of the intravascular volume or >300–400 mL), and/or the clinical condition of the patient (eg, underlying chronic diseases or comorbidities). Information about co-interventions or RBC transfusion triggers was not reported in 9 studies [13,17,27,28,31,33–35,38,43] and 4 studies [17,18,28,31], respectively.

Information on the included study protocols and trial registries can be found in **Appendix E**.

3.1.3. Risk of bias in included studies

3.1.3.3. Iron monotherapy. Three studies were at low risk of bias for all domains. [21,26,41] We scored five studies to have a low risk of bias for all but one or two domains, because no information was available for the following items: allocation concealment [25,29,30], and/or blinding of outcome assessment [14,19,25,29]. In one study, the outcome assessors were not blinded and no information was available on participant and personnel blinding. [23] The remaining items of this study were judged to be at low risk of bias. Finally, two studies had low risk of bias in only 3–4 domains [32,44]. In one study, it was unclear whether the randomization was performed appropriately, the outcome assessors were not blinded, and drop-out rates were higher in the intervention group compared to the control group[32]. In the second study, participants were not randomized and no information was provided concerning the allocation concealment, blinding of the outcome assessors and incomplete outcome data [44]. **Figs. 2A and 3A** provide an overview of the risk of bias across studies and domains, whereas detailed judgments per domain can be found for each included study in **Appendix F**.

3.1.3.4. Iron + ESA therapy. Two studies were at low risk of bias for all domains. [33,34,37] We scored three studies to have a low risk of bias for all but one domain, because personnel was not blinded for the intervention [36], no information was available whether the outcome assessors were blinded [40], or information regarding allocation concealment was lacking [42]. The majority of studies (n = 13, 68%) provided no information on at least 2 of the following domains: random sequence generation (selection bias, in 7 studies), allocation concealment (selection bias, in 11 studies), blinding of participants and personnel (performance bias, in 3 studies), blinding of outcome assessment (detection bias, in 13 studies), or incomplete outcome data (attrition bias, in 3 studies)[13,15–18,20,22,24,27,28,31,35,43]. One study was scored as having a high risk of performance bias, detection bias and attrition bias [38].

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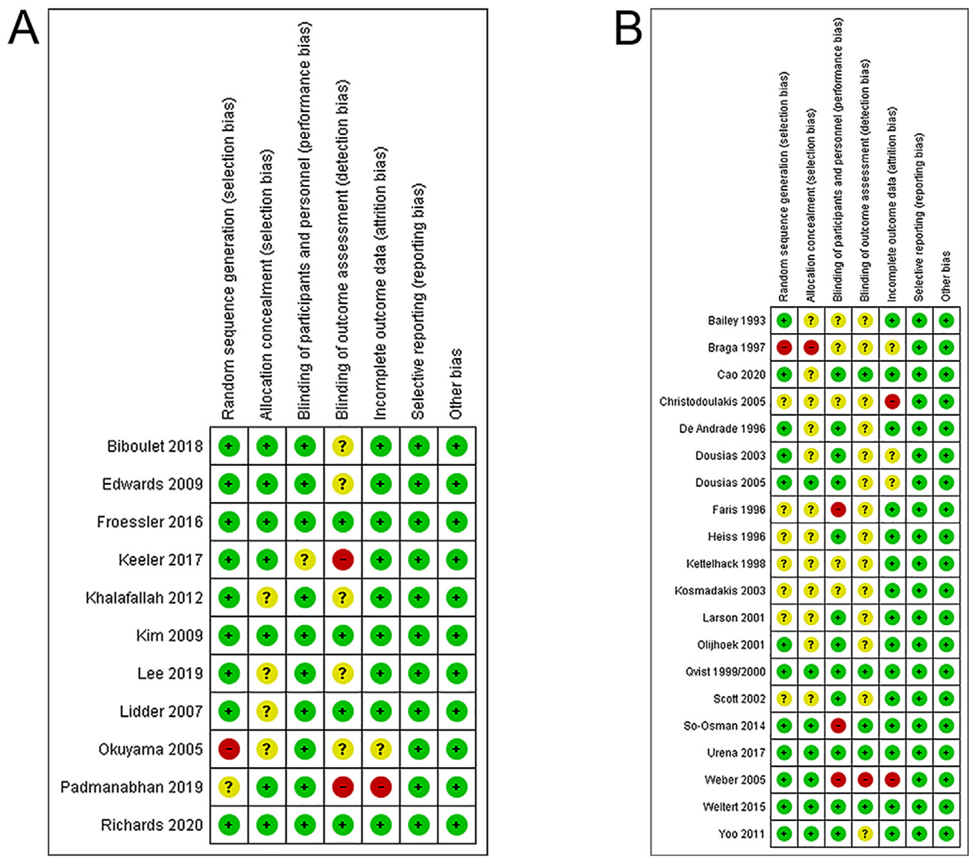

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study investigating the effectiveness of iron monotherapy (panel A) or the effectiveness of iron + ESA therapy (panel B) (green +, red - and yellow).

Figs. 2B and 3B provide an overview of the risk of bias across studies and domains, whereas detailed judgments per domain can be found for each included study in **Appendix G**.

3.1.4. Effects of interventions

Detailed Summary of Findings tables for the 4 comparisons can be found in **Appendices H, I, J, and K**.

4. Iron Monotherapy Versus Placebo, Usual Care or no Treatment (5 studies, 784 participants)

4.1. Primary Outcomes

4.1.1. Number of patients transfused

A difference in the number of patients transfused after IV iron administration, compared to placebo, standard of care or no treatment, could not be demonstrated (RR 0.65, 95% CI 0.31–1.35; P = 0.25; 3 studies [19,21,41]; low-certainty evidence). Similarly, a difference in the number of patients transfused after oral iron administration, compared to placebo, standard of care or no treatment, could not be demonstrated (RR 0.53, 95% CI 0.25–1.13; P = 0.10; 2 studies [30,44]; very low-certainty evidence) (Fig. 4). One of the 5 included studies, known as the PREVENTT trial, provided data on 3 additional outcomes which showed no statistical significant difference between preoperative IV iron administration and placebo: (1) the number of patients with ≥1 transfusion until 30 days post-surgery, excluding large blood transfusions (defined as ≥4 units of blood transfused in a single transfusion episode) (RR 1.03, 95% CI 0.77–1.38; P = 0.84; low-certainty evidence); (2) the number of patients with ≥1 transfusion until 6 months post-surgery, excluding large blood transfusions (RR 1.00, 95% CI 0.77–1.31; P = 0.98; low-certainty evidence); and (3) the number of transfusion episodes (MD 0.03, 95% CI -0.19–0.13; P = 0.72; low-certainty evidence) [41].

4.1.2. Number of units transfused

A difference in the number of RBC units transfused until 30 days and/or 6 months post-surgery after IV iron administration, compared to placebo, could not be demonstrated in the PREVENTT trial (30 days: MD -0.04, 95% CI -0.27–0.19; P = 0.74; 6 months: MD -0.15, 95% CI -0.49–0.19; P = 0.38). Two smaller studies found that significantly fewer units were transfused after administration of oral or IV iron monotherapy compared to usual care or placebo (median difference 1.5–2 units lower; P < 0.05; 2 studies) [19]. [30] [19, 30] The overall certainty of the evidence was considered as low.

4.1.3. Intraoperative transfusion volume

The intraoperative transfusion volume was increased after administration of oral iron therapy, compared to no treatment (MD 166 mL higher, 95% CI 101–231; P < 0.00001; 1 study; very low-certainty evidence)[44].

4.1.4. Summarized evidence conclusions

IV iron therapy may not result in a reduction in the number of patients transfused (low-certainty evidence). IV and/or oral iron therapy may not result in a reduction in the number of units transfused (low-certainty evidence). The evidence is very uncertain about the effect of oral iron therapy on the number of patients transfused and on the intraoperative transfusion volume (very low-certainty evidence).

