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Anemia in the Preoperative Patient

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Synopsis

Anemia is commonly encountered in the preoperative patient. With variable etiology, determination of the cause of the anemia can impact perioperative surgical and medical management and outcome. Red blood cell transfusions are often administered during the perioperative time period in patients with preoperative anemia, although evidence to support the optimal transfusion threshold is limited. We review the evaluation of anemia, as well as evidence regarding perioperative blood transfusions. Recommendations on the treatment of anemia, including perioperative blood transfusions, are outlined.

Keywords

anemia; erythrocyte transfusion; surgery; preoperative care

Introduction

Anemia

Anemia is the most common hematological problem in the preoperative patient. Often, it is a sign of an underlying disease or condition that could affect the surgical outcome.

Consequently, blood transfusions are commonly given perioperatively to anemic patients. In 2006 the supply of allogenic whole blood/red blood cells in the U.S. was estimated to be over 15.7 million units, and an estimated 14.6 million units were transfused.⁴⁷ It has been shown that 40 to 70% of all red cell units are transfused in the surgical setting.^{12,15,19,46}

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Therefore, an understanding of the causes and consequences of anemia, as well as any potential treatments, is crucial in the preoperative setting.

Evaluation of Anemia

History and Physical Examination—The evaluation of the anemic preoperative patient should always begin with a thorough history and physical examination. The history should first attempt to elicit symptoms of bleeding such as menstrual blood loss, hematochezia, melena, hematemesis, hemoptysis, or hematuria. It is also important to ask about symptoms related to the anemia and the body's compensatory mechanisms, that is, anginal chest pain, dyspnea, fatigue and palpitations. Any history of or symptoms of underlying illnesses, such as constitutional symptoms, malignancy, renal failure, endocrinopathies (thyroid disorders, for example), infections, or liver disease, should be targeted. Past history of anemia is also important, including previous hemoglobin values and therapies, onset, need for previous blood transfusions, splenectomy, and blood donations. The patient's family history may contain a history of anemia, bleeding and other hematological disorders, splenectomy, and early onset cholelithiasis, which may indicate congenital hemolytic disorders. The social history should take into account occupational hazards and exposures, dietary habits, alcohol and illicit drug use, and a detailed list of all prescription and non-prescription medications, including herbal and over-the-counter medications.

The physical examination should focus on manifestations and potential etiologies of the anemia, such as pallor of the skin and mucous membranes, jaundice, signs of bleeding, purpura, petechiae, hepatosplenomegaly, and lymphadenopathy. A heart murmur is sometimes heard, and this may be a flow murmur due to decreased blood viscosity and elevated cardiac output from the anemia, or it may indicate the presence of a prosthetic valve. A pelvic and rectal exam with stool guaiac may need to be performed to evaluate for possible sources of blood loss.

Diagnostic Evaluation—An approach to anemia is given in Figure 1. Initial laboratory testing should include a complete blood count (CBC), peripheral blood smear, and a reticulocyte count. In addition, stool guaiac, radiological, and endoscopic testing may be required in an effort to exclude blood loss. The reticulocyte count can be an indication of bone marrow production, but it usually needs to be corrected for differences in hematocrit and the effect of erythropoietin on the marrow. This is done by calculating a reticulocyte production index (RPI). [Figure 2]

An RPI of less than 2 usually indicates a hypoproliferative anemia, or an inappropriate/decreased marrow response to the anemia. The next step would be to look at the mean corpuscular volume (MCV) on the CBC to characterize the anemia as microcytic, normocytic, or macrocytic. Iron deficiency and thalassemia are the most common causes of microcytic anemia, and, therefore, initial work-up includes obtaining serum ferritin, serum iron, and total iron-binding capacity. Further tests may consist of hemoglobin electrophoresis or a bone marrow biopsy. In normocytic anemia, acute blood loss must first be excluded. Additional causes of normocytic anemia may include underlying renal or liver disease; early iron, vitamin B12, or folate deficiency; dimorphic anemia, such as concurrent

