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Research

Iron supplementation for patients undergoing cardiac surgery: a protocol for a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Iron administration has been evaluated in several randomized controlled trials for the potential of increasing baseline hemoglobin values and decreasing the incidence of red blood cell transfusion during cardiac surgery. We describe the protocol for a study aiming to evaluate the efficacy and safety of perioperative iron administration in patients undergoing cardiac surgery.

Methods: We will search MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and the Web of Science, from inception to Nov. 19, 2020, for randomized controlled trials in any language evaluating the perioperative administration of iron in adult patients undergoing cardiac surgery; we will also include the first 50 results from Google Scholar. The primary outcome will be the incidence of red blood cell transfusion from the study intervention time until 8 weeks postoperatively. The secondary outcomes will be the number of red blood cell units transfused; change in ferritin level, reticulocyte count and hemoglobin concentration after iron administration; and adverse events. We will assess the risk of bias with the Cochrane Collaboration Risk of Bias Tool, and will analyze the primary and secondary outcomes using a random-effects model.

Interpretation: This study will summarize the current evidence about perioperative iron administration in patients undergoing cardiac surgery, help determine whether this intervention should be included in enhanced-recovery protocols, and shape future research if needed. The final manuscript will be submitted to a peer-reviewed journal. **Trial registration:** PROSPERO no. CRD42020161927

Anemia is common in patients presenting for cardiac surgery. It may be present in up to 54% of cases.[1] Preoperative anemia is one of the most critical risk factors for patients requiring a red blood cell transfusion. Strategies have been sought to minimize the need for blood transfusion given its association with complications, such as surgical site infection,[2,3] pneumonia,[4] acute lung injury,[5] postoperative atrial fibrillation,[6] coronary artery graft occlusion[7] and risk-adjusted postoperative mortality.[8,9] Despite this, red blood cells are administered in 52%–73% of patients undergoing cardiac surgery.[10]

In up to half of patients undergoing cardiac surgery, the cause of anemia is iron deficiency.[1,11] In addition to causing anemia, iron deficiency has been independently associated with death, serious adverse events and prolonged hospital stay after cardiac surgery.[12] Give the essential role of iron in erythropoiesis and hemoglobin synthesis, iron supplementation has been evaluated to correct iron deficiency and anemia in the perioperative period.[13–18]

In a recent meta-analysis, Schack and colleagues[19] evaluated the available literature on iron supplementation for major noncardiac surgery and found a reduction in rates of blood transfusion and death, whereas a Cochrane review of iron therapy in the noncardiac surgery population showed no difference.[20] In the cardiac surgery population, 2 recent meta-analyses showed iron to be useful for reducing the need for blood transfusion, but only when administered in combination with erythropoietin.[21,22]

The primary objective of this systematic review and meta-analysis is to evaluate the efficacy and safety of perioperative iron supplementation in patients undergoing cardiac surgery.

Methods

This review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines.[23] The protocol is registered in the International

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Prospective Register of Systematic Reviews (PROSPERO) (trial registration number CRD42020161927). In the event of protocol amendments, we will provide the date of the amendment and the rationale, and describe the change.

Eligibility criteria

We will include randomized controlled trials evaluating iron therapy, without erythropoietin, compared to placebo or no treatment.

Trials that include patients aged 18 years or more who underwent cardiac surgery will be included. Cardiac surgery will be defined as coronary artery bypass grafting or valve surgery. We will include surgical approaches via median sternotomy or thoracotomy, or robotic-assisted cardiac surgery.

We will include trials that evaluated the use of iron therapy from 8 weeks before surgery to 8 weeks after surgery. We selected this time frame in an attempt to include all potential studies, as the current timeline for administration has not been well established, and in large studies in the noncardiac surgery population, such as the PREVENTT Trial,[24] this therapy has been administered up to 6 weeks before surgery. There will be no restriction on the dosing of iron or the administration route (oral or intravenous). Some iron therapy examples include iron isomaltoside (Monofer [Pfizer]) and iron sucrose (Venofer [Luitpold Pharmaceuticals]).

Trials that compared iron therapy alone, without erythropoietin, versus placebo or no treatment will be included. If an active control (i.e., another medication) was used as a comparator, it will be excluded.

Outcomes

The primary outcome will be the incidence of red blood cell transfusion from the study drug intervention time until 8 weeks postoperatively. Given the timeline for follow-up of up to 4 weeks observed in the noncardiac literature,[24] we selected 8 weeks to be inclusive of as many studies as possible.

Secondary outcomes will include the number of red blood cell transfusions received, the change in ferritin level after iron administration, the change in reticulocyte count after iron administration, the change in hemoglobin concentration after iron administration and adverse events.

Search strategy

The search for relevant studies will include the following databases, with no language limits: MEDLINE (via Ovid, 1946 to Nov. 19, 2020), Embase Classic + Embase (via Ovid, 1947 to Nov. 19, 2020), the Cochrane Central Register of Controlled Trials (via the Cochrane Library, Issue 11 of 12, November 2020), clinicaltrials.gov, the Web of Science and the first 50 results from Google Scholar. The search strategy was piloted in MEDLINE (Appendix 1, available at www.cmajopen.ca/content/9/2/E623/suppl/DC1) by a hospital librarian (A.A.-Z.), and searched both text words and relevant indexing, where available, to identify publications. The MEDLINE strategy design will be applied to all databases, with modifications to adapt to the other databases as necessary. The search strategy was developed by 1 of the authors (A.A.-Z.) and was peer-reviewed by 2 other hospital librarians.

