Anesthetic implications in sickle cell anemia

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Since approximately 50,000 or 1% of blacks in the United States are afflicted with sickle cell anemia, the anesthetist is likely to encounter the management of these patients. This article focuses on the history and pathophysiology of the disease, followed by the anesthetic implications and the treatment for the patient in crisis.

Sickle cell anemia is a hemoglobinopathy which for centuries has plagued the black population. Africans have long been painfully aware of the existence of this disease. Early African tribes marked their members to set them apart from those who were not carriers of this trait. The victims of the disease were identified by tattoos to facilitate diagnosis and prevent intermarriage with the healthy members of the group. This is remarkable in itself in that preventative medicine was being practiced by these primitive tribes.

Epidemiologic studies have suggested the reason why the trait is common among the blacks. It is most prevalent in West and Central Africa where most of the slave trade was carried on during colonial times; correlation studies have implied an inverse relationship of sickle cell trait to the malignant falciparum form of malaria. For reasons not understood, it has become apparent that the heterozygous sickle cell trait is advantageous in these regions because it protects the erythrocytes against invasion by the parasitic organism. Such protection is most effective in infants who have a greater chance of tolerating an attack of malaria, thus explaining the existence of an otherwise disadvantageous mutation. This may be the reason why black populations survived and thrived in an environment intolerable to other people.

Sickle cell trait also has been observed in Mediterranean peoples, however, with a much lower incidence. Specifically, it has been noted in Sicily, Turkey, and some of the Arab countries, where malaria was endemic; but the presence of the trait also may reflect the migration of ethnic groups originally from Africa toward the Mediterranean countries, Central Europe, North America, and the West Indies.

Pathophysiology

The disorder was first noted by J. B. Herrick in 1904 while examining a black student. However, it was not until 1927 that Hahn and Gillespie demonstrated that sickling was produced by a reduction of the oxygen tension and pH in blood, and that hemoglobin was the incriminating factor when erythrocyte "ghosts" from which the hemoglobin had been extracted would not sickle.

Normal hemoglobin synthesis occurs by the combination of globin with four heme radicals. The heme groups are metal complexes with an iron atom in the center of a porphyrin structure and give hemoglobin its red color. Globin is a colorless protein composed of four polypeptide...
chains. The polypeptide chains consist of two alpha chains and two beta chains. After iron is inserted into the porphyrin nucleus to form heme, the molecule combines with one of the globin peptide chains to form hemoglobin.5

All the variants of sickle cell disease share in the possession of various quantities of hemoglobin S. Hemoglobin S differs from normal adult hemoglobin A by the substitution of amino acid valine for glutamic acid at the sixth position of the beta chain in the hemoglobin molecule.5 Sickle cell anemia is present when the patient is homozygous for hemoglobin S. In the homozygous state, 70 to 98% of the hemoglobin is the S type resulting in severe hemolytic anemia.8 Estimation of the number of blacks afflicted with this disease in the United States differs from author to author, but the majority of estimates fall within the range of 0.2 to 1.3% of the black population being homozygous for hemoglobin S.

The deoxygenated form of hemoglobin S results in the deformation of the erythrocyte into the characteristic sickled shape. Molecularly, with the substitution of valine for glutamic acid in the beta chain, two reactive sites are formed when hemoglobin S releases oxygen. As a result, hemoglobin S molecules tend to bond with each other at these reactive sites, forming long aggregates or tactoids. These aggregates of deoxygenated hemoglobin molecules line up along their longitudinal axis thereby distorting the membrane of the cell and resulting in the sickled shape. Irreversible sickled cells become dehydrated and rigid and can cause tissue infarcts by impeding blood flow and oxygen to tissues.4 These erythrocytes typically have a short life span due to their increased fragility.

Classifications
Sickle cell disease is clinically considered to have two forms: (1) sickle cell anemia, and (2) sickle cell trait. Sickle cell trait is the heterozygous manifestation of sickle cell disease containing the hemoglobin genotype AS. Although various opinions exist, the general consensus is that erythrocytes of patients with sickle cell trait contain 20 to 50% hemoglobin S, with the remainder being hemoglobin A. The incidence of sickle cell trait among the black population of the United States is about 10%. People with the trait are usually asymptomatic because the life span of their red blood cells is normal.8

McNiece states that sickle crisis may occur in these individuals if they are exposed to a hypoxic environment. However, most researchers feel that sickle cell trait should not be considered a disease, because hemoglobin AS cells begin to sickle only when the oxygen saturation of hemoglobin is below 20%. With the exception of a 50% increase in pulmonary infarctions, no difference in survival rates or occurrence rates of severe disease has been found between normal persons (those with hemoglobin AA) and those with hemoglobin AS.4 Studies have also shown that erythrocytes found in the sickle cell trait are more resistant to acidosis than homozygous erythrocytes.5 Patients receiving anesthesia who have sickle cell trait should be treated with caution also, as single case reports of perioperative death and perioperative brain infarct do exist.5,6

