Optimizing Preoperative Anemia to Improve Patient Outcomes

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KEYWORDS

• Anemia • Hemoglobin • Outcomes • Transfusion

KEY POINTS

- Several studies have shown that preoperative anemia leads to increased morbidity and mortality following major surgery.
- The varying degrees of perioperative practice patterns and the health-related impact of preoperative anemia highlight the urgent need to identify new strategies to optimize preoperative anemia.
- Multiple published protocols recommend testing patients for hemoglobin at least 1 month before surgery, to allow intervention and treatment to take effect before surgery. This initial testing can be done at the preoperative clinic visit.
- Although professional society guidelines exist for the perioperative management of blood products, including transfusion triggers and cancellation guidance, less clear guidance exists on the perioperative optimization of patient red blood cell volume to improve clinical outcomes.

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INTRODUCTION

Anemia is a decrease in red blood cell mass, which leads to a reduction in oxygen delivery to tissues. The 2003 to 2012 National Health and Nutrition Examination Surveys (NHANES) estimated that an average of 5.6% of the United States population met the World Health Organization (WHO) criteria for anemia and 1.5% met the criteria for moderate to severe anemia during the study period.[1] In practice, a low hematocrit or hemoglobin concentration is widely used to screen and estimate the degree of anemia. The WHO defines anemia as a hemoglobin concentration less than 13 g/dL in men and less than 12 g/dL in women.[2] The WHO and the National Cancer Institute published revised cutoffs for the evaluation of anemia secondary to complications of cancer, in which anemia is defined as a hemoglobin concentration of less than 14 g/dL and less than 12 g/dL for men and women, respectively.[2]

Iron deficiency is the most common cause of anemia and can be caused by chronic blood loss, poor intake/absorption of iron from the gastrointestinal tract, or a functional state of iron deficiency induced by chronic disease. There are several other causes, such as anemia of chronic disease (eg, cancer, tuberculosis, human immunodeficiency virus), vitamin deficiencies (eg, folate and vitamin B_{12}), blood loss secondary to traumatic injury, chronic renal failure, and hemoglobinopathies. The WHO estimates that 50% of anemia cases are secondary to iron deficiency anemia,[2] However, this estimate is based largely on the geographic region and the population under study. Symptoms of anemia range from weakness and fatigue to angina and reduced cognitive performance. Anemia is the most common preoperative hematologic diagnosis and the reduced oxygen carrying capacity of the blood plays a critical role in causing perioperative morbidity and mortality. Estimates of anemia prevalence in the surgical population have been found to range from 25% to as high as 75% in orthopedic and colorectal surgeries, respectively.[3]

The increasing burden of chronic diseases (eg, heart disease, renal disease, cancer) coupled with an aging population pose unique challenges in optimizing preoperative anemia. Randomized controlled trials have established a hemoglobin concentration of less than 7 g/dL for transfusion, and, although transfusions are used perioperatively in the management of anemia, they are associated with inherent complications. Complications include acute/delayed hemolytic reactions, anaphylactic reactions, and transfusion associated with graft-versus-host disease.[4] Irrespective of degree of preoperative anemia, patients receiving perioperative transfusions were more likely to experience inpatient mortality.[5] As such, anemia and consequent blood transfusion pose a significant threat to postoperative rehabilitation and increases the risk of poor outcomes.

In a Web-based survey of preoperative anemia management practice patterns among liver surgeons and anesthesiologists, Bennet and colleagues[6] found that anesthesiologists (47%) relied heavily on hemoglobin concentration, whereas liver surgeons (33%) relied on hemodynamics when determining intraoperative transfusion. In their evaluation of 97,443 patients who underwent cardiac and noncardiac surgery, Sim and colleagues[7] showed that anemia predicted 1-year mortality. The varying degrees of perioperative practice patterns and the health-related impact of preoperative anemia highlight the urgent need to identify new strategies to optimize preoperative anemia. With this, an understanding of preoperative anemia and postoperative outcomes in various surgical settings is crucial. This article:

1. Reviews the relevant literature and highlights consequences of preoperative anemia in the surgical setting
2. Suggests strategies for screening and optimizing anemia in the preoperative setting

PREOPERATIVE ANEMIA AND POSTOPERATIVE OUTCOMES

The literature on preoperative anemia and postoperative outcomes is discussed here, based on surgical specialty, including cardiac surgery, general surgery, thoracic surgery, spine surgery, orthopedic (eg, joint arthroplasty), and vascular surgery.

