Sickle Cell and Anesthesia

Salvatore R. Goodwin, M.D.

Hemoglobin: Structure and Function

Hemoglobin (Hb) is composed of two pairs of sub-units containing protoheme and globin. The various globin chains differ in the number and sequence of amino acids and are designated by α, β, γ, δ, ε, ζ, and θ. Normal adult RBCs have three types of hemoglobin: HbA (α2β2) approx. 95%, HbA2 (α2δ2) approx. 2.5 %, and HbF (α2γ2). The spatial relationship of the four subunits determines oxygen affinity as well as physical properties such as Hb solubility and stability.

At birth red cells contain 70-90 % HbF until 2-4 months of age. Beta chain production begins shortly before birth and gamma chain production wanes resulting in a normal adult profile by age 4 months. Thus disorders of the beta chain will not manifest themselves in the first few months nor be identified by precipitation screening tests. Hemoglobinopathies can result from either production of an abnormal hemoglobin chain or by under production of a given chain. The most common mechanism of the former type is the result of a single substitution of one amino acid for another on the protein chain, which occurs with sickling disorders. Underproduction of a given chain results in a group of disorders known as thalassemias.

Sickle Cell Disease

Pathophysiology

Sickle cell disease (SCD) is the most common of all hereditary disorders with up to 0.2% of the adult African-American population with SCD, 8% with sickle cell trait (SCT), and approximately 50,000 children in the United States having SCD. A single amino acid substitution, valine for glutamate, at position 6 on the β chain is responsible for the condition. Sickle cell disease is inherited as an autosomal recessive disorder following a predictable Mendelian pattern. Thus heterozygote (HbAS) parents will have a 25 % chance of producing either a normal (HbAA) or sickle cell disease (HbSS) and a 50% chance of producing another heterozygote (HbSA, trait) child.

When lysine is substituted for glutamate, also at position 6 of the β chain, hemoglobin C is produced. HbSC disease produces similar pathophysiology but with fewer and often less severe clinical problems. Patients may also be double heterozygotes for SCD and β thalassemia, producing HbSβ disease. If they are coded to produce no normal β chains (β0) the disease is similar in severity to SCD. If they are coded to produce normal β chains in diminished quantities (β+) they have a milder form of the disease.

The single amino acid substitution creates an allosteric abnormality of the hemoglobin molecule rendering it unstable as well as less soluble when deoxygenated. The former causes accelerated breakdown and hemolytic anemia while the latter permits hemoglobin tetramers to form polymers. These hemoglobin polymers form long helical bands causing distorted red cells. Red blood cells with HbSS begin sickling when the oxygen saturation falls below 85%. Acidosis, hypoxia, intracellular dehydration, and vascular stasis increase the sickling process. Decreased cardiac output and hypovolemia lead to increased transit time through the hypoxic environment of the capillary bed, also increasing the sickling process. Historically, it was felt that this red cell pathophysiology was essentially solely responsible for SCD related problems. However, the interactions between red cells, platelets, leukocytes, thrombin, and endothelial cells
along with disturbances of nitric oxide (NO) biology are now known to be at least equally important in this complex pathophysiology.

There is reasonable evidence that there is decreased production and increased scavenging of NO in SCD patients. Through complex mediators this results in endothelial dysfunction, enhanced platelet aggregation, coagulation dysfunction, enhanced leukocyte endothelial adhesion, susceptibility to oxidant mediated injuries, and both acute and chronic pulmonary hypertension. Administration of inhaled NO has been shown to be beneficial in some patients suffering vasoocclusive crisis including stroke and acute chest syndrome (ACS).

The consequence of sickling and endothelial inflammation result in adhesion and occlusion of the microvasculature. As the cells sickle and reform the intricate balance of iron metabolism, ion transport, and cellular hydration is disturbed which alters the red cell membrane making them sticky. Thus the HbS red cell is unstable, sticky and insoluble resulting in early red cell destruction, sickling, and endothelial damage. It is this pathology that results in the acute crisis as well as the long-term chronic problems in these patients.

