Lesson S26: Preanesthetic Assessment of the Patient with Serum Antibodies – Part 2

Authored by: Sabrina Bhagwan, M.D., Assistant Professor, Mount Sinai School of Medicine; Elizabeth A.M. Frost, M.D., Clinical Professor, Mount Sinai School of Medicine, New York, NY
Reviewed by: Ram Roth, MD, Assistant Professor of Anesthesia, Mount Sinai Medical Center, New York, NY

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
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This is a 2 part series. Part 1 presents an update on blood transfusion and its complications. Methods of blood cross matching and identification of antibodies are described. In Part 2, the incidence and pathophysiology of sickle cell disease is reviewed. Antibody formation is particularly common in this group of patients and appropriate blood replacement and anesthetic management are outlined.

Needs Statement

The presence of antibodies in the blood of patients who require perioperative transfusion is not uncommon. Many anesthesiologists are unaware of which antibodies are significant and when a blood transfusion may cause complications that outweigh the benefit for the patient. This is especially true in patients with sickle cell disease.

Learning Objectives

At the end of this activity, the participant should be able to:

1. Outline a plan for anesthetic management of sickle cell disease (SCD) patients with identified antibodies
2. Identify issues in preoperative blood transfusions for the sickle cell patient
3. Distinguish between sickle cell disease and sickle cell trait
4. Prepare an anesthetic plan for an anemic patient with SCD
5. State the prevalence of SCD
6. List complications of SCD
7. Be aware of the anesthetic problems confronting a patient with SCD
8. Describe the pathophysiology of SCD
9. Know the major goal of blood transfusion
10. Present a plan for working with a blood bank
Case History

A 25 year old African-American woman with sickle cell disease (SCD) presented for an emergency appendectomy. She had frequent hospitalizations due to crisis episodes requiring red cell transfusions. She also had 4 pregnancies. Her hematocrit was 22%. The decision was made to transfuse the patient prior to surgery. The blood bank technician reported that the blood sample tested positive for antibodies.

Introduction

Sickle cell disease is a common and potentially fatal disease that is frequently encountered in anesthetic practice. Patients with sickle cell trait are more common and can present problems for the anesthesiologist who may be unfamiliar with the perioperative requirements. Antibody formation is common and attributable to multiple crises events that require transfusion.

Epidemiology

Sickle cell disease is a chronic hemolytic disease with a high prevalence among African Americans in the United States. The exact number of people living with SCD in the U.S. is unknown. In 2010, the Registry and Surveillance System for Hemoglobinopathies (RuSH) pilot project was implemented to collect state-specific, population-based data on people with SCD and thalassemia. The pilot is being conducted in collaboration with the National Institutes of Health’s National Heart, Lung, and Blood Institute. Currently, seven states are funded to participate in data collection: California, Florida, Georgia, Michigan, New York, North Carolina, and Pennsylvania. The purpose of the project is to ascertain the number of people living with SCD and better understand how the disease impacts their health.

It is estimated that SCD affects 90,000 to 100,000 Americans. It occurs among about 1 out of every 500 African-American births and 1 out of every 36,000 Hispanic-American births. The prevalence is about 1 in 12 African Americans. Eight to 10% of the African-American population in the United States have the sickle cell trait. These individuals are clinically asymptomatic carriers of one allele of the sickle cell gene. Worldwide, the disease affects Africans, where there is a 15 to 25% incidence of the carrier state. Arab, Indian and Southeast Asian populations are affected to a lesser degree.

Pathophysiology

Patients with SCD are primarily classified as HbSS variant. The SCD phenotype is also exhibited in patients with SC, S-β-thalassemia, SO Arab, SD and other rarer S-Hb subtypes. Those patients with HbSS comprise the greater portion of patients with SCD with 85 to 98% of their hemoglobin being HbS and the remaining being fetal hemoglobin (HbF) and HbA2. Very high HbF levels are protective against severe clinical manifestations of the disease. Hemoglobin S is composed of two normal alpha chains and two abnormal beta chains. The abnormal beta chain is the result of the substitution of glutamic acid with valine as the 6th amino acid on chromosome 11.