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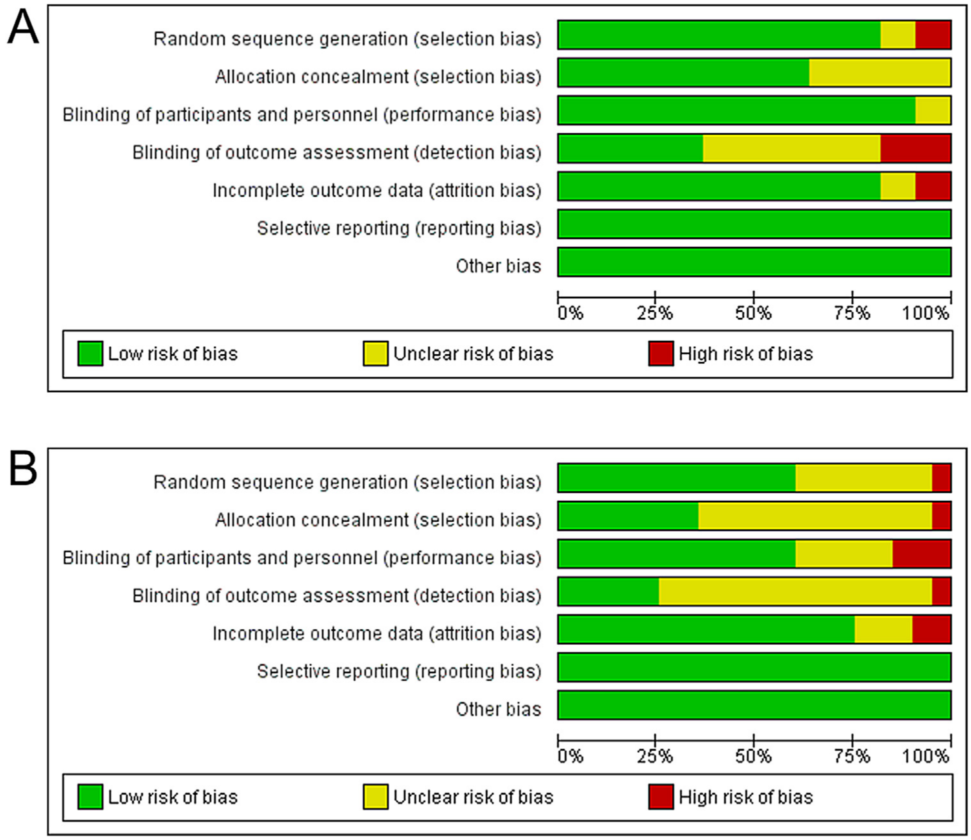

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies investigating the effectiveness of iron monotherapy (panel A) or the effectiveness of iron + ESA therapy (panel B).

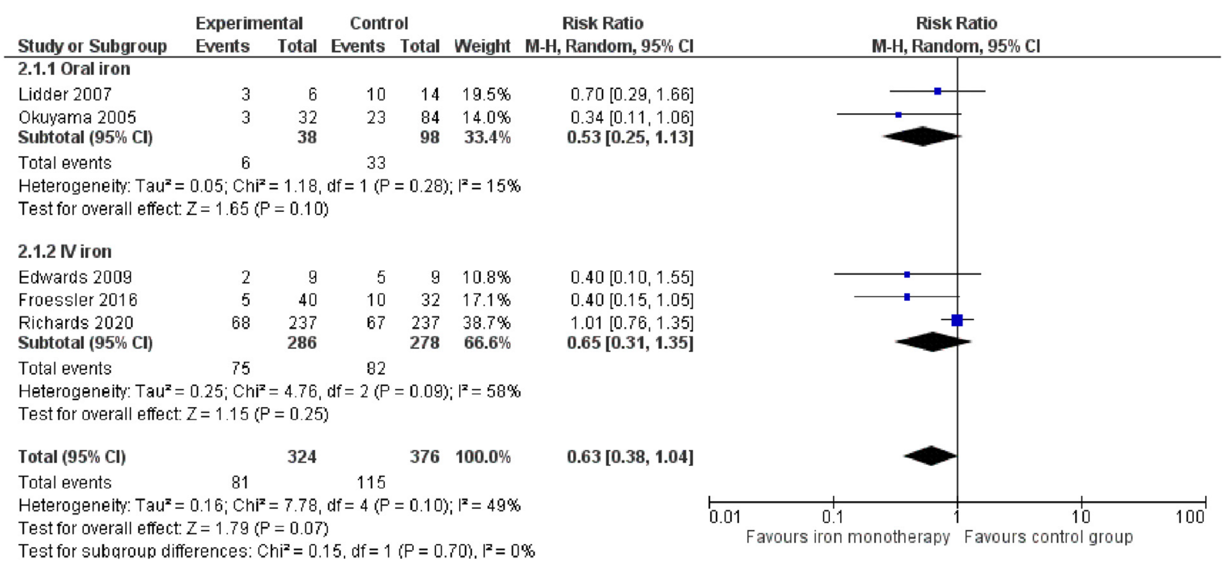

Fig. 4. Number of patients transfused: study-specific risk ratios (RRs) representing the effectiveness of iron supplementation versus control (placebo, usual care or no treatment). Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The two upper diamonds represent the pooled effect estimate (+95% CI) for the subgroups (oral iron and IV iron). The bottom diamond shows the pooled effect estimate (+95% CI) of the overall effect.

4.2. Secondary Outcomes

4.2.1. Preoperative/postoperative Hb levels

Oral or IV iron monotherapy tended to result in increased preoperative (change in) Hb levels, compared to placebo, usual care or no treatment (MD 0.54 g/dL, 95% CI 00.00–1.08; P = 0.05; 4 studies; moderate-certainty evidence) [19,21,41,44]. One study provided low-certainty evidence on the postoperative Hb levels, showing no statistically significant difference between IV iron administration and placebo at 4 different time points: (1) postoperative days 2–3: MD 0.20 g/dL, 95% CI -0.05–0.45; P = 0.12); (2) postoperative days 4–5: MD 0.10 g/dL, 95% CI -0.11–0.31; P = 0.36);

(3) postoperative days 6–7: MD 0.20 g/dL, 95% CI -0.12–0.52; $P = 0.22$); and (4) postoperative day 14: MD 0.40 g/dL, 95% CI -0.09–0.89; $P = 0.11$)[41]. In a smaller second study, a difference in postoperative Hb levels at hospital discharge after IV iron administration, compared to placebo, could not be demonstrated (MD -1.1 g/dL, 95% CI -2.85–0.65; $P = 0.24$; low-certainty evidence) [19], whereas a third study showed that the postoperative Hb levels from hospital discharge until 4 weeks post-surgery were significantly increased (MD 1 g/dL, 95% CI 0.31–1.69; $P = 0.006$; low-certainty evidence)[21]. At postoperative week 8 and month 6, Hb levels were found to be statistically significantly higher after IV iron administration, compared to placebo (week 8: MD 1.10 g/dL, 95% CI 0.81–1.39, $P < 0.00001$; 6-months: MD 0.80 g/dL, 95% CI 0.44–1.16, $P < 0.00001$; both low-certainty evidence)[41].

4.2.2. Preoperative/postoperative Hct levels

After oral iron therapy, preoperative Hct levels were increased, compared to no treatment (MD 3.5%, 95% 2.0–5.0; $P < 0.00001$; 1 study [44]; very low-certainty evidence), whereas a difference in preoperative Hct levels after IV iron administration, compared to placebo, could not be demonstrated (MD 2% lower; $P > 0.05$; 1 study [19]; low-certainty evidence). A difference in postoperative Hct at hospital discharge could not be demonstrated after IV iron administration, compared to placebo (MD 3% lower, $P > 0.05$; 1 study; low-certainty evidence)[19].

4.2.3. Preoperative/postoperative ferritin levels

A statistically significant difference in preoperative and postoperative ferritin levels after IV iron administration, compared to placebo, could not be demonstrated (preoperative levels: MD 46.8 µg/L higher, $P > 0.05$; postoperative levels: MD 80.5 µg/L lower, $P > 0.05$; both low-certainty evidence)[19].