Cardiac Surgery

Cardiac surgery patients with anemia commonly present with several comorbidities.[8,9] Studies have identified anemia as an independent predictor of postoperative morbidity and mortality in this surgical population.[10–13] Studies have also shown that anemia is associated with increased risk of postoperative renal dysfunction, for which patients may require renal replacement therapy.[11,14,15] In their evaluation of anemic patients with chronic kidney disease, Shavit and colleagues[16] showed that, for every 1 g/dL decrease in hemoglobin concentration, the odds of mortality, sepsis, postoperative hemodialysis, and cerebrovascular accident significantly increased.

The prevalence of anemia was 26% in a retrospective study that identified 10,589 patients who underwent elective cardiac operations. After adjusting for red blood cell transfusion, anemia remained a risk factor of renal failure, inpatient death, arrhythmias, and longer hospital and intensive care unit (ICU) length of stay.[17] Ranucci and colleagues[18] showed in a retrospective propensity-matched analysis of 401 severely anemic patients undergoing cardiac surgery that anemic patients had significantly higher rates of cerebrovascular accident, major postoperative morbidity, and operative mortality. Moreover, the severity of preoperative anemia and intraoperative blood transfusion both independently led to decreased long-term survival.[19] Hallward and colleagues[20] assessed the relationship between hemoglobin concentration and blood transfusion requirements, hospital length of stay, reoperation, and mortality. For every 1 g/dL increase in hemoglobin, there was a relative 11% decrease in red blood cell units transfused, an 8% decrease in number of platelets transfused, and a 3% decrease in fresh frozen plasma transfused. In addition, lower hemoglobin concentration has been shown to be associated with increased postoperative hospital and ICU length of stay. In a matched case-control study of 1170 cardiac surgery patients, Padmanabhan and colleagues[21] showed that anemic patients were significantly more likely to require postoperative airway support and had higher rates of surgical site infection and postoperative atrial fibrillation. Researchers have evaluated the impact of treating preoperative anemia with strategies other than transfusion. Cladellas and colleagues[22] showed that administration of recombinant human erythropoietin decreases postoperative mortality, blood transfusions, and hospitalization. Based on the existing data, prospective studies are needed to evaluate new strategies to optimally manage perioperative anemia in patients undergoing cardiac surgery.

General Surgery

Preoperative anemia is the most common hematologic disorder in many malignancies and its prevalence ranges from 30% to 90%.[23] In their single-institution retrospective evaluation of 2163 gastric surgery patients, Liu and colleagues[23] showed that preoperative anemia was associated with overall lower survival and an increased rate of perioperative transfusions and postoperative complications. Anemia has been identified as a marker of disease severity in inflammatory bowel disease (IBD), and the prevalence of colectomy for IBD is roughly 30% worldwide.[24] Michailidou and Nfonsam[24] showed that preoperative anemia predicted morbidity and increased hospital length of stay in patients with IBD following colorectal surgery. Preoperative anemia is also an independent risk factor of postoperative venous thromboembolism in patients with IBD following

colectomy.[25] After adjustment, preoperative anemia is associated with increases risk of morbidity following hepatectomy.[26] Similarly, Lucas and colleagues[27] showed that hepatopancreatobiliary surgery patients with preoperative hematocrit less than 36% were significantly more likely to require postoperative transfusion. Furthermore, in patients undergoing resection of colorectal liver metastases, correction of preoperative anemia with allogenic red blood cell transfusion was independently associated with lower recurrence-free survival.[28] Despite the well-understood pathology and ease of diagnosis, perioperative anemia continues to be a challenging issue. Physicians should continue efforts to develop guidelines for perioperative management of anemia.

