Can J Anesth/J Can Anesth (2022) 69:129–139
https://doi.org/10.1007/s12630-021-02113-z

REVIEW ARTICLE/BRIEF REVIEW

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

Supplémentation en fer pour les patients bénéficiant d'une chirurgie cardiaque : une revue systématique et une méta-analyse d'études randomisées contrôlées

Stephen Su Yang, MDCM, MSc · Latifa Al Kharusi, MD · Adam Gosselin, MDCM · Anissa Chirico, MDCM · Pouya Gholipour Baradari, MDCM · Matthew J. Cameron, MDCM, MPH

Received: 26 April 2021 / Revised: 11 August 2021 / Accepted: 12 August 2021 / Published online: 24 September 2021

Abstract

Purpose *Iron supplementation has been evaluated in several randomized controlled trials (RCTs) for its potential to increase baseline hemoglobin and decrease red blood cell transfusion during cardiac surgery. This study's main objective was to evaluate the current evidence for iron administration in cardiac surgery patients.*

Methods *We searched MEDLINE, EMBASE, CENTRAL, Web of Science databases, and Google Scholar from inception to 19 November 2020 for RCTs evaluating perioperative iron administration in adult patients undergoing cardiac surgery. The RCTs were assessed using a risk of bias assessment and the quality of evidence was assessed using the grading of recommendations, assessments, development, and evaluations.*

Results *We reviewed 1,767 citations, and five studies (n = 554) met the inclusion criteria. The use of iron showed no statistical difference in incidence of transfusion (risk ratio, 0.86; 95% confidence interval, 0.65 to 1.13). Trial sequential analysis suggested an optimal information size of 1,132 participants, which the accrued information size did not reach.*

Conclusion *The current literature does not support or refute the routine use of iron therapy in cardiac surgery patients.*

Trial registration *PROSPERO (CRD42020161927); registered 19 December 2019.*

Résumé

Objectif *La supplémentation en fer a été évaluée dans plusieurs études randomisées contrôlées (ERC) pour son potentiel à augmenter l'hémoglobine de base et à diminuer la transfusion d'érythrocytes pendant la chirurgie cardiaque. L'objectif principal de cette étude était d'évaluer les données probantes actuelles soutenant l'administration de fer chez les patients de chirurgie cardiaque.*

Méthode *Nous avons effectué des recherches dans les bases de données MEDLINE, EMBASE, CENTRAL, Web of Science et Google Scholar de leur création jusqu'au 19 novembre 2020 pour en extraire les ERC évaluant l'administration périopératoire de fer chez les patients adultes bénéficiant d'une chirurgie cardiaque. Les ERC ont été évaluées à l'aide d'une évaluation du risque de biais et la qualité des données probantes a été évaluée à l'aide du système de notation GRADE.*

Résultats *Nous avons examiné 1767 citations et cinq études (n = 554) répondaient aux critères d'inclusion.*

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12630-021-02113-z.

S. S. Yang, MDCM, MSc (✉) · M. J. Cameron, MDCM, MPH
Faculty of Medicine, McGill University, Montreal, QC, Canada
e-mail: stephen.yang@mail.mcgill.ca

Division of Critical Care, Department of Anesthesia, Jewish General Hospital, K1400-3755, Cote Sainte Catherine, Montreal, QC H3T 1E2, Canada

L. Al Kharusi, MD · A. Gosselin, MDCM · A. Chirico, MDCM · P. G. Baradari, MDCM
Faculty of Medicine, McGill University, Montreal, QC, Canada

L'administration de fer n'a montré aucune différence statistique dans l'incidence des transfusions (risque relatif, 0,86; intervalle de confiance à 95 %, 0,65 à 1,13). Selon l'analyse séquentielle des études, la taille d'information optimale serait de 1132 participants, une taille que l'information accumulée n'a pas atteint.

Conclusion *La littérature actuelle ne soutient ni ne réfute l'utilisation systématique d'une thérapie à base de fer chez les patients de chirurgie cardiaque.*

Enregistrement de l'étude *PROSPERO (CRD42020161927); enregistrée le 19 décembre 2019.*

Keywords Cardiac surgery · Iron · Anemia · Blood transfusion

Anemia is common in patients presenting for cardiac surgery, present in up to 54% of patients.[1] Preoperative anemia is a significant risk factor for perioperative red blood cell (RBC) transfusion, which is associated with various complications such as surgical site infection,[2, 3] pneumonia,[4] acute lung injury, postoperative atrial fibrillation,[5] coronary artery graft occlusion,[6] and risk-adjusted postoperative mortality.[7, 8] Strategies have been developed to minimize blood transfusion, but despite this, RBC transfusions are administered in 52–73% of cardiac surgery patients, with preoperative anemia contributing to this need for transfusion.[9]

In up to half of cardiac surgery patients, the etiology of preoperative anemia is iron deficiency.[1, 10] Iron deficiency is independently associated with postoperative mortality, serious adverse events, and prolonged hospital stay after cardiac surgery.[11] The ability of iron supplementation to correct iron deficiency anemia in non-cardiac surgery patients during the perioperative period has been evaluated because iron has an essential role in erythropoiesis and hemoglobin synthesis.[12–17] A recent meta-analysis in non-cardiac surgery found a reduction in transfusion and mortality rates in patients receiving iron supplementation. Nevertheless, a Cochrane review of the topic found no benefit in the same non-cardiac surgery population.[18, 19]

Despite the large number of cardiac surgery patients who present with iron deficiency anemia, the currently available evidence was insufficient to provide any recommendation in the most recent Guidelines for Perioperative Care in Cardiac Surgery.[20] Given the ease of administration and low incidence of side effects, perioperative iron administration would be an ideal therapy to include in future enhanced recovery programs for cardiac surgery.

This systematic review and meta-analysis's primary objectives were to determine the effectiveness and safety of iron supplementation in cardiac surgery. We evaluated the effect of iron administration on perioperative RBC transfusion, its potential upstream physiologic effects, and the adverse events associated with this therapy.

Methods

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020161927) on 19 December 2019. This review was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Electronic Supplementary Material [ESM] eAppendix 1).[21]

Eligibility criteria

Study design

Prospective randomized controlled trials (RCTs) were included in this review.