4.2.4. Length of ICU stay and length of hospital stay

A statistically significant difference in length of ICU or hospital stay after IV iron administration, compared to placebo, could not be demonstrated (ICU stay: median difference 1 day longer; hospital stay: median difference of 0 day; $P > 0.05$; 1 study) [41].

One other smaller study found that the length of hospital stay was reduced after IV iron administration, compared to usual care (median difference 3 days fewer; $P = 0.05$; 1 study [21]. The overall certainty of evidence was considered as low.

4.2.5. Summarized evidence conclusions

Preoperative IV and/or oral iron therapy probably results in an increase in preoperative (change in) Hb levels (moderate-certainty evidence). Preoperative IV iron therapy may not increase postoperative Hb levels in the first two weeks after surgery (low-certainty evidence), but may result in an increase in postoperative change in Hb levels at the longer-term (ie, until 4 weeks, 8 weeks or 6 months after surgery) (low-certainty evidence).

IV iron therapy may result in no difference in preoperative and postoperative Hct levels (low-certainty evidence). The evidence is very uncertain about the effect of oral iron therapy on preoperative Hct levels (very low-certainty evidence). IV iron therapy may not result in increased preoperative and postoperative ferritin levels (low-certainty evidence). IV iron therapy may not reduce the length of ICU or hospital stay (low-certainty evidence).

5. Intravenous Versus Oral Iron Therapy (5 studies, 380 participants)

5.1. Primary Outcomes

5.1.1. Number of patients transfused

A difference in the number of patients transfused after IV iron administration, compared to oral iron administration, could not be demonstrated (RR 1.05, 95% CI 0.69–1.59; $P = 0.83$; 4 studies; very low-certainty evidence) (Fig. 5) [23,25,32].

A difference in the number of patients requiring transfusion of multiple (2–3) units after administration of IV iron (+ Epoetin-α), compared to oral iron (+ Epoetin-α), could not be demonstrated (RR 0.34, 95%CI 0.04 to 3.16; $P = 0.34$; low-certainty evidence) [14].

5.1.2. Number of units transfused

Meta-analysis showed that the number of units transfused was not statistically significantly different after administration of IV iron compared to oral iron therapy (MD -0.35, 95%CI -1.10–0.40; $P = 0.36$; 2 studies) (Fig. 6) [23,25]. One additional study that was not included in the meta-analysis also found no statistically significant difference between IV iron therapy and oral iron therapy (median difference 0.5 units higher; $P = 0.16$) [32]. The overall certainty in these effect estimates was considered as low.

5.1.3. Summarized evidence conclusions

We are uncertain whether the administration route of iron monotherapy (IV vs oral) differentially affects the number of patients transfused (very low-certainty evidence). Compared to oral iron therapy, IV iron therapy may not result in a reduction in the number of units transfused or in the number of patients requiring multiple transfusions (low-certainty evidence).

5.2. Secondary Outcomes

5.2.1. Preoperative/postoperative Hb levels

IV iron therapy resulted in increased preoperative (change in) Hb levels, compared to oral iron therapy (MD 1.59 g/dL, 95% CI 0.42–2.77; $P = 0.008$; 2 studies). [25,26] Two additional studies, reporting medians, showed a similar effect (median difference 0.70–1.05 g/dL higher; $P < 0.001$) [14,23]. However, these findings were not corroborated by another study in patients receiving IV iron therapy, also reporting medians, where a difference in preoperative Hb levels could not be demonstrated, compared to oral iron therapy (median difference 0.2 g/dL lower, $P = 0.42$) [32]. The overall certainty in these effect estimates (ie preoperative (change) in Hb levels) was considered as low.

No statistically significant difference in Hb levels at postoperative day 2 was found after IV iron therapy, compared to oral iron therapy (MD 0.49 g/dL, 95% CI -0.34–1.32; $P = 0.25$; 1 study; low-certainty evidence) [25]. However, the same study found a statistically significant increase in postoperative Hb levels at postoperative week 6 (MD 1.2 g/dL, 95% CI 0.33–2.05; $P = 0.01$; 1 study; low-certainty evidence)[25].

5.2.2. Preoperative Hct levels

Higher preoperative Hct levels were observed after IV iron therapy (+ Epoetin-α), compared to oral iron therapy (+ Epoetin-α) (preoperative: median difference 1.6% higher, $P = 0.04$; 1 study; low-certainty evidence) [14].

5.2.3. Preoperative ferritin levels

IV iron therapy resulted in increased preoperative ferritin levels, compared to oral iron therapy: median difference 307 µg/L higher, $P < 0.001$, 1 study) [32]; median difference 530 µg/L higher, $P < 0.001$, 1 study) [23]; median difference 257 µg/L higher, 95% CI 199–315, $P < 0.001$, 1 study [14]. A difference in preoperative ferritin levels after IV iron therapy, compared to oral iron therapy, could not be demonstrated in one study (MD 166 µg/L higher, 95% CI -22–354; $P = 0.08$; 1 study) [26]. The overall certainty in these effect estimates (ie, preoperative (change) in ferritin levels) was considered as low.

Please cite this article as: H. Van Remoortel, J. Laermans, B. Avau et al., Effectiveness of Iron Supplementation With or Without Erythropoiesis-Stimulating Agents on Red Blood Cell Utilization in Patients With Preoperative Anaemia Undergoing Elective Surgery: A Systematic Review and Meta-Analysis, Transfusion Medicine Reviews, https://doi.org/10.1016/j.tmrv.2021.03.004

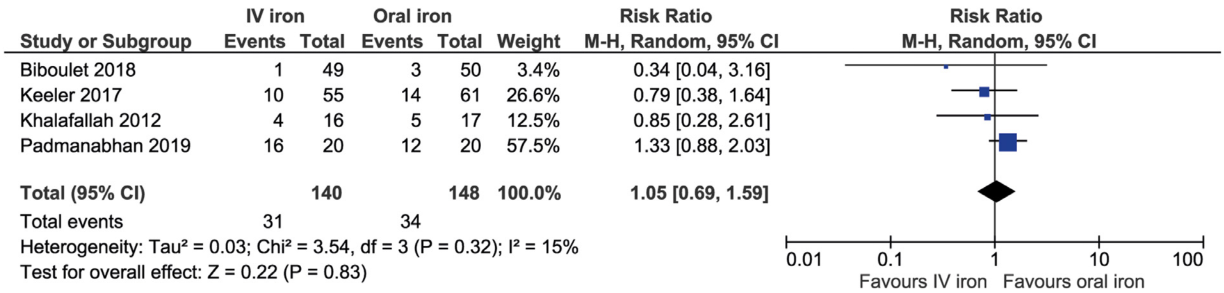

Fig. 5. Number of patients transfused: study-specific risk ratios (RRs) representing the effectiveness of IV iron versus oral iron therapy. Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The diamond represents the pooled effect estimate (+95% CI).

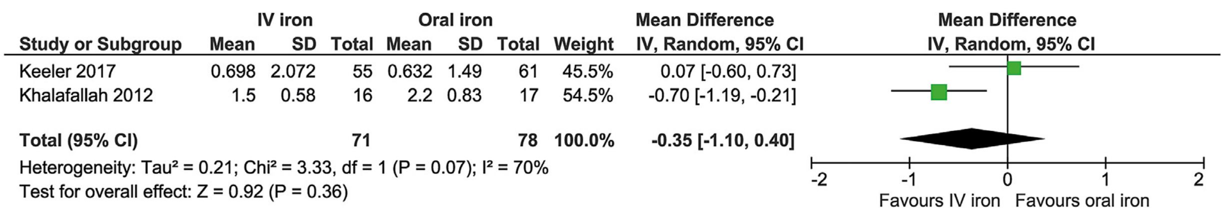

Fig. 6. Number of units transfused: study-specific mean differences (MDs) representing the effectiveness of IV iron versus oral iron therapy. Each dot represents the MD of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The diamond represents the pooled effect estimate (+95% CI).

