

## A review of perioperative anemia: A modifiable and not so benign risk factor

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### ABSTRACT

Anemia is a commonly encountered finding either during the preoperative assessment or during the postoperative management of the patient. Anemia often gets overlooked while more emphasis is paid to cardiovascular and pulmonary evaluation. Evidence, however, suggests that the presence of anemia in the perioperative period can predispose patients to other complications. Awareness of the consequences of anemia in the perioperative period can lead to better recognition and early management of this potentially modifiable risk factor. In this review, we focus on the effects of anemia on the cardiac, pulmonary, neurologic, cognitive, and functional status outcomes of patients. We also review management strategies that could be employed, depending on the available time and resources.

**Keywords:** Anemia, perioperative, risks

### Introduction

Perioperative medicine is a constantly evolving field and has been so for the last many decades. One of the common problems encountered in older patients and those with medical comorbidities perioperatively is anemia, especially iron deficiency anemia (IDA) and anemia of chronic disease (ACD). Anemia tends to be overlooked in the preoperative stages of evaluation, resulting in avoidable transfusions that carry their own set of potential risks.<sup>[1]</sup> Mild anemia as defined by the World Health Organization (WHO) is hemoglobin less than 13 gm/dL in men and less than 12 gm/dL in women, with moderate anemia defined as hemoglobin less than 11 gm/dL and severe anemia as hemoglobin less than 8 gm/dL in both genders.<sup>[2]</sup>

It is estimated that in patients undergoing major surgery, up to 50% are anemic preoperatively and 90% are anemic postoperatively.<sup>[3,4]</sup> When left unaddressed, anemia can increase

the risk of postoperative complications such as myocardial infarction, stroke, and cognitive dysfunction, as well as increased length of stay, mortality, and duration of ventilator requirement.<sup>[5-7]</sup> More detailed systemic numbers are quoted under the appropriate sections below. We believe one of the common reasons for anemia taking the back seat in the perioperative phase is the under-recognition of the potential risks of anemia. The goal of this review is to compile the evidence on the effects of anemia related to specific organ systems and to briefly discuss management strategies for the primary care physician (PCP) and Hospitalist. With more awareness about the perioperative risks of anemia and transfusions, it is likely that this risk factor will be addressed more preemptively.

### Methods

A PubMed search was conducted with different terminology including preoperative anemia, postoperative anemia, or perioperative anemia along with cardiovascular, pulmonary, neurological, cognitive, and functional status reviewed below. A total of 50 studies were included in this review article, ranging from 1997 to 2020. The studies reviewed included meta-analyses, retrospective and prospective reviews, randomized control trials,

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and other review articles. The studies that showed an outcome difference between anemic and control groups were selected for this discussion.

## Results/Discussion

### Cardiac

Anemia is directly and indirectly associated with increased perioperative cardiac complications. Older studies like the 1997 Swedish study of 811 men showed that on long-term follow-up, patients who underwent transurethral resection of the prostate (TURP) with preoperative hemoglobin of 10–13 gm/dL had an increased risk of the first time acute myocardial infarction postoperatively.<sup>[5]</sup> The association is even more pronounced in patients with a previous history of myocardial infarction. Later, hematocrit below 39% was found to be inversely associated with adjusted 30-day death or cardiac event risk.<sup>[6]</sup> Additionally, preoperative anemia is associated with increased mortality of all causes, including cardiac.<sup>[7]</sup> The studies in patients undergoing coronary artery bypass grafting (CABG) suggest that preoperative anemia may contribute to increased cardiac events but is not an independent risk factor.<sup>[8]</sup> The association is, therefore, thought to be due to comorbid cardiac risk factors that often accompany anemia, rather than the preoperative hemoglobin alone.<sup>[7-9]</sup> It is important to note that the presence of preoperative anemia is associated with an increased incidence of blood product transfusion, which in itself increases perioperative cardiac risk.<sup>[10-12]</sup>

