

# ANESTHESIOLOGY™ 2014

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## **Perioperative Management of the Anemic Patient**

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### **Stem Case and Key Questions Content**

A 63 year-old female with a past medical history notable for osteoarthritis, hypertension controlled with antihypertensives, obesity (BMI of 34), chronic kidney disease (CKD), and insulin dependent type 2 diabetes presents to your preoperative clinic for evaluation four weeks prior total hip arthroplasty (THA) for osteoarthritis.

Prior to experiencing hip pain severe enough to merit a THA, she walked briskly each day for 20 minutes (pace of 4 miles/hour). She denies a history of coronary artery disease (CAD), but due to her risk factors for CAD she takes an aspirin, statin, and metoprolol. Her HR in the preoperative clinic is 71 and her BP is 132/78. In addition to metoprolol, she also takes lisinopril for hypertension.

Her preoperative labs are notable for a serum creatinine of 2.0 mg/dl and a hemoglobin (Hb) concentration of 10.1 g/dl. The patient is post-menopausal. She denies vaginal bleeding, hematuria, melena, and blood streaked stool. She had a normal screening colonoscopy one year ago.

- 1) What is the most likely cause of her anemia?
- 2) Why is it important that the patient is anemic preoperatively?
- 3) What is patient blood management (PBM)?
- 4) If you were responsible for initiating a preoperative workup to identify the cause of her anemia, what additional laboratory tests would you order?
- 5) If you suspect that patient's anemia is the result of CKD, would you treat the patient with an erythropoietin-stimulating agent preoperatively to increase her Hb concentration?
- 6) If the patient was found to have iron deficiency anemia rather than anemia associated with CKD, how would you proceed?
- 7) If you encountered the patient in the preoperative clinic the day before surgery and discovered her anemia at that point (as opposed to four weeks prior to surgery), would you cancel the case to work-up the cause of the anemia and to potentially treat it? What if you

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learned of the anemia as you were reviewing your list the night before surgery? If that were the scenario, would you cancel the case on the day of surgery?

Serum ferritin and transferrin did not suggest iron-deficiency anemia, so the patient was referred to a nephrologist and treated with erythropoietin as well as iron supplementation to support erythropoiesis. She presents for surgery with a Hb concentration of 12.2 g/dl.

8) What are the risks of using erythropoietin in this patient?

9) What strategies can you use in the operating room to minimize the risk that the patient becomes anemic and requires a transfusion of red blood cells?

During the surgery, blood loss is greater than is typical for this orthopedic surgeon. The EBL is 1500 ml. Intraoperatively the patient was appropriately resuscitated, vital signs remained within 20% of baseline values, urine output was appropriate and phenylephrine boluses were only used prior to skin incision. Emergence was uneventful and the patient remained stable in PACU with normal vital signs and urine output greater than 0.5 ml/kg/hr. Because of the relatively large amount of EBL, a CBC was checked in PACU and the patient's Hb concentration was found to be 8.4 g/dl (platelet count was within normal limits).

10) Would you order a transfusion of packed red blood cells? What if her Hb concentration was 7.8 g/dl? If the patient complained of chest pain and had ST segment depression, would that change your transfusion strategy?

11) What are the risks associated with transfusion of packed red blood cells?

## **Model Discussion Content**

### *Risks of Preoperative Anemia*

Preoperative anemia has been shown to be an important predictor of both postoperative mortality and morbidity and is an important predictor of blood transfusion. Wu et al. showed an association between even mild degrees of preoperative anemia (< 39%) and 30-day postoperative mortality and cardiac events (Q-wave MI and cardiac arrest) in a population of elderly veterans having major noncardiac surgery. There was a 1.6% increase in mortality 30 days postoperatively "associated with every percentage-point increase or decrease in the hematocrit value from the normal range (1)." Being a retrospective study, this does not prove that treating anemia preoperatively would prevent these adverse outcomes, but it speaks to the significance of even small degrees of anemia (or polycythemia). Additionally, since anemia is an important risk factor for transfusion, a treatment with many known risks, avoiding preoperative anemia will reduce perioperative transfusion.

