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Preoperative iron therapy: Where are we?

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ABSTRACT

Preoperative anemia affects one-third of patients undergoing major surgery and is associated with worse perioperative and postoperative outcomes; including length of hospital stay, allogeneic blood transfusion, morbidity, and mortality. Iron deficiency is the most common cause of anemia, and associative data suggests that preoperative correction of iron deficiency anemia could improve postoperative patient outcomes. However, data from randomized controlled trials (RCTs) do not appear to support the routine use of iron therapy to treat preoperative anemia. We present a literature review of large RCTs examining the efficacy of preoperative intravenous iron. We discuss the observation that although preoperative intravenous iron treatment can increase hemoglobin concentration prior to surgery in certain patient groups, the data do not clarify whether there is a direct benefit to patients. We address that preoperative intravenous iron may not be a feasible option and highlight the need to explore the mechanism and management of iron deficiency anemia in surgical patients.

1. Rationale for the use of iron therapy before major surgery in anemic patients

Anemia is common in the general population, with variations in causality between age groups and comorbidities. While presenting symptoms and physiological effects can vary, overall, anemia is associated with reduced mental and physical health and increased patient morbidity and mortality [1]. Patients undergoing major surgery are at a high risk of preoperative anemia, which affects one-third of patients, with higher prevalence in specific cohorts such as patients undergoing colorectal surgery [2,3]. Preoperative anemia is recognized as an established marker for poor perioperative and postoperative outcomes; including 30-day morbidity and mortality [4]; length of hospital and ICU stay [5]; incidence of acute kidney injury and infection [6]; and allogeneic blood transfusion use [7].

Blood transfusions can be utilized to correct anemia, however, are independently associated with increased patient morbidity and mortality, even from a single unit transfusion [8]. Clinical recognition of the need to reduce blood product utilization was triggered by the problem of infectious transmission, particularly hepatitis and HIV [9]. In the late 1990s and early 2000s, researchers in Europe, Australia, and the United States began to examine transfusion practices and competing therapeutic modalities [10]. In addition, serious risks of transfusion include transfusion-related circulatory overload (TACO), transfusion-related acute lung injury (TRALI), hemolytic reactions, and more rarely, graft versus host disease [9,11].

The concept of patient blood management (PBM) was first introduced in 2005, referring to a multimodal multi-disciplinary patient-centered approach to minimize blood transfusion use and optimize clinical outcomes [12]. Australia introduced the first set of National

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PBM guidelines in 2009 [13]. In 2010, the World Health Organization (WHO) endorsed PBM [14], although, implementation has been gradual and variable geographically. South Korea initially implemented PBM in a few institutions a decade ago with national support provided for a broader approach more recently. Brazil, Saudi Arabia, and Switzerland fall on the other end of the spectrum, currently relying on 'grassroots' approaches led by local clinicians [13]. In the United States, The Joint Commission has been working on PBM measures since 2005 and partnered with the Association for the Advancement of Blood and Biotherapies to co-develop a voluntary two-year certification in 2016. Uptake has been slow with just seven certified programs as of February 2022 [15]. A multinational survey found that changing work practices, collaboration and communication, and lack of experience with PBM were the greatest barriers to implementation [13].

A central tenet of PBM is improvement in red cell mass. This is particularly relevant for the management of preoperative anemia. Iron deficiency is the most common cause of anemia, both in general and surgical populations: prior to major surgery, iron deficiency is found in three-quarters of patients with preoperative anemia and occurs in one-third of those without anemia [16]. Both oral iron and intravenous (IV) iron therapies are effective means of increasing hemoglobin concentration in iron deficiency anemia. It is therefore logical and plausible that iron therapy, particularly IV preparations that allow larger treatment doses, will be an effective treatment for preoperative anemia [17]. Observational data in selected patients has suggested that preoperative IV iron can correct anemia and reduce the need for blood transfusion with the implied potential to reduce surgical risk for patients [18]. However, data from randomized controlled trials (RCTs) has produced conflicting results. We therefore wished to undertake a literature review of the RCTs exploring iron therapy treatment for preoperative anemia.