Clinical manifestations
The clinical manifestations of sickle cell anemia are chronic anemia due to hemolysis and infarctive events resulting from occlusion of blood vessels with sickled cells. Virtually all organs are affected. The multiple organ dysfunction produced as a result of this is the major reason why survival beyond 30 years is unlikely in these patients.8

Factors that tend to exacerbate the sickling of red cells include hypoxia, infection, reduction in temperature, acidosis and dehydration. An arterial oxygen partial pressure below 40 torr is likely to initiate sickling of red cells in patients who are homozygous for hemoglobin S. Formation of sickle cells tends to be greater in veins than in arteries, probably because of the lower venous pH. Stasis of blood produced by low temperatures and the peripheral vasoconstriction and dehydration, which leads to increased viscosity, are also factors favoring the formation of sickle cells.8

Sickled red blood cells become fragile, dehydrated and rigid. Because of their odd shape, sickling cells are vulnerable to destruction by splenic phagocytes and reticuloendothelial cells. Hemolysis of the fragile red blood cells may cause jaundice. Marrow erythroid hyperplasia and increased reticulocyte counts in peripheral blood result from a compensatory mechanism which stimulates erythropoiesis. Despite attempts at compensation, the hemoglobin level remains around 8 gm/dl.5 The dehydration and rigidity of the erythrocyte causes an increased blood viscosity resulting in vascular occlusion. The vicious cycle continues as the vascular occlusion leads to further hypoxia, vasoconstriction, leakage of fluid, more sickling, and finally necrosis and infarct.1

Once sickling has occurred it is virtually an irreversible process. Some sickle cells, however, may undergo a retransformation to the biconcave
form upon oxygenation, provided cellular metabolic processes that control membrane rigidity have not been critically altered.8

Sickling crises are clinically divided into two groups: (1) hematologic crises, and (2) vaso-occlusive crises. Hematologic crises include: (1) a hemolytic type, in which the primary triggering episode results in destruction of sickled erythrocytes and an acute loss of circulating cells, and (2) an aplastic type, in which bone marrow enters an aplastic phase with no erythropoiesis and a rapid reduction of hemoglobin. Vaso-occlusive or painful crisis is triggered by hypoxemia and/or acidosis. The resultant sluggish circulation, caused by increased viscosity of the blood, aggravates the decreased blood flow to peripheral tissues. Eventually, if the process advances, complete vascular occlusion results, which is manifested primarily by severe pain localized in the involved area, frequently the extremities and abdomen.9

At present, treatment of vaso-occlusive crises is symptomatic. Analgesics are given to relieve the pain along with appropriate fluids and electrolytes to combat dehydration and acidosis.

In the steady state, the hemoglobin concentration is 5 to 10 gm per dl. The cardiac output is generally increased and the oxyhemoglobin dissociation curve is shifted to the right (Pt 2 O 2 about 31 torr), reflecting an increased erythrocyte concentration of 2,3-diphosphoglycerate. This shift facilitates the unloading of oxygen, but, at the same time, it places the S-containing erythrocyte in greater jeopardy of sickle cell formation because the critical degree of deoxygenation is reached at a higher arterial oxygen partial pressure (PaO 2).

The infarctive events are responsible for the end organ damage produced in sickle cell anemia. Cardiomegaly is frequently associated with cor pulmonale resulting from repeated pulmonary emboli. An increased alveolar-to-arterial difference for oxygen (A-aDO 2) is often present presumably due to pulmonary infarctive events. The total lung capacity and vital capacity are commonly reduced. The renal medulla is a frequent site of vascular occlusion which in turn leads to papillary necrosis and hematuria, and ultimately to renal failure.

The liver is mildly enlarged due to vascular occlusion. Chronic hemolysis of erythrocytes is reflected in elevated levels of serum bilirubin. The increased bilirubin load is associated with a high incidence of cholelithiasis. The need for periodic transfusions increases the risk of viral hepatitis. In severe cases, iron deposited in the liver as hemosiderin can lead to cirrhosis.

Splenomegaly is often present in infants; however, a gradual reduction in the size of the spleen follows secondary to repeated thrombosis and infarction. By 6 years of age, most patients with sickle cell anemia are, for all practical purposes, asplenic. The absence of splenic function is associated with a decreased production of antibodies and an increased risk for developing bacterial infections. Neurological dysfunction is also likely in patients with this disease, manifested most often as cerebral infarction in children and as intracranial hemorrhage in adults.8 No major organ is left unaffected by sickle cell anemia.

