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Review Article

Treatment Strategies in Anemic Patients Before Cardiac Surgery

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Both preoperative anemia and the transfusion of red blood cells have been associated with increased morbidity and mortality after cardiac surgery. To reduce the need for blood transfusion during surgery and improve patient outcomes, patient blood management programs have been developed. A primary focus of patient blood management in the preoperative period is the identification, diagnosis, and treatment of preoperative anemia, as anemia is associated with an increased risk of preoperative blood transfusion. In this narrative review, the authors focus on the laboratory screening of anemia before surgery and the evidence and limitations of different treatment strategies in anemic patients scheduled for cardiac surgery. To accurately correct preoperative anemia, the timely detection and definition of the etiology of anemia before elective cardiac surgery are crucial. Multiple randomized studies have been performed using preoperative iron supplementation and/or administration of erythropoiesis-stimulating agents in patients undergoing cardiac surgery. Although preoperative iron substitution in patients with iron deficiency is recommended, the evidence of its effectiveness is limited. In patients with nonpure iron deficiency anemia, combined therapy with erythropoiesis-stimulating agents and intravenous iron is recommended. Combined therapy might effectively reduce the need for red blood cell transfusion, even if applied shortly before cardiac surgery. The therapeutic effect on morbidity and mortality remains unclear. Nonetheless, the timely preoperative assessment of anemia and determination of iron status, eventually leading to targeted therapy, should become a standard of care and might potentially improve patient outcomes.

Key Words: anemia; cardiac surgery; red blood cells; transfusion; outcome

CARDIAC SURGERY IS associated with high rates of transfused allogeneic blood products.[1] Red blood cells (RBC) are administered to about 30%-to-50% of all patients.[2-8] Former studies have shown impaired outcomes with RBC transfusion in cardiac surgery.[9-11] In order to reduce RBC transfusion and improve patient outcomes, patient blood management (PBM) has been developed.[12-14] Patient blood management is an evidence-based concept aiming for preoperative conservation or boosting of a patient's own blood reserves, optimization of perioperative hemostasis, and minimization of blood loss. The clinical introduction of PBM programs has reduced the rate of allogeneic RBC transfusion and hospital length of stay in several studies,[15,16] but did not result in relevantly lower morbidity and mortality.[15,17] Further, the cost-effectiveness of PBM interventions has been questioned.[15] Nonetheless, PBM is an important concept and might eventually improve patient outcomes,[13] especially in cardiac surgery.[18] One important cornerstone of PBM in cardiac surgery is the diagnosis and treatment of preoperative anemia. In this narrative review, the authors focused on the laboratory screening of anemia before surgery and the evidence and limitations of different treatment strategies in anemic patients scheduled for cardiac surgery.

Search Strategy

An extensive literature search in PubMed was performed using the following terms: (preoperative) AND (anemia) AND

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(cardiac surgery) on May 1, 2022. The search identified 720 publications. The authors excluded publications that were written in languages other than English and pediatric cardiac surgery studies, and focused on clinical studies, clinical trials, meta-analyses, randomized controlled trials (RCTs), and systematic and nonsystematic reviews published after 2012. After reading the abstracts, the authors identified 65 publications investigating the potential impact of preoperative anemia on postoperative outcomes and interventions to improve RBC mass in patients before cardiac surgery. Publications of potential interest were assessed critically and eventually included in this review.

Impact of Anemia in Cardiac Surgery Patients

The World Health Organization (WHO) definition of anemia (hemoglobin values <13 g/dL in men, <12 g/dL in women) is most commonly used for diagnosing preoperative anemia.[19] When assessed according to these criteria, about 20%-to-50% of patients undergoing cardiac surgery suffer from preoperative anemia,[2,4,5,18,20,21] with especially high incidences in older patients or in patients with chronic diseases and/or multiple comorbidities.[22] Preoperative anemia can be divided into mild (hemoglobin 11-12.9 g/dL in men, 11-11.9 g/dL in women) and moderate-to-severe anemia (hemoglobin <11 g/dL in men and women).[2,23,24]

Multiple studies have shown preoperative anemia to be associated with increased perioperative RBC transfusion, postoperative morbidity, including stroke, myocardial infarction, acute kidney injury (AKI), infections, and reduced short- and long-term survival after cardiac surgery.[2,6,8,18,20,21,25] When compared with mild anemia (hemoglobin >11 g/dL), severe preoperative anemia was associated repeatedly with a higher risk of perioperative transfusion and postoperative morbidity and mortality.[2,23,24] These findings were confirmed recently by a large nation-wide Dutch observational study including >35,000 patients. Preoperative anemia was associated independently with 120-day mortality (adjusted odds ratio 1.7; 95% CI: 1.4-2.0; $p < 0.001$). Furthermore, anemia increased the risk of AKI, postoperative myocardial infarction, redo thoracotomy, pneumonia, prolonged tracheal intubation, and readmission to the intensive care unit. Finally, severe anemia was associated with worse postoperative outcomes compared to moderate or mild anemia.[2]