2. Evidence from randomized controlled trials

A literature review was conducted to discuss large ($n > 50$) RCTs investigating the use of iron therapy for patients with preoperative anemia. RCTs administering preoperative iron therapy were sourced from an update of a broader systematic review (PROSPERO registration: CRD42019148956), inclusion and exclusion criteria are defined in Table 1. The update follows from the previous search, spanning from inception to June 1, 2019 [19–21]. On the February 1, 2023, the search was conducted in PubMed, MEDLINE, EMBASE, CINAHL Plus, CENTRAL, ISI Web of Science: SCI-EXPANDED, and CPCI–S. Key search terms included anemia, iron, ferrous and ferric. Detailed search terms are listed in the primary publication of this search by Gurusamy et al. [19]. Two reviewers independently screened to full text for eligible articles.

The search yielded 8493 articles, of which 3367 were duplicates (Fig. 1.). Of the remaining 5126 articles, 12 articles on the topic of preoperative iron therapy were screened to full text, and of these, 4 were excluded for recruiting non-anemic patients and 3 were excluded for having cohorts with $n < 50$. With the addition of 2 eligible studies and 1 associated secondary analysis identified from the previous searches [19–21], there was a total of 5 RCTs included with 3 associated secondary analysis publications (Table 2).

The included RCTs range from those exploring the introduction of iron into clinical practice to those comparing different iron preparations to compare efficacy. We present them as follows:

3. The important role of intravenous iron in perioperative patient blood management in major abdominal surgery, Froessler et al. [22]

Between 2011 and 2014, Froessler et al. recruited 72 patients undergoing major abdominal surgery with iron deficiency anemia (IDA). The trial included those with a hemoglobin concentration (Hb) < 130 g/L in men and Hb < 120 g/L in women with ferritin <300 μg/L and transferrin saturation (TSAT) < 25 %. Patients were preoperatively randomly allocated (1:1) to receive either IV ferric carboxymaltose (FCM) (15 mg/kg bodyweight up to a maximum dose of 1000 mg) or usual care in an unblinded manner 4–21 days prior to major abdominal surgery. The IV iron group received a second IV iron dose 2 days postoperatively if operative blood loss exceeded 100 mL (0.5 mg of iron per mL of blood loss). The study found a reduction in blood transfusions in the IV iron group compared with usual care (31.25 % vs 12.5 %). Prior to admission, Hb improved by 8 g/L in the IV iron group compared to 1 g/L in the usual care group ($p = 0.01$). Similarly, at 4 weeks after surgery, Hb improved by 19 g/L in the IV iron group compared with 9 g/L in the usual care group ($p = 0.01$). There was no difference in Hb at discharge, mortality, morbidity, or quality of life (QoL), however, length of stay (LOS) was shorter in the IV iron group (7.0 vs 9.7, $p = 0.026$). It should be noted that the rate of blood transfusion reported in this trial was unusually high, resulting in early termination of the trial.

Table 1
Literature review PICO. Large RCTs treating patients with preoperative anemia, as defined by the authors, with iron therapy administered preoperatively were included. Studies were excluded for having a cohort with $n < 50$, chronic kidney disease patients, patients < 18 years old, antenatal patients, or cohorts with non-anemic patients.