The effect of intraoperative and postoperative anemia on perioperative cardiac events is clearer. In a study of 190 men undergoing radical prostatectomy who were monitored for ischemic cardiac events, those who suffered an ischemic event had lower postoperative day 1 hematocrit ( $P = 0.03$ ).<sup>[13]</sup> The postoperative decrease in hemoglobin is significantly associated with a composite endpoint of cardiac death, myocardial infarction, coronary revascularization, or heart failure admission within 3 months.<sup>[14]</sup> Furthermore, in those undergoing cardiopulmonary bypass (CPB), myocardial infarction, cardiac arrest, and low cardiac output are all significantly increased when the intraoperative hematocrit nadir reaches below 22%.<sup>[15]</sup> Similarly, intraoperative hematocrit nadir below 25% and RBC transfusion were both independent risk factors for increased troponin levels, and exposure to both low intraoperative hematocrit and transfusion conferred the highest risk of all. The group exposed to both anemia and blood transfusion had the highest mortality rate ( $P = 0.0007$ ), while the group that neither had anemia or received transfusion was associated with the lowest morbidity risk.<sup>[16]</sup>

In summary, preoperative anemia may be a potential but not independent risk factor for cardiac events postoperatively, but transfusions postoperatively definitively led to adverse outcomes. Postoperative hemoglobin drop, especially on day 1 was predictive of negative cardiac outcomes, especially in CABG.

### Pulmonary

The relationship between anemia and perioperative pulmonary complications runs much in the same vein as cardiac, but complications relating to blood transfusions play a bigger role. Hemoglobin below 10 g/dL increases the risk of postoperative pulmonary complications (PPCs) nearly three-fold and is identified as an independent risk factor for PPCs on multivariate analysis.<sup>[17]</sup> Additionally, the incidence of prolonged mechanical ventilation and pulmonary edema increased as hematocrit nadir during CPB decreased.<sup>[15]</sup> On the other hand, in patients who underwent noncardiac surgery with mechanical ventilation, the average preoperative hemoglobin levels of those who developed pulmonary complications, 12.1 g/dL, were statistically lower than those who did not at 12.5 g/dL ( $P = 0.01$ ).<sup>[18]</sup> In a 2012 study of 1,170 noncardiac surgical patients, perioperative anemia (hemoglobin <10 g/dL) is associated with increased risk for PPC on univariate, but not multivariate analysis.<sup>[19]</sup>

Studies agree that respiratory complications are increased by the transfusion of blood products. Transfusion is known to cause a host of pulmonary issues, including transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM), and related nosocomial pneumonia.<sup>[20]</sup> Hematocrit under 25% and red blood cell transfusion are both associated with longer ventilator support times, and exposure to both is associated with the longest ventilator requirements.<sup>[16]</sup> In a multivariate analysis of pulmonary complications after pneumonectomy, the odds of suffering a respiratory complication are increased by 47% after a single unit blood transfusion (OR 1.47; 95% CI 1.06-2.05).<sup>[21]</sup> Despite the aforementioned findings that the presence of preoperative anemia is associated with an increased risk of blood transfusions, blood transfusion is an independent risk factor for pulmonary complications regardless of preoperative hemoglobin levels. In addition, patients who suffer perioperative pulmonary complications experienced greater perioperative blood loss and required more hemodynamic support with colloids, blood products, and vasopressors.<sup>[18]</sup>

In summary, although preoperative anemia is associated with increased PPCs, such complications may be more reliably predicted by the transfusion of blood products during this period. Commonly used tools that predict pulmonary risk identify anemia as a significant risk factor for PPCs.