Of note, the WHO criteria for anemia might not be an ideal preoperative risk assessment tool. The optimal preoperative hemoglobin levels and targets to avoid or minimize perioperative RBC transfusion and postoperative complications have yet to be defined.[26-28] They might vary with the type of surgery, sex, age, and dynamics of preoperative hemoglobin decline.[29] A recent retrospective health data analysis has suggested that the calculated RBC mass, rather than the absolute hemoglobin value, might be better suited to predict the probability of perioperative transfusion.[4] Thereby, differences between the sexes could be, at least partially, eliminated.[26,30]

Both the presence of anemia and the perioperative transfusion of RBC are predictors of organ injury, adverse outcomes, and mortality after cardiac surgery.[9,10,24,31,32] Comorbidities, such as heart failure, chronic diseases, renal failure, and cancer, are more common in anemic patients and have a relevant impact on postoperative outcomes.[2,19,33] It remains difficult to determine whether anemia is a direct risk factor or whether it is a sign of the severity of associated comorbidities.[19] Furthermore, separating the risk of increased postoperative morbidity and mortality as a result of preoperative anemia from the risk associated with perioperative RBC transfusion remains difficult.[19,24] Although some publications have suggested a relevant additional impact of RBC transfusion in anemic patients,[10,32] other studies have not been able to demonstrate that transfused anemic patients had higher mortality compared with transfused nonanemic patients.[2,31]

Diagnostic Assessment in Preoperative Anemia

Anemia before cardiac surgery is often multifactorial.[2,4,5,18,20,21] Common causes of anemia include chronic bleeding (especially gastrointestinal), the deficiency of specific substrates, including iron, folic acid, or vitamin B_{12}, erythropoietin deficiency (eg, in chronic renal failure patients), chronic hemolysis, concomitant chronic diseases (anemia of chronic disease), and advanced age (anemia of the older patient) (Fig 1).[34-37] Timely detection and defining the etiology of anemia before elective cardiac surgery are crucial to allow for preoperative treatment. Ideally, diagnostic testing followed by corrective measures should be initiated 4-to-6 weeks before elective surgery for the potentially successful correction of anemia, or at least a relevant increase of RBC mass.[38,39]

Multiple screening algorithms have been described to differentiate among the different etiologies of anemia. Table 1 shows typical laboratory findings with different types of anemia. It is commonly recommended to perform a full blood count, including reticulocyte count, ferritin levels, transferrin concentration, transferrin saturation, and levels of soluble transferrin receptor. More elaborate laboratory tests might be helpful in specific hematologic patients to exclude particular hematologic diseases (eg, myelodysplastic syndromes). It might also be recommended to determine C-reactive protein (CRP) and creatinine levels.

Despite different pathophysiologic pathways, many or even most of these etiologies will result in an absolute or functional iron deficiency. Absolute iron deficiency can be found in patients with reduced dietary iron intake or chronic blood loss, whereas functional iron deficiency is caused mainly by chronic inflammation, malignancy, renal failure, and advanced age. It has been described that inflammatory cytokines will activate hepatic hepcidin expression, eventually leading to impaired iron absorption from the gut and iron integration into hemoglobin. This cytokine-mediated functional iron deficiency might be common in patients presenting for cardiac surgery due to multiple comorbidities and chronic inflammatory reactions.[36,40] It has been suggested that about one-third of patients scheduled for cardiac surgery present with iron deficiency anemia. These patients might have a higher risk for