Thoracic Surgery

Postoperative complications directly influence postoperative mortality following thoracic surgery. Using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP), Jean and colleagues[29] evaluated 6434 lung resection patients and showed that the odds of 30-day mortality were 53% higher in patients with preoperative anemia compared with those without. Likewise, in their retrospective analysis of 125 patients with non–small cell lung cancer, Yovino and colleagues[30] found that preoperative hemoglobin level less than 12 g/dL predicted worse relapse-free and overall survival. Berardi and colleagues[31] found that perioperative anemia predicted postoperative mortality and this relationship remained after correction of anemia with red blood cell transfusion. In contrast, Melis and colleagues[32] showed that preoperative anemia was not associated with poor outcomes in patients undergoing esophagectomy, but preoperative anemia was independently associated with increased rate of perioperative blood transfusions, and such transfusions were associated with higher risk of overall complications and surgical site infections.

Spine Surgery

Over the last decade, the prevalence of spine surgeries has dramatically increased. With an increasing elderly population, there is also an increase in perioperative comorbidities that consequently increase the risk of postoperative morbidity and mortality.[33] Patients with anemia are significantly more likely to have several preoperative risk factors of poor outcomes, including diabetes mellitus, American Society of Anesthesiologists physical status classification greater than or equal to 3, and dependent functional status.[34] In patients undergoing posterior cervical fusion, preoperative anemia was associated with roughly a 3-fold increase in any complications, pulmonary complications, perioperative transfusions, reoperation, readmission, and extended hospital length of stay (ie, >5 days).[34] Similarly, in a retrospective study using data from ACS NSQIP, 3500 patients undergoing anterior cervical discectomy and fusion were included in the final analysis. Preoperative anemia was a prognostic indicator of any complication, pulmonary complications, intraoperative blood transfusions, reoperation, and hospital length of stay greater than 5 days.[35] Moreover, low preoperative hematocrit (ie, <40%) was shown to be associated with hospital stay greater than 5 days in patients receiving lumbar spinal procedures.[36] In adult patients undergoing elective spine surgeries, anemic patients had an increased risk of perioperative blood transfusion, which was associated with morbidity and mortality.[33] Preoperative hematocrit was also identified as an independent risk factor of postoperative 30-day reintubation in a cohort of 8648 cervical spine surgery patients.[33]

Orthopedic Surgery

In patients undergoing total hip and knee arthroplasty, preoperative anemia was associated with postoperative complications, extended hospital length of stay, and increased

rates of allogenic red blood cell transfusions.[37] Similarly, after total knee arthroplasty in noncardiac patients, preoperative anemia was shown to be associated with higher odds of transfusions and pulmonary and renal postoperative complications.[38] After controlling for potential confounders, preoperative hematocrit less than 38% was associated with short-term inpatient complications following total shoulder arthroplasty.[39] Perioperative red blood cell transfusion is also associated with significantly higher rates of myocardial infarction, pneumonia, sepsis, venous thromboembolism, and cerebrovascular accident in patients undergoing shoulder arthroplasty.[40] Dix and colleagues[41] evaluated 39 patients who underwent hindfoot and ankle arthrodesis and found that preoperative anemia was associated with surgery-specific complications (ie, delayed union, nonunion, and malunion), postoperative infection, and longer hospital stay.

Elderly anemic patients are at increased risk of postoperative adverse events secondary to the aging process and the comorbidity burden associated with perioperative anemia. Furthermore, anemia is common in orthopedic surgery. A systematic literature review of perioperative anemia in hip or knee arthroplasty showed that preoperative anemia was prevalent in 24% to 44% of the patients and postoperative anemia occurred in 51% of patients.[42] Furthermore, that review showed that anemic patients had significantly higher rates of red blood cell transfusion, postoperative infection, and mortality, as well as poor postoperative recovery and increased hospital length of stay.[42] In their assessment of postoperative outcomes after total hip and knee arthroplasty in patients more than 85 years old, Pittert and colleagues[43] found that preoperative anemia was associated with 90-day readmission. In Medicare patients, Bozic and colleagues[44] showed that several comorbidities along with preoperative anemia were associated with an increased risk of periprosthetic joint infections and postoperative 90-day mortality following total hip arthroplasty.