5.2.4. Length of hospital stay – postoperative stay – ICU stay

A difference in hospital stay in patients receiving IV iron therapy could not be demonstrated ((MD -1.76 days, 95% CI -3.88–0.36; $P = 0.12$; 1 study; very low-certainty) [25], (median difference 2 days fewer; $P = 0.71$; 1 study; very low-certainty evidence) [32]. One additional study found no difference in postoperative stay between IV and oral iron therapy (median difference 0 days; $P = 0.95$; 1 study; very low-certainty evidence) [23]. Finally, patients receiving IV iron therapy tended to have a prolonged stay at the ICU (median difference 19 days more; $P = 0.05$; 1 study; very low-certainty evidence) [32].

5.2.5. Summarized evidence conclusions

Compared to oral iron monotherapy, IV iron monotherapy may result in increased preoperative Hb levels, increased preoperative Hct levels and increased preoperative ferritin levels (all low-certainty evidence). Preoperative IV iron monotherapy may not result in increased postoperative Hb levels at 48 hours, whereas it may result in increased postoperative Hb levels at 6 weeks (low-certainty evidence).

We are uncertain whether administration route of iron (IV versus oral) differentially affects the lengths of ICU stay, postoperative stay and hospital stay (all very low-certainty evidence).

6. Intravenous Ferric Carboxymaltose Versus Intravenous Iron Sucrose Monotherapy (1 study, 101 participants)

6.1. Primary Outcomes

6.1.1. Number of patients transfused

A difference in number of patients transfused between IV ferric carboxymaltose and IV iron sucrose could not be demonstrated (no patients transfused in both groups, RR not estimable; 1 study; low-certainty evidence) [29].

6.1.2. Summarized evidence conclusion

IV ferric carboxymaltose monotherapy may not result in a difference in the number of patients transfused compared to IV iron sucrose monotherapy (low-certainty evidence).

6.2. Secondary Outcomes

6.2.1. Hb levels 2 weeks after the first treatment administration

A difference in Hb levels 2 weeks after the first treatment administration in the IV ferric carboxymaltose group, compared to the IV iron sucrose group, could not be demonstrated (MD 0.3 g/dL, 95% CI -0.09–0.69; $P = 0.14$; 1 study; low-certainty evidence)[29].

6.2.2. Summarized evidence conclusion

IV ferric carboxymaltose monotherapy may not result in a difference in Hb levels 2 weeks after the first treatment administration, compared to IV iron sucrose therapy (low-certainty evidence).

7. Iron + ESA Therapy Versus Placebo, Usual Care (Oral/IV Iron) or no Treatment (20 studies, 2151 participants)

7.1. Primary Outcomes

7.1.1. Number of patients transfused

There was a reduction in the number of patients transfused after iron with ESA therapy as compared to placebo and/or oral/IV iron or no treatment (ESAs + oral iron: RR 0.55, 95% CI 0.41–0.74, $P < 0.0001$, 14 studies, moderate-certainty evidence [13,15–18,20,22,24,28,33–36,38,39,42]; ESAs + IV iron: RR 0.67, 95% CI 0.49–0.92, $P = 0.01$, 5 studies, low-certainty evidence [27,37,40,43] (Fig. 7). The asymmetrical appearance of the funnel plot of the effect estimates indicated a potential risk of bias due to missing results, ie, smaller studies without statistically significant effects may have been remained unpublished, which could lead to overestimation of this overall effect estimate (Fig. 8). However, the Egger regression test was not significant ($P = 0.71$) and the Duval & Tweedie's trim-and-fill procedure resulted in no significant difference between the calculated overall pooled RR (RR = 0.57) and the trimmed pooled RR (RR = 0.59). Therefore, no further downgrading for publication bias was considered.

Two studies reported both intra-operative and post-operative transfusion data. [15,27] The intra-operative transfusion data were included in the meta-analysis (Fig. 7), the number of patients transfused postoperatively were not included in this meta-analysis

Study or Subgroup	ESA+iron Events	ESA+iron Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 ESA + oral iron						
Bailey 1993	7	12	11	11	7.0%	0.60 [0.37, 0.97]
Christodoulakis 2005 (150/300 IU/kg - periop)	59	136	36	68	8.4%	0.82 [0.61, 1.10]
De Andrade 1996 (100/300 IU/kg)	11	57	13	26	5.7%	0.39 [0.20, 0.74]
Dousias 2003	0	23	5	27	0.7%	0.11 [0.01, 1.82]
Dousias 2005	0	20	3	18	0.7%	0.13 [0.01, 2.34]
Faris 1996 (100/300 IU/kg)	12	45	21	27	6.7%	0.34 [0.20, 0.58]
Heiss 1996	9	17	4	10	4.3%	1.32 [0.55, 3.20]
Kettelhack 1998	16	48	15	54	6.2%	1.20 [0.67, 2.16]
Larson 2001	0	15	1	16	0.6%	0.35 [0.02, 8.08]
Qvist 1999/2000	13	38	23	43	6.7%	0.64 [0.38, 1.08]
Scott 2002	19	29	24	29	8.3%	0.79 [0.58, 1.08]
So-Osman 2014	13	125	32	138	6.1%	0.45 [0.25, 0.82]
Weber 2005	41	450	87	235	8.1%	0.25 [0.18, 0.34]
Weltert 2015	64	249	135	240	8.8%	0.46 [0.36, 0.58]
Subtotal (95% CI)		**1264**		**942**	**78.1%**	**0.55 [0.41, 0.74]**
Total events	264		410			
Heterogeneity: Tau² = 0.19; Chi² = 57.31, df = 13 (P < 0.00001); I² = 77%						
Test for overall effect: Z = 4.00 (P < 0.0001)						
1.1.2 ESA + IV iron						
Braga 1997	1	10	5	10	1.3%	0.20 [0.03, 1.42]
Cao 2020	0	35	1	32	0.6%	0.31 [0.01, 7.24]
Kosmadakis 2003 (intraop)	9	31	19	32	5.9%	0.49 [0.26, 0.91]
Urena 2017	13	48	13	52	5.6%	1.08 [0.56, 2.10]
Yoo 2011	22	37	32	37	8.4%	0.69 [0.51, 0.92]
Subtotal (95% CI)		**161**		**163**	**21.9%**	**0.67 [0.49, 0.92]**
Total events	45		70			
Heterogeneity: Tau² = 0.02; Chi² = 4.77, df = 4 (P = 0.31); I² = 16%						
Test for overall effect: Z = 2.45 (P = 0.01)						
Total (95% CI)		**1425**		**1105**	**100.0%**	**0.57 [0.44, 0.72]**
Total events	309		480			
Heterogeneity: Tau² = 0.16; Chi² = 65.25, df = 18 (P < 0.00001); I² = 72%						
Test for overall effect: Z = 4.56 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%						

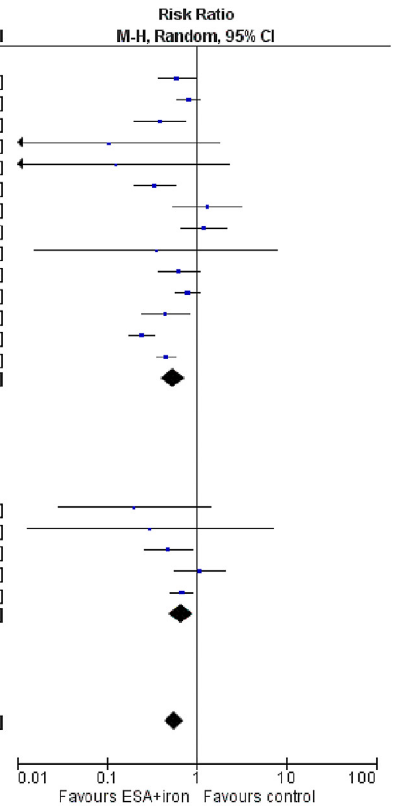

Fig. 7. Number of patients transfused: study-specific risk ratios (RRs) representing the effectiveness of ESAs in addition to oral or IV iron supplementation versus control (placebo and/or oral/IV iron or no treatment). Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The two upper diamonds represent the pooled effect estimate (+95% CI) for the subgroups (ESAs + oral iron and ESAs + IV iron). The bottom diamond shows the pooled effect estimate (+95% CI) of the overall effect.