Similar results have also been published more recently in a large non-veterans administration cohort. Musallam et al. (2) obtained data for 227,425 patients from the National Surgical Quality Improvement Program database, of whom 69,229 had preoperative anemia. After adjustment, 30-day postoperative mortality was higher in patients with anemia. This difference was present even with mild anemia as well as with moderate-to-severe anemia. Mild anemia was defined as a hematocrit >29% but <36% in women. Thirty-day postoperative morbidity was also

higher in patients with anemia. The increased morbidity was present in patients with mild anemia and moderate-to-severe anemia. Preoperative anemia has also been shown to be associated with higher mortality and morbidity prior to cardiac surgery (3).

### Causes of Preoperative Anemia

Preoperative anemia has numerous causes, but common causes of preoperative anemia are probably already familiar to you. Knowledge of several basic laboratory tests will allow you to identify the etiology of anemia in most patients and to potentially treat it. In this particular case, the patient is most likely anemic due to her CKD since she denies hematuria, vaginal or gastrointestinal bleeding and recently had a normal colonoscopy. However, an occult upper gastrointestinal source of bleeding is certainly possible.

Common causes of preoperative anemia are: iron deficiency anemia, CKD, anemia of chronic disease, and anemia due to deficiency of folate or vitamin B12. There are numerous other causes of anemia, but diagnosis and workup of these conditions is beyond the scope of this PBLD. If one of these common diagnoses fails to explain the patient's anemia, I would recommend a hematology consultation.

### Diagnosing the Cause of Anemia

In the case for this PBLD, it is already known that the patient has CKD, which is a likely cause of her anemia. I would also assess the patient's iron status to rule-out iron deficiency anemia by ordering a serum ferritin and transferrin saturation (4). Goodnough et al. recently reviewed the detection, evaluation, and management of preoperative anemia (4) and the review contains a nice figure (see figure 2 of reference 4) outlining a diagnostic approach to preoperative anemia using common laboratory tests. According to these Network for Advancement of Transfusion Alternatives (NATA) guidelines, there would not be an indication to perform upper endoscopy assuming that the patient's lab results did not suggest iron deficiency. Because of her CKD and associated anemia, the NATA guidelines recommend that the patient be referred to a nephrologist for consideration of using an erythropoietin-stimulating agent (ESA) to increase her hematocrit prior to surgery.

On the other hand, if the patient's laboratory tests revealed iron deficiency anemia, she should be referred to a gastroenterologist for upper endoscopy since other common causes of occult bleeding seem less likely given the recent normal colonoscopy and lack of vaginal bleeding or hematuria. While the cause of the iron deficiency is being investigated, the patient's iron deficiency should be treated to facilitate erythropoiesis and increase her hematocrit prior to surgery.

### Patient Blood Management (PBM)

According to the Society for the Advancement of Blood Management (5), PBM is "the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome." PBM by definition will minimize transfusion, which is important since transfusion of

even one unit of red blood cells has risk and each additional unit transfused adds to the risk (6). Spahn and Goodnough (7) presented a simple conceptual framework (see Figure 1 in reference 7) for PBM with broad goals of optimizing erythropoiesis, minimizing blood loss, and managing anemia. Each of these goals must be achieved throughout the perioperative period to maximally improve patient outcome. Implementing this strategy requires buy-in from a multidisciplinary team (i.e. anesthesia, surgery, perfusion, and nursing). Kotzé et al. (8) showed that a PBM program in patients presenting for total knee (TKA) and hip arthroplasty (THA) reduced the prevalence of anemia (26% to 10%), percentage of cases with transfusion (23% to 7% in THA and 7% to 0% in TKA), length of hospital stay, cost, and 90 day readmission rate from 14% to 8%.