Criteria	
Population	Adult patients with preoperative anemia
Intervention	Iron therapy (intravenous or oral)
Comparator	Placebo, standard of care, no treatment, differing iron therapy (preparation, dose, or frequency)
Outcomes	Red blood cell transfusion, hematological outcomes, length of stay, readmissions, quality of life
Exclusion	Chronic kidney disease, children, pregnant or postpartum women, non-anemic patients, small cohort ($n < 50$)

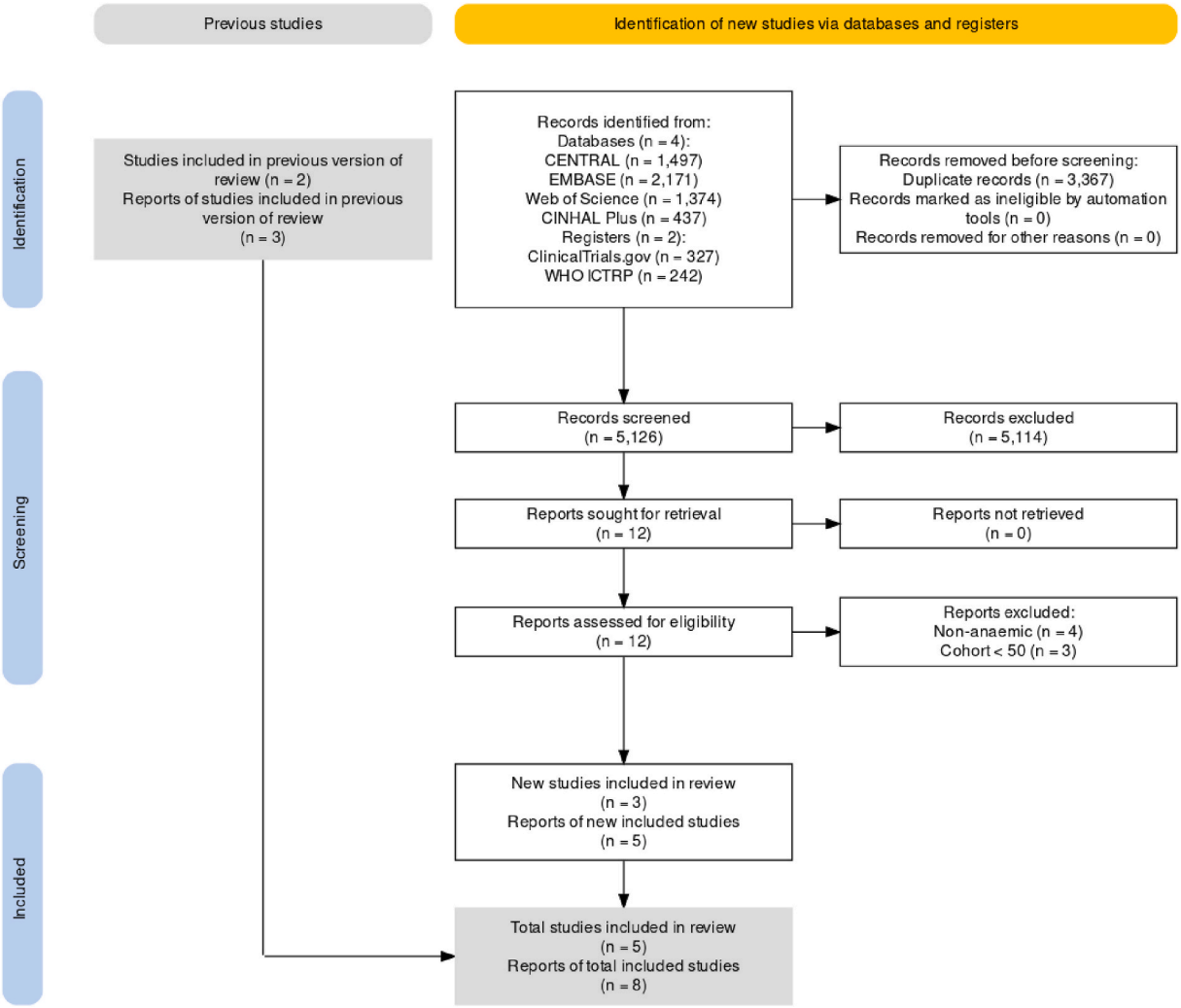

Fig. 1. PRISMA flow diagram. The flowchart above describes the search process conducted in the updated systematic review conducted by JL and BM. The diagram was created using software by Haddaway et al. [41].