**Acute crisis**

While the most concerning crises during the perioperative period are the vaso-occlusive crisis of acute chest syndrome and stroke, one should also be aware of the other crises which sickle cell patients may suffer. Other less severe vaso-occlusive crises include episodes of ischemia, pain, and priapism. **Splenomegaly crisis** can occur between 5 months to 2 years of age when large amounts of blood pool within the spleen resulting in profound anemia and shock. **Aplastic crisis** presents as an acute decrease in RBC production often as a result of infection frequently with Parvovirus B19. **Hyperhemolytic crises** may occur secondary to coexisting conditions such as viral infection, transfusion reaction, or to glucose-6-phosphate dehydrogenase deficiency which is present in 10% of the African-American population.

**Acute chest syndrome** (ACS) is a common and important perioperative complication, occurring in 10% of surgical patients. Acute chest syndrome has complex pathophysiology likely resulting at least in part from pulmonary vaso-occlusion and sequestration. Symptoms of fever, tachypnea, pleuritic pain, and cough are difficult to distinguish from pneumonia, and in fact, may begin as pneumonia. Infected and/or fat emboli may lead to vaso-occlusion and sequestration. Chest radiograph can range from normal to complete opacification but usually demonstrates a new lobar infiltrate. The mortality rate of patients with acute chest syndrome is from 2 to 12% depending on the series, is the second most common cause of hospitalization in sickle cell patients and accounts for 25% of deaths in these patients. They may rapidly develop respiratory failure and should be treated with hydration, oxygen, antibiotics, and in many cases exchange transfusion. As noted earlier, there is likely a role for inhaled nitric oxide in treating severe cases.

**Cerebral vascular accidents** occur in about 5% of children with SCD. Most CVAs in children are due to ischemic infarcts while adults are often hemorrhagic. It has recently been recognized that as many as 15-25 percent of asymptomatic children have radiographic evidence of silent cerebral infarcts. In many centers children with SCD are screened with transcranial doppler and those with elevated flow velocities in the middle cerebral and terminal internal carotid arteries are placed on hyper-transfusion regimens. Children with known previous CVA are placed on transfusion regimens usually for a period of 10 years. We are now observing that those children coming off of these transfusion programs are experiencing recurrence.

Vaso-occlusive crises occur with greater frequency during the perioperative period and are the primary concern when deciding the best transfusion and anesthetic approach. Patients who
have had either ACS or CVA should be considered high-risk patients and may benefit from aggressive preoperative transfusion with a target HbS level.

**Chronic problems.**
A lifetime of intermittent vaso-occlusion and endothelial damage results in a host of chronic problems in most patients. These include: decreased growth and maturation, increased nutritional requirements, retinopathy, hearing loss, stroke, high output cardiac failure, pulmonary insufficiency, loss of renal concentrating ability, icterus, bone and joint destruction, leg ulceration, splenic infarction (infection risk), to name but a few. Since one can consider this disease to be as much an endothelial disease as a red blood cell disease, every vascular bed in every organ is affected.

The common complications seen in individuals with sickle cell disease are summarized by the mnemonic "**HBSS PAIN CRISIS**: From Georgia Comprehensive Sickle Cell Web Site www.scinfo.org/prod05.htm

<table>
<thead>
<tr>
<th>H</th>
<th>P</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis, Hand-Foot syndrome</td>
<td>Pain episodes, Priapism, Psychosocial problems</td>
<td>Cholelithiasis, Cardiomegaly, Congestive heart failure, Chest syndrome</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>R</td>
</tr>
<tr>
<td>Bone Marrow Hyperplasia/Infarction</td>
<td>Anemia, Aplastic crisis, Avascular necrosis</td>
<td>Retinopathy, Renal failure, Renal concentrating defects</td>
</tr>
<tr>
<td>S</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>Stroke: Thrombotic or hemorrhagic, Subarachnoid bleeds</td>
<td>Infections: CNS, Pulmonary, GU, Bone, Joints</td>
<td>Infarction: Bone, Spleen, CNS, Muscle, Bowel, Renal</td>
</tr>
<tr>
<td>S</td>
<td>N</td>
<td>S</td>
</tr>
<tr>
<td>Skin ulcers (primarily leg)</td>
<td>Nocturia, urinary frequency from hyposthenuria</td>
<td>Sequestration crisis involving spleen or liver</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased fetal loss during pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td></td>
</tr>
</tbody>
</table>

**Anesthetic Management**

**Preoperative Preparation**

Historically, perioperative mortality rates as high as 10% and morbidity rates as high as 50% have been reported. More recent studies have reported a mortality of around 1%. Sickle cell disease causes such widespread organ damage, that it is difficult to give a single critical pathway for standardized preoperative care, which will apply, to all patients. The patient’s hematologist should be intimately involved in the preoperative preparation. Together the hematologist, anesthesiologist and surgeon can assess the patient’s perioperative risk and determine any special requirements.