iron and vitamin B12 deficiency; myelodysplasia/aplastic anemia; or anemia of chronic disease due to an underlying inflammatory condition. The testing for normocytic anemia may entail many of the serologies discussed for microcytic anemia, assessment of renal and liver function, and bone marrow biopsy. Macrocytic anemia can be characterized as megaloblastic and nonmegaloblastic anemia. Megaloblastic anemia may be due to vitamin B12 or folate deficiency, drugs such as chemotherapeutic agents or anticonvulsants, and myelodysplasia. Nonmegaloblastic anemia includes alcohol ingestion, liver disease, or hypothyroidism. Initial work-up should comprise measurement of vitamin B12 and folate levels. Further tests may include thyroid or liver function tests and a bone marrow biopsy.

An RPI of greater than 2 demonstrates an appropriate marrow response to blood loss or may indicate hemolysis. Initial studies would include direct and indirect bilirubin, lactate dehydrogenase, haptoglobin level, and direct and indirect Coomb's test. The peripheral smear should also be reviewed for clues to the underlying process. Polychromasia, basophilic stippling, and nucleated red blood cells can all be seen in hemolytic anemia. In addition, several findings may point towards a specific cause. For example, schistocytes are generally associated with microangiopathic hemolytic anemias, such as those due to disseminated intravascular coagulation, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, and hemolysis from prosthetic valves. Spherocytes may be seen in hereditary spherocytosis, autoimmune hemolytic anemia, and also in microangiopathic hemolytic anemias.

Risk of Anemia in Surgical Patients

The risk of anemia in patients can be ascertained from studies involving those who decline blood transfusions. The largest such study was a retrospective cohort study performed on 1958 consecutive surgical patients who refused transfusions based on religious reasons. The overall 30-day risk of mortality increased with decreasing preoperative hemoglobin concentrations, especially in those patients with a hemoglobin level of less than 6 g/dL.⁶ The risk of death was much greater, however, in patients with underlying cardiovascular disease and preoperative hemoglobin value of 10 g/dL or less. A subsequent study on the same population showed that none of the 99 patients with postoperative hemoglobin concentrations between 7 and 8 g/dL died, whereas there was a sharp rise in mortality in those patients with a hemoglobin concentration less than 5 to 6 g/dL.⁸

These results are consistent with a series of studies in which healthy subjects underwent acute isovolemic reduction to a hemoglobin level of 5 g/dL.^{28,41,44,45} Two of these studies found evidence of asymptomatic and reversible ST-segment changes suggestive of myocardial ischemia in 5 of the 87 combined patients at hemoglobin concentrations between 5 to 7 g/dL.^{28,45} Another study evaluated eight healthy volunteers during isovolemic reduction and found self-assessed fatigue at a hemoglobin level of 7 g/dL, which then decreased further at hemoglobin levels of 6 g/dL and 5 g/dL.⁴¹ Minor and reversible cognitive changes were seen in nine healthy subjects, including decreased reaction times at hemoglobin concentration of less than 6 g/dL and impaired immediate and delayed memory at hemoglobin levels less than 5 g/dL.⁴⁴ These studies show that even healthy subjects can exhibit clinical changes at hemoglobin concentrations between 5 and 7 g/dL.

Elderly patients, however, may respond to and tolerate preoperative anemia differently than younger patients. In one study of twenty patients over the age of 65 and free from known cardiac disease, isovolemic anemia to a mean hemoglobin concentration of 8.8 g/dL was well tolerated.³⁹ Another study examined patients with known coronary artery disease and found that isovolemic anemia was well tolerated to hemoglobin value of 9.9 g/dL. In addition, the increase in cardiac index and oxygen extraction during hemodilution was found to be independent of age.³⁸ The results of these studies should be interpreted with caution as they involved small numbers of patients and very few were over the age of 80 years.³¹

A more recent study analyzed preoperative hematocrit levels in over 310,000 elderly veterans undergoing noncardiac surgery.⁴⁹ In contrast to the two previous studies, even mild anemia was associated with an increased risk of thirty-day morbidity and mortality. There was a monotonical rise in mortality and cardiac events when the hematocrit level was less than 39%. These results, however, may not be able to be generalized to elderly females. Moreover, it is unclear whether the anemia is causal or associated with the increased morbidity and mortality, and whether this risk may be corrected with transfusion.³⁶