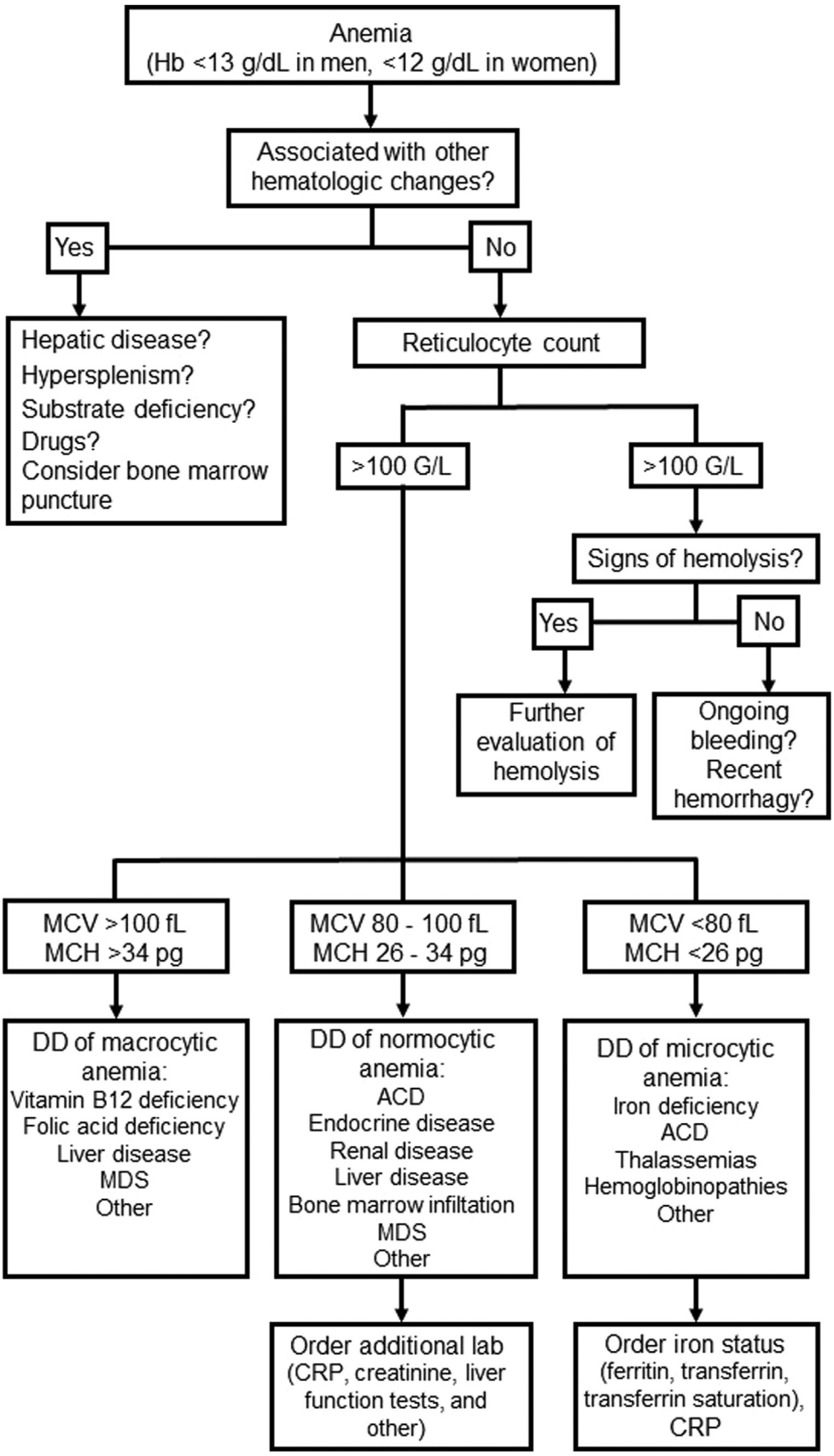

Fig 1. Diagnostic approach to anemia. The algorithm shows a laboratory-based approach to anemic patients in the general population. This algorithm might not be applicable in most patients before surgery due to time requirements (several weeks) and the need for specific consultations with hematologists. ACD, anemia of chronic disease; CRP, C-reactive protein; DD, differential diagnosis; Hb, hemoglobin; MCH, mean cell hemoglobin; MCV, mean cell volume; MDS; myelodysplastic syndrome.

Table 1
Laboratory Characteristics of Iron-Deficiency Anemia and Anemia of Chronic Disease[36]

Variable	Iron-Deficiency Anemia	Anemia of Chronic Disease	Anemia Due to Both Conditions
Hemoglobin	↓	↓	↓
Mean corpuscular volume	↓	↓/normal	↓
Reticulocyte count	↓	↓	↓
Serum iron level	↓	↓	↓
Ferritin	↓	normal/↑	↓/normal
Transferrin	↑	↓/normal	↓/normal
Transferrin saturation	↓	↓	↓
Soluble transferrin receptor	↑	normal	normal/↑
Erythropoietin levels	↑	normal/slightly ↑	↑/normal
C-reactive protein	normal	↑/normal	normal/↑

NOTE. Modified after Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011-23.[36]

RBC transfusion than non-iron deficient anemic patients with similar hemoglobin values.[41] The above-mentioned laboratory tests might also be helpful in defining absolute or functional iron deficiency in patients not fulfilling the WHO criteria for anemia.

Some laboratories offer the determination of erythropoietin levels (Table 1). Hypoxia is the basic stimulant in the production of erythropoietin, eventually resulting in the increased production of erythrocytes. The increased capacity to carry oxygen to peripheral organs, resulting in reduced hypoxic stimulus, provides negative feedback for stopping erythropoietin production. In a recent study including 562 patients with and without renal insufficiency, erythropoietin levels were correlated negatively with hemoglobin values (ie, erythropoietin levels were lower with higher hemoglobin concentration) in patients with normal or slightly impaired renal function.[42] In patients with chronic renal failure, hypo-regenerative anemia is commonly due to inadequate erythropoietin production. Accordingly, no correlation between hemoglobin values and erythropoietin levels was found in patients with relevantly impaired renal function.[42] However, erythropoietin levels are difficult to interpret in patients with chronic anemia, and determination of erythropoietin levels might have limited benefits in the perioperative setting.