With the pathological processes and end organ damage produced by this disease, sickle cell anemia patients present in the operating room for various procedures. These patients most common surgical procedures include skin grafting of chronic leg ulcers, cholecystectomy resulting from pigment stones, relief of persistent painful priapism secondary to sickling in the sinusoids of the penis, currettage of osteomyelitic bone cavities, and splenectomy because of hypersplenism.2

Treatment
The treatment of sickle cell disease is primarily symptomatic despite intensive efforts during the last decade to provide more definitive therapy. Analgesics for the relief of pain, fluid and electrolytes to combat dehydration and acidosis, and oxygen therapy are the treatments of choice for most sickle cell crises. Mild alkalinization of blood has also been advocated both preoperatively (for prophylactic measures) and during a sickle cell crisis (to diminish the acidosis).2 Pulmonary hyperventilation, as long as it is not carried to extremes, affords relative protection.

Exchange blood transfusions are another course of treatment but should be limited to a severe crisis. Partial exchange transfusions with erythrocytes containing hemoglobin A will reduce the concentration of hemoglobin S, and thereby decrease the likelihood of further infarctive damage.8 The goal of the exchange transfusion is to increase the hemoglobin A concentration to 40% and the hematocrit to 35%. The 40% figure is an arbitrary one, because no controlled studies have examined ratios of hemoglobin A to S that prevent the blood from sickling in vivo. To achieve the 40% ratio about 4 units of washed erythrocytes must be exchanged in a 70 kg adult.4 However, bone marrow depression resulting in a decreased erythrocyte production is a major complication.2

Post-transfusion reactions also have been reported up to a few days after blood administration.
Delayed hemolytic reactions in patients receiving frequent transfusions are due to red cell antigens differing from recipient and donor. Donors were largely from the white population. Increasing the frequency of black blood donors because of the similarity of red blood cell antigens may lower the incidence of hemolytic transfusion reactions.

Iron overload is another complication following transfusion and requires chronic and intensive chelation to prevent. Deferoxamine administered subcutaneously by infusion pump is being used for the treatment of iron overload. Increased blood viscosity and viral hepatitis are other possible complications of exchange transfusions.

Exchange transfusions are useful in selected situations however. Strokes tend to recur in over 60% of the cases without a hypertransfusion program and may recur once the transfusions are discontinued. Packed red blood cells given at regular intervals have been recommended to keep the hemoglobin S levels below 30%. It is usually possible to keep bone marrow suppressed if the hemoglobin is maintained between 9-11 g/dl. Two units of packed red blood cells every 3-4 weeks accomplishes this.

Selective apheresis is a method of selectively removing those cells containing hemoglobin S on the basis of differences in buoyant density. These cells are then replaced with neocytes. These young red blood cells have a mean age of 30 days and have a 50% longer survival rate than routine red blood cell preparations. The longer survival of the red cells increases the interval between transfusions and reduces the hazard of iron deposition in the tissues.

Long-term cryopreservation of red blood cells from 1 to 3 years has been reported with positive results. This may make autologous transfusions a possibility during anemic episodes not due to sickling. However, the results are not definitive and controversy still exists.

Magnesium sulfate has vasodilating properties and prolongs the bleeding time. As a result, its use has been suggested to prevent thrombus formation and sludging of erythrocytes. Optimizing the peripheral circulation with fluids combined with the use of a mild alpha adrenergic blocking agent to prevent capillary sludging and sickling has also been recommended. Inducing hyponatremia has been shown to abort acute sickle cell crises by causing the erythrocytes to swell, thereby reducing the incidence of sickle cell formation. This treatment, however, is still experimental.

The use of urea, both prophylactically and in the treatment of sickle cell crises, also has been advocated. It has been shown that less urea is required to block sickling than is actually needed to reverse the sickling event. Since urea induces a diuresis, fluids should be replaced promptly in a volume equivalent to, or greater than, the urinary output. A side effect of intravenous urea is sedation, which is actually a desirable effect in treatment of painful sickle cell crises, decreasing or eliminating the need for narcotics and analgesics.

Other agents which may be useful in sickle cell anemia include the phenothiazines (inhibit sickling in vitro), alkalines or alkalinizing agents, anti-sludging agents, anti-sickling agents (zinc and imidoesters), defibrinating agents (Arvin®), and cyanide derivatives (Cyanate®) (which increases hemoglobin affinity for oxygen). However, none have satisfied criteria for efficiency, safety, and dependability to date.