Identification and selection of studies

The search strategy results will be uploaded to the Rayyan Web application, which facilitates article identification and screening.[25] The titles and abstracts will be independently screened for eligibility by 4 reviewers (A.G., A.C., L.A.K., P.G.B.) in duplicate. We will perform calibration exercises to pilot the screening process. A random sample of 50 articles will be chosen. The reviewers will apply inclusion and exclusion criteria and will meet to discuss the level of agreement. Once a level of agreement greater than 90% is reached, formal screening will begin. If a reviewer believes that the citation fulfils the eligibility criteria, the manuscript will undergo a full-text review, which will be independently performed by 2 reviewers based on the eligibility criteria. In cases of disagreement, the reviewers will discuss and come to a consensus. If the reviewers are unable to agree, a third reviewer (S.S.Y. or M.J.C.) will make the final decision. A preconsensus level of agreement (Cohen κ coefficient) will be reported.

Data extraction

Two reviewers (S.S.Y. and M.J.C.) will independently perform data extraction in Microsoft Excel. Calibration exercises will be done to ensure consistency. Any discrepancies will be resolved through consensus.

For any missing or unclear data, we will contact the authors of the trial in question. Only complete data will be included in the systematic review and meta-analysis.

Risk of bias assessment

Two reviewers (S.S.Y. and M.J.C.) will independently assess the risk of bias. They will use the Cochrane Collaboration Risk of Bias Tool[26] to assess the following: random sequence generation and allocation concealment for selection bias, blinding of participants and personnel for performance bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting bias and other potential sources of bias. The risk of bias will be categorized as high, low or unclear. A consensus process will be used to resolve any discrepancies.

Quality of evidence

The quality of each outcome will be evaluated with the GRADE guidelines.[27] Two reviewers (S.S.Y. and M.J.C.) will examine the risk of bias, consistency, directness, imprecision and reporting bias of each outcome. Randomized controlled trials will initially be assumed to be of high quality and will then be downgraded based on the described criteria. The quality of the evidence will be categorized as high (the reviewers are confident that the estimated effect is close to the real effect), moderate (the reviewers are moderately confident that the result is close to the real effect), low (the reviewers have low confidence that the estimated effect is close to the true effect) or very low (the reviewers feel that the effect estimate is likely substantially different from the true effect).

Statistical analysis

To measure the treatment effect, the description of the administration route, dosage and timing of iron therapy for each trial will be provided in a table. We will analyze primary and secondary outcomes using a random-effects model (DerSimonian and Laird method) and Review Manager 5.3 (The Cochrane Collaboration). Point estimates and 95% confidence intervals will be reported. We will present continuous outcomes using mean difference, and dichotomous outcomes using risk ratio or risk difference. If the article provides a median and interquartile range, we will convert them to mean and standard deviation using the method described by Wan and colleagues.[5]

We will evaluate the included studies for statistical heterogeneity using the I^2 statistic. If substantial heterogeneity ($I^2 \geq 50\%$) is identified, we will perform subgroup analyses to explain the source of heterogeneity. The following subgroups, defined a priori, will be examined: male versus female, timing of iron administration, dosing of iron therapy, and presence of preoperative anemia versus absence of preoperative anemia.

Trial sequential analysis

Trial sequential analysis will estimate the required information size, as it accounts for study-level heterogeneity.[28] We will use TSA software, version 0.9 (Copenhagen Trial Unit) for the primary outcome. The calculation, defined a priori, will be based on an expected relative risk reduction of 30% with a 2-sided α of 0.05 and a power of 80%. The heterogeneity level will be assumed to be 30% within the cardiac surgery population, and the control event rate from the meta-analysis will be used.

Sensitivity analysis

We will perform sensitivity analysis to evaluate potential sources of bias resulting from trials that are deemed as having a high risk of bias. We will also construct a funnel plot to verify for any publication bias.

Ethics approval

Ethics approval is not required for this systematic review and meta-analysis.

Interpretation

This systematic review and meta-analysis will summarize the current evidence for the preoperative administration of iron without erythropoietin in patients undergoing cardiac surgery. Currently, preoperative administration of iron is not standard for patients with anemia who present for cardiac surgery. The findings of this systematic review and meta-analysis may support the creation of formal recommendations regarding iron therapy for patients undergoing cardiac surgery and help with future research design if needed.

It is possible that a positive result may be shown in our study but that the studies included will be of insufficient quality to support the creation of a formal recommendation, similar to what was observed by Schack and colleagues[19] in their meta-analysis evaluating a similar therapy in patients undergoing noncardiac surgery. The Intravenous Iron for the Treatment of Anaemia Before Cardiac Surgery (ITACS) trial, aimed at determining the efficacy, safety and cost-effectiveness of preoperative iron therapy in patients with anemia before elective cardiac surgery, is currently underway (NCT-02632760); however, it is not expected to be completed before October 2023.

The results of our study will be submitted for presentation at a conference and to a peer-reviewed journal.

Limitations

Limitations include the difficulty to account for all confounding factors leading to perioperative blood transfusion, including baseline hemoglobin values, transfusion thresholds, and coagulation status and management. Also, the potential heterogeneity of the studies included may limit the ability to answer our study question correctly. Finally, there is the possibility that some of the grey literature may be missed.

Conclusion

This study will have potential implications for the roughly 50% of patients undergoing cardiac surgery who have anemia, and may potentially help guide prehabilitation protocols before cardiac surgery.

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