If the patient in this case had presented for surgery without having her anemia identified and treated, the literature discussed above shows she is at higher risk for death and morbidity in the perioperative period. The NATA guidelines suggest canceling an elective case due to anemia (GRADE 2C), but due to lack of consensus among the guideline working group this is a suggestion, not a recommendation (4). If you decide to cancel the case, doing so will only benefit the patient if you have buy-in from the surgeon on the risk of proceeding with elective surgery in an anemic patient. The surgeon and patient will also have to be prepared to wait up to a month to reschedule the surgical procedure, while the etiology and treatment of the anemia are pursued. Assuming you and your department can achieve this understanding with your surgical colleagues, the situation of not knowing about a patient's anemia until the day of surgery (or the night prior to surgery) can be avoided by having patients seen early enough preoperatively to address anemia without having to cancel cases. The NATA guidelines cited above recommend that patients presenting for elective orthopedic surgery have a Hb level checked 28 days prior to surgery (4). If your institution has a preoperative clinic, your department can take charge of managing the work-up of anemic patients. If that is not the case, the surgeons can learn this same protocol or have the patient's PCP address preoperative anemia. However, having anesthesiologists take charge of managing anemia would seem to provide a perfect opportunity for us to adhere to the principles of the surgical home that the ASA is promoting. Also, there is no reason a few champions of PBM in a practice could not assist surgeons in working up anemic patients even in the absence of a preoperative clinic. In addition to having buy-in from your surgical colleagues, you must have the other members of your practice on-board so the surgeon will not just schedule the case the next day with a different anesthesiologist. If that occurs, you will not have achieved anything other than making yourself the villain in the eyes of the patient and surgeon.

### Risks of Treating Anemia

Since the risks of perioperative anemia have been discussed above, we will now turn our attention to the risk of treating anemia. Red cell transfusion has been the traditional treatment for anemia, but it should be noted that blood transfusion has never undergone FDA safety and efficacy evaluation. There are numerous risks associated with red cell transfusion which include mortality, transfusion related acute lung injury, volume overload, transfusion reactions, immunomodulation leading to increased risk for postoperative infection and/or tumor

progression for patients undergoing cancer surgery, ischemic complications, transmission of infectious disease, delayed wound healing, increased length of hospital stay, and non-Hodgkin lymphoma (7 and 9). These risks of transfusion have not been proven in prospective randomized trials, but Bradford-Hill criteria suggest that the link between transfusion and the above risks is causal (9). Treating anemia preoperatively will reduce transfusion and the associated risks.

In some cases, treating the underlying etiology for preoperative anemia also has risk. Traditionally the risk of hypersensitivity reactions associated with intravenous iron replacement has relegated this method of iron-repletion to a second-line treatment behind oral iron supplementation, although it has been recommended that this trend be reconsidered (10). Parenteral iron makes it possible to more rapidly replete diminished iron stores compared with oral iron, making it an attractive treatment option for patients who need urgent surgery, and it is the preferred route of iron supplementation for patients being treated ESAs such as erythropoietin. Treating patients with deficiencies of folate or vitamin B12 with supplemental folate or vitamin B12 is safe.

Erythropoietin is the only ESA with a specific indication to reduce transfusion in anemic patients having elective noncardiac/nonvascular surgery, but it does carry a black-box warning for thrombotic risks such as stroke, myocardial infarction, and venous thromboembolism. Targeting a Hb concentration in the normal range (4) and using DVT prophylaxis during erythropoietin use can minimize this risk (11 and 12).

### *Intraoperative Application of PBM*

In the operating room and post-operatively, using restrictive transfusion thresholds and the intraoperative components of PBM outlined above can minimize the risk of transfusion. Meticulous attention to hemostasis will minimize blood loss and cell salvage should be used where appropriate to minimize the risk of transfusion of allogeneic red blood cells. A 2003 meta-analysis (updated in 2009) of topical fibrin sealant in 18 trials showed it to reduce red cell transfusion by 37% (13).