This trial showed that IV iron resulted in a reduction in blood transfusion and LOS providing evidence to support the use of IV iron in the preoperative setting. However, the intervention was provided in an open-label approach, enabling the potential for treatment bias to occur, for example, clinicians may have decided not to transfuse a patient knowing that the patient had received IV iron. In addition, the secondary dosing strategy used in the postoperative setting could arguably compromise the applicability to the preoperative setting alone. Nonetheless, this was the first large trial on the use of preoperative IV iron and provided an important starting point for further RCTs to explore preoperative iron use.

4. Intravenous iron in colorectal cancer-associated anemia (IVICA) trial, Keeler et al. [23,24] and Dickson et al. [25]

Between 2012 and 2014, the IVICA Trial Group recruited 116 patients with non-metastatic cancer prior to elective colorectal cancer resection surgery. The trial included those with Hb < 110 g/L for women and Hb < 120 g/L for men. Patients were randomly allocated (1:1) at least 2 weeks preoperatively to a patient-tailored dose of IV FCM (up to 2000 mg) or 2 daily oral doses of 200 mg ferrous sulfate, taken until the day of surgery. The interventions were not blinded to the participants. There was no difference in units of blood transfused in the IV iron group compared with the oral iron group (0.632, 95 % CI 0.258–1.006 vs 0.698, 95 % CI 0.151–1.246, p = 0.841), nor the number of patients transfused (14 vs 10, p = 0.470). The IV iron group showed a greater increase in preoperative Hb (15.5 g/L vs 5.0 g/L, p = 0.001) with a greater proportion of normalized Hb by the date of surgery (25 % vs 10 %, p = 0.048). No difference in LOS was observed between groups, nor mortality, complication rate, or grade. Longitudinal analysis (n = 110), with a median follow-up duration of 61 months (IQR 46–67), found no difference in mortality (hazard ratio (HR) 1.22, 95 % CI 0.65–2.28, p = 0.522) nor disease-free survival (HR 1.08, 95 % CI 0.61–1.92, p = 0.79) [25]. A small subgroup of those with

Table 2
Summary of RCT characteristics. The table describes the period of data collection for each trial, the trial identifier (by trial name or author group), and surgical cohort that patients were recruited from. Inclusion parameters are described, including hemoglobin concentration (Hb), ferritin and transferrin saturation (TSAT) where included. The intervention column describes the intervention and control/comparator while the intervention window describes the time from intervention administration to the day of surgery, reported as a median + interquartile range (IQR) and range where indicated.

Trial Period	Trial/ Author	n	Surgery	Inclusion Parameters	Intervention	Intervention Window (Days)
2011–2014	Froessler et al.	72	Major abdominal	Men Hb < 130 g/L Women Hb < 120 g/L, ferritin <300 μg/L, TSAT <25 %	IV FCM (15 mg/kg up to 1000 mg, if > 100 mL blood loss, secondary dose 2 days postop of 0.5 mg/mL of blood) or usual care	4–21 (range)
2012–2014	IVICA	116	Elective colorectal cancer	Men Hb < 120 g/L Women Hb < 110 g/L	FCM (up to 2000 mg) or 2 × 200 mg ferrous sulfate daily	21 Oral group IQR 15 - 33 IV group IQR 15 - 34
2014–2018	PREVENTT	487	Major abdominal	Men Hb < 130 g/L Women Hb < 120 g/L	1000 mg IV FCM or saline	10–42 (range) 15 days (IQR 12–22)
2014–2021	FIT	202	Elective colorectal cancer	Men Hb < 130 g/L Women Hb < 120 g/L + TSAT <20 %	1000 - 2000 IV FCM or 3 × 200 mg oral ferrous fumarate	Oral group: 19 (IQR 13–27) IV group: 14 (IQR 11–22)
2019–2020	Shokri and Ali	80	Elective cardiac	Men Hb < 130 g/L Women Hb < 120 g/L	1000 mg IV FCM or saline	7

preoperatively corrected anemia showed improved 5-year survival (HR 3.38, 95 % 1.07–11.56, p = 0.044).