Complications of SCD are directly related to the deformation, adhesion and hemolysis of red cells. The abnormal hemoglobin S responds poorly to repeated cycles of deoxygenation, and polymerizes into...
rod like structures that distort red cells into a sickle shape. Sickled cells decrease blood flow and oxygen to tissues, leading to ischemia and chronic end organ destruction. These cells adhere to vascular endothelium causing chronic inflammation, abnormal vasomotor tone favoring vasoconstriction, and hypercoagulability.

Acute chest syndrome is one of the many clinical complications of this process and has a mortality rate of 1.1% in children and 4.8% in adults.\textsuperscript{20} It manifests as a new pulmonary infiltrate accompanied by fever, respiratory symptoms, or chest pain and can be precipitated by infection, fat embolism, pulmonary infarction and surgical procedures. Acute chest syndrome is also the most common perioperative sickle-cell related complication and occurs as a vaso-occlusive crisis of the pulmonary vasculature. Studies indicate that a higher steady state blood viscosity is associated with a greater rate of vaso-occlusive crises in children with sickle cell anemia but not in those with Hb sickle cell disease.\textsuperscript{21} A higher steady state red blood cell disaggregation was associated with a previous history of acute chest syndrome in children with HbSC disease and boys with sickle cell anemia. Transfusion is a recommended treatment to decrease the incidence of acute chest syndrome.\textsuperscript{22,23}

The next most common variant of SCD is HbSC. These patients experience less severe and fewer vaso-occlusive crises. Even so, large scale studies have demonstrated similar rates of perioperative complications as their HbSS counterparts. Neumayr et al found an increased incidence of sickle cell-related complications in patients with HbSC disease who underwent intra-abdominal procedures without a preoperative transfusion - 35% versus 0%.\textsuperscript{24}

Patients with sickle cell trait (HbSA) have at least 50% normal hemoglobin (HbA.) Red cell polymerization does not occur in these patients until oxygen saturations are below 40%. Blood transfusions are usually not required.

\textbf{Sickle Cell Anemia, Anesthesia and Transfusion}

Patients with SCD requiring general anesthesia have an increased risk of intra- and post-operative vaso-occlusive crises, including acute chest syndrome. There may also be an increased risk of non-SCD specific complications such as fever, bleeding and pulmonary embolism. An observational study over a 10 year period found a 1.1% perioperative mortality rate for 717 patients with SCD undergoing 1079 procedures.\textsuperscript{25} Type of surgery, increasing age, frequency and severity of crises, organ failure, and pulmonary disease are all risk factors for perioperative morbidity.

There is right shift in the hemoglobin-oxygen dissociation curve for patients with SCD. Sickling increases with low pH, hypoxia and increasing temperature; and decreases with higher levels of non-S hemoglobin. Thus, avoidance of hypovolemia, hypoxia, tourniquets, and hyperthermia, and preoperative transfusions of non-HbS blood, are most important. Surgical stress and microvascular ischemia-reperfusion contributes to endothelial stress.

When compared to the general population, SCD patients have a greater likelihood of complications from blood transfusions as the risk of alloimmunization and autoimmunization is increased.\textsuperscript{24} Alloimmunization is a process where antibodies (i.e. alloantibodies) are created in when exposed to foreign antigens as is in allogenic blood transfusion. In autoimmunization, warm-antibodies (autoantibodies active at body temperature) are created to act against the patient’s own red cells. A retrospective review of the records of SCD patients who received transfusions over a 10-year period
showed that among pediatric patients, 29% developed clinically significant alloantibodies and 8% developed autoantibodies. In the adult group, 47% developed alloantibodies and almost 10% had autoantibodies.

Sickle cell patients can be transfused intermittently (e.g., for symptomatic anemia or aplastic crisis) or transfused on a chronic basis (e.g., for prevention of stroke or acute chest syndrome) with simple or exchange transfusions. Exchange transfusions are performed in a manner to prevent significant increases in blood volume and viscosity by simultaneously removing some of the patient’s blood while infusing a volume of RBCs. The major goal of red cell transfusion is to increase the oxygen carrying capacity of the blood, which is critical during a sickle cell crisis. Chronic transfusions decrease the incidence of both acute chest syndrome and pain crises in children, the two most frequent causes of hospital admissions and stroke. Chronic transfusions also suppress the endogenous production of HbS by increasing tissue oxygenation.