Population

Adult patients (≥ 18 yr of age) who underwent elective cardiac surgery were included. Cardiac surgery was defined as coronary artery bypass grafting and/or valve surgery.

Intervention

Trials that evaluated iron therapy were selected, including intravenous or oral administration, regardless of the dosing regimen. The timing of iron administration was restricted from eight weeks before surgery to eight weeks after surgery.

Comparators

Trials that compared iron therapy with a placebo or a no-treatment control group were included. Trials that used an active control as a comparator, i.e., another medication, were excluded.

Outcomes

The primary outcome was the incidence of perioperative RBC transfusion. Secondary outcomes included the number of RBC transfusions received, postoperative hemoglobin levels, postoperative ferritin levels, postoperative reticulocyte count, postoperative transferrin saturation, and adverse events.

Search strategy

The search for relevant studies included: MEDLINE, Embase, The Cochrane Central Register of Controlled Trials, Web of Science, and Google Scholar. The search was conducted from database inception to 19 November 2020 and the search strategy was developed in MEDLINE and applied to all databases with modifications (ESM eAppendix 2). There were no language limits. Search strategies were peer-reviewed by two other librarians.

Data management and selection process

The search strategy results were uploaded to Rayyan QCRI, a web-based application allowing the independent evaluation of citations and abstracts by multiple independent reviewers.[22] Titles and abstracts were independently screened in duplicates by two of the four reviewers (L.A.K., A.G., A.C., P.G.B.) using pre-defined eligibility criteria. If either of the two reviewers believed that the citation fulfilled the pre-specified eligibility criteria, the manuscript underwent a full-text review. The full-text review of each article was independently performed by two reviewers (S.S.Y., M.J.C.) to determine if it fulfilled the eligibility criteria. In the case of a disagreement between two reviewers, a consensus discussion was completed. If the reviewers were unable to agree, a third reviewer (L.A.K.) would make the final decision.

Data extraction process

Two reviewers (S.S.Y., M.J.C) independently performed data extraction in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Calibration exercises were undertaken to ensure consistency. Any discrepancies were resolved through a consensus. For any missing or unclear data, we contacted the authors of the trials. Only complete data were included in the final analysis.

Risk of bias assessment

Two reviewers (S.S.Y., M.J.C.) independently performed the risk of bias assessment. The Cochrane Collaboration Risk of Bias Tool[23] was used 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 was categorized as high risk, low risk, or unclear. A consensus process was used to resolve any discrepancies.

Quality of evidence

The quality of each outcome was evaluated using the grading of recommendations, assessments, development and evaluations (GRADE) guidelines.[24] Two reviewers examined the risk of bias, inconsistency, indirectness, imprecision, and publication bias of each outcome. The quality of the evidence was categorized as high (the reviewers were confident that the estimated effect is close to the real effect), moderate (the reviewers were moderately confident that the result is close to the real effect), low (the reviewers had low confidence that the estimated effect is close to the true effect), or very low (the reviewers felt that the effect estimate is likely substantially different from the true effect).

Trial sequential analysis

Trial sequential analysis (TSA) was used to estimate the required information size for the primary outcome[25] (TSA software version 0.9, Copenhagen Trial Unit, Copenhagen, Denmark). The calculation defined *a priori* was based on an anticipated 30% relative risk reduction using a two-sided alpha of 0.05 and a power of 80%. The heterogeneity level was assumed to be 30% within the cardiac surgery population, and the control event rate from the meta-analysis was used.

Statistical analysis

Primary and secondary outcomes were analyzed using a random-effects model (DerSimonian and Laird method) using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).[5] Point estimates and 95% confidence intervals (CI) are reported. Continuous outcomes are presented using mean differences (MD), and dichotomous outcomes are presented using the risk ratio (RR) or risk difference (RD). If an article provided a median and interquartile range, it was converted to mean and standard deviation using the method described by Wan *et al.*[26]

Assessment of heterogeneity

The included studies were evaluated for statistical heterogeneity using the I^2 statistic. If substantial heterogeneity ($I^2 \geq 50\%$) was identified, subgroup analyses, defined *a priori,* were performed to explain the source of heterogeneity. *P* values for subgroup analyses were presented based on a test of interaction between the groups.

Sensitivity analysis

Sensitivity analysis was used to evaluate potential sources of bias resulting from trials deemed at high risk of bias.

Results

A total of 2,039 articles were identified from the primary electronic databases (564 from MEDLINE, 1,092 from EMBASE, 106 from CENTRAL, and 277 from Web of Science), and 50 articles were identified from Google Scholar. After removing duplicates, 1,767 articles were screened, and 46 articles were retrieved for full-text review. Five articles were identified for inclusion in the meta-analysis (Fig. 1).[13, 17, 27–29] The agreement between two independent reviewers during the screening process showed moderate agreement ($\kappa = 0.73$), and during the full-text review was considered in almost perfect agreement ($\kappa = 0.87$).

Included trials

Five trials were included, with a total of 554 participants.[13, 17, 27–29] All studies were RCTs with a placebo[13, 17, 27–29] or no-treatment[27] control arm. The trials were conducted in the following countries: USA,[27] Spain,[28] Denmark,[17] Lebanon,[29] and China.[13] The mean age of participants ranged from 54.4 to 65.0, and the proportion of males ranged from 45% to 90%. All trials included cardiac surgery using cardiopulmonary bypass.[13, 17, 27–29] One trial included only valve surgery[13] and another trial included only coronary artery bypass surgery.[27] Four trials used intravenous iron[13, 17, 28, 29] and three trials used oral iron supplementation.[27–29] Two trials gave iron therapy preoperatively[17, 28] and three trials gave iron therapy postoperatively (Table 1).[13, 27, 29]

Risk of bias and GRADE assessment

Three trials were judged to be at low risk of bias in all domains. One trial had a high risk of bias related to incomplete outcome data (attrition bias) and other sources