In 2019, the IVICA Trial Group published further longitudinal data from IVICA to report on QoL measures assessed at recruitment, immediately prior to surgery and at the outpatient review 3 months postoperatively [23]. The self-report questionnaires included the EuroQoL 5-dimension 5-level (EQ5D5L), Short Form 36 (SF36), and Functional Assessment of Cancer Therapy – Anemia (FACT-An). At 3 months post-operation, 11 QoL components significantly improved in the IV iron group while only one component improved in the oral iron group. Hb was found to be positively correlated with 6 QoL components.

The IVICA trial showed that IV iron was more effective at improving preoperative Hb for anemic patients but, contrary to initial thoughts, oral iron was also quite effective. As this study was conducted in patients with colorectal cancer, there is an assumed hypothesis that the underlying cause of anemia was chronic gastrointestinal blood loss, leading to absolute iron deficiency [26]. This may explain the effectiveness of both oral and IV iron interventions, which showed a greater treatment effect (increased Hb) than that observed in similar RCTs.

The postoperative QoL improvements observed in the IV iron group suggest a direct patient benefit compared to using oral iron. This combined with the observed greater efficacy for improved preoperative Hb suggests that IV iron may be the preferred iron therapy choice in the preoperative setting for colorectal cancer patients. However, as with the trial conducted by Froessler et al. [22], the unblinded and open-label nature of this trial has the potential for reporting bias in QoL assessments due to the subjective nature of these measurements.

Interestingly, the long-term follow-up finding that 5-year survival was improved in those with preoperatively corrected anemia, regardless of treatment strategy, reflects associative data in the literature [4], reiterating that preoperative anemia is a risk factor for mortality. This follow-up finding highlights the need to address preoperative anemia in surgical patients, although questions remain regarding optimal timing and therapy.

5. Preoperative intravenous iron to treat anemia before major abdominal surgery (PREVENTT) trial, Richards et al. [32, 33]

Between 2014 and 2018, Richards et al. preoperatively recruited 487 patients undergoing major open abdominal surgery across 46 UK centers in the PREVENTT trial. The trial included patients with anemia (Hb < 120 g/L for women and Hb < 130 g/L for men) with a predefined subgroup of those with iron deficiency (ferritin <100 μg/L or TSAT <20 %). Between 10 and 42 days before their operation, patients were randomized to 1000 mg of IV FCM or saline in a double-blind manner. Preoperative IV iron did not reduce the risk of death or blood transfusion within 30 days after surgery (risk ratio 1.03, CI 0.78–1.37, p = 0.84), nor was there a difference in blood transfusion events between groups (rate ratio 0.98, 95 % CI 0.68–1.43, p = 0.93). Anemia was corrected in 21 % of the IV iron group vs 10 % of the control group preoperatively and preoperative Hb significantly increased in the IV iron group (mean difference (MD) 4.7 g/L, 95 % CI 2.7–6.8). There was a significantly lower rate of readmissions in the IV iron group within the first 8 weeks postoperatively (risk ratio 0.61, 95 % CI 0.40–0.91). This was associated with improved Hb in the IV iron group at 8 weeks (MD 10.7 g/L, 95 % CI 7.8–13.7) and 6 months (MD 7.3 g/L, 95 % CI 3.6–11.1) postoperatively. There was no difference in adverse events, LOS or 6-month mortality between groups.