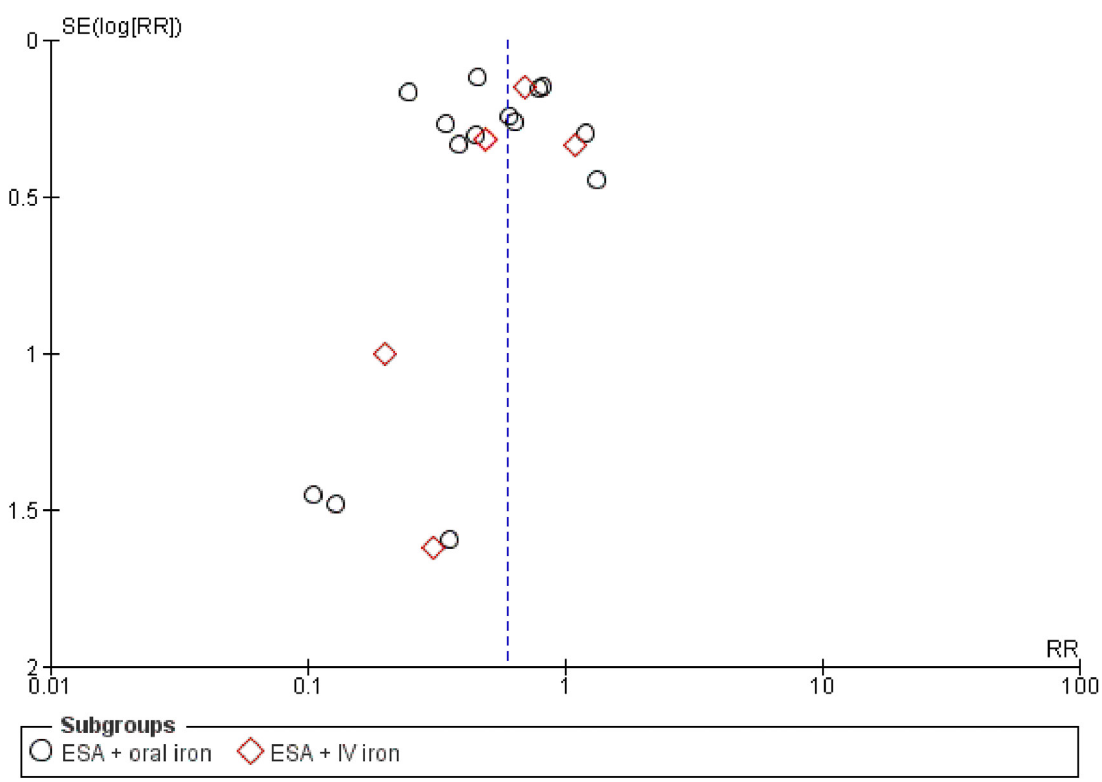

Fig. 8. Funnel plot of the effect estimates (RR: risk ratios) against their standard errors (SE) for the studies included in the meta-analysis on the number of patients transfused in response to iron + ESA therapy versus placebo, usual care (oral/IV iron) or no treatment.

Study or Subgroup	ESA + oral iron Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Braga 1997	0.2	0.63	10	1.3	1.49	10	6.9%	-1.10 [-2.10, -0.10]
Christodoulakis 2005 (150/300 IU/kg - periop)	1	1.356	136	1.34	1.59	68	15.8%	-0.34 [-0.78, 0.10]
De Andrade 1996 (100/300 IU/kg)	0.44	1.086	57	1.14	1.432	29	12.6%	-0.70 [-1.29, -0.11]
Heiss 1996	1.82	0.8	17	1.8	0.97	10	10.6%	0.02 [-0.69, 0.73]
Scott 2002	2.07	2.76	29	3.41	3.04	29	3.8%	-1.34 [-2.83, 0.15]
So-Osman 2014	0.25	0.9	125	0.64	1.6	138	18.6%	-0.39 [-0.70, -0.08]
Weltert 2015	1.21	0.358	249	1.81	0.597	240	22.3%	-0.60 [-0.69, -0.51]
Yoo 2011	1	1.1	37	3.3	2.2	37	9.4%	-2.30 [-3.09, -1.51]
Total (95% CI)			**660**			**561**	**100.0%**	**-0.69 [-1.01, -0.37]**

Heterogeneity: Tau² = 0.12; Chi² = 25.67, df = 7 (P = 0.0006); I² = 73%
Test for overall effect: Z = 4.26 (P < 0.0001)

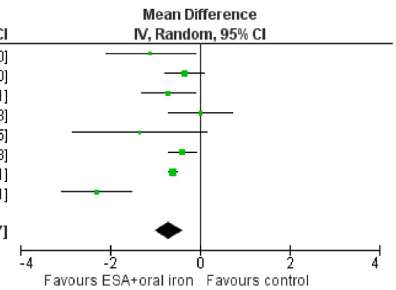

Fig. 9. Number of units transfused: study-specific risk ratios (RRs) representing the effectiveness of ESAs in addition to oral iron supplementation versus control (placebo and/or oral iron or no treatment). Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The diamond represents the pooled effect estimate (+95% CI).

but reported separately (oral iron + ESA: RR 0.83, 95% CI 0.62−1.12, $P = 0.22$ [15]; IV iron + ESA: RR 0.11, 95% CI 0.01−0.85, $P = 0.03$ [27]).

A difference in number of patients requiring transfusion of multiple (at least 2) RBC units after oral and/or IV iron administrations + ESAs, compared to placebo (+ oral iron), could not be demonstrated (RR 0.57, 95% CI 0.21−1.57; $P = 0.28$; 4 studies; very-low certainty evidence) [16,22,24,40].

7.1.2. Number of units transfused

A meta-analysis of 8 studies showed that fewer RBC units were transfused after administration of oral iron + ESA therapy compared to placebo and/or oral iron or no treatment (MD -0.69, 95% CI -1.01−-0.37, $P < 0.0001$; moderate-certainty evidence) (Fig. 9). [15,16,22,33−36,39,43] One study reported both intra-operative and postoperative transfusion data [15]. The intra-operative transfusion data were included in the meta-analysis (Fig. 9), the number of units transfused postoperatively were not included in this meta-analysis but reported separately (oral iron + ESAs: MD -0.36, 95% CI -0.80−0.08, $P = 0.08$) [15]. One additional study found that fewer units were transfused after administration of oral iron + ESA therapy (MD -1.3 [range 0−3), $P < 0.05$)] [33,34].

Pooled data from 2 studies found that fewer units were transfused in transfused patients after iron + ESA therapy (MD: -1.79, 95% CI -2.78−-0.8, $P = 0.004$, moderate-certainty evidence) [35,40]. In one additional study, a difference in the number of units transfused in transfused patients could not be demonstrated (median difference 1 unit lower, $P = 0.99$) [37].

7.1.3. Summarized evidence conclusions

The use of oral iron + ESA therapy probably results in a reduction in the number of patients transfused, the number of units transfused, and the number of units transfused in transfused patients (all moderate-certainty evidence). IV iron + ESA therapy may result in a reduction in the number of patients transfused (low-certainty evidence). We are uncertain about the effect of oral and/or IV iron + ESA therapy on the number of patients requiring transfusion of multiple (at least 2) RBC units (very low-certainty evidence).