Findings in laboratory testing might differ in patients before cardiac surgery as compared to the general population. It has been shown that about 45% of patients have above upper normal level CRP values before cardiac surgery, suggesting an increased inflammatory state.[43] Similarly, about one-fourth of patients have low endogenous erythropoietin levels before cardiac surgery. Accordingly, algorithms and thresholds used in the general population (Fig 1) might not be transferred directly to patients before cardiac surgery. Simplified algorithms, including full blood count, ferritin, transferrin saturation, creatinine, and CRP, might be better suited in the preoperative patient for reasons of time, therapeutic opportunities, and cost-effectiveness.[21,38,39,43] Thereby, patients usually can be assigned to groups of iron deficiency without anemia, iron-deficiency anemia, renal anemia, anemia of inflammation, and non-iron-deficient nonanemic patients. The latter might allow for simplified and rapid treatment decisions without the consultation of a hematologist. The treatment of preoperative anemia in cardiac surgery based on simple laboratory screening tests should become a standard of care. Figure 2 shows the modified version of an algorithm used at the authors' institution. The algorithm primarily aims to identify patients with iron-deficiency anemia who might be treated easily with iron infusion shortly before surgery. As the use of erythropoiesis-stimulating agents (ESA) before cardiac surgery requires specific time-consuming approvals by the insurance providers in Switzerland, these agents are used only in a minority of patients in the authors' institution.

Treatment Strategies

Defining the subtypes of anemia based on laboratory testing (Table 1) seems to be the key for specific and individualized therapy. However, the hemoglobin thresholds at which to start treating are not well- defined and might differ considering the underlying pathology and patient conditions.

Iron deficiency is common before cardiac surgery, but exclusive iron substitution only might be beneficial for specific subtypes of anemia. Iron supplementation should be initiated as soon as possible according to published formulas that

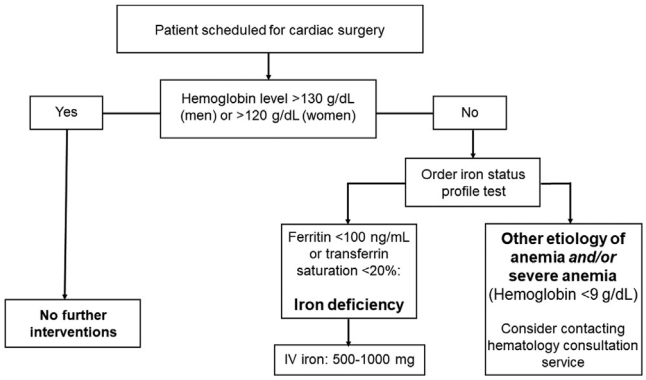

Fig 2. Modified algorithm from the Pre-Anesthesia Clinic at the University Hospital Basel. The authors' algorithm primarily aims to identify patients with iron-deficiency anemia and patients with severe anemia. Intravenous iron therapy can be directly performed after rapid laboratory testing in the preoperative anesthesia clinic. IV, intravenous.

calculate the iron deficit. Although preoperative iron substitution in patients with iron-deficiency anemia scheduled for surgery with a transfusion probability >10% is recommended,[44,45] the evidence of its effectiveness with respect to reduction of perioperative RBC transfusion and improved outcomes is scarce.[46] Oral iron therapy has long been the standard way of treatment in iron-deficient therapy, and is still recommended in some guidelines. However, the longer duration of therapy, the lower bioavailability, and the limited tolerance to oral iron in many patients often render this approach insufficient for rapid and effective preoperative iron substitution.[7] Intravenous (IV) iron therapy is favored for replenishing iron stores and for improving hemoglobin values shortly before surgery,[7,45] but might be associated with a higher risk of anaphylactic reactions and higher costs.

Iron deficiency without anemia also has been identified as a risk factor for adverse outcomes in cardiac surgery patients.[47] A prospective observational study with 730 patients undergoing elective cardiac surgery showed that the diagnosis of preoperative iron deficiency increased the risk of 90-day mortality from 2%-to-5% in patients without anemia, and from 4%-to-14% in patients with anemia. Moreover, iron deficiency led to an increased incidence of serious adverse events, including major adverse cardiac and cerebrovascular events, increased transfusions, and prolonged hospital stay.[47] Thus, iron supplementation might be indicated even in nonanemic patients before cardiac surgery.[48]