In a preplanned secondary analysis [33], Richards et al. confirmed the hypothesis that most (82 %) patients in the PREVENTT trial were iron deficient (ferritin <100 μg/L or TSAT <20 %). The greatest preoperative treatment effect from IV iron, producing a greater

preoperative Hb spike, was seen in those with absolute iron deficiency anemia (ferritin <30 μg/L; MD 8.9 g/L, 95 % CI 5.3–12.5) compared to those with functional iron deficiency anemia (ferritin <100 μg/L or TSAT <20 %; MD 2.8 g/L, 95 % CI 0.01–5.7) or without iron deficiency. However, despite this, there was no difference in risk of death or blood transfusion at 30 days postoperatively nor number of blood transfusions based on baseline ferritin or TSAT data.

PREVENTT was the first large double-blind RCT on the use of preoperative iron therapy for anemic patients. The risks of treatment bias and reporting bias were mitigated by the study design. In contrast to the trial by Froessler et al. [22] and in line with the findings of IVICA [24], there was no difference in blood transfusion observed. Similar to both trials, IV iron improved Hb prior to surgery, suggesting that IV iron is an effective means of preoperative Hb optimization, however, PREVENTT suggested that no direct benefit to patients could be observed until 8 weeks after surgery. This may reflect that simply swapping one intervention (i.e. blood transfusion) for another, such as IV iron, has little benefit in isolation, or that both interventions may be appropriate within that time frame of a patient's surgical journey.

The longitudinal increase in Hb observed during recovery, coupled with a reduction in readmissions, could indicate that there are long-term protective effects from treating preoperative anemia with IV iron. This is a concept supported by the improved 5-year survival observed in IVICA [23]. However, these longitudinal observations were secondary outcomes to both trials and therefore suggest that correspondingly powered future research is required to further explore these outcomes.

6. Ferric carboxymaltose infusion versus oral iron supplementation for preoperative iron deficiency anemia in patients with colorectal cancer (FIT), Talboom et al. [34]

Between 2014 and 2021, the FIT trial recruited 202 patients undergoing elective colorectal non-metastatic cancer resection surgery. The trial included those with iron deficiency anemia (Hb < 120 g/L for women and Hb < 130 g/L for men and TSATS <20 %), who were randomly allocated to receive a patient-tailored dose of IV FCM (1000–2000 mg) or 3 × 200 mg oral ferrous fumarate taken daily until the day before surgery. Preoperative IV iron was not superior to oral iron in normalizing Hb levels on the day of admission (RR 1.08, 95 % CI 0·55–2.10, p = 0.83), however, it was superior at 30 days after surgery (RR 2.92, 95 % CI 1.87–4.58, p < 0.0001). There was no difference in blood transfusion, postoperative complications, LOS, and mortality between the groups. Treatment-related adverse events were higher in the oral iron group compared to IV iron (22 % vs 8 %, effect size 0.38, 95 % CI 0.18–0.82, p = 0.0085), with the most prevalent event being discolored feces in the oral iron group.

The results of the FIT trial echo that of PREVENTT [32], finding no benefit of preoperative IV iron in terms of blood transfusion, LOS, and mortality outcomes [32]. Notably, the FIT trial was unblinded, so despite the potential biases associated with unblinded trials, the results remained consistent with the PREVENTT trial. The increase in Hb preoperatively reflects the observations of Froessler et al. [22], PREVENTT [32], and IVICA [23]. Interestingly, between these trials, the preoperative Hb increase is observed despite an intervention window of between at least 4–42 days before operation (Table 1.). This range in preoperative treatment window merits further exploration, for example, iron administered in closer proximity to the date of surgery may differ in absorption efficacy as a result of the inflammatory response experienced in surgery and the consequent upregulation of hepcidin [35]. Furthermore, the increase in Hb postoperatively in the FIT trial reflects similar findings observed in PREVENTT and the trial by Froessler et al. [22,32]. The effect was seen at 30 days after surgery compared to the reported finding at 8 weeks in PREVENTT. This treatment effect could reflect the timing for follow-up testing or differences in initial IV iron dosing.