In general the patient should be admitted to the hospital the day before surgery to permit assessment by hematology, anesthesiology, and surgery. An elective surgical procedure should not proceed in a sickle cell patient with an ongoing infection such as urinary track infection or respiratory tract infection since these could lead to a painful crisis, ACS, or CVA. Intravenous fluids should be administered while the patient is fasting. While the recommendation of an infusion rate of one and a half times maintenance fluid requirement of a balanced salt solution is frequently made, there is no evidence that excessive hydration is beneficial. The goal of intravenous fluid therapy is to prevent dehydration throughout the peri-operative period.
The role of preoperative transfusion continues to be somewhat controversial. Based on the concern of high mortality and morbidity rates hematologists and anesthesiologists in the 1980s and 1990s provided aggressive transfusion practices with target Hb of 10 mg/dl and HbS concentration of 30% or less. This was considered by many to be the standard of care for most patients until the Preoperative Transfusion in Sickle Cell Disease Study Group published their findings in 1995. This group determined that the complication rate, including death and ACS, was equal in a group that underwent aggressive transfusion with a target Hb of 10 mg/dl and HbS of 30% compared to those who had a simple correction of anemia to a Hb of 10mg/dl. There has never been a randomized controlled study comparing complication rates where a group was randomized to no transfusion at all. However, most authors recommend simple transfusion pre-operatively in all but very low risk patients undergoing low risk procedures. In fact the National Institutes of Health’s 2002 publication on “The Management of Sickle Cell Disease” recommends: “In patients with SCD-SS and SCD-β Thalassemia, simple transfusion to achieve a hemoglobin of 10g/dl should be performed before all but the lowest risk procedures.” Transfusion provides improved oxygen carrying capacity and dilutes the percentage of sickle cells with RBCs containing HbA. Very high-risk patients may require the more aggressive transfusion approach. This should be decided in concert with the hematologist. However, this increases the risk of transfusion related complications. Transfusion related complications include hemolytic reactions, transfusion associated acute lung injury, alloimmunization, iron overload, allergic reactions to leukocyte antigens, and transmission of viral pathogens. Alloimmunization occurs in as many as 30% of adult sickle cell patients requiring frequent transfusions. This complication can be reduced by the use of phenotypically antigen matched blood for at least the C, E, and Kell antigens and leuko-reduction. The hemoglobin should not be permitted to rise above 11g/dl, since this can increase blood viscosity, delay transit time, promote sickling and precipitate a stroke.

In our institution only very low risk patients having low risk procedures avoid transfusion. This is by common agreement with the anesthesiologist, hematologist and surgeon.

Intraoperative Management

No particular anesthetic or technique has proven to be more or less advantageous for sickle cell disease patients. Arguments can be made for and against regional techniques for sickle cell patients. In The Cooperative Study of Sickle Cell Disease series the non-sickle cell disease related complications of fever and infection were higher in the regional group. However this group contained a large portion of obstetric patients receiving epidural anesthesia. This subpopulation is known to have a higher complication rate than other surgical groups. Some authors suggest that the compensatory vasoconstriction in non-blocked areas, lack of control of ventilation, and potential for stasis during regional anesthesia creates an environment in which sickling can occur. Others feel that regional techniques do not create this milieu. In fact, in one series epidural anesthesia and analgesia was successfully used to treat painful vaso-occlusive crisis. Suffice it to say that the technique of anesthetic is likely much less important than the meticulous attention to detail in the areas of preoperative preparation, perfusion, temperature control, and oxygenation.

