Sickle cell diseases comprise a group of inherited disorders that alter hemoglobin, ultimately causing hemolytic anemia and recurring instances of vascular occlusion that produce acute and chronic pain. Many patients with sickle cell disease require surgery for conditions associated with their disease. Painful vasculocclusive episodes, which can be debilitating and require long hospital stays, are often precipitated by the stress of surgery. Poorly controlled postoperative pain also can worsen an impending painful crisis. Traditional therapy for patients with sickle cell disease undergoing surgery has included preoperative transfusion and postoperative opioid therapy.

Recent studies have demonstrated that aggressive preoperative transfusion therapy is not beneficial over a more conservative approach. Postoperative pain control trends include nonsteroidal anti-inflammatory drugs such as ketorolac and opioid agonist-antagonist agents such as nalbuphine, as well as epidural analgesia to minimize respiratory depression. New preventive therapy for vaso-occlusive crisis includes hydroxyurea, a chemotherapeutic agent that stimulates the production of fetal hemoglobin. Inhaled nitric oxide is being used in clinical trials with success in slowing the sickling process and unsickling cells. Phase III clinical trials are in progress for 2 drugs that decrease sickling: poloxamer 188 and fructose 1-6 diphosphate. These new therapies should help improve the anesthetic course of the patient with sickle cell disease, reduce postoperative complications, and shorten hospital stays.

Key words: Anesthesia, pain, sickle cell anemia.

The clinical manifestations of sickle cell anemia result from the increase in blood viscosity, red cell adherence to vascular walls, and vascular occlusions. The sickled erythrocytes impede blood flow to target tissues, causing infarctions and ischemic necrosis (Figure 3). Damage can occur to any organ in the body, including the heart, lungs, liver, kidneys, spleen, and brain. This is the genesis of the pain associated with sickle cell disease.

Figure 1. Continuation of amino acids

Hemoglobin S has a tendency to form long strands when deoxygenated, which contort the erythrocytes into the distinctive “sickle” shape. Normal red blood cells have a life span of about 120 days. In contrast, sickle red blood cells have a life span of about 15 days.

Figure 2. Normal and sickle red blood cells under scanning electron microscope


New advances in the treatment of sickle cell disease: Focus on perioperative significance

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2000 Student Writing Contest Winner

Sickle cell diseases comprise a group of inherited disorders that alter hemoglobin, ultimately causing hemolytic anemia and recurring instances of vascular occlusion that produce acute and chronic pain. Many patients with sickle cell disease require surgery for conditions associated with their disease. Painful vasculocclusive episodes, which can be debilitating and require long hospital stays, are often precipitated by the stress of surgery. Poorly controlled postoperative pain also can worsen an impending painful crisis. Traditional therapy for patients with sickle cell disease undergoing surgery has included preoperative transfusion and postoperative opioid therapy.

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associated with sickle cell vaso-occlusive crisis. As blood flow further decreases due to the sickled cells, hypoxia and acidosis develop, which subsequently increase the degree of sickling. These painful vaso-occlusive crises vary widely among patients in severity and duration but have been reported to correlate with early death in adult patients (as a measure of the severity of disease). In fact, a painful crisis is the most common environment in which death occurs for the sickle cell anemia patient. Precipitating factors related to the painful vaso-occlusive crisis include fever, infection, acidosis, hypoxia, stress (physical and/or psychological), sleep apnea, physical exhaustion, and exposure to cold.

Of particular concern to the anesthetist is the high incidence of perioperative sickling and vaso-occlusive crisis, as these patients frequently require surgery. Some of the procedures that patients with sickle cell disease undergo are cholecystectomy, splenectomy, femoral head reconstruction due to avascular necrosis, joint replacement, and craniotomy due to subarachnoid hemorrhage. The perioperative period is critical for the patient with sickle cell disease and frequently a formidable challenge to the anesthetist. The expected decrease in PaO₂, high incidence of pulmonary complications, incisional pain requiring the use of opioid respiratory depressants, fluid compartmental shifts, and disruption in thermoregulation all place the patient at high risk for postoperative vaso-occlusive crisis.

History/review of the literature

Traditional preoperative preparation of the patient with sickle cell disease has included antibiotics, hydration, and aggressive transfusion therapy to achieve a hematocrit of 35% to 40% with 50% to 70% normal hemoglobin. Intraoperative care has focused on the prevention of a potential sickling crisis. Postoperative care has focused on pain management, most commonly with opioids, supplemental oxygen, and fluid maintenance. However, some very promising new developments made over the past 6 years have the potential to improve the perioperative care of the patient with sickle cell disease dramatically.