Most patients undergoing cardiac surgery, however, present with anemia of chronic disease and with absolute or relative erythropoietin deficiency. In these patients, anemia treatment should include ESA in combination with low-dose IV iron to stimulate erythropoiesis and increase hemoglobin levels. Anemia treatment with ESA generally can be divided into 2 different regimens. First, short-term intervention with 200 to 500 U/kg ESA for 1-to-3 days in combination with or without iron substitution; and second, long-term interventions with 100-to-150 U/kg once to twice per week over 2-to-4 weeks in combination with iron substitution.[49,50] It is currently unclear which strategy is more efficacious. Such a therapeutic strategy also should be considered in patients with mild anemia (11 g/dL in women and in men) before cardiac and major noncardiac surgery[51] and in patients with renal insufficiency. Of note, therapeutic strategies, including ESAs, are often expensive, and cost-effectiveness remains questionable.[15] Furthermore, such treatment strategies might be associated with relevant side effects, including thromboembolic events, myocardial infarction, and anaphylaxis.[12,13,51]

If substrate deficiencies other than iron are supposed or confirmed, treatment with the respective agent (eg, subcutaneous vitamin B_{12} or oral folic acid) should be considered. An indiscriminate administration of these vitamins is not recommended.

In case of a primary blood disorder as the underlying cause of anemia, referral to a hematologist is advised. Further diagnostic tests might include bone marrow investigation, including molecular testing to characterize and treat primary hematologic disease (eg, plasma cell disorders, mature B-cell neoplasms, myelodysplastic syndromes, and other malignancies). If a primary blood disease is diagnosed, interdisciplinary approaches are suggested on how to best proceed with the treatment of both the hematologic and the cardiac disease.

Studies With Perioperative Interventions in Anemia

Iron Supplementation

Preoperative iron supplementation in iron-deficient patients might offer a special window of opportunity, and appears to be an attractive and simple intervention that might apply to a relevant proportion of anemic patients undergoing cardiac surgery.[18,24] Recent international PBM guidelines for adult cardiac surgery support preoperative iron supplementation in mildly and in severely anemic patients (recommendation IIA[52] and IIB[53]). The recent review by Meybohm et al. nicely summarized the current evidence.[18] The authors reported on 3 retrospective and 4 randomized interventional trials that included nearly 2,500 patients. Of these patients, about 40% were treated with pure iron supplementation, and about 60% were treated with a combination of iron and ESA. In most patients with preoperative iron supplementation, the IV application was used. The above-mentioned review partially found evidence that preoperative iron supplementation might increase hemoglobin values and reduce the requirements for perioperative RBC transfusions.[18] A recent and more restrictive systematic review and meta-analysis including just 5 RCTs with 554 patients found only some effects on surrogate laboratory parameters (eg, improved transferrin saturation) but no effect on hemoglobin values or avoidance of RBC transfusion.[54] Of note, the application and dosages of iron supplementation were rather heterogeneous among the different studies.[54] For example, Garrido-Martin et al. administered iron either orally (105 mg/d preoperatively and postoperatively), intravenously (3 doses of 100 mg IV iron/d during preoperative and postoperative hospitalization), or as a combination of both.[55] It might be speculated that the iron treatment partially was ineffective due to the oral application or due to low IV doses.[55] A recent Canadian retrospective analysis suggested that preoperative IV iron dosages >600 mg were necessary to effectively increase hemoglobin before cardiac surgery.[56]

Although IV iron supplementation might increase postoperative hemoglobin values and reduce requirements for RBC transfusion, the benefits of more rapid hemoglobin recovery after cardiac surgery or higher hemoglobin values in the early postoperative period on patient outcome remain unclear.[54,57] The evidence for improved patient-centered outcomes or reduced adverse events and mortality after cardiac surgery by perioperative iron supplementation is very limited.[18,57,58] One retrospective cohort study suggested less renal failure in patients with iron supplementation in combination with erythropoietin.[59] In major noncardiac surgery, a recent meta-analysis suggested that preoperative iron substitution reduced the risk of transfusion ($p = 0.0004$) but also the rate of postoperative infections and even mortality ($p = 0.04$).[60]

Although there is no evidence to support or refute the routine use of iron therapy at the moment,[54] the indiscriminate application of IV iron to all patients before cardiac surgery does not seem to be beneficial.[61] In a recent RCT, 204 patients undergoing complex cardiac surgery were randomized to receive either 20 mg/kg of IV iron twice (3 days before surgery and after surgery) or placebo.[61] The authors found that IV iron supplementation replenished iron stores and increased erythropoiesis, resulting in higher postoperative hemoglobin values, but failed to show reduced requirements for RBC transfusion during hospitalization. Preoperative laboratory testing and iron supplementation might be most beneficial in selected high-risk patients.[54] Finally, the combined use of iron and ESA seems indicated, especially in patients with anemia due to inflammation or chronic disease.[62,63]