The wisdom of the use of a tourniquet in patients with sickle cell disease has been debated. Although no prospective studies have been performed to address this issue there are several small retrospective reports touting its safety. If one chooses to use a tourniquet the extremity should be carefully exsanguinated prior to inflation.

Postoperative Management
Most of the serious sickle cell disease related complications occur in the postoperative period. Vaso-occlusive crises are among the most frequent and include painful crisis, acute chest syndrome and stroke. For these reasons the author suggests compliance with the paradigm used in The Preoperative Transfusion in Sickle Cell Disease Study Group, which includes postoperative oxygen supplementation, hydration, and pulse oximeter monitoring. This has obvious implications on the advisability of outpatient surgery for these patients.

**Sickle Trait (HbSA)**

By definition HbSA patients have at least 50% Hb A. Under physiologic conditions problems are very rare. While intracellular polymerization begins below oxygen saturations of 85% in HbSS this does not occur in HbSA until saturations are below 40%. Thus it is generally accepted that children with sickle trait do not require transfusions. However attention to hydration, perfusion, ventilation, and temperature control is prudent as always.

**Sickle Hb C Disease (HbSC)**

In general patients with both HbS and HbC (HbSC or S-C disease) have less frequent and usually milder vaso-occlusive episodes. In the Preoperative Transfusion in Sickle Cell Disease Study Group there were 92 patients with HbSC disease. This group was reported separately. Non-transfused patients undergoing intra-abdominal procedures had a higher incidence of sickle cell related complications (35%) compared to those who were transfused (0%). There were two deaths in the non-transfused group and none in the transfused group. The authors concluded that transfusion appears to be beneficial in HbSC disease patients undergoing abdominal procedures but is not necessary in minor procedures. Because these patients are usually only mildly anemic partial exchange transfusions may be required to keep hemoglobin levels to less than 12 g/dl.

**Screening**

At this point all states in the United States provide newborn screening programs and as such most newborns in the United States are tested at birth for multiple genetic abnormalities including a newborn electrophoresis. Unfortunately the degree to which this information is communicated to and understood by the parents is quite variable. In the older infant, child or adult, a more rapid solubility test, which promotes formation of insoluble sickle hemoglobin, is available. A positive solubility test then requires a hemoglobin electrophoresis to determine the type of hemoglobinopathy. A few facts may be helpful in deciding on the wisdom of a pre-operative screening program. The overall mortality rate for adults undergoing anesthesia and surgery has reached the lofty 6-sigma level of 1 in 300,000. Mortality rates for children overall is considerably worse at about 1 in 80,000. The mortality rate for sickle cell patients undergoing surgery is 1 in 100. For this reason we feel it is crucial to identify these children, who are at much higher risk, prior to administering their anesthetic.

When the sickle cell status of a child coming to our operating room who is in an at risk population is unknown, we follow a standard procedure to determine the sickle cell status: newborn screen from the state lab, a report from the child’s pediatrician, a reliable report from the parent coupled with a hemoglobin determination of 10 gm/dl or greater, a sickle cell prep and, if positive, a hemoglobin electrophoresis. Since 95% of all sickle cell patients will have had some clinical manifestations by age 9 we do not screen beyond this age. If a child is found to have sickle cell disease, sickle hemoglobin C disease, or sickle β thalassemia they should be seen by their hematologist who will assist in the preparation for surgery.
Summary

With the completion of the Preoperative Transfusion of Sickle Cell Disease Study Group data we now have reasonable guidelines to approach most surgical situations. If we are to adopt a simple transfusion practice it seems prudent to also adopt the issues of preoperative hydration, intraoperative vigilance, and postoperative oxygen supplementation and oxymetry monitoring, which was provided to all patients in this study. Until randomized controlled studies comparing transfusion to no transfusion are performed, simple transfusion to achieve a hemoglobin of 10g/dl should be performed before all but the lowest risk procedures. Special circumstances with high-risk procedures and high-risk patients will continue to require careful consideration and consultation. Only through effective communication between the surgery, anesthesiology, and hematology specialists will the individual unique patient considerations be optimally managed.

Bibliography


Sullivan, KJ, Goodwin SR et al.: Nitric oxide successfully used to treat acute chest syndrome of