7.2. Secondary outcomes

7.2.1. Preoperative/postoperative Hb levels

Oral and/or IV iron + ESA therapy resulted in increased preoperative (change in) Hb levels, compared to placebo and/or oral/IV iron (MD 0.79 g/dL, 95% CI 0.30−1.27, $P < 0.0001$, 8 studies) [17,18,28,31, 35,37,40,42]. Four additional studies, not included in this meta-analysis, showed increased preoperative Hb levels during oral and/or IV iron + ESA therapy (MD 0.61−1.20 g/dL, $P < 0.004$ in 1 study [15], $P > 0.05$ in 1 study [27]; median difference 0.30−0.97 g/dL, $P < 0.05$ in 1 study [33,34], $P = 0.28$ in 1 study [22]). The overall certainty in these effect estimates (ie, preoperative (change) in Hb levels) was considered as low.

Patients receiving IV iron + ESA therapy experienced significantly lower Hb drops on postoperative day 1 and day 5, compared to patients receiving IV iron only (day 1: MD -0.53 g/dL, 95% CI -0.95−-0.11, $P = 0.01$, low-certainty evidence; day 5: MD -0.77 g/dL, 95% CI -1.2 −-0.34, $P = 0.0004$, low-certainty evidence) [42]. A meta-analysis of 2 studies showed no difference in postoperative (change in) Hb levels on post-operative days 3−4 after preoperative IV iron + ESA administration (MD -0.13 g/dL, 95% CI -0.96−0.71, $P = 0.77$, very-low certainty evidence)[40,42]. On the contrary, four studies investigating the effectiveness of preoperative oral iron + ESA therapy found higher Hb levels on postoperative days 3-4 days, compared to oral iron only and/or placebo (MD 1.20 g/dL, 95% CI 0.87− 1.52, $P < 0.00001$, 3 studies [17, 18, 39]; median difference 0.8 g/dL, $P = 0.01$, 1 study [33, 34], moderate-certainty evidence).

Significantly higher postoperative Hb levels were also found 10−14 days after surgery in patients treated with oral iron + ESAs (MD 0.94 g/dL, 95% CI 0.10−1.78, p = 0.03, 3 studies [17,18,28], very low-certainty evidence) and at hospital discharge (MD 1.00 g/dL, 95% CI 0.69−1.31, $P < 0.00001$, 1 study [22]; median difference 0.97 g/dL, $P < 0.002$, 1 study [33,34], low-certainty evidence). One additional study found that postoperative Hb levels at hospital discharge after IV iron + ESAs administration were not significantly different compared to placebo (MD -0.1 g/dL, 95% CI -0.53−0.33, $P = 0.65$, 1 study [37]).

7.2.2. Preoperative/postoperative Hct levels

A difference in preoperative (change in) Hct after oral and/or IV iron + ESA therapy, compared to placebo and/or oral/IV iron, could not be demonstrated in 3 studies (MD 0.75 %, 95% CI -2.45 to 3.96, p = 0.64, 2 studies [35, 42]; MD 2.00 %, 95% CI -0.82 to 4.82, p = 0.16, 1 study [28]; all low-certainty evidence). One additional study reported that the preoperative change in Hct levels was not statistically significant, without providing the specific effect estimate. [27] Two other studies found statistically significantly increased preoperative Hct levels after oral/IV iron + ESA therapy (MD 1.93 %, $P < 0.005$, 1 study [15]; MD 3.5−4.5 %, $P = 0.0001$, 1 study [31]; both low-certainty evidence).

One study found significantly higher Hct levels on postoperative days 1, 3 and 5 in patients treated with preoperative IV iron + ESAs, compared to IV iron only (day 1: MD 1.55%, 95% CI 0.46−2.64, $P = 0.0061$; day 3: MD 1.92%, 95% CI 0.68−3.16, $P = 0.0033$; day 3: MD 2.63%, 95% CI 1.14−4.12, $P = 0.0009$). [42]

Another study showed that Hct was increased after IV iron + ESA administration at hospital discharge (MD 3.00%, $P = 0.0001$) [27], whereas a third one found no difference 14 days after surgery after oral iron + ESA administration (MD 0.00%, 95% CI -2.25−2.25, P = 1.00). [28] The overall certainty of the evidence on postoperative Hct levels was rated as low.

Please cite this article as: H. Van Remoortel, J. Laermans, B. Avau et al., Effectiveness of Iron Supplementation With or Without Erythropoiesis-Stimulating Agents on Red Blood Cell Utilization in Patients With Preoperative Anaemia Undergoing Elective Surgery: A Systematic Review and Meta-Analysis, Transfusion Medicine Reviews, https://doi.org/10.1016/j.tmrv.2021.03.004

7.2.3. Preoperative/postoperative reticulocyte count

A higher preoperative reticulocyte count was present after oral/IV iron + ESA therapy, compared to placebo and/or oral/IV iron (MD 2.9%, 95% CI 1.68–4.12, $P < 0.00001$, 1 study [17]; MD 10.18/1000 erythrocytes, $P < 0.001$, 1 study [33,34]; MD 101.84 × 10^3/mm^3, 95% CI 74.73–127.95, $P < 0.00001$, 1 study [35]; MD 9 × 103/µL, 95% CI 2.84–15.16, $P = 0.005$, 1 study [40]; median difference 7.6–8.5%, $P = 0.03$, 2 studies [22, 24]; MD 1.96–2.86%, $P = 0.0001$, 1 study [31]; low-certainty evidence).

Postoperative reticulocyte count was increased after receiving oral/IV iron + ESA therapy at the following time points:

- Postoperative day 1: MD 21.70 × 10^{12}/µL, 95% CI 9.30–34.10, $P = 0.0013$, 1 study [42];
- Postoperative days 3–4: MD 2.95%, 95% CI 2.75–3.15, $P < 0.00001$, 1 study [17]; MD 24 × 10^3/µL, 95% CI 11.91 to 36.09, $P = 0.0002$, 1 study [40]; MD 37.51 × 10^{12}/µL, 95% CI 22.85–52.17, $P < 0.00001$, 1 study [42];
- Postoperative day 5: MD 64.48 × 10^{12}/µL, 95% CI 46.99–81.97, $P < 0.00001$, 1 study [42];
- Hospital discharge (MD 6.7%, $P = 0.0001$, 1 study [27]);
- Postoperative days 10-14 (MD 1.94%, 95% CI 1.79–2.09, $P < 0.00001$, 1 study [17]).

The overall certainty of evidence on the effect on postoperative reticulocyte count was rated as low.

7.2.4. Preoperative/postoperative ferritin levels

Preoperative and postoperative ferritin levels were lower after oral and/or IV iron + ESA administration, compared to placebo and/or oral/IV iron (preoperative ferritin levels: MD -32.3 ng/mL, 95% CI -49.9–-14.69, $P = 0.003$, 4 studies [17,18,28,31], low-certainty evidence; postoperative ferritin levels at day 3-4: MD -27.22 ng/mL, 95% CI -31.46–-22.98, $P < 0.0001$, 2 studies [17,18] and MD -0.25 ng/mL, $P > 0.05$, 1 study [40], very-low certainty evidence; postoperative ferritin levels at hospital discharge: -5 mg/dL, $P = 0.90$, 1 study [27], and median difference -38 µg/L, $P > 0.05$, 1 study [33, 34], low-certainty evidence; postoperative ferritin levels at day 14: MD -18.28 ng/mL, 95% CI -30.12–-6.45, $P = 0.002$, 3 studies [17,18,28], very low-certainty evidence).

7.2.5. Length of ICU stay, hospital stay, postoperative hospitalization

Patients receiving IV iron + ESAs tended to stay fewer days at the intensive care unit, compared to the placebo group (MD -16.4 hours, 95% CI -33.67–0.87, $P = 0.06$, 1 study [40], low-certainty evidence).

A reduced length of hospital stay was observed in patients that received oral/IV iron + ESAs, compared to placebo and/or oral/IV iron (MD -2.98 days, 95% CI -3.33–-2.62, $P < 0.00001$, 3 studies [27,28,40], and MD -0.4 days, $P > 0.05$, 1 study [33, 34]; low-certainty evidence).