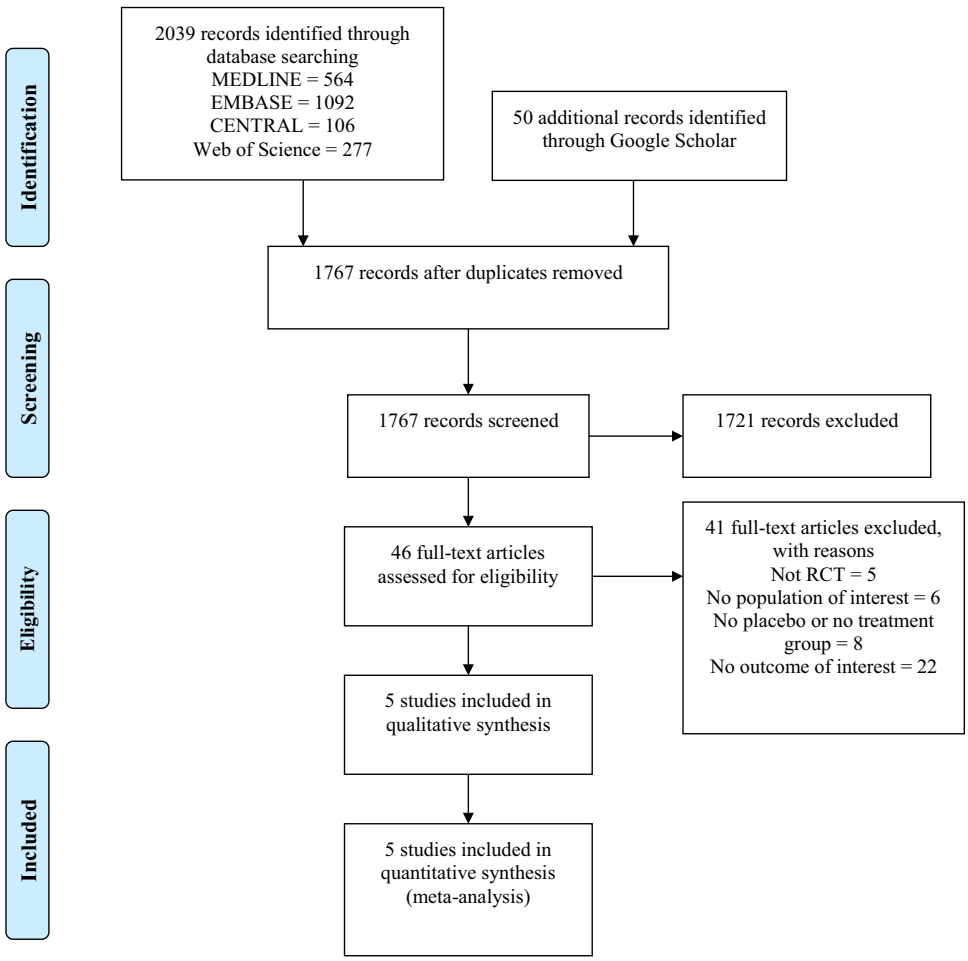

Fig. 1 Flow diagram of trial selection

Table 1 Study characteristics

Trial	Country	Age (mean)	% male	Sample size	Surgery	Intervention/comparator	Timing of iron administration	Outcomes
Crosby 1994[27]	USA	64.7	83	121	CABG	*Intervention* 1. 50 mg oral elemental iron 2. 200 mg oral elemental iron *Comparator* 1. Placebo 2. No-treatment control	8 weeks post surgery	1. Hemoglobin 2. Ferritin 3. Adverse events
Garrido-Martin 2012[28]	Spain	65.0	73	159	Cardiac surgery using cardiopulmonary bypass	*Intervention* 1. IV iron(III)-hydroxide sucrose complex, three doses of 100 mg 2- Oral ferrous fumarate iron *Comparator* Oral and IV placebo	24 hr preoperatively	1. Transfusion 2. Hemoglobin 3. Ferritin 4. Reticulocyte count 5. Adverse events
Johansson 2015[17]	Denmark	65.0	87	60	1. CABG 2. Valve surgery 3. Combination of CABG and valve surgery	*Intervention* Iron isomaltoside 1,000 mg IV single-dose over 15 min *Comparator* Placebo	Preoperative: day before or same day as surgery	1. Transfusion 2. Number of pRBC units 3. Hemoglobin 4. Transferrin saturation 5. Adverse events
Madi-Jebara 2004[29]	Lebanon	57.4	90	94	Cardiac surgery using cardiopulmonary bypass	*Intervention* IV iron sucrose 100 mg *Comparator* Placebo	Postoperative day 1	1. Transfusion 2. Hemoglobin 3. Ferritin 4. Reticulocyte count 5. Adverse events
Xu 2019[13]	China	54.4	45	150	Valve surgery using cardiopulmonary bypass	*Intervention* IV iron sucrose 200 mg *Comparator* Placebo	Postoperative day 1	1. Transfusion 2. Hemoglobin 3. Ferritin 4. Transferrin saturation 5. Adverse events

CABG coronary artery bypass surgery; *IV* intravenous; *pRBC* packed red blood cells