A recent meta-analysis of 129 trials from 1972 to 2011 concluded that the antifibrinolytic medication tranexamic acid reduces blood transfusion by about one-third with no significant increased risk of thrombotic complications (14). However, many of the trials were of low quality, so the authors felt the risk of thromboembolic complications is uncertain. I would suggest that given the uncertain thromboembolic risk associated with using antifibrinolytics, it makes sense to use these medications in cases where it is expected that there will be a large amount of blood loss (increasing the likelihood of patient benefit from decreased blood loss by avoiding or minimizing transfusion), in cases where the patient is presenting to the operating room with a hemorrhage and has or may have ongoing fibrinolysis, and/or where fibrinolysis is going to occur (i.e. cases involving cardiopulmonary bypass). Goodnough has recently reviewed the use of antifibrinolytics in PBM (15).

## Transfusion Threshold

It is often not completely clear when it is appropriate to transfuse red blood cells to an anemic patient, but the traditional Hb target of 10 g/dl is likely unnecessary and even harmful for many patients. Numerous trials over the past 15 years have shown that restrictive transfusion criteria are safe in selected patient populations and that restrictive transfusion practice decreases transfusion and the associated complications (16 and 17). Additionally transfusion guidelines have recently been published (18) and provide a more updated set of criteria than either the 2006 ASA transfusion guidelines (19) or the 2009 trauma and critical care guidelines (20), although both sets of guidelines are worth reading. Of note, the ASA guidelines do provide advice on other areas of transfusion medicine apart from red cell transfusion, unlike the two more recent guidelines, which focus solely on red blood cell transfusion.

In the Transfusion Requirements in Critical Care (TRICC) trial, Hébert et al. (21) enrolled 838 euvolemic ICU patients (mix of medical and surgical patients) with Hb concentrations of < 9.0 g/dl within 3 days of ICU admission and randomly assigned patients to either a restrictive (transfused if Hb < 7 g/dl, Hb then maintained 7 - 9 g/dl) or a liberal transfusion strategy (transfused if Hb < 9 g/dl; Hb then maintained 10-12 g/dl). Overall, 30-day mortality was not significantly different between the two groups, but mortality was lower in the restrictive group among the subgroup of patients who were less ill (Acute Physiology and Chronic Health Evaluation II score of  $\leq 20$  [8.7% in the restrictive group and 16.1% in the liberal group,  $P=0.03$ ]) and among younger patients (age < 55; 5.7% and 13.0%, respectively;  $P=0.02$ ). There was no significant mortality difference in the subgroup of patients with clinically significant cardiac disease.

More recently several large randomized controlled trials have also been published comparing restrictive and liberal transfusion approaches in elderly patients at risk for cardiovascular disease who were having hip fracture surgery (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair or FOCUS) and in patients with acute upper gastrointestinal bleeding (UGIB). In the FOCUS trial (22), 2016 patients with a Hb < 10 g/dl following hip fracture surgery were randomly assigned to a liberal transfusion strategy (transfusion at a Hb < 10 g/dl) or a restrictive transfusion strategy (transfusion at a Hb < 8 g/dl or at physician discretion for symptoms of anemia [cardiac related chest pain, congestive heart failure, and unexplained tachycardia or hypotension not responsive to fluid replacement]). The rates of the primary outcome (death or an inability to walk across a room without human assistance on 60-day follow-up) were not significantly different between the two groups. The authors concluded “a liberal transfusion strategy, as compared with a restrictive strategy, did not reduce rates of death or inability to walk independently on 60-day follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk.” On the other hand, the trial did not achieve its enrollment goal to meet its prespecified power calculation due to difficulty in enrolling the requisite number of patients, increasing the chance that this trial failed to detect a benefit of a liberal transfusion strategy.

The most recent high-profile large randomized trial to compare a liberal and restrictive

transfusion strategy enrolled patients having severe acute UGIBs (23). The investigators enrolled 921 patients and randomly assigned them to a restrictive strategy (transfused when Hb < 7 g/dl) or a liberal strategy (transfused when Hb < 9 g/dl). As expected, more patients in the restrictive group avoided transfusion (51%) compared with those in the liberal group (15%;  $P < 0.001$ ). Additionally, patients in the restrictive group had a higher likelihood of survival at 6 weeks, fewer recurrent bleeds, and fewer adverse events.