Vascular Surgery

Anemic patients undergoing vascular surgery are at higher risk of several postoperative adverse events. Bodewes and colleagues[45] evaluated 5081 patients with chronic limb-threatening ischemia undergoing infrainguinal bypass surgery and showed that anemic patients tended to be older with higher comorbidity burden. Severe preoperative anemia was associated with increased odds of short-term mortality, major amputation, adverse postoperative cardiovascular events, and reoperation. The relationship between preoperative anemia and mortality remains significant for patients following carotid endarterectomy.[46] It is well established that blood transfusions are common among patients receiving vascular surgery. Obi and colleagues[47] investigated the impact of perioperative transfusions on 30-day morbidity and mortality in 2964 patients undergoing peripheral arterial disease procedures and aneurysm repair and found a 25% transfusion rate with preoperative anemia predicting perioperative transfusions. With advancements in technology, there is an increasing prevalence of elderly patients undergoing vascular surgery. Peripheral arterial disease is estimated to occur at a rate of 29% in this population. Using the ACS NSQIP database to evaluate 31,857 patients 65 years of age or older, Gupta and colleagues[48] found an inverse relationship between postoperative mortality and preoperative hematocrit following elective vascular procedures. Moreover, there is a lower perioperative hematocrit following open surgery versus endovascular repair of ruptured abdominal aortic aneurysm.[49]

ANEMIA SCREENING IN THE PREOPERATIVE ASSESSMENT CLINIC

Patient blood management is defined by the Society for the Advancement of Blood Management as the timely application of evidence-based medical and surgical

concepts designed to maintain hemoglobin concentration, optimize hemostasis, and minimize blood loss to improve patient outcome. The 3 pillars include the optimization of red blood cell mass, reduction of blood loss and bleeding, and optimization of the patient's physiologic tolerance of anemia (Fig. 1).[50]

In the setting of the preoperative clinic, integrating the principles of patient blood management focuses on the first pillar: optimization of red blood cell mass to reduce perioperative transfusions. The preoperative clinic identifies patients with anemia before major elective surgery (Fig. 2). Once these patients are identified, the anemia can be evaluated and treated per protocols before surgery. These protocols vary by institution, but common approaches to these protocols are discussed later. Correcting anemia before surgery reduces the risk of perioperative transfusion in joint arthroplasty patients, with a relative risk of 0.48 in a meta-analysis.[51] It is reasonable to consider that patient outcomes should be improved by avoiding the known risks of severe anemia and transfusion as well as by treating underlying diseases. In addition, reductions in perioperative transfusion can result in reduced costs to the blood bank and health care system.[52] The Duke Perioperative Enhancement Team implemented a thorough financial modeling of a perioperative anemia screening program that showed a positive net value of more than $2.5 million over 5 years.[53]

Time Frame: When to Screen

Treatment of anemia in the preoperative period has a stronger level of evidence in improving anemia and transfusion-related outcomes than in the immediate perioperative period or the postoperative period.[52] Accordingly, multiple published protocols recommend testing patients for hemoglobin at least 1 month before surgery, to allow intervention and treatment to take effect before surgery.[54,55] This initial testing can be done at the preoperative clinic visit with a point-of-care test for a real-time result, or by ordering a complete blood count (CBC) as part of the preoperative laboratory tests.

Surgery Types: Who to Test/Screen

The decision regarding which patients to screen varies by institution. Screening all patients for hemoglobin is one approach, but several institutions make the decision to screen all patients presenting for specific surgeries with higher blood loss (>500 mL) or higher transfusion rates (>10%).[55] Most commonly, this includes major orthopedic (eg, total joint) and spine surgeries.[53] A third approach is to screen all patients for whom surgical orders include a crossmatch order.

What to Do with Identified Anemic Patients

The WHO criteria for anemia are hemoglobin level less than 13 g/dL in men and less than 12 g/dL in women.[56] Despite the gender differences in the WHO definition of anemia, some algorithms choose a hemoglobin level of 13 g/dL as the screening criteria

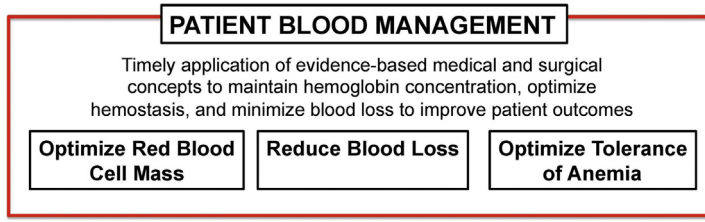

Fig. 1. Patient blood management goals.