7. Intravenous iron supplementation treats anemia and reduces blood transfusion requirements in patients undergoing coronary artery bypass grafting – a prospective randomized trial, Shokri and Ali [36]

Between 2019 and 2020, Shokri and Ali preoperatively recruited 80 anemic patients (Hb < 130 g/L for men and < 120 g/L for women) undergoing elective coronary artery bypass grafting. Patients were double-blind randomized to receive either 1000 mg of IV FCM or saline 7 days before their operation date. The primary outcome was the incidence of anemia at 4 weeks after surgery. In the IV iron group, the incidence of anemia at 4 weeks was 32 % compared with 80 % in the placebo group (p < 0.001). The IV iron group had a higher Hb preoperatively (127.6 ± 8.8 g/L vs 100.3 ± 8.3 g/L, p < 0.001), postoperatively (91.0 ± 6.3 g/L vs 75.5 ± 6.0 g/L, p < 0.001) and 4 weeks after discharge (124.4 ± 7.1 g/L vs 112.6 ± 11.3 g/L, p < 0.001), though measurements at 1 week after discharge were comparable between groups (103.5 ± 8.9 g/L vs 101.8 ± 8.5 g/L: p = 0.397). Postoperatively, more units of blood were transfused in the placebo group compared to the IV iron group (5 units vs 22 units, p < 0.001). Length of ICU stay was 1.28 ± 0.45 days in the IV iron group compared with 2.23 ± 0.95 days in the placebo group (p < 0.001) while hospital LOS was respectively 4.33 ± 1 days compared with 8.68 ± 1.1 days (p < 0.001).

This trial further supports the use of IV iron as a means of preoperatively improving Hb, reflecting the similar observations in IVICA, the trial by Froessler et al., and PREVENTT [22,24,33], compounding our understanding that IV iron is an effective means of increasing preoperative Hb in patients with assumed blood loss-related anemia before surgery. There are similar improvements observed with postoperative Hb in this trial, however, postoperative Hb is poorly defined as an outcome within the trial and can only be deduced as occurring sometime between surgery and 1 week after discharge. This trial also feeds into a lack of consensus on whether preoperative iron can reduce blood transfusion use, however, it should be noted that in this trial this finding is reported exclusively in the postoperative period despite randomization occurring 7 days prior to surgery; it would be more comparable to trials in the area if this outcome was reported from randomization.

8. Where are we now?

The above RCTs took a long time to recruit and, due to the short timelines in normal clinical practice, implementing preoperative iron treatment can prove difficult. This was highlighted in a snapshot audit of 2730 patients undergoing major surgery at 56 centers in Australia and New Zealand, where < 6 % of patients with preoperative anemia received treatment, despite well-established pathways [37]. From the above trials, we can observe a feasible preoperative iron treatment range between 4 and 42 days prior to the date of surgery (Table 1).

Ultimately, we must question whether hospitals should implement routine preoperative IV iron into patient blood management programs. The application of preoperative IV iron to treat anemia appears to be a sensible idea for patients undergoing major surgery as the majority of these patients are iron deficient [18,33]. The use of IV iron does increase Hb preoperatively and, in selected cases such as colorectal cancer with absolute iron deficiency, probably reduces the use of blood transfusions. However, the fundamental principle of an intervention is to mediate patient benefit, and the current data have not shown an immediate benefit to treating patients before surgery.

There are several unanswered questions, particularly the definition of iron deficiency anemia in surgical patients. The results of PREVENTT reflected that IV iron was more beneficial for improving preoperative Hb in the more iron-deficient subgroup (ferritin < 30 μg/L) [32], however, the array of confounders existing in the surgical population makes it unclear whether the thresholds for absolute iron deficiency or concept of functional iron deficiency are even applicable to surgical patients. This is also highlighted by the range of hematological inclusion criteria (Table 1) between the RCTs, with many trials simply including patients with anemia. This heterogeneity is not unique to the preoperative population and can be observed across all RCTs utilizing iron therapy to treat anemia [17]. The variation observed in the above RCTs could be addressed in an individual patient meta-analysis or through achieving a consensus on the definition of iron deficiency; including defining absolute iron deficiency, functional iron deficiency, or even the long-anticipated review of Hb thresholds for diagnosing anemia in women [38,39].

