Transfusion Medicine Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

The Efficacy of Postoperative Iron Therapy in Improving Clinical and Patient-Centered Outcomes Following Surgery: A Systematic Review and Meta-Analysis☆

Iris Perelman [a,b], Remington Winter [a], Lindsey Sikora [a], Guillaume Martel [b,c], Elianna Saidenberg [b,c], Dean Fergusson [a,b,*]

[a] University of Ottawa, Ottawa, Ontario, Canada
[b] Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[c] Ottawa Hospital, Ottawa, Ontario, Canada

ARTICLE INFO

Available online xxxx

Keywords:
Systematic review
Elective surgery
Postoperative iron therapy
Oral iron
Intravenous iron
Efficacy
Safety
Hemoglobin
Patient-centered outcomes

ABSTRACT

Postoperative anemia is a common occurrence in surgical patients and leads to an increased risk for allogeneic blood transfusions. The efficacy of iron therapy in treating postoperative anemia has not been firmly established. The objective of this systematic review was to evaluate the efficacy of postoperative oral and intravenous (IV) iron therapy in increasing hemoglobin levels and improving patient outcomes following elective surgery. The databases Medline, EMBASE, CENTRAL, the Transfusion Evidence Library, and ClinicalTrials.gov were searched. Eligible studies were randomized controlled trials or prospective cohorts having a control group, where postoperative oral or IV iron was administered to elective surgery patients. Primary outcomes were hemoglobin levels and patient-centered outcomes of quality of life and functioning. Secondary outcomes were the safety of postoperative iron and blood transfusion requirement. Meta-analysis using a random-effects model was performed. Seventeen relevant studies were identified, of which 7 investigated IV iron, 7 investigated oral iron, and 3 compared IV with oral iron. Postoperative oral and IV iron therapies were ineffective in improving quality of life and functioning (the Grading of Recommendations Assessment, Development and Evaluation [GRADE]: moderate-low quality). Compared with control, IV iron increased mean hemoglobin levels by 3.40 g/L (95% confidence interval [CI]: 1.18-5.62) (GRADE: moderate quality); however, this increase is likely not clinically meaningful. Overall, oral iron was ineffective in increasing hemoglobin concentrations compared with control (mean difference = 0.77, 95% CI: −1.48-3.01) (GRADE: moderate quality). Postoperative iron therapy did not significantly reduce the risk of blood transfusion (relative risk = 0.75; 95% CI: 0.53-1.07) (GRADE: low quality). IV iron was not associated with a significantly increased risk of adverse events (relative risk = 4.50, 95% CI: 0.64-31.56). There was insufficient information to determine the risk of adverse events for postoperative oral iron. This systematic review found no evidence to support the routine use of postoperative iron therapy in all elective surgery patient populations; however, results are based largely on studies with non–iron-deficient patients preoperatively. Further research on the role of postoperative IV iron is warranted for certain high-risk groups, including patients with iron deficiency or anemia prior to surgery. This systematic review is registered in PROSPERO (CRD42017057837).

Anemia is a common occurrence in surgical patients, and may already be present prior to surgery or may be caused or exacerbated by intra- and postoperative blood loss [1]. Preoperative anemia can be due to iron deficiency, or it can be the result of chronic disease whereby chronic inflammatory states lead to altered iron metabolism and iron-deficient production of red blood cells [2-5]. The determinants of postoperative anemia include the presence of preoperative anemia, intra- and postoperative blood loss, postsurgical inflammatory responses leading to altered use of iron stores, or a combination of factors [6,7]. The prevalence of preoperative and postoperative anemia varies by study, depending on the surgical procedure, the patient population, and the definition of anemia used [1,8-10]. Preoperative anemia has been found to occur in 5% to 75.8% of patients, whereas the rate of postoperative anemia is often more frequent [1].

Anemia prior to surgery has been independently associated with multiple adverse outcomes postoperatively, including infection, stroke,

☆ Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding author at: Dr Dean Fergusson, PhD MHA, Clinical Epidemiology Program, Ottawa Hospital Research Institute, 501 Smyth Rd, Ottawa, Ontario, Canada K1H 8L6.
E-mail address: dafergusson@ohri.ca (D. Fergusson).

https://doi.org/10.1016/j.tmrv.2017.10.002
0887-7963/

acute kidney injury, longer hospitalization, higher odds of readmission, decreased disease-free survival for cancer patients, and mortality [8,9,11-17]. Postoperative anemia can be a risk factor for infection, poor functional outcomes, increased length of hospitalization, and decreased quality of life for certain patient populations [8,10,18]. Importantly, both preoperative anemia and postoperative anemia are known to increase the risk of allogeneic red blood cell transfusion, with its attendant health risks [1,8,19-21]. In general, it is recommended that the use of blood transfusions be minimized in treatment of anemia, and avoidance of transfusion is especially recommended when other, safer therapy such as iron replacement would be effective [19,22,23].