The original thought behind preoperative transfusion therapy was that raising the hematocrit and increasing the percentage of normal hemoglobin in the blood would help to prevent perioperative hypoxia, thereby decreasing the likelihood of a sickling crisis. However, patients were placed at increased risk for transfusion-related complications such as disease transmission and anaphylaxis from delayed transfusion reaction. While most patients with sickle cell disease are of African ancestry, most of the blood available for transfusion comes from donors of European ancestry. Antigens are found in varying frequencies in the blood of Africans and Europeans. Delayed transfusion reactions arise from an antibody-antigen reaction, which can destroy a large portion of circulating erythrocytes. This underscores the importance of recent research analyzing the benefits of aggressive versus conservative transfusion therapy.

Intraoperative management of the patient with sickle cell disease is an anesthetic challenge. Because, to date, the reversal of the sickling process has been difficult, the anesthetist has focused on prevention. Measures to protect the patient with sickle cell disease from a potential vaso-occlusive crisis include ensuring adequate hydration, anticipating blood loss and fluid shifts, providing systemic oxygenation and avoiding acidosis, maintenance of normothermia, and meticulous positioning in order to avoid circulatory stasis. However, recent pharmacological advances may dramatically alter the intraoperative care of the patient with sickle cell disease. New drugs, which are now in phase III clinical trials, appear to decrease erythrocyte aggregation and treat vaso-occlusive crisis at its source. Furthermore, inhaled nitric oxide also is being investigated for its role in the prevention and treatment of vaso-occlusion due to sickled cells.

Key goals in the postoperative management of the
patient with sickle cell disease are oxygenation, hydration, and pain control. Supplemental oxygen therapy must be continued well into the postoperative course due to the expected decrease in \( \text{PaO}_2 \) after surgery. Traditionally, meperidine and morphine have been the agents of choice for postoperative pain control in patients with sickle cell disease.\(^{12}\) However, the respiratory depressant effects of these drugs have been known to cause acidosis and hypoxia, which can precipitate additional sickling. Meperidine also may have theoretical drawbacks related to its pro-epileptic metabolite normeperidine.\(^{13}\) Nonopioid analgesic agents such as ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), and nalbuphine, a narcotic agonist-antagonist, are becoming increasingly popular in the management of postoperative pain in the patient with sickle cell disease.

Another consideration in the control of postoperative/vaso-occlusive pain in the patient with sickle cell disease is the administration of epidural analgesia. Analgesics administered epidurally have the unique ability, when administered carefully, to provide relief from pain without altering respiratory function. Recently completed and ongoing research has examined and continues to examine the efficacy of epidural analgesia in relieving vaso-occlusive pain in adults with sickle cell disease.\(^{14}\)

**Discussion of the state of the art**

Sickle cell disease is currently the focus of cutting-edge research that has some definite anesthetic implications. New treatments and preventive therapy that have been accepted for practice in the past 3 years include hydroxyurea for pain prevention and new guidelines for preoperative transfusion.\(^{10}\) Current research in pharmacology includes 3 very promising new therapies for the treatment, and in some cases preclusion of painful vaso-occlusive episodes.\(^{11}\) All 3 experimental therapies have the potential to benefit the patient. Also, a new trend toward the use of NSAIDs and narcotic agonist-antagonist drugs, as well as epidurally administered analgesics, in lieu of parenteral morphine and meperidine may help to decrease the respiratory depression and consequent acidosis that may exacerbate the frequency and severity of postoperative vaso-occlusive crisis.

- **Preoperative transfusion.** A 1998 multicenter study compared the number of perioperative complications among patients who received either aggressive preoperative transfusion or a more conservative regimen. Out of the 604 participants, 14% of the aggressive transfusion group had transfusion-related complications, compared with 7% in the conservative regimen group.\(^{10}\) Moreover, there was no appreciable difference in the rate of serious complications (not transfusion-related). It is now generally accepted that for patients with sickle cell disease, conservative preoperative transfusion is the safest and most reasonable method to optimize hematological status preoperatively.\(^{9,10}\)

  - **Hydroxyurea** (Droxea [Bristol-Meyers Squibb, Princeton, NJ]). The chemotherapeutic agent hydroxyurea was approved by the United States Food and Drug Administration in 1998 for use in the adult patient with sickle cell disease experiencing more than 3 painful vaso-occlusive events in 1 year.\(^{11}\) Hydroxyurea fosters HbF production and increases mean corpuscular volume.\(^{15}\) The importance of HbF and sickle cell disease was first understood by Janet Watson, a pediatrician, in 1948. Dr. Watson noticed that infants with sickle cell disease did not exhibit symptoms of the disease. She hypothesized that HbF, which remains in high levels for the first year of life, had a protective mechanism against sickle cell crisis.\(^{11}\)