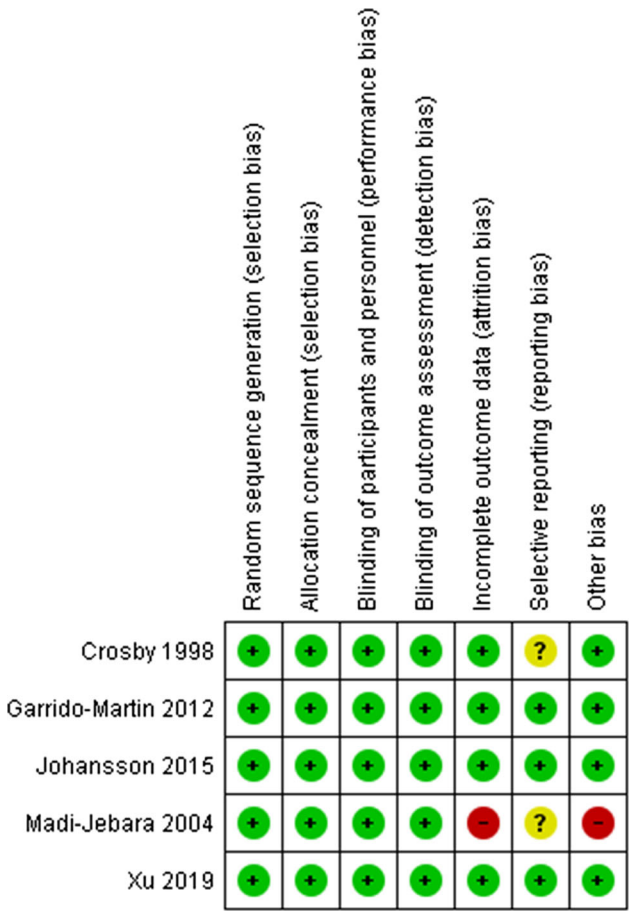

Fig. 2 Risk of bias assessment for randomized controlled trials

of bias (i.e., excluded patients who received transfusion). One trial was deemed an unclear risk of bias related to selective reporting (reporting bias) (Fig. 2 and ESM eAppendix 3). The GRADE assessment showed an overall moderate level of evidence for the following outcomes: incidence of transfusion, hemoglobin level on postoperative day 5, transferrin saturation on postoperative day 0–1, and serious adverse events. The levels of evidence were considered low for the following outcomes: hemoglobin on discharge, number of packed red blood cells transfused, ferritin on postoperative day 0–1, ferritin on postoperative day 5, ferritin on discharge, transferrin saturation on postoperative day 5, and transferrin saturation on discharge. The levels of evidence were considered very low for hemoglobin on postoperative day 0–1, reticulocyte count on postoperative day 0–1, reticulocyte count on postoperative day 5, and reticulocyte count on discharge (ESM eAppendix 4).

Reported outcomes

Primary outcome

Based on the pooling of data from four trials (n = 449), the use of iron showed no statistical difference in the incidence of transfusion (RR, 0.86; 95% CI, 0.65 to 1.13). There was low heterogeneity between studies (I^2 = 0%) (Fig. 3). The TSA suggested an optimal information size of 1,132 participants, which the accrued information size did not reach (Fig. 4).

Secondary outcomes

One trial (n = 60) reported a significant decrease in the number of red blood cells transfused (MD, -1.0 units; 95% CI, −1.6 to −0.3) (ESM eAppendix 5 and Table 2).

Three trials with 368 participants showed iron therapy led to no statistical difference in early postoperative hemoglobin change (i.e., postoperative day 0–1) (MD, −1.5 $g{\cdot}L^{-1}$; 95% CI, −7.7 to 4.7). There was high heterogeneity between studies (I^2 = 78%). Sensitivity analysis showed no statistical difference after removal of high risk of bias studies (MD, 1.7 $g{\cdot}L^{-1}$; 95% CI, −1.5 to 5.0). Five trials examined postoperative hemoglobin day 5 with 552 participants. There was no statistical difference between iron therapy and the control group (MD, −1.8 $g{\cdot}L^{-1}$; 95% CI, −4.0 to 0.4) with moderate heterogeneity (I^2 = 51%). The pooling of the data from five trials (n = 552) that examined hemoglobin level at the time of discharge showed that iron therapy did not lead to a change in hemoglobin level (MD, 1.4 $g{\cdot}L^{-1}$; 95% CI, −3.9 to 6.6) with a high level of heterogeneity (I^2 = 93%) (ESM eAppendix 6).

Pooling the data from four trials (n = 489) showed that iron therapy did not lead to a difference in ferritin levels on postoperative day 0–1 (MD, 13.8 $ng{\cdot}mL^{-1}$; 95% CI, −22.5 to 50.1) with a substantial heterogeneity (I^2 = 75%). On postoperative day 5, pooling of the data from three trials (n = 368) showed a large increase in ferritin level with the use of iron therapy (MD, 375.4 $ng{\cdot}mL^{-1}$; 95% CI, 252.7 to 498.2) with a substantial level of heterogeneity (I^2 = 68%). At the time of discharge, four trials (n = 489) showed that iron therapy led to a large increase in ferritin level (MD, 173.4 $ng{\cdot}mL^{-1}$; 95% CI, 2.9 to 343.9) with a high level of heterogeneity (I^2 = 97%) (ESM eAppendix 7).

The two trials (n = 220) reporting reticulocyte count showed that iron therapy did not lead to any difference on postoperative day 0–1 (MD, −0.1%; 95% CI, −0.5 to 0.3) with substantial heterogeneity (I^2 = 73%). On postoperative day 5, two trials (n = 220) reported no difference in reticulocyte count (MD, 0.1%; 95% CI, −0.4 to 0.6) with moderate heterogeneity (I^2 = 53%). At the time of