Alternatives to blood transfusion in the management of anemia include erythropoiesis-stimulating agents, replacement of deficient nutrients such as iron and B12, and combinations of the above [13,24]. Although these methods have been shown to be effective in preoperative anemia management, the efficacy of iron therapy for postoperative anemia management has not yet been clearly established, and literature reviews have come to conflicting conclusions [6,19,24-27]. In addition to inconsistent and conflicting results, most of the reviews on postoperative iron replacement therapy are outdated and are missing recent studies done in the field. As such, a synthesis of the literature on the efficacy of iron supplementation following surgery is timely.

The primary purpose of this systematic review was *to determine the efficacy of postoperative iron, intravenous (IV) or oral, in increasing hemoglobin levels and improving patient-centered outcomes for elective surgery patients, as compared with placebo, no intervention, or active comparator, based on clinical trials and prospective observational studies.* A secondary objective of interest was *to evaluate the safety and tolerability of postoperative IV and oral iron therapy in managing anemia following elective surgery*.

1. Methods

The protocol for this systematic review is registered in PROSPERO (registration number: CRD42017057837). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and checklist were followed throughout the reporting of this systematic review [28].

1.1. Inclusion Criteria

The population of interest was patients of any age who had undergone elective surgery and had developed postoperative anemia, including patients who were preoperatively anemic. We included studies where the intervention consisted of iron therapy, oral or IV, administered within 30 days after surgery. Any dose, frequency, and duration of iron treatment were accepted. Studies that administered iron both preoperatively and postoperatively were included as long as all patients received iron following surgery. We included studies that compared oral or IV iron to no intervention, placebo, an active comparator, or each other. The primary outcomes of interest were hemoglobin levels following iron therapy, and patient-centered outcomes of quality of life and functioning. These were chosen as primary end points because they are meaningful and important to both patients and clinicians. Our secondary outcomes included blood transfusion requirement and the safety of iron therapy (number of adverse events, infections, general medical complications, surgical site complications, length of hospitalization, reoperation rate, time to chemotherapy for cancer surgeries). We included studies that reported at least one of our primary or secondary outcomes. With respect to study design, full-text, peer-reviewed randomized controlled trials (RCTs) and prospective cohort studies written in any language were included in this systematic review. We restricted studies to RCTs and prospective observational studies to maximize the quality of data obtained.

1.2. Exclusion Criteria

Studies were excluded if they did not meet one or more of the inclusion criteria. We excluded studies where the patient population consisted fully or partially of nonsurgical patients, or where not all participants received postoperative iron. Studies lacking a control group were not included. We excluded retrospective study designs, as well as animal studies, abstracts, conference publications or proceedings, letters, and duplicate publications.

1.3. Search Strategy

A comprehensive and systematic search strategy was developed with guidance from an information specialist. The databases Medline (Ovid), EMBASE (Ovid), the Transfusion Evidence Library, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched from inception until February 2017 using combinations of relevant keywords and Medical Subject Headings. Searches were run without any filters, limits, and publication date or language restrictions. The complete search strategy for Medline (Ovid) can be found in Appendix A. Database searches were supplemented by manual screening of reference lists of relevant studies and systematic reviews identified in the literature searches.

1.4. Study Screening and Data Abstraction

Two reviewers performed all stages of study screening and data abstraction independently and in duplicate. Disagreements were settled by discussion, and where necessary, a third study author was consulted. Titles and abstracts of studies identified in the literature search were screened by the 2 reviewers using the eligibility criteria. Relevant citations were obtained and read in full text. Eligible studies were abstracted using a standardized, piloted form. Study authors were contacted by e-mail if important and necessary information was found to be missing from the article.

1.5. Risk of Bias Assessment

Risk of bias was assessed at the study level and was done independently and in duplicate by 2 reviewers using the Cochrane tool for RCTs [29] and the Newcastle-Ottawa scale for prospective cohort studies [30]. Data from the risk of bias assessment were used (*a*) to compare studies based on their quality, (*b*) to perform a sensitivity analysis excluding high risk of bias studies, and (c) to help evaluate the overall quality of evidence synthesized in this systematic review.

1.6. Overall Quality of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was conducted to evaluate the overall strength of evidence of this systematic review and to determine the confidence with which conclusions and recommendations could be made [31]. The overall quality of the body of evidence was rated as being very low, low, moderate, or high.

Meta-biases that could affect the overall quality of evidence were also assessed. Publication bias was appraised using funnel plots, and selective reporting bias was evaluated within individual studies in the risk of bias assessment.

1.7. Analysis Plan

1.7.1. Study Synthesis

A narrative synthesis of all eligible studies was performed, describing the study origin (year of publication, country), methodological characteristics (study design, blinding, duration of follow-up, study arms, dosage regimen), clinical and patient characteristics (type of surgery,

Please cite this article as: Perelman I, et al, The Efficacy of Postoperative Iron Therapy in Improving Clinical and Patient-Centered Outcomes Following Surgery: A Systematic Rev..., Transfus Med Rev (2017), https://doi.org/10.1016/j.tmrv.2017.10.002