Clinical transfusion practices are disparate among medical centers. Two preoperative patients with sickle cell disease and similar clinical histories may have different transfusion histories and a different rate of developing alloantibodies that will interfere with the transfusion plan and cross matching.

The ASA has not yet established guidelines for perioperative blood transfusions for SCD patients. Most centers encourage individual practitioners to review current literature before deciding to transfuse. A Cochrane review revealed that a conservative transfusion regimen is as effective as an aggressive regimen for preventing perioperative complications and that further research is required to examine the optimal regimen for different types. Other studies have suggested that low risk procedures (e.g. herniorraphy, dental/oral procedures, tympanostomy) in adults and children can be done safely without preoperative transfusion.

The National Institutes of Health’s most recent policy recommended transfusion to a hemoglobin of 10g/dl for patients undergoing all but very low risk procedures, based on review of the literature. Perhaps the most influential study affecting contemporary perioperative transfusion practices was conducted in 1995 by the Preoperative Transfusion in Sickle Cell Disease Study Group. In this randomized prospective study in 36 centers, 604 surgical cases were randomized to receive either a simple conservative transfusion to a hemoglobin level of 10g/dL or exchange or serial transfusions to a HbS level of 30%. No significant benefit was found in the more aggressive transfusion group and a similar (15%) incidence of SCD related complications existed in both groups. The study did not include a group that was not transfused.

In 1997, Haberken et al were able to confirm these findings in their prospective study of patients undergoing cholecystectomies. They also found that, in their non-transfused group, there was an incidence of SCD-related events (including acute chest syndrome) that was twice that of the simple and aggressive approaches. One caveat was that the non-randomized, non-transfused group was also more likely to be older, female and smokers which likely introduced bias. The value of the study was that the findings suggested no difference in the conservatively and aggressively transfused groups. Another 10 year retrospective study of 60 children had a smaller (6.6%) incidence of acute chest syndrome than reported in many previous studies, a finding that the authors felt was attributable to the fact that 95% of the patients in their study had been transfused to hemoglobin of 10 g/dl.
Even though solid evidence of the benefits of prophylactic transfusions is lacking, transfusion is indicated to replace significant blood loss or to correct severe anemia and hypoxia. Once the anesthesiologist decides to transfuse a patient, the complications of transfusion must be anticipated. In addition, difficulties with cross matching blood for SCD patients with alloantibodies can delay urgent, lifesaving blood transfusions.

**Sickle Cell Antibodies**

Sickle cell patients are more likely to develop unexpected antibodies compared to other chronically transfused patients, with an 8% to 40% rate of alloimmunization and a disproportionally elevated rate of alloimmunization with larger numbers of transfusions. Vichinsky et al found a 30% incidence of alloimmunization in SCD patients who received multiple transfusions compared to 5% for multiply transfused white patients with other types of anemia. Antigenic differences between the population of sickle cell patients and the primarily white blood donor pool may be one reason for increased alloimmunization. However, SCD patients may also have a higher rate of autoantibody production. Autoantibodies have been found in approximately 8 - 10 of alloimmunized sickle cell patients.

Antibodies in the sickle cell patient can delay blood availability for transfusion and also place the patient at risk of acute or delayed hemolytic transfusion reactions (HTRs). Delayed HTRs in the SCD population are estimated to occur at a frequency of 4 - 11% in varying studies. Problems with detection and identification of antibodies suggest that up to 30% may become undetectable over time, and there is no single procedure that currently exists that is able to detect all known antibodies.