Treatment With ESA

A recent meta-analysis, including 8 RCTs published between 2009 and 2016, with a total of 610 cardiac surgery patients, showed that preoperative ESA administration significantly reduced intraoperative RBC transfusion, the incidence of perioperative AKI, and hospital length of stay. When ESAs were administered during and after surgery, such effects could not be found.[64] Of note, the primary aim of that meta-analysis was to evaluate the effect of ESA on AKI in cardiac surgery. Six of 8 included studies were performed in countries in Eastern Asia and 2 in Europe, potentially limiting the generalizability of the findings of this meta-analysis. Furthermore, ESAs were given within 3 days before surgery in 6 of these studies, and between anesthesia induction and surgical incision in two-thirds. Nevertheless, it remains questionable whether this short time interval allows for improved perioperative hematopoiesis. The meta-analysis found a mean difference of -0.3 (95% CI -0.55 to 0.05) for intraoperative RBC transfusion, as evaluated in 3 of the 8 included studies. Similarly, postoperative RBC transfusion was reduced, but the meta-analysis did not report on perioperative hemoglobin values.[64] Finally, no effect on mortality was found.

Based on the present evidence, the optimal timing and dosing for ESA administration in cardiac surgery remain poorly defined. The effects of ESA with respect to increased erythropoiesis might require several days-to-weeks, but most studies evaluated the ESA administration close to surgery.[7] In addition, a retrospective Canadian analysis suggested that erythropoietin alfa at doses of at least 80,000 U were necessary to increase hemoglobin values in patients before cardiac surgery.[56] Finally, the administration of ESA might be associated with potential adverse effects such as hypertension and thromboembolic events in patients with stable congestive heart failure and coronary artery disease.[65,66]

Combined Iron and ESA Supplementation

In the recent PBM guidelines, the combined therapy of ESA and iron supplementation in patients with non-pure iron-deficient anemia has been recommended (recommendation IIA).[52,53] These recommendations were supported by a meta-analysis and a large cohort study in cardiac surgery patients, showing that iron supplementation was effective in reducing the need for RBC transfusion when combined with ESA.[67,68] The above-mentioned recommendations are further supported by a very recent single-center RCT comparing the administration of 1,000 mg IV iron in combination with 200 μg darbepoetin subcutaneously with 600 mg oral iron daily.[69] Therapy was started 2-to-10 weeks before cardiac surgery. The combined single-dose treatment was more effective at increasing hemoglobin values and decreasing the proportion of patients who received a perioperative blood transfusion as compared to oral iron substitution.[69]

The optimal timing and dosing of concomitant supplementation of IV iron and ESA are poorly defined. A recent retrospective analysis suggested that IV iron at a dose of at least 600 mg and erythropoietin alfa doses of at least 80,000 U are necessary to increase hemoglobin values in patients before cardiac surgery.[56] These doses are relevantly higher than those used in earlier studies.[55,70] Of note, treatment should start as early as possible. Two recent studies applied regimens with combined iron and ESA supplementation shortly before surgery. Yoo et al. administered a single IV dose of 500 U/kg ESA in combination with 200 mg of IV iron 16-to-24 hours before valvular heart surgery.[71] Using this regimen, they found a significantly decreased incidence of perioperative RBC transfusion and postoperative AKI.[71] Similarly, the acute treatment of anemia using combined therapy on the day of admission was evaluated by a large single-center study by Spahn et al. In their RCT, about 500 cardiac surgery patients with anemia or isolated iron deficiency were randomized to either combination therapy with 20 mg/kg of IV iron, 40,000 U of subcutaneous erythropoietin alpha, 1 mg of subcutaneous vitamin B12, and 5 mg of oral folic acid or placebo on the day before surgery.[17] The authors found higher hemoglobin values and reduced RBC transfusion (median minus one RBC) in the intervention group. Furthermore, the proportion of patients exposed to any allogeneic blood products within the first 7 postoperative days was reduced from 54% in the control group to 46% in the intervention group. However, no beneficial effects on morbidity or mortality were reported.[17]

Preoperative RBC Transfusion

A small RCT found that the preoperative transfusion of 2 units of RBCs reduced intraoperative RBC transfusion by a median of 2 units of RBCs.[72] No effect on AKI was found, but the study was not powered for this outcome.[72] Based on this very limited evidence, 2 recent PBM guidelines recommended not to administer preoperative RBC transfusion in anemic patients except in case of emergent surgery or life-threatening anemia.[52,53] Furthermore, preoperative autologous blood donation is not recommended in anemic patients.