9. What is next?

Recent publication of the ICCAMS Consensus on the use of iron in the surgical setting recommends that all patients undergoing major surgery be screened preoperatively for anemia, with corresponding etiology-specific anemia treatment conducted preoperatively where possible [16]. The consensus further details that regardless of the strong correlative data between preoperative anemia and poor patient outcomes, there is potential that anemia may not be the risk factor for these outcomes and may simply be a marker of the underlying comorbidities [16].

The imbalance between associative data and level-one evidence from RCTs may also reflect a lack of understanding of the interplay among iron, inflammation, and blood loss in the surgical setting. Though IV iron may be effective at increasing Hb preoperatively and postoperatively, the magnitude of these effects may be restricted by inflammation-induced hepcidin upregulation, resulting in the sequestration of iron which could ultimately restrict erythrogenesis [40]. However, blood loss at operation may lead to an upregulation of erythroferrone, which inhibits hepcidin production and could consequently allow for a greater response to iron therapy after perioperative blood loss [40]. Therefore, there is potential for iron therapy to show greater efficacy at different time points in a patient's surgical journey. Further mechanistic research is required from the preoperative period through to the postoperative period: exploring the impact of the timing of iron administration and its effects on blood transfusion and hematological markers of iron absorption, red blood cell production, and inflammation. Aside from exploring the impacts of iron efficacy around the time of surgery, a study such as this could explore options for iron administration time points if preoperative administration is not feasible.

Finally, several RCTs have identified a potential benefit for long-term patient outcomes by treating anemia with IV iron preoperatively [25,32], meriting further exploration. Longitudinal studies on preoperative iron could build on previous explorations of clinical outcomes such as blood transfusion, readmissions, mortality, and morbidity; or further explore the impact on mental well-being and QoL; or examine unknown patient-focused aspects such as implications on physical function and frailty; and aspects developed through collaboration with patients. Future RCTs should explore the role of iron therapy in postoperative patient recovery after discharge from hospital and explore whether increasing Hb during recovery can improve patient-reported outcomes.

For now, the benefit to patients of preoperative iron therapy to correct iron deficiency anemia remains unclear. Furthermore, the certainty of the optimal timing of IV iron, or indeed the definition of perioperative iron deficiency, thereby identifying those patients who may benefit most, may not yet be understood. Further double-blind RCTs are required to explore the use of IV iron to treat preoperative anemia to inform clinical practice.

10. Practice points

- Preoperative anemia is a risk factor for worse patient outcomes
- IV iron is an effective means of increasing hemoglobin concentration preoperatively
- Oral iron is less effective than IV iron in the properative period
- Preoperative IV iron is effective for increasing hemoglobin concentration in the postoperative period

11. Research agenda

- A confirmed definition of iron deficiency anemia in the preoperative period

- An exploration of the optimal timing of iron therapy in patients undergoing major surgery
- Evaluation of long-term outcomes in patients treated with preoperative IV iron, including both clinical and patient-centered outcome measures

12. Summary

Preoperative anemia is a risk factor for worse patient outcomes. Randomized controlled trials have shown that preoperative intravenous iron is an effective means of improving hemoglobin concentration before the day of surgery and in the postoperative period. Though improvements in hemoglobin concentration are observed, these do not necessitate interventional success, and more evidence of direct-patient benefit should be observed to determine the role of IV iron in preoperative patient blood management. The impact of preoperative iron on blood transfusion, length of stay, readmission, quality of life, morbidity, and mortality outcomes remains unclear.

Declaration of competing interest

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