A means to decrease the high frequency of alloimmunization in the SCD population and the inadequacy of the current means of antibody detection in the SCD population is to phenotypically match for clinically significant antigens. Sickle cell patients are most likely to demonstrate alloantibodies to the Rh (C and E), Kell (K), Duffy (Fya,) Kidd (Jkb), and MNS (M and S) antigens, all of which are associated with HTRs. The relevance of Rh variants must also be considered as variant antigens found in individuals of African descent are common. In some centers SCD patients prophylactically receive blood that is negative for Rh and Kell antigens, or in addition, Duffy, Kidd and MNS antigens. Others advocate phenotype-matched red cells only after the first antibody is detected. Matching for C, E, K, Fy, Jk and S antigens in already alloimmunized recipients has been reported to decrease the rate of further alloimmunization to 1% - 5%. Extensive antigen matching programs, however, are expensive and not widely available.

When faced with a patient with SCD and antibodies, it is helpful to know which antibodies are detected and potential reactions associated with the antibodies. (Table 1) It is also important to know the most common presentations and the clinical course of transfusion reactions.
Table 1: Working with the Blood Bank

- In an emergency, request at least Sickle-negative, C, D, E and Kell negative and leukoreduced blood.
- Inform the blood bank of the last place the patient was transfused to allow the identification of any new RBC alloantibodies.
- Know that patients with SCD and alloantibodies are at higher risk of developing more alloantibodies.
- A patient is considered alloimmunized for life to any identified antibody.
- Type and screens expire (as an inpatient after 3 days, as an outpatient after 10 days if the patient has not been transfused in the last 3 months, has not been pregnant in the last 3 months, and does not have a history of a transfusion reaction in the last 3 months) because alloantibodies are not detectible immediately following transfusion.
- Alert the blood bank immediately of any signs or symptoms of a delayed or acute transfusion reaction so they can begin an appropriate work-up.

Delayed HTRs present within hours to several weeks following a transfusion, with symptoms ranging from pain to significant hemolysis and renal failure. Delayed reactions occur because antibody levels are too low to be serologically detectable at the time of transfusion; and re-exposure to the antigen triggers an anamnestic response, causing amplification of the antibody. In most instances no new antibodies are identified, underlining the complexity of the pathophysiology of SCD. Delayed HTRs in a postoperative, recently transfused patient with SCD should always be considered. Fortunately, most symptoms of delayed HTRs can be treated with primary supportive care.

Hyperhemolysis is a rare but severe and possibly fatal transfusion reaction that may occur in association with an allogenic HTR. In this syndrome, the hemoglobin level falls lower than the pre-transfusion value and the patient may present with profound anemia, hemoglobinuria and hyperbilirubinemia. In addition to hemolysis of transfused red cells, hemolysis of autologous red cells or suppression of endogenous erythropoiesis is thought to occur. Hemolysis of autologous red cells may be due to “bystander” hemolysis of autologous red cells and not necessarily due to the production of autoantibody. Direct antibody tests may be negative and no new alloantibodies may be present. Successful treatment with corticosteroids and intravenous immunoglobulin (IVIG) or erythropoietin has been reported.

Finally, the risk of febrile non-hemolytic transfusion reactions in sickle cell patients, like other patients, is directly related to the number of transfusions. These reactions present with symptoms similar to pain crises and infections, with fever and chills. Accordingly, patients with SCD should receive leukoreduced blood, in which the leukocyte count is less than 5x10⁶ WBC/unit thereby reducing the risk of HLA alloimmunization and also WBC cytokine release. Management of patients with this type of
reaction includes administration of antipyretic medication.

**Treatment**

The Center for Disease Control and the National Heart Lung and Blood Institute (NHLBI), proposed the following evidence based guidance for the management of SCD:

- Penicillin prophylaxis should be administered to children to prevent pneumococcal sepsis.
- Pneumococcal vaccine should be administered to children to prevent pneumococcal infection.
- In surgical settings, simple transfusions to increase hemoglobin (Hb) levels to 10 g/dL are as good as or safer than aggressive transfusions to reduce sickle hemoglobin (Hb S) levels to below 30 percent.
- The risk of complications of pregnancy is not reduced by transfusing to maintain a hematocrit of more than 36 percent.
- Transfusions can be used to reduce Hb S levels to below 30 percent to prevent strokes in children with high central nervous system blood flow.
- Hydroxyurea is useful in decreasing the risk of crises in patients with SCD.