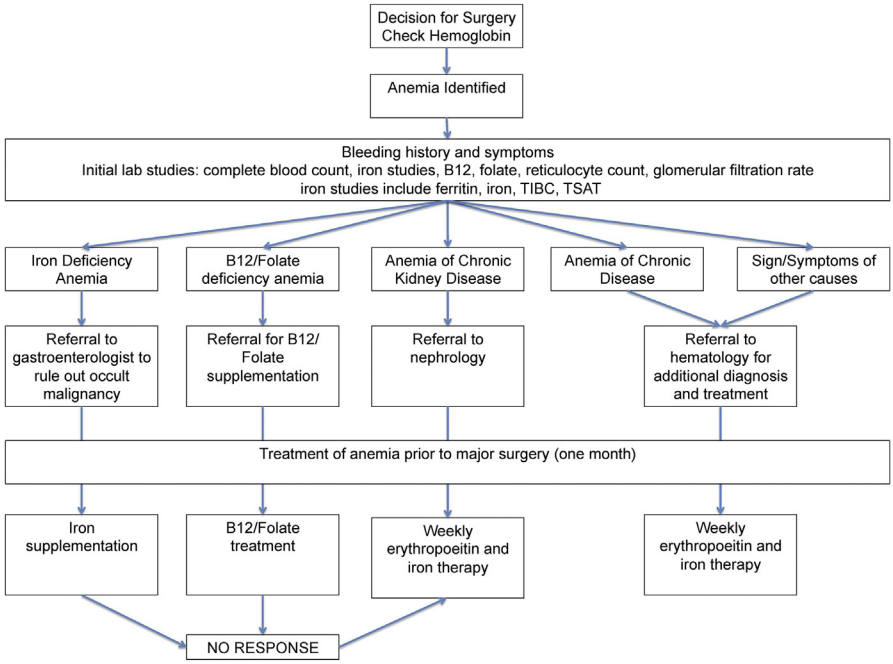

Fig. 2. Proposed evaluation and treatment algorithm for preoperative anemia. TIBC, total iron-binding capacity; TSAT, transferrin saturation.

for both genders. The reasoning is that female patients have a lower circulating blood volume, therefore a given amount of surgical blood loss would have a larger impact on perioperative anemia.[52] Once the syndrome of anemia is identified by these initial criteria, the triage of initial assessment and referral is summarized in **Fig. 2**. In parallel to referral for follow-up, the patient can also start treatment in the preoperative clinic for preoperative correction of the anemia before surgery.

TREATMENT OF ANEMIA FOR PREOPERATIVE OPTIMIZATION

Although professional society guidelines exist for the perioperative management of blood products, including transfusion triggers and cancellation guidance, less clear guidance exists on the perioperative optimization of patient red blood cell volume to improve clinical outcomes.[57–60] Preoperative anemia is clearly associated with worsened outcomes postoperatively. A holistic approach to perioperative blood management focuses on preoperative optimization of red blood cell mass, minimization and mitigation of intraoperative blood loss, and goal-directed management of postoperative anemia.[61] This article focuses on preoperative management and therefore the optimization of red blood cell mass. Treatment strategies can be broadly broken down into correction of reversible causes of anemia, enhanced red blood cell production, and preoperative transfusion.

Assessment of Anemia

Recommendations from the European Society of Anaesthesiology recommend that hemoglobin concentrations be measured 4 to 8 weeks before surgery, particularly if the patient is at risk for perioperative bleeding.[62] The goal of early identification is to

allow time for preoperative interventions to result in meaningful increases in the hemoglobin concentration. At this time, no recommendation can be made regarding a target hemoglobin level preoperatively. Although increasing severity of anemia is associated with worsened postoperative outcomes, a clear causal link between preoperative optimization and improved outcomes has not been definitively shown.