### Neurologic

The association between anemia and cerebrovascular events (CVEs) has been well established due to compromised tissue oxygen delivery to the central nervous system. Specifically, IDA has been linked to ischemic stroke through numerous mechanisms. It has been suggested that the hyperkinetic state associated with anemia elicits endothelial adhesion molecular genes to form thrombi, thereby, increasing the risk of stroke. In addition, IDA stimulates erythropoietin (EPO) levels, which can cause reactive thrombocytosis. “Anemic hypoxia” from impaired

oxygen tissue delivery can lead to ischemic tissue damage in the brain, as evidenced by neuroimaging of anemic stroke patients.<sup>[22]</sup>

Anemia and stroke are closely intertwined. Zeng *et al.*<sup>[23]</sup> found that 26% of the anemic patients with hemoglobin <10 g/dL died within 6 months of stroke versus 19.7% of the non-anemic patients after adjusting for potential confounders ( $P < 0.05$ ). Even among pediatric patients without classical risk factors for stroke, IDA was associated with a 3.8-fold increased risk of developing an ischemic stroke or venous thrombosis following a viral prodrome.<sup>[22]</sup> That said, anemia is also found to be a risk factor for perioperative stroke, which is defined as an ischemic or hemorrhagic brain infarction occurring during surgery or within 30 days after surgery. The incidence of perioperative stroke can be up to 10% in high-risk cardiac or brain surgery versus 0.1–1.9% in nonmajor surgeries. A study of patients undergoing mitral valve surgery identified anemia as a risk factor associated with perioperative stroke.<sup>[24]</sup>

Cerebral hypoxia from anemia is one proposed mechanism of ischemic perioperative stroke. In the setting of anemia, cardiac output and cerebral blood flow are expected to increase as compensatory mechanisms to maintain tissue oxygenation. Anemia elicits a hyperkinetic response which increases cardiac output through decreased systemic vascular resistance, reduced blood volume, and shift in the oxyhemoglobin dissociation curve to allow increased tissue consumption of oxygen. However, the use of nonspecific beta-blockers in the setting of anemia may inhibit the appropriate compensatory mechanisms, and therefore, result in cerebral tissue hypoxia. This mechanism was demonstrated in animal models, and clinical data have also confirmed increased stroke risk in patients with hemoglobin below 9 g/dL who are on beta-blockers.<sup>[25]</sup>

## Cognitive

Postoperative cognitive dysfunction is a common occurrence after major cardiac, vascular, and orthopedic surgeries, occurring at a rate of 40–60%.<sup>[26]</sup> The literature on the association between acute anemia and postoperative cognitive function has yielded mixed results. In a study of 108 elderly subjects undergoing cardiopulmonary bypass, those with severe anemia (defined as hematocrit <18%) experienced a higher degree of cognitive impairment than those with mild anemia (defined as hematocrit >27%).<sup>[26]</sup> Even in a study of healthy nonsurgical human subjects who underwent phlebotomy to achieve desired hemoglobin levels of 5.5–6.0 g/dL, acute anemia has been found to cause cognitive impairment.<sup>[27]</sup>

Intermittent hypoxia (as defined by nonsustained recurrent episodes of hypoxia in between periods of normal oxygenation with subsequent reoxygenation), has been shown to impair synaptic plasticity and synthesis of neuronal proteins essential for learning.<sup>[26]</sup> Therefore, it is no surprise that prolonged periods of sustained hypoxia associated with sleep apnea and high-altitude exposure have been shown to impair memory and

learning.<sup>[28]</sup> On the other hand, a large study of 653 older adults in the acute surgical setting found no statistical association between anemia (as defined by hemoglobin <12.9 g/dL) and delirium. Patients were evaluated with the Confusion Assessment Method (CAM) and Montreal Cognitive Assessment (MoCA) cognitive function tests, and performance was not different in patients with anemia and those without (OR 1.00 (95% CI 0.48–2.10)).<sup>[29]</sup> A more recent secondary analysis of the prospective multicenter observational CESARO-study that included 800 patients showed that postoperative anemia was associated with a much higher incidence of delirium and hospital stays.<sup>[30]</sup> Despite mixed results, cell hypoxia is commonly encountered in major surgeries, especially in anemic patients, and its potential role in postoperative cognitive dysfunction is important to consider.