  Hemoglobin F is composed of \( \gamma \)-globulin chains rather than \( \beta \)-chains. The \( \gamma \)-globulin chains are not affected by the genetic alterations present in sickle cell disease. It is now understood that HbF prevents disease manifestation by disrupting the polymerization of deoxygenated HbS.\(^{16}\) Therefore, increased levels of HbF inside sickle RBCs may prevent the RBCs from becoming rigid and clogging blood vessels.\(^{10}\)

  The 1995 Multicenter Study of Hydroxyurea in Sickle Cell Anemia was actually interrupted by the National Institutes of Health because the participants treated with hydroxyurea had momentous results.\(^{15}\) Adult patients who received hydroxyurea reported a 50% decrease in the number of painful vaso-occlusive episodes. (Figure 4). In addition, patients treated with hydroxyurea required fewer blood transfusions and hospitalizations than those in the placebo arm of the study (Figure 5).\(^{10,11,15}\)

  Hydroxyurea is given orally at a starting dose of 10 mg/kg, increasing on a weekly basis by 5 mg/kg until a maximum dose of 35 mg/kg is reached or toxicity develops. No decision regarding the efficacy of hydroxyurea is made until the patient has completed 6 to 9 months of therapy. Hydroxyurea-related toxicity is manifested as reversible bone marrow suppression. However, it is imperative that patients treated with this drug are monitored on a weekly to biweekly basis because life-threatening cytopenia can develop if blood levels are not assessed and dosage adjusted. Limiting factors for hydroxyurea treatment are pregnancy, neutropenia (neutrophil count less than 2,500/mm\(^3\)), platelet count less than 80,000/mm\(^3\), and hemoglobin concentration less than 4.5 g/dL. These
laboratory values must be carefully considered when preoperatively evaluating the patient with sickle cell disease being treated with hydroxyurea.17

- **Purified poloxamer 188 (Flocor, [CytRx Corporation, Norcross, Ga]).** The first of the 3 latest therapies for sickle cell vaso-occlusion is purified poloxamer 188 (Flocor), a rheologic, anti-adhesive, antithrombotic drug that is currently in Phase III clinical trials. It has been widely studied and shown to decrease the aggregation and endothelial adhesion of erythrocytes in patients with sickle cell disease. Purified poloxamer 188 also has the ability to enhance the deformability of normal/sickle erythrocytes and to decrease the membrane rigidity of irreversibly sickled cells. Purified poloxamer 188 creates a slippery overlay on sickled cells, which allows them to slide over each other, thereby improving blood flow to target tissues. Purified poloxamer 188 has no anticoagulant effects, yet it does possess antithrombotic effects.18

Studies have shown that sickle cell disease patients with vaso-occlusive crisis treated with intravenous purified poloxamer 188 have had shorter hospital stays and decreased analgesic requirements.11 For example, a 1997 study19 designed to evaluate the safety and efficacy of purified poloxamer 188 had promising results. Patients treated in the study group required less narcotic analgesic than those in the placebo group. In addition, the patients treated with purified poloxamer 188 demonstrated a net reduction in length of hospital stay when compared with those in the placebo group.

Purified poloxamer 188 is administered intravenously at a rate of 15 to 30 mg/kg per hour. The most commonly reported adverse effects are backache and nausea. The only consistent manifestation of toxicity reported is a dose-dependent osmotic nephrosis, which is completely reversible.18 CytRx Corporation hopes to submit a New Drug Application for Flocor to the US Food and Drug Administration in 2001.11 The perioperative significance of purified poloxamer 188 is great. By facilitating blood flow and improving oxygen delivery, this drug has the potential to decrease postoperative vaso-occlusive complications and improve outcome.

- **Fructose 1-6 diphosphate (Cordox [Cypros Pharmaceutical Corp, Carlsbad, Calif]).** Fructose 1-6 diphosphate (Cordox) is another recent development in the treatment of sickle cell disease. It is a naturally occurring intermediate of anaerobic energy generation in cells. Fructose 1-6 diphosphate is produced intracellularly, as glucose is metabolized for energy. It may have the ability to sustain energy levels (via adenosine triphosphate) in hypoxic cells. If fructose 1-6 diphosphate does indeed have the ability to maintain adenosine triphosphate levels in hypoxic cells, these cells may be able to recover more quickly from a vaso-occlusive event.20 It acts directly at the cellular level by reducing sickling and thus protecting the target tissues. Fructose 1-6 diphosphate helps RBCs maintain their shape, avoiding the sickle architecture. Consequently, blood flow is improved, and the vaso-occlusive episode is treated at its source.10

Fructose 1-6 diphosphate is unique in that it is the first drug confirmed to reduce both the sickling and pain caused by vaso-occlusion.10 Double-blind studies have confirmed that patients with sickle cell disease treated with fructose 1-6 diphosphate experiencing pain related to vaso-occlusive crisis have had signifi-
cantly lower pain scores (on 2 scales) compared with patients treated with placebo.\textsuperscript{10} This makes fructose 1-6 diphosphate an attractive option for use by the anesthetist in the intraoperative and postoperative periods for the patient with sickle cell disease who has high potential for vaso-occlusive crisis. Fructose 1-6 diphosphate is undergoing phase III clinical trials.