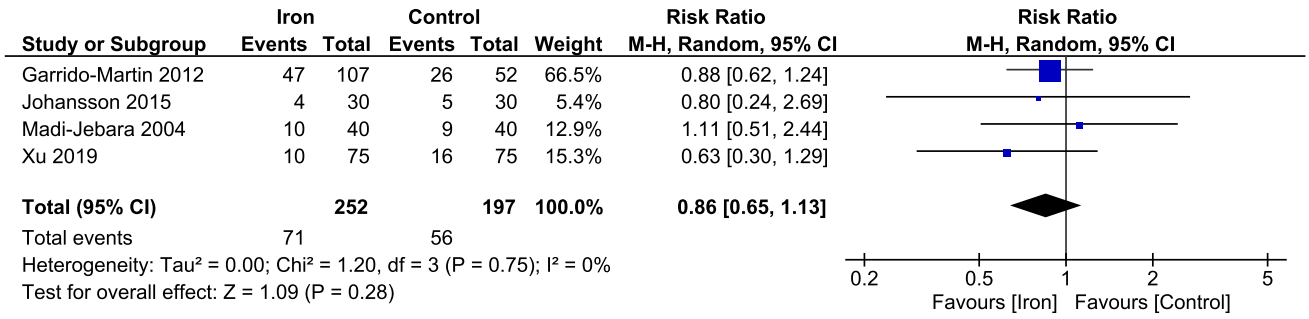

Fig. 3 Incidence of transfusion

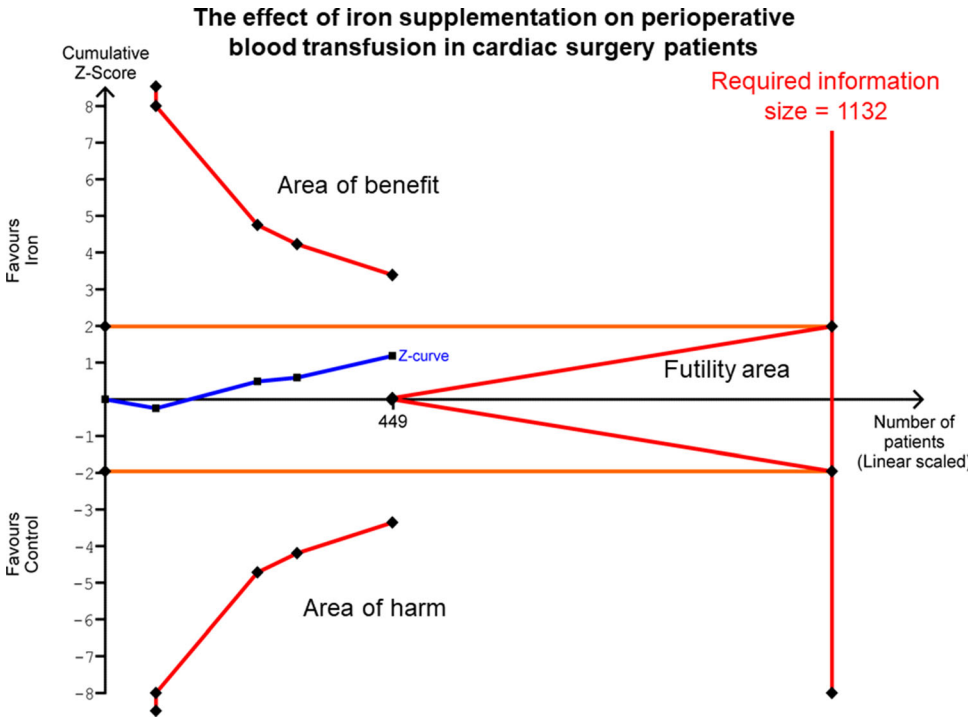

Fig. 4 Trial sequential analysis on perioperative blood transfusion

discharge, pooling of the data from two trials (n =220) showed no difference in reticulocyte count (MD, 0.8%; 95% CI, −0.7 to 2.3) with a high level of heterogeneity (I^2 = 94%) (ESM eAppendix 8).

Two trials (n = 208) reported transferrin saturation on postoperative day 0–1 and showed a considerable reduction with the use of iron therapy (MD, −1.8%; 95% CI, −2.6 to −0.9) with a low level of heterogeneity (I^2 = 0%). The pooling of the data from two trials (n = 208) showed no difference in transferrin saturation on postoperative day 5 (MD, 7.5%; 95% CI, −3.3 to 18.3) with a high level of heterogeneity (I^2 = 99%). At the time of discharge, two trials showed that the use of iron did not lead to any difference in transferrin saturation (MD, 3.6%; 95% CI, −1.1 to 8.3) with a high level of heterogeneity (I^2 = 95%) (ESM eAppendix 9).

All five trials (n = 554) showed no difference in serious adverse events using iron therapy (RD, 0.0; 95% CI, −0.0 to 0.0) (Fig. 5). One trial reported adverse events in both the iron and control groups, including atrial fibrillation, pericardial effusion, and post-procedural hemorrhage. Another trial reported death in two patients in the placebo group.

Subgroup analyses

Oral vs intravenous iron

Hemoglobin level on postoperative day 0–1 and on day 5 did not show a statistically significant subgroup difference with regards to the route of iron administration (P = 0.37 and P = 0.13). The hemoglobin level on discharge was not statistical significant between intravenous iron administration (MD, 2.8; 95% CI, −3.3 to 8.9) compared with oral iron administration (MD, −1.5; 95% CI, −4.4 to 1.5; P = 0.22). Ferritin level on postoperative day 0–1 did

Table 2 Summary of meta-analysis; results by outcome

Outcomes	Studies	Participants	Statistical methods	Effect estimate	I^2
Incidence of transfusion	4	449	Risk ratio (random, 95% CI)	0.86 (0.65 to 1.13)	0%
Number of RBC transfusions	1	60	Mean difference (random, 95% CI)	− 1.0 (− 1.6 to − 0.3)	NA
Hemoglobin—postoperative day 0–1	3	368	Mean difference (random, 95% CI)	− 1.5 (− 7.7 to 4.7)	78%
Hemoglobin—postoperative day 5	5	552	Mean difference (random, 95% CI)	− 1.8 (− 4.0 to 0.4)	51%
Hemoglobin—on discharge	5	552	Mean difference (random, 95% CI)	1.4 (− 3.9 to 6.6)	93%
Ferritin—postoperative day 0–1	4	489	Mean difference (random, 95% CI)	13.8 (− 22.5 to 50.1)	75%
Ferritin—postoperative day 5	3	368	Mean difference (random, 95% CI)	375.4 (252.7 to 498.2)	68%
Ferritin—on discharge	4	489	Mean difference (random, 95% CI)	173.4 (2.9 to 343.9)	97%
Reticulocyte count—postoperative day 0-1	2	220	Mean difference (random, 95% CI)	− 0.1 (− 0.5 to 0.3)	73%
Reticulocyte count—postoperative day 5	2	220	Mean difference (random, 95% CI)	0.1 (− 0.4 to 0.6)	53%
Reticulocyte count—on discharge	2	220	Mean difference (random, 95% CI)	0.8 (− 0.7 to 2.3)	94%
Transferrin saturation—postoperative day 0–1	2	208	Mean difference (random, 95% CI)	− 1.8 (− 2.6 to − 0.9)	0%
Transferrin saturation—postoperative day 5	2	208	Mean difference (random, 95% CI)	7.5 (−3.3 to 18.3)	99%
Transferrin saturation—on discharge	2	208	Mean difference (random, 95% CI)	3.6 (− 1.1 to 8.3)	95%
Serious adverse events	5	554	Risk difference (random, 95% CI)	0.0 (− 0.0 to 0.0)	0%

CI confidence interval; *RBC* red blood cell; *NA* not applicable.