## Functional status

There is a lot of literature showing an association between anemia and functional capacity, risk of fracture, and mortality in the elderly.<sup>[31–33]</sup> Baseline physical performance was assessed in 1,146 older adults with standing balance, a timed walk, and a timed test of five chair rises. Physical performance was reassessed over 4 years for functional decline. The mean decline of physical performance was found to be significantly higher in subjects with anemia (2.3%) compared to non-anemic older adults (1.4%) ( $P = 0.003$ ). This association was observed even in otherwise healthy participants without other medical comorbidities as confounders, suggesting that anemia is an independent risk factor for physical performance decline.<sup>[34]</sup> A later study confirmed similar findings among elderly women over 11 years with similar tests of physical function. Worse physical performance and increased mortality were observed in elderly women with hemoglobin below 12 g/dL than their non-anemic counterparts.<sup>[35]</sup>

In terms of risk for injury, anemic patients were twice as likely to sustain an intertrochanteric fracture (OR 2.0; 95% CI 1.3–2.9,  $P = 0.001$ ). Anemia at hospital admission was associated with increased hospital length of stay ( $P < 0.01$ ), however, not with postoperative complications. After undergoing surgical intervention for hip fracture, anemic (defined as admission hemoglobin levels <12 g/dL for females and <13 g/dL for males) and non-anemic patients had similar recovery of physical performance at 3, 6, and 12 months. However, increased mortality was observed at 6 and 12 months after hip surgery in anemic patients. This association became more pronounced in severely anemic patients (defined as admission hemoglobin <10 g/dL), who were five times more likely to die after hip surgery compared to non-anemic patients ( $P = 0.01$ ).<sup>[31]</sup>

Furthermore, anemia has been linked to the length of stay and mortality in hospitalized patients. In a cohort study of 550 patients who had surgery for hip fracture, the hemoglobin levels on admission were inversely correlated with length of hospital stay ( $r = -0.42$ ,  $P < 0.05$ ), odds of mortality (OR = 0.72, 95% CI

0.56–0.93) and readmission (OR = 0.86, 95% CI 0.75–0.98) after controlling for pre-fracture patient characteristics. Postoperative hemoglobin was inversely correlated with length of hospital stay ( $r = -0.97$ ,  $P < 0.05$ ) and odds of readmission (OR = 0.85, 95% CI 0.73–0.99), however, had no association with mortality (OR = 0.94, 95% CI 0.70–1.26). Neither preoperative nor postoperative anemia was associated with mobility scores estimating functional status in this study.<sup>[33]</sup>

## Management

Given that the evidence largely suggests favorable outcomes when packed red cell transfusions (PRCT) are prevented, it is important that management of anemia be considered from this perspective.

Preoperative evaluation should occur at the earliest opportunity to ensure adequate time for interventions.<sup>[36]</sup> This visit should begin with a focused history to elicit symptoms such as hematochezia, melena, hematemesis, heavy menstrual bleeding, hematuria, hemoptysis, weight loss, history of gastrointestinal surgery, and poor nutrition. Pertinent medical history includes the previous PRCT, inherited/acquired coagulopathy, and venous thromboembolism. Comorbid conditions such as cardiorespiratory disease may increase the risk for organ ischemia and influence PRCT thresholds. One should carefully review all medications with special attention to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, proton pump inhibitors, anticoagulants, antiplatelet agents, vitamins, and supplements.<sup>[37,38]</sup> After reviewing the indications for each medication, the patient should be given specific instructions on how to take them in the perioperative period based on available evidence and guidelines. Review recent labs and order additional studies as indicated based on the history, exam, and risk factors.

If surgery is emergent, proceed with surgery and initiate concurrent evaluation and treatment of anemia. Studies have shown that administration of iron and erythropoietin, even as a single dose before surgery can limit the overall perioperative PRCTs needed in a patient.<sup>[39,40]</sup> When reasonable, elective surgery should be deferred to allow for appropriate evaluation and treatment of anemia.