Identification of Reversible Causes of Anemia

Once anemia is identified on preoperative laboratory screening and the patient is scheduled to undergo a surgery with moderate to high blood loss, further evaluation of potential reversible causes of anemia is warranted. Initial laboratory evaluation should focus on common, easily reversible causes, with assessment of serum iron and transferrin levels, total iron binding capacity, and ferritin levels to identify potential iron deficiency anemia. A CBC with assessment of the mean corpuscular volume can identify macrocytosis and should prompt assessment of vitamin B_{12} and folic acid levels, as well as prompting further assessment of patient alcohol consumption. A measure of systemic inflammation, such as the C-reactive protein or erythrocyte sedimentation rate, is often useful in the interpretation of iron studies. In addition, a marker of renal function, such as the serum creatinine level, should be assessed. This evaluation allows determination of the major, most common causes of anemia, as shown in **Fig. 2**: iron deficiency, other nutritional deficiency, anemia of chronic disease, anemia of chronic kidney disease, or the category of other less common hematologic or oncologic causes. If this testing is done and treatment is started in the preoperative clinic, patients still need to be referred for follow-up of the underlying cause of anemia. Iron deficiency anemia is the most common cause of anemia in preoperative patients, accounting for approximately 33% of cases.[2] If iron deficiency anemia is identified as the cause, referral may be made to a gastroenterologist to rule out occult malignancy, and the primary care provider should be notified. If glomerular filtration rate is less than 60 mL/min, a referral is made to nephrology. If folate or B_{12} levels are low, referral is made to primary care or nutrition for treatment. If these are all normal, the diagnosis of anemia of chronic disease is considered. If the anemia is severe (hemoglobin level <8 g/dL), other components of the CBC are abnormal, or history and physical suggest other causes of anemia, referral is made to primary care or hematology.

Management of Iron Deficiency Anemia

Iron deficiency anemia is a common cause of preoperative anemia and is readily corrected with administration of exogenous iron. Both oral and intravenous (IV) formulations of iron exist. Oral iron is an easily accessible, low-cost method of iron repletion that has been shown to decrease the likelihood of perioperative blood transfusion.[63] However, oral iron administration is limited by several factors, including patient adherence because of induced gastrointestinal upset, poor bioavailability, and the need for prolonged oral administration to restore adequate iron stores.

IV iron formulations have shown equivalent efficacy to enteral iron in the treatment of iron deficiency anemia, with fewer adverse effects and decreased time to efficacy. IV iron may be preferred in situations in which oral iron is not practical, such as when the time to surgery is less than 6 to 8 weeks, or the required intake is impossible because of patient adherence. IV iron has been shown to decrease the need for perioperative blood transfusion and improve hospital stay in several studies.[64,65]

Enhanced Red Blood Cell Production

In patients with adequate iron stores and without evidence of other macronutrient deficiencies, preoperative anemia is often assumed to be caused by impaired

erythropoiesis. Use of recombinant human erythropoietin has been shown in several meta-analyses to effectively increase the preoperative hemoglobin level and reduce the need for perioperative blood transfusions.[66,67] The precise dosing, route of administration, frequency, and duration of treatment remain unknown. The most frequent dosing regimen is once-weekly erythropoietin injections, and usually results in an increase in hemoglobin level of between 0.5 g/dL and 1 g/dL per week. Clinicians considering implementation of erythropoietin treatment in the preoperative clinic should be aware of the contraindications to erythropoietin treatment, which include uncontrolled hypertension; severe or recent coronary, cerebral, or peripheral disease; and uncontrolled seizure disorder.[68] Erythropoietin is avoided in patients with cancer not on myelosuppressive chemotherapy because of increased risk of recurrence and progression in several cancers. In addition, although the adverse effects of erythropoietin administration have been well described in multiple other populations, the specific risks of preoperative administration are unclear.[69–71] Specifically, whether erythropoietin increases the rates of perioperative thrombotic events, including venous thromboembolism and myocardial infarction, in patients receiving erythropoietin is uncertain.[66,72]

Preoperative Blood Transfusion

Routine preoperative blood transfusion is not routinely recommended except in situations of symptomatic anemia in which transfusion is recommended by guidelines, or in cases of hemoglobinopathies such as sickle cell anemia.[73] The optimal method of transfusion for patients with sickle cell disease remains unknown. Consultation with a hematologist is recommended in these situations.[74]

SUMMARY

Anemia is a common preoperative finding in surgical populations. With only subtle clinical symptoms except when anemia becomes severe, a systematic approach to the screening and clinical assessment of anemia is needed when performing a preoperative assessment. Given the association between the severity of anemia and increased complication rates, mortality, and hospital length of stay, it is important to identify and optimize these patients. The risk factors associated with transfusion of blood products during the perioperative period mean that preoperative treatment of anemia is a key strategy for improving postsurgical outcomes.

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