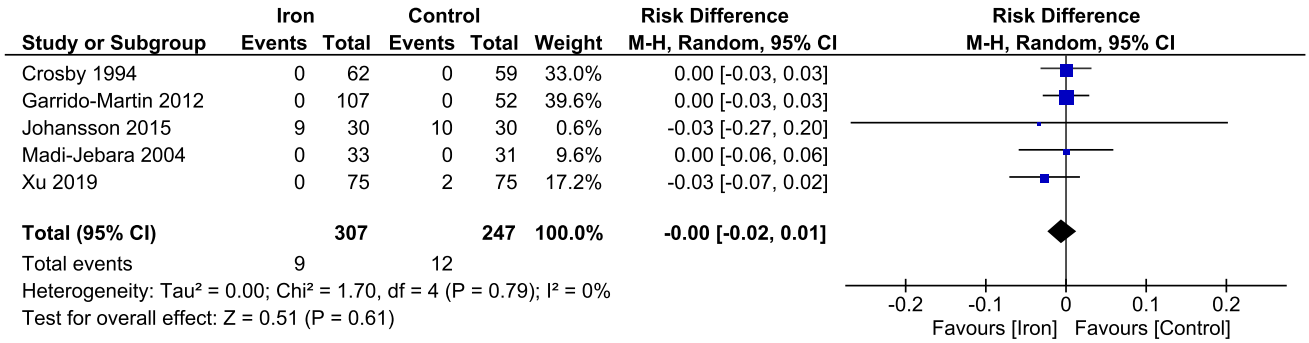

Fig. 5 Serious adverse events

not have a subgroup effect related to the oral *vs* intravenous iron administration (P = 0.78). Nevertheless, intravenous administration of iron led to a greater increase in in ferritin level on postoperative day 5 (MD, 511.2; 95% CI, 200.0 to 822.4 *vs* MD, 56.0; 95% CI, −99.5 to 211.5; P = 0.01) and on discharge (MD, 294.7; 95% CI, 216.2 to 373.1 *vs* MD, 3.3; 95% CI, −4.0 to 10.6; $P < 0.001$). There was no subgroup effect concerning reticulocyte count on postoperative day 0–1 (P = 0.28), on day 5 (P = 0.76), and on discharge (P = 0.22) (ESM eAppendix 10).

Preoperative vs postoperative iron

There was no subgroup effect for hemoglobin level on postoperative day 0–1 (P = 0.51), on day 5 (P = 0.09), and on discharge (P = 0.09). Preoperative iron led to a higher ferritin level on postoperative day 0–1 (MD, 83.7; 95% CI, 32.6 to 134.9) compared with postoperative iron administration (MD, −6.8; 95% CI, −15.6 to 2.0; $P <$ 0.001). This effect on ferritin was not sustained on postoperative day 5 (P = 0.34) and on discharge (P = 0.82). There was a small increase in reticulocyte count on postoperative day 0–1 in the preoperative administration group (MD, 0.1; 95% CI, −0.2 to 0.3) compared with postoperative iron (MD, −0.4; 95% CI, −0.7 to −0.0; P = 0.05). There was no subgroup effect on postoperative day 5 in terms of reticulocyte count (P = 0.14). On discharge, postoperative iron led to a higher reticulocyte count (MD, 1.6; 95% CI, 0.9 to 2.3) compared with preoperative iron (MD, 0.1; 95% CI, −0.1 to 0.3; $P < 0.001$). There was no subgroup effect on transferrin saturation on postoperative day 0–1. On postoperative day 5, there was a strong effect favouring preoperative iron (MD, 13.0; 95% CI, 12.2 to 13.8) compared with postoperative iron (MD, 2.0; 95% CI, 0.3 to 3.7; $P < 0.001$). A similar effect was seen on discharge favouring preoperative iron (MD, 6.0; 95% CI,

4.5 to 7.5 *vs* MD, 1.2; 95% CI, −0.3 to 2.7; $P < 0.001$) (ESM eAppendix 11).

Discussion

This systematic review and meta-analysis of RCTs on perioperative iron administration in cardiac surgery patients did not show any effects on the postoperative outcomes of interest.[18] This indicates that there are currently insufficient RCTs to justify the routine perioperative administration of iron to cardiac surgery patients. The TSA showed that more than twice the currently available number of patients studied would be required for a meta-analysis to conclude whether there is a difference in perioperative blood transfusion's primary outcome. Nevertheless, when examining the laboratory values, the impact of iron administration led to important efficacy endpoints. The hemoglobin level, ferritin level, reticulocyte count, and transferrin saturation appeared to increase with time postoperatively. These findings are hypothesis-generating to suggest the importance of ensuring an appropriate time to onset of action with iron therapy. This is further shown in our subgroup analysis of preoperative iron *vs* postoperative iron administration. Preoperative iron led to a higher hemoglobin level, ferritin level, and transferrin saturation. The duration of treatment for iron deficiency anemia differs among experts. Some would treat for six to eight weeks, while others continue for as long as six months to replete iron stores.[30] Both the trend in laboratory findings and this subgroup analysis showed the importance of starting iron therapy as early as possible to ensure it has time to take effect before the insult of cardiac surgery.