Limitations of Preoperative Anemia Treatment in Cardiac Surgery

Despite the fact that multiple studies showed the negative effect of preoperative anemia on blood transfusion requirements and on postoperative morbidity and mortality, the studies investigating the treatment of preoperative anemia widely failed to show relevantly improved patient outcomes. Table 2 Effective anemia treatment is limited by different intrinsic issues. First, preoperative anemia clinics, which are

Table 2
Randomized Controlled Trials with Perioperative Iron Supplementation (#1-5), Administration of Erythropoiesis-Stimulating Agents (#6-11) or Combination Therapy (#12-15)

	First Author, Year	Sample	Intervention	Control	Timepoint of Intervention	Results in Primary Outcome	Additional Findings
1	Garrido-Martin, 2012[55]	159 (54/53/52)	A.100 mg IV iron 3 × 100 mg/d (n = 54) + 100 mg oral iron/d B. 100 mg oral iron/d + IV placebo (n = 53)	IV and oral Placebo	During pre- and postoperative hospitalization, oral iron until 1 mo after discharge	No difference in postoperative hemoglobin between groups	Higher serum ferritin levels in the IV iron group at hospital discharge and 1 mo later, no difference in RBC transfusion
2	Johansson, 2015[57]	60 (30/30)	1000 mg IV iron, single-dose	Placebo	Day before surgery or directly before surgery	Hemoglobin higher in iv iron group after 4 wk	No differences in RBC transfusion, higher ferritin levels/transferrin saturation in iv iron group
3	Padmanabhan, 2019[31]	50 (25/25)	1000-2000 mg IV iron in 1 to 2 doses	200 mg oral iron twice daily until surgery	3-8 wk before surgery	No difference in hemoglobin increase after treatment	No difference in patients who remained anemic, higher ferritin and lower transferrin levels in the IV iron group
4	Song, 2022[61]	204 (103/101)	20 mg/kg IV iron before and after surgery	Placebo	3 d before and after surgery	No difference in RBC transfusion up to postoperative day 10	Hemoglobin levels, 3 wk after surgery, reticulocyte count at postoperative day 10, transferrin saturation, and serum ferritin were higher in IV iron group
5	Xu, 2019[77]	150 (75/75)	200 mg IV iron once daily until calculated dose (according to iron deficiency) was reached	Placebo	Start on the day after surgery	Hemoglobin levels on postoperative day 14 higher in IV iron group	Proportion of patients with corrected anemia on postoperative day 14 higher, ferritin levels higher in IV iron group
6	Song, 2009[78]	71 (35/36)	300 U/kg ESA, single-dose	Placebo	Before surgical skin incision	Less AKI in ESA group	Lower postoperative serum creatinine levels
6	Oh, 2012[79]	71 (36/35)	300 U/kg ESA, single-dose	Placebo	Before surgical skin incision	Less AKI in ESA group	Lower postoperative serum creatinine levels
7	de Seigneux, 2012[80]	80 (20/20/40)	A. 20,000 U ESA single-dose (n = 20) B. 40,000 U ESA, single-dose (n = 20)	Placebo	Directly after surgery	No difference in AKI	No differences in urinary NGAL, serum creatinine levels, and RBC transfusion
8	Tasanarong, 2013[81]	100 (50/50)	200 U/kg ESA before and 100 U/kg ESA during surgery	Placebo	3 d before surgery and intraoperatively	Less AKI in ESA group	No difference in serum creatinine levels
9	Kim, 2013[82]	98 (49/49)	300 U/kg ESA, single-dose	Placebo	Before surgical skin incision	No difference in AKI	No difference in serum creatinine levels
10	Dardashti, 2014[83]	70 (35/35)	400 U/kg ESA, single- dose	Placebo	Before surgical skin incision	No difference in AKI	No difference in plasma cystatin levels
11	Kim et al, 2016[84]	60 (31/29)	500 U/kg ESA, single- dose	Placebo	During surgery	No difference in AKI	No difference in serum creatinine levels and frequency of RRT
12	Karkouti, 2006[85]	38 (13/13/12) (cardiac, orthopedic and spinal surgery)	A: 600 U/kg ESA on POD 1 and 3 + 200 mg IV iron on POD 1.2 and 3 B: 200 mg IV iron on POD 1.2 and 3	Placebo	After surgery	No difference in postoperative increase of hemoglobin levels	No difference in RBC transfusion, higher reticulocyte count in combination group
13	Yoo, 2011[71]	74 (37/37)	500 U/kg ESA + 200 mg IV iron, single-dose	Placebo	Day before surgery	Lower proportion of transfused patients and less RBC requirements in intervention group	Higher reticulocyte count in intervention group
14	Spahn, 2019[17]	484 (243/241)	20 mg/kg IV iron + 40,000 U ESA sc + 1 mg vitamin B_{12} sc + 5 mg folic acid orally	Placebo	Day before surgery	Less RBC transfusion in intervention group	Higher postoperative hemoglobin levels and reticulocyte count
15	Kong, 2022[69]	158 (79/77)	1,000 mg IV iron + 200 mg ESA, single dose	600 mg oral iron	2-10 wk before surgery	Fewer RBC transfusion in intervention group	Higher increase in preoperative hemoglobin levels