A newly described agent with some promise is Cetiedil®. It has been found to inhibit sickling by more than 80%, acts as a peripheral dilator, decreases blood viscosity, and is known to be nontoxic. Results, however, are still inconclusive.

Bone marrow transplantation offers another method for management of sickle cell disease, however this modality should be contemplated only in certain selected cases, as this procedure is associated with a high risk.

Finally, anti-natal diagnosis and gene manipulation of sickle cell anemia are possible. Gene manipulation, in which a chemotherapeutic agent (5-azacytidine) is used, offers promising results. However, 5-azacytidine must be used with extreme caution due to its toxicity. Research with this type of drug offers the potential that less toxic means of gene manipulation will be developed.

Anesthetic considerations

Anesthetic considerations require a thorough understanding of the implications involved in this already compromised patient. Preoperatively, inhaled oxygen therapy of at least 30% is of good therapeutic measure but not required unless the patient's condition so dictates. Preoxygenation prior to induction is essential. Preoperative medications should not depress respiratory function in order to avoid respiratory acidosis. Intravenous fluids should be warmed and given in amounts that assure adequate hydration, prevent erythrocyte sludging, and promote good urinary flow. The anesthetist should ensure that the patient is hydrated while at the same time should avoid fluid overload, as most of these patients will have some aspect of cardiac involvement.

These patients must be kept warm in order to prevent a crisis. Use of warm blankets preo-
tively and intraoperatively, warming the surgical suite, warming of intravenous fluids and preventing unnecessary exposure of the patient intraoperatively are essential. Aseptic technique is required at all times because these patients have an increased risk of infection. They are especially vulnerable to pulmonary infections.

Routine monitoring equipment should include an oxygen analyzer, temperature probe, and an electrocardiogram in lead V5 for early diagnosis of hypoxia shown as inferior wall ischemia. Homi suggests the use of transcutaneous oxygen measurements but the results seem to be inconclusive, most likely because of the pigmentation of the skin. However, the use of an O2 saturation monitor is recommended.

Intraoperatively, conditions which promote sickling of erythrocytes must be avoided. For this reason, a local anesthetic with intravenous sedation is the technique of choice. Regional anesthesia is the second choice but it has been shown that regional blocks, including axillary, epidural, or subarachnoid, produce compensatory vasoconstriction and a decreased PaO2 in the nonblocked areas, creating a milieu for infarction in these areas.17 Spontaneous respirations are maintained with these techniques, and the stresses of general anesthesia are not induced.

If a general anesthetic is mandated, an inhalation agent with high oxygen flows is utilized. A very low flow of nitrous oxide may be used. Muscle relaxants must be used with caution and prolonged immobilization should be avoided. The use of succinylcholine is modified by the occasional occurrence of decreased serum cholinesterase activity in these patients.18

Treatment of a crisis with magnesium sulfate will potentiate muscle relaxants, and the use of a peripheral nerve stimulator is prudent in all patients. Adequate alveolar ventilation and normal cardiac output must be maintained to avoid ventilation-perfusion ratio alterations. Positional changes and the use of tourniquets are undesirable/contraindicated because of the likelihood of intravascular stasis. Movement of the patient's extremities, if possible, in long procedures is also recommended to relieve stasis. Deliberate hypotension is one technique that should be avoided at all costs because this promotes sludging and pooling of erythrocytes in the extremities. There is some evidence that general anesthesia may actually decrease the number of circulating sickle cells during and immediately following the anesthetic.19,20

Postoperatively the patient should be kept warm. Inhaled oxygen therapy is recommended for transport of the patient to the recovery room. In the postoperative area, oxygen should be administered through an aerosol mask at an FIO2 of 35%. The sickle cell patient should be frequently assessed for hypoventilation and cooling. Early mobilization is essential for the patient.

Once recovery from anesthesia is complete, oxygen should be administered only intermittently, or as needed, rather than continuously. Two of three patients given oxygen at 5 L/minute over 5 days were reported to have developed painful episodes following discontinuation of oxygen.21 With oxygen administration, there is a rapid decline in erythropoietin, a fall in reticulocytes, and a fall in the number of irreversibly sickled cells. After cessation of oxygen therapy, the erythropoietin levels and number of irreversibly sickled cells increased promptly, producing the painful episodes.

Conclusion
Most surgical procedures in the sickle cell anemia patient are a result of the disease process itself. However, this is a disease which rapidly can turn the most routine operation into a deleterious situation. Most of the anesthetic implications focus on the prevention of an undesirable outcome. The anesthetic protocol should be developed using techniques that will least compromise the patient. Appropriate monitoring and management of these patients are essential.

REFERENCES


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