The introduction of the 7-valent pneumococcal conjugate vaccine has significantly decreased SCD mortality among African American children. Also, according to the CDC, hydroxyurea is underused and may replace some blood transfusions.

**Management of the Case**

The medical center treating the patient did not have aggressive transfusion practices. Patient are not routinely transfused perioperatively, especially patients at low risk, children, patients with stable cardiorespiratory status and hemoglobin near baseline, elective or low risk procedures. Because of the patient’s age, history of frequent acute chest syndrome, low hemoglobin, and the procedure planned, the medical and surgical team felt transfusion was indicated. There was concern about the risk of transfusing non-cross matched blood. The blood bank estimated that it would take more than an hour from antibody identification to completion of the serologic cross match.

Surgical expediency was also a concern. Appendicitis was placing this patient at a risk of a vasocclusive crisis and acute chest syndrome, and possibly a hyperhemolytic crisis. The decision to proceed without transfusion and anticipate postoperative transfusion was made. A laparoscopic surgical technique was planned as this approach is known to decrease hospital stay without increasing SCD complications.

The patient was well hydrated preoperatively and was given oral antipyretics. Temperature and
oxygenation were monitored and maintained within normal limits. The surgery and anesthesia proceeded uneventfully and the patient was discharged without incident. She did not require a postoperative transfusion.

**Conclusion**

Sickle cell disease has a complex pathology. It affects a significant proportion of the American population. Transfusion remains an integral part of management. Key to providing the correct blood depends an understanding of the disease process and a close relationship with the blood bank.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of *Clinical Anesthesia in Neurosurgery* (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, *Preanesthetic Assessment, Volumes 1 through 3* (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).
REFERENCES


Post-test

1. The hemoglobin-oxygen disassociation curve for sickle cell anemia is:
   a. Unaffected
   b. Shifted to the left
   c. Shifted to the right
   d. Not applicable to sickle cell anemia

2. Which of the following is not associated with a protective clinical effect in sickle cell disease?
   a. High fetal hemoglobin concentration
   b. Temperature regulation
   c. Regional anesthesia
   d. High oxygen concentration intraoperatively

3. The most common genotype of SCD is
   a. Hemoglobin SC
   b. Hemoglobin SS
   c. Hemoglobin Sβ-thalassemia
   d. Hemoglobin SA

4. Delayed Hemolytic Transfusion Reactions are:
   a. Always fatal
   b. Treatable with diphenhydramine
   c. Treatable with primary supportive care
   d. Preventable with appropriate antibody testing

5. Red cell sickling:
   a. Decreases at low pH
   b. May be triggered by hypoxia
   c. Is increased by hypothermia
   d. Is potentiated by non-S Hb
6. **The CDC and NHLBI suggest which of the following as part of the management of SCD?**
   a. Pneumococcal vaccine for children
   b. Rifampin prophylaxis for children
   c. Aggressive transfusions to reduce sickle HbS levels to < 30 percent
   d. Transfusing a pregnant patient to maintain a hematocrit of more than 36 percent

7. **Transfusions:**
   a. Suppress the endogenous production of HbS
   b. Decrease the incidence of acute chest syndrome and pain crises
   c. Increase the oxygen carrying capacity
   d. All of the above

8. **Hyperhemolysis**
   a. Occurs commonly
   b. Is a syndrome where the HB level falls below pre transfusion values
   c. Increases erythropoiesis
   d. Is usually due to the production of autoantibodies

9. **A true statement regarding sickle cell disease:**
   a. Significant advantages are found in aggressive blood transfusion
   b. Preoperative transfusions are recommended in almost all cases
   c. There is a disproportionally elevated rate of alloimmunization with multiple transfusions
   d. Pediatric patients rarely develop antibodies before age 10

10. **Alloantibodies:**
    a. Are detected immediately after transfusion
    b. Remain the same over the life span of the patient
    c. Have been detected in up to 29% of pediatric patients over a 10 year period
    d. Are warm-antibodies that are active at body temperature