Abbreviations: AKI, acute kidney injury; ESA, erythropoiesis-stimulating agents; IV, intravenous; NGAL, neutrophil gelatinase-associated lipocalin; POD, postoperative day; RBC, red blood cell; RRT, renal replacement therapy; sc, subcutaneous.

able to determine and treat anemic patients before cardiac surgery according to specific treatment protocols, are not yet established in many countries and institutions. Recently, a prospective study in the United Kingdom showed that it was feasible to develop a pathway for IV iron treatment in cardiac surgery patients in 7 out of 11 hospitals over a period of 2 years.[58] The IV iron treatment before cardiac surgery was limited to selected high-risk patients in most of these institutions, and the number of included patients in this study was low.[58]

Second, the timely assessment and treatment of cardiac surgery patients, even with effectively functioning preoperative anemia clinics, remains challenging. An estimated percentage of up to 40% of patients are nonelective in some centers.[21] Furthermore, the access of elective patients to preoperative anemia clinics is limited. A recent retrospective analysis included only about 530 patients recruited over about 10 years at a large Canadian center.[56] A recent Italian study reported that only about 20% of elective surgery patients had access to preoperative anemia screening clinics due to organizational and time issues.[21] Ultimately, a large proportion of patients undergo cardiac surgery without preoperative anemia correction despite recommendations to treat preoperative anemia treatment with iron supplementation and/or ESA administration by many important societies.[52,53,73,74]

Third, time intervals between the initial visit and the day of surgery are usually short, potentially limiting effective anemia treatment. In a recent study including nearly 800 patients who underwent elective cardiac surgery at a Canadian tertiary hospital, the median interval between the initial visit and the day of surgery was 7 days.[75] Only 8% of patients with anemia were referred preoperatively to the blood conservation clinic, and treatment was initiated in only 3% of anemic patients,[75] mostly probably due to time restriction.

Fourth, optimal thresholds and targets of interventions remain poorly defined. The WHO criteria for anemia might not be ideal for preoperative patients undergoing high-risk cardiac surgery and should not be applied universally. For example, preoperative hemoglobin optimization might be important but also insufficient to reduce the transfusion of allogeneic blood products in patients with low body mass index.[4] It is essential to understand the individual interaction of hemoglobin values, body mass index, and total RBC mass. The latter might help to predict better which patients are at increased risk of perioperative transfusion and might benefit most from preoperative blood optimization.[4]

Fifth, the optimal treatment strategy remains unclear. Pure iron supplementation seems not to be very effective in most cardiac surgery patients. Combined therapy, including IV iron and subcutaneous ESA at higher doses, seems most promising to increase RBC mass and reduce transfusion requirements.[56,69] However, higher doses of IV iron and ESA might increase the risk of adverse side effects and question the cost-effectiveness of such interventions.[15] In many European countries and in North America, the indication of erythropoietin administration is currently limited to anemia related to chronic kidney diseases and chemotherapy in cancer patients. For use in cardiac surgery patients, specific approvals are often required.[64] Given the limited evidence of improved patient outcomes in cardiac surgery patients with preoperative administration of IV iron and/or ESA, such therapies potentially should be used primarily in high-risk patients after individual assessment.[56,58]

Finally, missing the effects of preoperative hemoglobin optimization in many studies in cardiac surgery patients might arise from the ambiguity of hemoglobin as a marker for adequate oxygenation of sensitive organs.[19,76] Markers of inadequate balance between tissue oxygen delivery and demand, such as central venous oxygen saturation, lactate, or near-infrared spectroscopy, potentially should be implemented in transfusion decision-making and might be beneficial for the patient[19] rather than hemoglobin values in the range between 7 and 10 g/dL.[12,13] Finally, low hemoglobin values during and after surgery might not have the same impact on patient outcomes as preoperative anemia.

Conclusions

Patients presenting for cardiac surgery are often at high risk of anemia due to age and multiple comorbidities. Given the strong association between low preoperative hemoglobin values and postoperative complications, the timely diagnosis and therapy of treatable forms of anemia (especially iron deficiency anemia) are recommended to improve patient outcomes.[52,53] However, anemia in cardiac surgery is often multifactorial and might be a surrogate of reduced patient conditions, comorbidities, and chronic diseases. Correcting anemia remains difficult and is often unsuccessful. A combined administration of IV iron and ESA seems most promising. However, even with intensified therapies, positive effects in published studies have been limited generally to a reduction in RBC requirements during and after surgery. Nonetheless, the preoperative assessment of anemia and determination of the anemic patient's iron status, eventually leading to targeted therapy, should become standard of care. Clinics must advise facilities to screen for anemia and the cause thereof. Although therapeutic interventions shortly before surgery have been suggested,[17] treatments should be initiated within several weeks before surgery to effectively improve RBC mass and hemoglobin values. Hopefully, the remaining questions can be answered, and limiting factors might be managed successfully in the next years, eventually leading to improved outcomes.

Conflict of Interest

None.

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