Current Evidence Relevant to Transfusion

Observational Studies—There have been many observational studies documenting the effect of anemia and red blood cell transfusions on clinical outcomes of patients undergoing surgery, those with acute coronary syndromes, and those admitted to intensive care units. A recent systematic review of the literature identified 45 cohort studies including 272,596 patients.³² With the exception of three studies, the risks of transfusion appeared to outweigh the benefits. Transfusion was associated with an increase risk of death, infection, multiorgan dysfunction syndrome, and acute respiratory distress syndrome. However, this analysis has important limitations including that the analysis did not take into account the hemoglobin concentration before transfusion and very high likelihood of uncontrolled confounding.⁹ Those requiring blood transfusions are more severely ill than the patients that do not require them and it is impossible to completely adjust for these differences between the patients who have received transfusions and those who have not. Therefore, the decision to transfuse a preoperative patient must rest on the strength of randomized clinical trials.

Randomized Clinical Trials—There are ten randomized clinical trials in adults to date that distinguish the consequences of various transfusion thresholds.^{4, 5, 18, 20, 25, 30, 40} The clinical settings of the studies were diverse, but each of the studies did randomize patients to receive transfusions based on a “restrictive” versus a “liberal” strategy. Of the ten clinical trials, five took place within a surgical setting. One study evaluated 39 patients after myocardial revascularization and found no difference in morbidity between the conservative and liberal group, but mortality was not evaluated.²⁵ Another study involved 428 patients undergoing coronary artery bypass grafting who were randomized to receive transfusion for a hemoglobin threshold less than 9 g/dL and less than 8 g/dL.⁵ There was no difference in mortality, morbidity, and clinical outcomes between the two groups. A third study included 127 patients undergoing knee arthroplasty who were assigned to receive either two units of autologous red blood cells immediately postoperatively or to be transfused only if the hemoglobin fell below 9 g/dL.³⁰ The mean postoperative hemoglobin values between both

groups only differed by 0.7 g/dL. There were more nonsurgical complications in the conservative transfusion group. In another study 84 hip fracture patients were randomized to receive blood transfusion either when the hemoglobin fell below 10 g/dL or if they became symptomatic (this also included transfusion if the hemoglobin level was less than 8 g/dL).¹⁰ There were no statistical differences in morbidity, mortality, or functional recovery between the two groups, although a trend of increased 60-day mortality was seen in the liberal transfusion group (11.9% vs. 4.8% in the restrictive group).

The largest randomized clinical trial, and the only one with adequate power to assess clinical outcomes related to transfusion triggers, is the Transfusion Requirements in Critical Care (TRICC) trial.²⁰ 838 normovolemic, critically ill patients were randomized to a restrictive transfusion strategy or a liberal strategy. In the restrictive transfusion group, patients were transfused if the hemoglobin concentration dropped below 7 g/dL and were maintained between 7 and 9 g/dL. In the liberal transfusion group, patients received transfusion for hemoglobin levels less than 10 g/dL, and their hemoglobin values were maintained between 10 and 12 g/dL. Consistent with other studies, the average hemoglobin value and red cells units transfused were significantly lower in the restrictive trigger group. There was no statistical difference in 30-day mortality between the two groups, although there was a trend towards lower mortality in the restrictive transfusion group (18.7% vs. 23.3%). The restrictive transfusion group did have lower rates of myocardial infarction (0.07% vs. 2.9%, $p=0.02$) and pulmonary edema (5.3% vs. 10.7%, $p<0.01$) than the liberal-strategy group. Those patients with underlying ischemic heart disease showed no difference in the 30-day mortality rate between the two transfusion groups. Although this study took place in the critical care setting, it provides useful information even for perioperative patients.