- **Nitric oxide.** Inhaled nitric oxide has been used with much success in the laboratory treatment of sickle cell disease. Nitric oxide acts by causing smooth muscle relaxation in the vascular wall as well as vasodilation. It helps the sickled hemoglobin to bind oxygen with greater affinity, theoretically slowing the formation of additional sickled cells.\textsuperscript{10,11,20} Their results indicate that nitric oxide shifts the oxygen binding capacity of HbS toward that of HbA. Dr. Head is studying the effect of nitric oxide administration on the severity of existing sickle cell crisis. Initial data show that nitric oxide may retard the sickling process and even cause the return to normal architecture of a previously sickled cell. The anesthetic implications of these initial results are considerable. Intraoperative use of inhaled nitric oxide may offer us yet another intervention targeted at reducing sickle cell disease-related morbidity.

- **Nonopiate analgesics.** Effective postoperative pain management is critical for the patient with sickle cell disease. A slowly growing body of evidence shows that NSAIDS, such as ketorolac, and agonist-antagonist agents, such as nalbuphine and butorphanol, can effectively control postoperative pain without the undesirable respiratory depression produced by opioids. Both ketorolac and nalbuphine have been proven to be effective in the treatment of acute vaso-occlusive pain in the patient with sickle cell disease.\textsuperscript{22,23}

Ketorolac is classified as an NSAID, which is a group of drugs that are reversible inhibitors of cyclooxygenase, the enzyme that is responsible for the conversion of arachidonic acid endoperoxide compounds. Ketorolac acts upon pain peripherally through its effects on inflammation. Inflammation is reduced by decreasing the release of chemical mediators from mast cells, granulocytes, and basophils. The NSAIDS also decrease the sensitivity of vessels to histamine and bradykinin. However, recent research indicates that ketorolac’s strong analgesic properties are not exclusively due to cyclooxygenase inhibition, but rather from another mechanism, perhaps at opioid receptors.\textsuperscript{24,25}

Nalbuphine, a powerful narcotic agonist-antagonist provides pain relief similar to that of morphine. Nalbuphine is a kappa agonist, with weak mu receptor antagonist activity. The main advantage of nalbuphine over morphine is its respiratory depression ceiling effect. It has been shown that a variable degree of respiratory depression occurs in doses up to 0.15 mg/kg, where additional dosing does not result in greater depression.\textsuperscript{26,27} Morphine has no such ceiling effect.

- **Epidural analgesia.** Recently, the use of epidural analgesia has proven to be a viable alternative to intravenously administered opioid analgesics. Epidurally administered analgesics have the ability to control pain up to mid-chest level without risk of respiratory compromise, thereby allowing optimal oxygenation.\textsuperscript{20} Taking these factors into consideration, epidural analgesia would seem ideal for the patient with sickle cell disease. Despite the fact that sickle cell vaso-occlusive pain is commonly generalized in nature, the most critically affected areas are the lower extremities, abdomen, and lower back. In 1994, Yaster and associates\textsuperscript{19} concluded from their retrospective observational study that epidural analgesia is an effective technique for the safe management of the vaso-occlusive pain of sickle cell disease. The principal benefits of properly applied epidural pain management lie in the preservation of normal respiratory function and lack of central nervous system depression and sedation. By optimizing respiratory function and avoiding sedation, tissue oxygenation is optimized, and theoretically, further sickling is averted. For that reason, epidural anesthesia and analgesia are viable alternatives that should be strongly considered by the anesthetist, when appropriate, in planning the perioperative management of the patient with sickle cell disease.

**Summary**

Recent developments in the treatment of sickling and resultant vaso-occlusion, as well as new trends in pain control, have the potential to improve dramatically the anesthetic course of the patient with sickle cell disease. A new, more conservative approach to preoperative transfusion therapy should reduce the incidence of transfusion-related complications.\textsuperscript{10} Hydroxyurea has shown to reduce the incidence of painful vaso-occlusive crisis and consequent hospitalization.\textsuperscript{15} Purified poloxamer 188, fructose 1-6 diphosphate, and inhaled nitric oxide are being studied clinically and have promising applications to perioperative care. Alternatives to opiates, in the form of NSAIDs and agonist-antagonists, avoid the adverse effects that may exacerbate or increase the frequency of sickling crisis. In
addition, epidural analgesia is being investigated to validate its promising applications in the treatment of painful events in patients with sickle cell disease. With the advent of these new therapies, the anesthetic course of the sickle cell disease patient should become less complicated, postoperative complications decreased, and hospital stays shortened.

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