In terms of route of administration, our subgroup analyses showed that intravenous iron may be more efficacious and led to a consistent increase in hemoglobin, ferritin level, and reticulocyte count. This may be because oral formulation, such as ferrous sulfate, is often poorly tolerated and can lead to significant gastrointestinal side effects in up to 70% of individuals.[30] This would significantly impact patient's compliance with the medication. Furthermore, some patients may be nonresponsive to the oral formulation. Patients with high levels of hepcidin may be nonresponsive to oral iron supplement, but may subsequently respond to intravenous iron.[31]

More importantly, our study showed that there was no increase in adverse events. Cardiac surgery patients with iron deficiency have been shown to be independently at risk of increased mortality, serious adverse events, and major cardiac and cerebrovascular events.[11] These findings highlight the importance of preoperative screening for iron deficiency. Although unclear at this time, its replacement may improve outcomes in the at-risk population. In the non-cardiac surgery population, the current evidence is mixed. In a systematic review of 13 studies, the use of intravenous iron led to a decrease in 30-day mortality and a reduction in blood transfusion.[18] In the PREVENTT trial, a double-blinded RCT that randomized patients undergoing major abdominal surgery to intravenous iron *vs* placebo, there was no difference between the two groups with related to death and blood transfusion.[32] Nevertheless, in terms of secondary outcomes, there was a significant decrease in readmission in the iron group. This suggests that there may be additional clinical benefits seen with iron therapy other than to increase hemoglobin level.

There are some limitations to this meta-analysis. First, cardiac surgeries are often performed during the same hospital admission that a cardiac lesion is found, which may not leave enough time for hemoglobin levels to rise. Recent iron therapy trials have typically administered the study drug at least ten days before surgery.[32] Furthermore, different forms of iron were administered in the studies included, which used varying doses and timing relative to surgery. More consistency in the timing, dose, and formulation of iron would likely reduce heterogeneity and subsequently reduce the optimal information size required, allowing a better chance for such a meta-analysis to be conclusive.[33] Also, commonly accepted transfusion thresholds have changed over time and likely varied in the different studies included in this meta-analysis. A consistent transfusion threshold in all patients would be essential in reducing the potential confounding of this outcome. The included studies also lacked outcomes, allowing patient-centred outcomes, such as functional status, discharge home, and mortality, to be evaluated. Finally, although iron deficiency is among the most common causes of anemia, there are other potential causes that would not be adequately treated by iron supplementation. Spahn *et al.* completed an RCT comparing a combination therapy of intravenous iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid *vs* placebo. They showed that this combination was effective at reducing blood product transfusion in patients with preoperative anemia or iron deficiency anemia.[14] This suggests that iron alone may be adequate to prevent blood transfusion.[34] This is supported by a systematic review of 25 studies looking at all types of surgeries, the combination of erythropoietin and iron led to a reduction in blood transfusion.[35] Another systematic review examining cardiac and elective orthopedic patients showed a reduction in blood transfusion with the use of preoperative erythropoietin.[36] While this approach has the advantage of treating multiple potential causes of anemia, this combination comes with a significant additional

expense – the need for intravenous access and therefore hospital admission. Erythropoetin in particular has a Food and Drug Administration black box warning for the potential increased risk of deep vein thrombosis. In addition, without evaluating these treatments separately, it is not possible to understand their individual influences on outcomes.

Our systematic review has identified a critical knowledge gap given the large number of anemic patients presenting for surgery, the high rate of transfusion in cardiac surgery, and the elevated relative risk of postoperative morbidity. A relatively simple intervention such as preoperative iron supplementation would be ideal for routine inclusion in enhanced recovery protocols for cardiac surgery, which are currently in development. The ITACS trial is a randomized controlled, double-blind study comparing iron to placebo in 1,000 cardiac surgery patients. Recruitment is currently underway, but the study is only due to be completed in October 2023 (ClinicalTrials.gov, NCT02632760; last checked 3 June 2021). Anemia is a complex disorder with a very heterogenous pathophysiology. Some treatments of anemia have led to cardiovascular and cellular changes as well as a reduction in RBC transfusion. Nevertheless, the more important question remains as none of the treatments reduced organ injury or mortality in large prospective trials.[37]

Conclusion

The current evidence does not support or refute the routine use of iron therapy in cardiac surgery patients for the purpose of transfusion avoidance. Nevertheless, there is evidence of a significant surrogate laboratory effect with iron therapy and this may be beneficial in a specific high-risk population, such as those identified with iron deficiency anemia preoperatively. The data accumulated do not confirm the improved patient outcomes shown in non-cardiac surgery. A large-scale, prospective RCT on this topic is merited.

Author contributions *Stephen Su Yang*, *Matthew J. Cameron*, *Latifa Al Kharusi*, *Pouya Gholipour Baradari*, *Adam Gosselin*, and *Anissa Chirico* contributed to study conception and design and drafting the manuscript. *Stephen Su Yang*, *Matthew J. Cameron*, *Latifa Al Kharusi*, *Pouya Gholipour Baradari*, and *Anissa Chirico* contributed to acquisition and analysis of data. *Stephen Su Yang* and *Matthew J. Cameron* contributed to interpretation of data.

Disclosures None.

Funding statement Matthew J. Cameron holds a foundation grant from *la Fondation d'anesthésiologie and réanimation du Québec*.

Editorial responsibility This submission was handled by Dr. Philip M. Jones, Deputy Editor-in-Chief, *Canadian Journal of Anesthesia/ Journal canadien d'anesthésie*