A meta-analysis evaluated all ten randomized clinical trials pertaining to red cell transfusion triggers.^{7, 23} Several important conclusions were drawn from data that was pooled from the various studies. Firstly, a restrictive transfusion trigger had a lower likelihood of RBC transfusion by 42% (relative risk [RR] 0.58; 95% confidence interval [CI] 0.51-0.77), saving an average of 0.93 units of red cells per transfused patient. Secondly, there were 24% fewer cardiac events in the restrictive trigger groups, although the statistical significance was borderline (RR 0.76, 95% CI 0.57-1.00). Thirdly, patients in the restrictive trigger groups had, on average, 5.6% lower hematocrit levels than the liberal trigger groups. Fourthly, there was no statistically significant difference in the length of hospital stay between the restrictive and liberal trigger groups. Finally, there was no increase in mortality seen in the restrictive trigger groups when compared to those with liberal transfusion triggers. Actually, restrictive transfusion triggers were associated with a one fifth lower mortality (RR 0.80, 95% CI 0.63-1.02), although this was not statistically significant ($p=0.07$). It should be noted that 83% of the data on mortality was taken from the TRICC trial. This meta-analysis, however, found insufficient evidence pertaining to restrictive transfusion triggers in the setting of cardiovascular disease, hematological disorders, and renal failure. The authors of the review concluded that additional randomized clinical trials need to be done in various clinical settings and especially in those with underlying cardiovascular disease.

There is a multicenter, randomized clinical trial called FOCUS currently underway that is evaluating red cell transfusion strategy in hip fracture patients with cardiovascular disease or

cardiovascular disease risk factors in up to 2000 patients.¹¹ The results should be available in 2009.

Treatment of Anemia

Reversible Causes—In the case of iron deficiency anemia, the underlying cause, such as blood loss, should be identified and treated. Therefore, a thorough gastrointestinal evaluation is often indicated. The supplementation of iron, however, should also be initiated. Iron is most easily given in the oral form, the least expensive of which is ferrous sulfate. Ferrous sulfate provides 65 mg of elemental iron per 325 mg tablet. It is recommended that adults receive 150 to 200 mg of elemental iron per day in deficiency states. Oral iron is more readily absorbed in an acidic gastric environment and, therefore, often given with ascorbic acid and while avoiding antacids. Reticulocytosis is generally seen in seven to ten days, and the hemoglobin level should increase by 1 g/dL every two to three weeks. If patients have failed oral iron therapy, or if iron loss exceeds capacity for oral iron absorption, intravenous iron therapy may be necessary. Common clinical scenarios in which this occurs include patients with inflammatory bowel disease, intestinal malabsorption from celiac disease, patients intolerant to oral iron therapy, or patients undergoing cancer chemotherapy. Of the intravenous iron preparations ferric gluconate and iron sucrose are generally thought to have the best safety profile. Recent studies and systematic reviews, however, suggest that low-molecular-weight iron dextran may have a comparable toxicity profile to iron sucrose.^{2, 13, 33, 35}

Anemia due to vitamin B12 or folate deficiency is also easily treated with supplementation. Folate deficiency should be treated with folic acid, 1 mg per day for up to four months, or until the patient's anemia is corrected. Vitamin B12 deficiency is usually treated with intramuscular cobalamin injections. The dosage of cobalamin may vary depending on the severity of the anemia and symptoms, from 1000 mcg daily for seven days, to 1000 mcg every one to four weeks. Studies have also shown that oral cobalamin supplementation of 1000-2000 mcg per day for four months, may be at least as effective as parenteral cobalamin, but this requires greater patient compliance.^{16, 26} Reticulocytosis may be expected in three to five days, and hemoglobin levels should rise within ten days.

Patients with anemia of chronic disease, chronic renal insufficiency, zidovudine-treated HIV-infected patients and other hematological diseases may benefit from use of erythropoietin prior to surgery. In many patients erythropoietin will raise the hemoglobin concentration enough to reduce the need for allogeneic blood transfusion after surgery.^{17, 27} The target hemoglobin concentration should be no greater than 12 g/dL to avoid potential risks associated with erythropoietin (i.e., thromboembolism^{3, 34}, serious cardiovascular events^{14, 37}, and mortality³⁴), and all patients should receive thromboembolism prophylaxis. We recommend against using erythropoietin in patients with cancer since there are some studies demonstrating increase risk of tumor progression or recurrence.^{21, 22, 29}