Perioperative management of anticoagulants and antiplatelet agents is dependent on the indications for therapy, the risk of holding therapy, and the surgery-specific risk of perioperative blood loss. The patient should be given clear, specific instructions about whether to hold such agents, the need for bridging anticoagulation, and when to resume medication based on current recommendations. For patients with anemia due to nutritional deficiencies, initiate nutrient replacement as soon as possible. The response occurs in about 1–2 weeks and correction is expected in 6–8 weeks. Replace vitamin B12 and/or folate, when indicated, in conjunction with iron. Iron therapy is recommended for patients with IDA and for non-anemic patients with low iron stores (ferritin <100, transferrin

saturation <20%) scheduled for surgery with predicted total preoperative hemoglobin loss >3 g/dL (>1,200 mL in 70 kg adult) to protect against IDA.<sup>[36]</sup> If time permits (4 weeks or more), oral iron supplementation can be considered.<sup>[41]</sup> Ferrous and ferric formulations are equally efficacious but ferrous salts are more cost-effective.<sup>[42]</sup> However, a higher iron level is often achieved when intravenous formulations are used. Practical problems may arise when arranging for these infusions from the PCP's office without the appropriate resources.

Consider erythropoietin analogs (EPO) with or without iron for perioperative management in most anemic patients.<sup>[43]</sup> Based on previous studies in different surgical specialties, it appears that giving a dose of IV iron (up to 1,000 mg) either as iron carboxymaltose or dextran along with high doses of EPO, B12, and folate will decrease the need for PRCT postoperatively.<sup>[44]</sup> Even when hemoglobin is in the normal range, this strategy can still be used to mitigate postoperative anemia when the anticipated blood loss during surgery is high. European guidelines recommend preoperative EPO with or without iron for all patients with hemoglobin less than 14.5 g/dL and without iron deficiency who are undergoing cardiac surgery. This is based on three RCTs demonstrating reduced perioperative PRCT compared to placebo in this population.<sup>[39,45]</sup> EPO should not be given to patients with chemotherapy-associated anemia for whom treatment is intended to be curative. In such patients, EPOs are associated with decreased survival, increased mortality, and increased risk of cancer progression or recurrence.<sup>[46]</sup> For patients with chronic kidney disease, follow the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for EPO use in consultation with the patient's nephrologist. It is important to ensure iron repletion before EPO therapy. Do not start EPO unless hemoglobin is less than 10 g/dL, and aim for a goal of 10–11.5 g/dL.<sup>[37]</sup>

Initiate or continue IV iron/EPO treatment in the postoperative period as well.<sup>[47]</sup> Given the clinical risks, limited resources, and cost, limit phlebotomy to when clinically necessary and transfuse unit by unit unless the patient is clinically unstable. Set transfusion thresholds for the patient: in general, a restrictive PRCT threshold of 7 g/dL is recommended, but for patients undergoing cardiac surgery, a PRCT threshold of 7.5 g/dL is recommended.<sup>[48,49]</sup> Monitor for signs of transfusion reaction during and after transfusion such as ABO incompatibility (hyperthermia, hemoglobinuria, microvascular bleeding); TRALI (a leading cause of transfusion-associated fatalities) or TACO (hypoxemia, respiratory distress, increased peak airway pressure); bacterial contamination (hyperthermia, hypotension); an allergic reaction (urticaria); and citrate toxicity (hypocalcemia).<sup>[50]</sup> Anemia should be monitored and addressed beyond the immediate postoperative period as well. Patients who need PRCT could become anemic again beyond the lifespan of the transfused red cells. Keeping these patients on supplemental oral iron, B12, and folate for a few weeks may be beneficial with close monitoring. Many institutions have protocols that incorporate part of many of these guidelines for anemia management.



## Conclusions

In summary, anemia in the perioperative period can result in or predispose patients to a myriad of complications involving different organ systems. This review raises awareness of the impact of perioperative anemia on cardiac, pulmonary, neurological, cognitive, and functional statuses in an effort to promote prompt treatment and prevention of intraoperative and postoperative complications. Early recognition of the problem and proactive interventions including the use of intravenous iron infusions and use of erythropoietin analogs can go a long way in preventing transfusions and transfusion-related problems. Anemia is one modifiable risk factor that can improve postoperative outcomes in high-risk patients and procedures.

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## Conflicts of interest

There are no conflicts of interest.

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