A difference in the period of postoperative hospitalization after oral iron + ESAs, compared to placebo + oral iron, could not be demonstrated (MD -0.68 days, 95% CI -1.66–0.3, p = 0.17, 2 studies [17,18]; low-certainty evidence).

7.2.6. Summarized evidence conclusions

<u>Oral/IV iron</u> ± <u>ESA therapy</u> may result in (all low-certainty evidence):

- increased (change in) preoperative Hb levels and reticulocyte counts
- increased postoperative Hb levels at hospital discharge
- increased postoperative reticulocyte counts at day 3–4
- reduced preoperative ferritin levels
- a reduced length of hospital stay

Oral/IV iron + ESA therapy may not result in result in increased (changes in) preoperative Hct levels, nor in changes in postoperative ferritin levels at hospital discharge (both low-certainty evidence). We are uncertain about the effect of oral/IV iron + ESA therapy on postoperative ferritin levels at day 3–4 (very low-certainty evidence).

<u>IV iron</u> ± <u>ESA therapy</u> may result in (all low-certainty evidence):

- reduced postoperative Hb level drops at day 1 and day 5
- increased postoperative Hct levels at day 1, 3, 5, and at hospital discharge
- increased postoperative reticulocyte counts at day 1, 5, and at hospital discharge

We are uncertain about the effect of IV iron + ESA therapy on postoperative Hb levels at day 3–4 and on length of stay in the intensive care unit (very low-certainty evidence).

<u>Oral iron</u> ± <u>ESA therapy</u>:

- probably results in increased postoperative Hb levels at day 3–4 (moderate-certainty evidence)
- may result in increased postoperative reticulocyte counts at day 10–14 (low-certainty evidence)
- may not result in increased postoperative Hct levels at day 14 (low-certainty evidence)
- may not result in a shorter period of postoperative hospitalization (low-certainty evidence)

We are uncertain about the effect of oral iron + ESA therapy on postoperative Hb levels at day 10-14 and on postoperative ferritin levels at day 14 (very low-certainty evidence).

8. Discussion

8.1. Summarized Findings

The present systematic review identified 29 RCTs and 2 non-RCTs comparing the absolute or relative effectiveness of preoperative oral and/or IV iron therapy with or without ESAs in adult patients with anaemia regardless of its etiology, scheduled for elective surgery. It was shown that:

- Iron monotherapy may not result in a reduced number of units transfused (low-certainty evidence);
- IV iron monotherapy may not result in a reduced number of patients transfused (low-certainty evidence);
- It is uncertain how oral iron monotherapy affects the number of patients transfused and the intraoperative transfusion volume (very low-certainty evidence);
- It is uncertain whether the administration route of iron therapy (IV versus oral) differentially affects the number of patients transfused (very low-certainty evidence);
- Compared to oral iron therapy, IV iron may not result in a reduction in the number of units transfused or in the number of patients requiring multiple transfusions (low-certainty evidence);
- IV ferric carboxymaltose monotherapy may not result in a difference in number of patients transfused compared to IV iron sucrose monotherapy (low-certainty evidence);
- Oral iron + ESAs therapy probably results in a reduction in the number of patients transfused, the number of units transfused and the number of units transfused in transfused patients (moderate-certainty evidence);
- IV iron + ESA therapy may result in a reduction in the number of patients transfused (low-certainty evidence);
- We are uncertain about the effect of oral/IV iron + ESAs on the number of patients requiring transfusion of multiple units (very low-certainty evidence).

8.2. Comparison to Previously Published Work and Reviews

This systematic review serves as a direct scientific basis and confirms, with moderate-certainty evidence, the ICC-PBM 2018 conditional recommendation to consider ESAs in addition to iron supplementation to reduce RBC transfusion rates in adult preoperative anaemic patients undergoing elective (major orthopedic) surgery [6]. In contrast, this review shows that iron monotherapy may not result in a reduction in the number of patients or units transfused (predominantly based on the results of the large and recently-published PREVENTT trial) [41]. Therefore, the ICC-PBM 2018 conditional recommendation to use iron supplementation to reduce RBC transfusion rates is not supported by the most up-to-date body of evidence.

Until now, several published systematic reviews (and meta-analyses) have identified RCTs investigating the effectiveness of iron and/or ESA therapy on blood product utilization in patients with preoperative anaemia undergoing (non-) elective surgery.

8.2.1. Iron therapy

A Cochrane review by Ng *et al.* included 6 RCTs that compared preoperative iron monotherapy to placebo, no treatment or standard care in anaemic patients (according to the WHO definition) undergoing both elective or non-elective surgery [83]. In line with our findings, it was concluded that the use of iron therapy for preoperative anaemia did not show a clinically significant reduction in the proportion of patients who received an allogeneic blood transfusion compared to no iron therapy. Three other systematic reviews, including RCTs until 2015, formulated conflicting conclusions that iron supplementation in patients undergoing (non-)elective surgery resulted in a non-statistically significant trend towards fewer blood transfusions compared to no treatment, placebo or usual care. [84–86] Therefore, updating existing systematic reviews and inclusion of recent scientific evidence is of utmost importance to formulate robust and up-to-date evidence-based conclusions.

8.2.2. iron + ESA therapy

Our review confirmed that ESAs in addition to iron supplementation were effective to reduce blood product utilization (moderate-certainty evidence for ESAs + oral iron, low-certainty evidence for ESAs + IV iron). Although only 7 studies were directly performed in major orthopedic surgery, 10 of the 13 other studies were considered to be relevant to the major orthopedic surgery setting since colorectal, head or neck cancer surgery (in 7 studies) and cardiac surgery (in 3 studies) are also categorized as procedures with a major risk of bleeding. [87] The threshold of Hb <13 g/dL, stated in the ICC-PBM recommendation, can be justified because the majority of the studies (13 studies, 72%) included patients with baseline Hb <13–13.5 g/dL.

Over the past 2 decades, several published systematic reviews (and meta-analyses) identified RCTs that investigated the efficacy of preoperative administration of ESAs in addition to iron supplementation on blood product utilization in anaemic adults undergoing elective surgery. In 1998, Laupacis *et al.* identified 21 RCTs and concluded that EPO, when given alone or to augment autologous donation, decreased the exposure to perioperative allogeneic transfusion in orthopaedic and cardiac surgery [88]. The review and meta-analysis (of 26 trials) by Alsaleh *et al.* focused on the efficacy of ESAs (with concomitant use of iron) in patients undergoing elective hip or knee arthroplasty (both anaemic and non-anaemic) and showed that the allogeneic blood transfusion was decreased [89]. A 2009 Cochrane review synthesized 4 RCTs that investigated the preoperative administration of subcutaneous rHuEPO, specifically in anaemic adults (Hb <14.0 g/dL for men and <12.5 g/dL for women) undergoing surgery for colorectal cancer and found no statistically significant difference in the proportion of patients transfused [90]. Finally, a recent Cochrane review by Kaufner *et al.* concluded that preoperative rHuEPO + iron therapy reduced the need for RBC transfusion in anaemic adults prior to non-cardiac surgery, whereas no reduction in the mean number of RBC units transfused per patient was found [91]. Compared to this Cochrane review, our systematic review answered a similar research question (ie effectiveness iron and ESA therapy) and used similar selection criteria in terms of the intervention (ie, preoperative administration of iron and ESA administration), primary outcomes (ie, number of patients transfused) and study design (ie. RCTs). The most important difference is that we included patients that underwent elective surgery in all settings (cfr. ICC-PBM 2018 recommendation) compared to Kaufner *et al.* who included both elective and non-elective non-cardiac surgery.