Red Cell Transfusion Guidelines—The old adage of transfusing red cells such that the hemoglobin is greater than 10 g/dL and the hematocrit is more than 30% prior to operations no longer applies. The evidence to date suggests that a more conservative threshold for

transfusion can be used in most patients. Recently updated guidelines from the American Society of Anesthesiology recommend transfusion if hemoglobin level is less than 6 g/dL and that transfusion is rarely necessary when the level is more than 10 g/dL.¹ When hemoglobin concentrations fall between 6 and 10 g/dL, the guidelines state that transfusion decisions should be based on indication of organ ischemia, risk of or ongoing bleeding, intravascular volume status, and susceptibility to complications of inadequate oxygenation.

A special mention should be made about preoperative transfusions in patients with sickle cell disease, as the perioperative complication rate in this patient population can be as high as 67%.⁴³ Surgical stress and trauma can increase the rate of anemia and sickle cell formation, and red cell transfusions are often used to preserve oxygen-carrying capacity and to dilute the sickle cells. A randomized clinical trial evaluated transfusion regimens in patients undergoing 602 surgical procedures.⁴² Patients were randomly assigned to either an aggressive transfusion strategy, which maintained a preoperative hemoglobin level of 10 g/dL and a hemoglobin S level of 30% or less, or a conservative strategy, in which transfusions were given to maintain a hemoglobin concentration of 10 g/dL regardless of the hemoglobin S level. There was no difference in the rate of serious complications between the two groups, but transfusion-related complications were twice as likely in the aggressive strategy group (odds ratio 2.15; 95% confidence interval, 1.23-3.77). A Cochrane Database review concluded that although a conservative transfusion strategy appears as effective in preoperative patients as an aggressive regimen, further studies are needed to determine the best possible course of therapy and whether preoperative transfusion is required in all surgical settings.²⁴

In our opinion a transfusion threshold of 7 g/dL can be used safely in most perioperative patients, provided that they have no underlying ischemic heart disease and are asymptomatic. The optimal threshold is unknown in patients with cardiovascular disease for there is no randomized evidence available. We recommend carefully evaluating each patient's symptoms and signs and not basing the transfusion decision solely on a hemoglobin concentration. Those patients who are symptomatic from their anemia should be transfused as needed. The optimal rate of red cell administration should be guided by the clinical situation. Active exsanguination may require transfusion rates as high as five to ten units of red cells over ten to fifteen minute, whereas, those patients at risk for volume overload should be transfused at one mL/kg/hour. Most patients may be transfused at one unit of red cells every one to two hours, and a hemoglobin level rise of 1 g/dL should be expected per unit of red cells transfused.⁴⁸ After each red cell unit is transfused, a repeat hemoglobin level should be obtained, and the patient should be reevaluated.

Summary

Anemia produces a unique set of challenges in the preoperative patient. An efficient evaluation of anemia relies on a detailed history and physical examination and a systematic approach to the diagnostic testing. The presence of anemia, as well as the use of perioperative blood transfusions, has potential ramifications on the surgical outcome. While the current evidence suggests a lower transfusion threshold may be appropriate in most

preoperative patients, the decision to transfuse must be individualized to the patient and the clinical setting.

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Figure 1.

Approach to anemia. RPI, reticulocyte production index; DIC, disseminated intravascular coagulation; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; RBC, red blood cell; G6PD, glucose-6-phosphate dehydrogenase.

$$\text{Reticulocyte Production Index} = \text{Retic Count} \times \frac{\text{Patient's Hematocrit}}{\text{Normal Hematocrit (45)}} \times \frac{1}{\text{Maturation Correction}}$$

(RPI)

<u>Hematocrit (%)</u>	<u>Maturation Correction</u>
36-45	1.0
26-35	1.5
16-25	2.0
≤ 15	2.5

RPI < 2 indicates an inappropriate/decreased marrow response to anemia

RPI > 2 indicates an appropriate marrow response to anemia, usually due to blood loss or hemolysis

Figure 2.

Calculating the Reticulocyte Production Index (RPI).