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The Impact of Perioperative Iron on the Use of Red Blood Cell Transfusions in Gastrointestinal Surgery: A Systematic Review and Meta-Analysis

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ABSTRACT

Perioperative anemia is common, yet detrimental, in surgical patients. However, red blood cell transfusions (RBCTs) used to treat anemia are associated with significant postoperative risks and worse oncologic outcomes. Perioperative iron has been suggested to mitigate perioperative anemia. This meta-analysis examined the impact of perioperative iron compared to no intervention on the need for RBCT in gastrointestinal surgery. We systematically searched Medline, Embase, Web of Science, Cochrane Central, and Scopus to identify relevant randomized controlled trials (RCTs) and nonrandomized studies (NRSs). We excluded studies investigating autologous RBCT or erythropoietin. Two independent reviewers selected the studies, extracted data, and assessed the risk of bias using the Cochrane tool and Newcastle-Ottawa scale. Primary outcomes were proportion of patients getting allogeneic RBCT and number of transfused patient. Secondary outcomes were hemoglobin change, 30-day postoperative morbidity and mortality, length of stay, and oncologic outcomes. A meta-analysis using random effects models was performed. The review was registered in PROSPERO (CRD42013004805). From 883 citations, we included 2 RCTs and 2 NRSs (n = 325 patients), all pertaining to colorectal cancer surgery. Randomized controlled trials were at high risk for bias and underpowered. One RCT and 1 NRS using preoperative oral iron reported a decreased proportion of patients needing RBCT. One RCT on preoperative intravenous iron and 1 NRS on postoperative PO iron did not observe a difference. Only 1 study revealed a difference in number of transfused patients. One RCT reported significantly increased postintervention hemoglobin. Among 3 studies reporting length of stay, none observed a difference. Other secondary outcomes were not reported. Meta-analysis revealed a trend toward fewer patients requiring RBCT with iron supplementation (risk ratio, 0.66 [0.42, 1.02]), but no benefit on the number of RBCT per patient (weighted mean difference, −0.91 [−1.61, −0.18]). Although preliminary evidence suggests that it may be a promising strategy, there is insufficient evidence to support the routine use of perioperative iron to decrease the need for RBCT in colorectal cancer surgery. Well-designed RCTs focusing on the need for RBCT and including long-term outcomes are warranted.

Contents

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Up to 34% of noncardiac surgical patients present with preoperative anemia, a number rising to 46% in colorectal cancer (CRC) [1,2]. Anemia thus appears as a common, yet detrimental, problem in patients undergoing gastrointestinal (GI) surgery, as it is associated with increased postoperative mortality and morbidity [1,3-5]. The most common treatment for anemia, allogeneic red blood cell transfusion (RBCT), is also associated with significant risks and worse outcomes in terms of morbidity, recovery, and even cancer recurrence [6-10]. In addition to associated clinical risks, transfusions are a scarce and expensive resource that contributes a significant cost to health care through prolonged length of stay and hospital charges [11]. In 2012, blood transfusion was identified as 1 of 5 overused medical treatments at the National Summit on Overuse of the Joint Commission and American Medical Association, further highlighting the dangers of blood transfusions and the need for effective strategies to minimize its use [12].

Recently, alternatives or cotreatments to reduce the need for perioperative RBCT have been examined. No difference was observed in RBCT with erythropoietin used before CRC surgery in a meta-analysis of 4 randomized controlled trials (RCTs) [13]. Although autologous blood transfusion decreased the risk of receiving allogeneic transfusions, it did not modify the need for any blood transfusion or result in improved postoperative outcomes. Furthermore, it is challenging to use in patients with preexisting anemia [14]. Pooled data on intraoperative cell salvage devices revealed a decrease in RBCT, but its use is limited outside of benign and noncontaminated cases [15]. Finally, perioperative iron supplementation has been suggested as well and found useful in reducing RBCT in orthopedic surgery [16,17]. However, in GI surgery, results of this strategy remain controversial. Therefore, evidence regarding the clinical benefits of perioperative iron supplementation in GI surgery remains insufficient.

We undertook a systematic review and meta-analysis of observational nonrandomized studies (NRSs) and RCTs to examine the impact of perioperative iron supplementation on the need for postoperative RBCT in GI surgery.

Methods

Search Strategy

We systematically searched Medline (1966 to May 2013), EMBASE (1974 to May 2013), the Cochrane Register for Controlled Trials, Web of Knowledge (Web of Science and BIOSIS), and the Scopus database (1966 to May 2013), without restrictions regarding language or type of publication. We also searched the gray literature through OpenSIGLE, Intute (until closing in July 2011), the Trip database, and Google Scholar, as of May 2013. With assistance from an information specialist, the search strategy was initially developed for Medline and then adapted to each database's thesaurus (see Appendix 1). Keywords and MeSH (or EMTREE) terms were gathered into 3 categories: (1) GI pathology (population), (2) surgery (population), and (3) iron supplementation (intervention). To increase search sensitivity, we exploded each keyword. We also searched conference proceedings of national and international meetings in surgery and transfusion medicine to identify relevant abstracts (see Appendix 2). Finally, we reviewed bibliographies of all included studies for any additional relevant publications.

Study Selection

We included RCTs and comparative NRSs reporting on the impact of perioperative (within 30 days before and/or after surgery) iron supplementation, administered intravenously (IV) or orally (PO), on the need for postoperative RBCT, compared to placebo or no intervention. Studies including at least 10 adults (≥18 years old) undergoing GI surgery (surgical procedure for benign or malignant disease, on the esophagus, stomach, small bowel, liver, pancreas, colon, or rectum) were included. We excluded studies that were designed to specifically evaluate the use of erythropoietin or preoperative autologous blood donation, to focus on the effects of iron supplementation. Studies that included patients meeting our inclusion criteria were excluded if we were unable to distinguish those patients from the larger study population. In the event of duplicate publication, we included the most relevant and the most informative study.

Data Abstraction

We developed and pilot tested a standardized extraction form following the recommendations of the Cochrane Effective Practice and Organization of Care Review Group [18]. We determined study design using the Cochrane Group checklist [18]. The following patient characteristics were captured: indication for and site of surgery, cotreatments (eg, preoperative chemotherapy), age, sex, and comorbidities. We collected intervention, and comparator information was collected, including type of iron medication, IV or PO administration route, dosage, dosing interval, timing of administration (preoperative or postoperative), type of comparator (placebo or no treatment), and use of cointervention (eg, erythropoietin). We recorded the transfusion protocol used for the administration of RBCT. We contacted the corresponding authors of each study to obtain additional details about missing or incomplete data when deemed necessary, using the email provided in the article.

Outcome Measures

Our primary outcome was the proportion of patients requiring at least 1 U of allogeneic RBCT and the number of RBCT units per transfused patient. Our secondary outcomes were mean changes in hemoglobin (Hb) level between preoperative (closest value before surgery) and postoperative (latest value before discharge or within 30 days after surgery) periods, postoperative morbidity (within 30 days),