References

1. *Hung M, Besser M, Sharples LD, Nair SK, Klein AA.* The prevalence and association with transfusion, intensive care unit stay and mortality of pre-operative anaemia in a cohort of cardiac surgery patients. Anaesthesia 2011; 66: 812-8.
2. *Gulack BC, Kirkwood KA, Shi W, et al.* Secondary surgical-site infection after coronary artery bypass grafting: a multi-institutional prospective cohort study. J Thorac Cardiovasc Surg 2018; 155: 1555-62.e1.
3. *Cutrell JB, Barros N, McBroom M, et al.* Risk factors for deep sternal wound infection after cardiac surgery: influence of red blood cell transfusions and chronic infection. Am J Infect Control 2016; 44: 1302-9.
4. *Likosky DS, Paone G, Zhang M, et al.* Red blood cell transfusions impact pneumonia rates after coronary artery bypass grafting. Ann Thorac Surg 2015; 100: 794-800; discussion 801.
5. *Alameddine AK, Visintainer P, Alimov VK, Rousou JA.* Blood transfusion and the risk of atrial fibrillation after cardiac surgery. J Card Surg 2014; 29: 593-9.
6. *Engoren M, Schwann TA, Jewell E, et al.* Is transfusion associated with graft occlusion after cardiac operations? Ann Thorac Surg 2015; 99: 502-8.
7. *Tantawy H, Li A, Dai F, et al.* Association of red blood cell transfusion and short- and longer-term mortality after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2018; 32: 1225-32.
8. *LaPar DJ, Hawkins RB, McMurry TL, et al.* Preoperative anemia versus blood transfusion: which is the culprit for worse outcomes in cardiac surgery? J Thorac Cardiovasc Surg 2018; 156: 66-74.e2.
9. *Mazer CD, Whitlock RP, Fergusson DA, et al.* Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 2017; 377: 2133-44.
10. *Patel KV.* Epidemiology of anemia in older adults. Semin Hematol 2008; 45: 210-7.
11. *Rössler J, Schoenrath F, Seifert B, et al.* Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. Br J Anaesth 2020; 124: 25-34.
12. *Silverberg DS, Iaina A, Peer G, et al.* Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. Am J Kidney Dis 1996; 27: 234-8.
13. *Xu H, Duan Y, Yuan X, Wu H, Sun H, Ji H.* Intravenous iron versus placebo in the management of postoperative functional iron deficiency anemia in patients undergoing cardiac valvular surgery: a prospective, single-blinded, randomized controlled trial. J Cardiothorac Vasc Anesth 2019; 33: 2941-8.
14. *Spahn DR, Schoenrath F, Spahn GH, et al.* Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. Lancet 2019; 393: 2201-12.
15. *Lee SH, Shim JK, Soh S, et al.* The effect of perioperative intravenously administered iron isomaltoside 1000 (Monofer®) on transfusion requirements for patients undergoing complex valvular heart surgery: study protocol for a randomized controlled trial. Trials 2018; DOI: https://doi.org/10.1186/s13063-018-2545-3.

16. *Koch TA, Myers J, Goodnough LT.* Intravenous iron therapy in patients with iron deficiency anemia: dosing considerations. Anemia 2015; DOI: https://doi.org/10.1155/2015/763576.
17. *Johansson PI, Rasmussen AS, Thomsen LL.* Intravenous iron isomaltoside 1000 (Monofer®) reduces postoperative anaemia in preoperatively non-anaemic patients undergoing elective or subacute coronary artery bypass graft, valve replacement or a combination thereof: a randomized double-blind placebo-controlled clinical trial (the PROTECT trial). Vox Sang 2015; 109: 257-66.
18. *Schack A, Berkfors AA, Ekeloef S, Gögenur I, Burcharth J.* The effect of perioperative iron therapy in acute major non-cardiac surgery on allogenic blood transfusion and postoperative haemoglobin levels: a systematic review and meta-analysis. World J Surg 2019; 43: 1677-91.
19. *Ng O, Keeler BD, Mishra A, et al.* Iron therapy for preoperative anaemia. Cochrane Database Syst Rev 2019; DOI: https://doi.org/10.1002/14651858.CD011588.pub3.
20. *Engelman DT, Ben Ali W, Williams JB, et al.* Guidelines for perioperative care in cardiac surgery: enhanced recovery after surgery society recommendations. JAMA Surg 2019; 154: 755-66.
21. *Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; DOI: https://doi.org/10.1371/journal.pmed.1000097.
22. *Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A.* Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016; DOI: https://doi.org/10.1186/s13643-016-0384-4.
23. *Sterne JA, Savovic J, Page MJ, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; DOI: https://doi.org/10.1136/bmj.l4898.
24. *Guyatt GH, Oxman AD, Kunz R, et al.* What is "quality of evidence" and why is it important to clinicians? BMJ 2008; 336: 995-8.
25. *Wetterslev J, Jakobsen JC, Gluud C.* Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 2017; DOI: https://doi.org/10.1186/s12874-017-0315-7.
26. *Wan X, Wang W, Liu J, Tong T.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014; DOI: https://doi.org/10.1186/1471-2288-14-135.
27. *Crosby L, Palarski VA, Cottington E, Cmolik B.* Iron supplementation for acute blood loss anemia after coronary artery bypass surgery: a randomized, placebo-controlled study. Heart Lung 1994; 23: 493-9.
28. *Garrido-Martín P, Nassar-Mansur MI, de la Llana-Ducrós R, et al.* The effect of intravenous and oral iron administration on perioperative anaemia and transfusion requirements in patients undergoing elective cardiac surgery: a randomized clinical trial. Interact Cardiovasc Thorac Surg 2012; 15: 1013-8.
29. *Madi-Jebara SN, Sleilaty GS, Achouh PE, et al.* Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. J Cardiothorac Vasc Anesth 2004; 18: 59-63.
30. *Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ.* Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One 2015; DOI: https://doi.org/10.1371/journal.pone.0117383.
31. *Bregman DB, Morris D, Koch TA, He A, Goodnough LT.* Hepcidin levels predict nonresponsiveness to oral iron therapy in patients with iron deficiency anemia. Am J Hematol 2013; 88: 97-101.
32. *Richards T, Baikady RR, Clevenger B, et al.* Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet 2020; 396: 1353-61.
33. *Garcia-Alamino JM, Bankhead C, Heneghan C, Pidduck N, Perera R.* Impact of heterogeneity and effect size on the estimation of the optimal information size: analysis of recently published meta-analyses. BMJ Open 2017; DOI: https://doi.org/10.1136/bmjopen-2017-015888.
34. *Rössler J, Hegemann I, Schoenrath F, et al.* Efficacy of quadruple treatment on different types of pre-operative anaemia: secondary analysis of a randomised controlled trial. Anaesthesia 2020; 75: 1039-49.
35. *Kei T, Mistry N, Curley G, et al.* Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: a systematic review and meta-analysis. Can J Anesth 2019; 66: 716-31.
36. *Cho BC, Serini J, Zorrilla-Vaca A, et al.* Impact of preoperative erythropoietin on allogeneic blood transfusions in surgical patients: results from a systematic review and meta-analysis. Anesth Analg 2019; 128: 981-92.
37. *Hare GM, Mazer CD.* Anemia: perioperative risk and treatment opportunity. Anesthesiology 2021; DOI: https://doi.org/10.1097/ALN.0000000000003870.