In summary, the aggregate evidence for transfusion thresholds has shown that a lower transfusion threshold reduces red blood cell transfusion and has not been shown to cause harm. In some trials, patients treated with a restrictive transfusion strategy had lower morbidity and mortality. Salpeter et al. recently performed a systematic review and meta-analysis of restrictive transfusion strategies on clinical outcomes (24). In the primary analysis, pooled data from 3 randomized trials (21, 23, 25) with 2,364 participants comparing a restrictive hemoglobin transfusion trigger of <7 g/dL, with a more liberal transfusion trigger showed that restrictive transfusion “resulted in reduced in-hospital mortality (risk ratio [RR], 0.74; confidence interval [CI], 0.60-0.92), total mortality (RR, 0.80; CI, 0.65-0.98), rebleeding (RR, 0.64; CI, 0.45-0.90), acute coronary syndrome (RR, 0.44; CI, 0.22-0.89), pulmonary edema (RR, 0.48; CI, 0.33-0.72), and bacterial infections (RR, 0.86; CI, 0.73-1.00), compared with a more liberal strategy. The number needed to treat with a restrictive strategy to prevent 1 death was 33. Pooled data from randomized trials with less restrictive transfusion strategies showed no significant effect on outcomes.” (24) It should be noted that reference 25, one of the three trials included in the analysis, was carried out in a PICU patient population.

One common concern with lower transfusion thresholds is that they will lead to adverse cardiac outcomes (17). While this adverse outcome has not been shown, many of the trials in the recent Cochrane review (16) were not large enough to exclude anything smaller than a two-fold increased risk of myocardial infarction associated with a lower transfusion threshold (17). On the other hand, a recent systematic review and meta-analysis of blood transfusion in patients with acute myocardial infarction (26) showed red cell transfusion was associated with a higher risk for mortality independent of baseline Hb concentration, nadir Hb, and change in Hb during hospitalization, as well as a doubling of the risk for subsequent myocardial infarction (risk ratio, 2.04; 95% CI, 1.06-3.93;  $P = .03$ ). This study was limited by the fact that the studies analyzed were observational in nature, but hopefully this meta-analysis along with other trials showing that a restrictive transfusion strategy is safe will lay the groundwork for a large randomized trial testing a restrictive versus liberal transfusion strategy in patients with acute myocardial infarction. Two pilot studies testing restrictive versus liberal transfusion triggers in patients with symptomatic coronary heart disease (27) and acute MI (28) have recently been published with conflicting outcomes results, further highlighting the need for a definitive, larger trial in this patient population. While this PBLD is not a discussion of the management of transfusion in patients having cardiac surgery, since we are discussing transfusion practices in patients with cardiac disease, I also feel that it is important to note that the TRACS trial recently showed that a restrictive transfusion strategy (hematocrit goal  $\geq 24\%$ ) in patients undergoing cardiac surgery with cardiopulmonary bypass is non-inferior to a liberal strategy (hematocrit goal  $\geq 30\%$ ) for a

composite outcome 30-day all-cause mortality and severe morbidity (6).

In this particular patient (who is euvoletic and not bleeding), I would not transfuse her with red blood cells with a Hb concentration of 8.4 g/dl provided that she was not showing any signs of symptomatic anemia. Alternatively if her Hb concentration were 7.8 g/dl, unless she had symptoms of anemia, the decision is less clear-cut based on the trials discussed above. This patient has numerous risk factors for CAD given her past medical history of hypertension, diabetes, obesity, and age > 45 (29) and her revised cardiac index is 2 (for a history of insulin dependent diabetes and CKD) giving her a low, but not insignificant risk for a perioperative cardiac event. She fits the patient population of the FOCUS trial (22) and with a Hb concentration of 7.8 g/dl, you could argue that she should be transfused red blood cells based on the protocol used in the FOCUS trial. Alternatively, while she is not critically ill like the patient population in the TRICC trial (21), it seems that she is euvoletic and not bleeding like the patients in the TRICC trial. In the TRICC trial, even in patients who had significant cardiac disease, there was no increased mortality with a restrictive transfusion strategy using a transfusion threshold of 7 g/dl (21).

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