8.3. Strengths, limitations and recommendations for future research

The major strength of this systematic review is the use of high-quality methodological standards to provide the most direct and up-to-date body of evidence to further scientifically underpin the ICC-PBM 2018 recommendations. Indeed, We conducted a systematic review (and meta-analyses) by using the Cochrane methodology that adheres to strict standards aiming to minimize bias, improve the accuracy of summarized data and maximize transparency and reproducibility [7]. In addition to the GRADE approach (to assess the certainty of evidence for each outcome), GRADE's Guideline Development Tool software (to construct Synthesis of Findings tables) [92] and informative statements (recommended by the GRADE working group [11] and recently added in the Cochrane Handbook [12]) to communicate the findings of systematic reviews of interventions, provide a rigorous, transparent and applicable evidence-based information source for both patients, researchers, clinicians, guideline developers or decision-makers.

A major limitation of the current review is the heterogeneity in definitions on anaemia and iron-deficiency, the different treatment modalities used (ie, dose, frequency and duration), or the RBC transfusion threshold used. This prevented us from conducting additional subgroup analyses in order to elucidate which definition of anaemia or iron-deficiency is the most appropriate to apply and which iron modalities (dose, frequency, duration) should be recommended. Moreover, insufficient reporting, for example, on the iron-deficiency status of the patients in the studies, hindered us from exploring the impact of the cause of anaemia on the results. It therefore must be emphasized that this review's findings apply to the entire population of patients with preoperative anaemia, regardless of the causes of the anaemia (eg, iron-deficiency, renal insufficiency). The current systematic review is therefore unable to provide specific recommendations on the use of iron therapy in patients with iron deficiencies. Currently ongoing trials relevant to our PICO question [52,54,57,60,62,68,69,72,74,76,93] could provide additional data to conduct these analyses and to further scientifically support the current (or future/updated) ICC-PBM 2018 recommendations or NATA guidelines, that recommend nutritional deficiencies to be treated and recommend iron supplementation in the presence of confirmed preoperative iron deficiency anaemia. [94] Based on the non-significant Egger-test and Duval & Tweedie's trim-and-fill procedure, we did not downgrade for publication bias. However, since 9 out of 11 of the prematurely-ended registered clinical trials on iron and/or ESA therapy were directly industry-sponsored, attention is needed to rule out potential publication bias in future updates of this systematic review.

We acknowledge and understand that some of the secondary outcome results (ie, haematological parameters) are unexpected or may seem counter-intuitive. A first unexpected result was that preoperative iron monotherapy resulted in increased Hb levels at postoperative weeks 4−8 and month 6 [21,41], whereas no differences were observed in the first 2 postoperative weeks. [19,41] Froessler *et al.* commented that "this demonstrates that perioperative iron repletion has substantial benefit in the post-operative recovery period, potentially due to the iron repletion allowing bone marrow to increase erythropoiesis, compared with transfused RBC units which are rapidly cleared from the circulation and have a shorter lifespan than normal RBCs"[21]. Richards *et al.* mentioned that "this effect might reflect an underlying mechanism of functional or absolute iron deficiency and anaemia of chronic disease with inflammation, and subsequent stimulus of blood loss at operation"[41] A second unexpected result was that uncertainty exists about the postoperative Hb levels at day 3−4 after IV iron + ESA therapy, compared to IV iron only, whereas reduced postoperative Hb levels at day 1 and day 5 were observed [42]. A possible explanation in the latter study is that the blood loss in the iron only group could lead to an increase of the endogenous erythropoietin level which could stimulate erythropoiesis coordinated with the iron treatment while the ESA therapy still need time to promote the Hb level after surgery. A third and final counter-intuitive result was that the observation that oral/IV iron + ESA therapy resulted in decreased preoperative ferritin levels. A first possible explanation is that iron administration might mobilize iron stores for erythropoiesis. [17,18,31] A second explanation is that a higher proportion of patients with lower ferritin levels (eventually defined as patients with iron-deficiency) were included in the iron + ESA group [17,18]. It must be noted that the certainty of evidence of these unexpected or counter-intuitive secondary outcome results was generally considered as low certainty evidence, meaning that further research is very likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.

The best available and most up-to-date scientific evidence thus indicates that preoperative iron monotherapy may not be effective and that preoperative iron + ESA therapy is probably effective to reduce blood product utilization in patients scheduled for elective surgery. Other important items, that are not covered by this review but are equally important to consider when moving from the evidence to the formulation of a public health recommendation are the safety (adverse events) and cost-effectiveness of the treatment intervention [95]. These aspects were beyond the scope of this systematic review but will be discussed and published later.

9. Overall Conclusions

The evidence synthesized in this systematic review of 29 RCTs and 2 non-RCTs showed that, in patients with preoperative anaemia of any cause scheduled for elective surgery, the preoperative administration of iron may not result in a reduction in the number of units transfused (low-certainty evidence). IV iron monotherapy may not result in a reduced number of patients transfused (low-certainty evidence). It is uncertain whether the administration route of iron therapy (IV versus oral) differentially affects the number of patients transfused (very low-certainty evidence). Oral iron + ESA therapy probably results in a reduction in the number of patients transfused and the number of units transfused (moderate-certainty evidence). IV iron + ESA therapy may result in a reduction in the number of patients transfused (low-certainty evidence). This review serves as a direct scientific basis to formulate or update evidence-based and clinically-relevant recommendations in this PBM domain.

Author contributions

HVR: Investigation, Formal analysis, Writing – Original draft, Visualization. JL: Conceptualization, Investigation, Formal analysis, Writing – Original draft, Visualization, Supervision, Project administration, Funding acquisition. BA: Validation, Writing – Review & Editing. GB: Validation, Writing – Review & Editing. JG: Validation, Writing – Review & Editing. PMM: Validation, Writing – Review & Editing. PM: Validation, Writing – Review & Editing. YO: Validation, Writing – Review & Editing. EDB: Conceptualization, Writing – Review & Editing, Supervision. VC: Conceptualization, Writing – Review & Editing. PV: Conceptualization, Resources, Writing – Review & Editing, Supervision.

Funding

Funding for this project has been provided partly through an Agreement with the European Blood Alliance (EBA) and partly by the Foundation for Scientific Research of the Belgian Red Cross. The contents of this document do not necessarily reflect the views and policies of the EBA, nor does mentioning of trade names or commercial products constitute endorsement or recommendation of use. We are grateful to Ehsan Sadeghian for helping with the full-text screening of a Persian paper, and Olga Krasnoukhova for helping with the full-text screening of a Russian paper.

Conflict of Interest

Relevant financial conflicts of interest directly related to this review

PMM received personal fees from Ethos Srl (Advisory Board on PBM) and SUMMEET Srl (Speaker in a meeting on PBM).

PM received grants from Vifor Pharma, SerumWerke Bernburg, csl Behring, Fresenius Medical, and B.Baun. PM received personal fees from Vifor Pharma and Pharmacosmos.

HVR, JL, BA, EDB, GB, JG, VC, YO and PV declared not having any relevant direct financial conflict of interest.

Relevant financial conflicts of interest not directly related to this review

HVR, JL, BA, EDB, VC and PV are employees of Belgian Red Cross-Flanders, which is responsible for supplying adequate quantities of safe blood products to hospitals in Flanders and Brussels on a continuous basis and is being paid for this activity by the Ministry of Social Affairs. Belgian Red Cross-Flanders received a grant from the European Blood Alliance to conduct this review.

PMM received personal fees from Editree Srl (creation of training course on porphyria), Eleuthera Srl (AHP Advisory Board), Collage SpA (speaker in a meeting on Erythrocytosis), IQVIA (Advisory Board on porphyria), Alnylam (Advisory Board on porphyria).

GB, JG, PM, YO declared not having any other financial conflicts of interest.

HVR, JL, BA, GB, PMM, YO, EDB, VC and PV declared not having any intellectual conflict of interest.

PM declared to be involved in the implementation of Patient Blood Management programs.

JG declared to be involved in The Danish Health Authority – National Clinical Guideline – Indication for Transfusion with Blood Components – Copenhagen 2018 – https://www.sst.dk/da/udgivelser/2018/nkr-indikation-for-transfusion-med-blodkomponenter

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tmrv.2021.03.004.

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