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Managing the Pain of Sickle Cell Anemia

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The life expectancy of an individual with sickle cell disease (SCD) has increased dramatically in the last 30 years, from an average of 14 years in 1973 to a current estimate of about 50 years. Therefore, clinicians will be confronted with new management challenges from infrequently observed disease sequelae as the current cohort of SCD patients reaches adulthood. This issue of *Anesthesiology Rounds* summarizes the pathophysiology of sickle cell pain, and the current strategies for prevention and management of acute pain crises. Some factors that interfere with ideal pain management are discussed. The comprehensive management of SCD, however, is beyond the scope of this paper and the reader is directed to recent reviews.[1,2]

GENETICS

SCD is an inherited disorder of the β-hemoglobin chain. Normal adult hemoglobin (HbA) consists of two α- and two β-globin chains. In SCD, valine is substituted for glutamic acid in the 6th position on the β-globin chain. This mutated globin combined with an α chain produces sickle cell hemoglobin (HbS). The 4 most common SCD genotypes in North America are SCD-SS, SCD-SC, SCD-Sβ$^+$thal and SCD-Sβ°thal. In general, SCD-SS (two genes for HbS) and SCD-Sβ°thal (one gene for HbS and one gene for β°thalassemia) are the most severe phenotypes followed by SCD-SC (one gene for HbS and one gene for HbC) and SCD-Sβ$^+$thal (one gene for HbS and one gene for β$^+$ thalassemia). However, there is considerable overlap in severity and individuals with the same genotype even members of the same family may have a markedly different clinical course. Individuals who inherit one gene for the normal β chain and one gene for the sickle cell β chain are said to have "sickle cell trait" and, in general, have few health problems except for increased risk of heat exhaustion, splenic infarction after exercise, and renal tumours.[3] Individuals identified with the sickle cell trait should receive genetic counselling.

EPIDEMIOLOGY

SCD has classically been associated with people of West African ancestry. In West Africa, 10%-30% of people have the sickle cell trait.[4] The hemoglobin S gene is not confined to Africa, however. The genetic mutation that causes SCD arose in areas where malaria is or has been endemic, ie, Africa, Mediterranean countries, Saudi Arabia, and India. It is also found in countries that had African or Indian colonies or participated in the slave trade. In the black population of North America, it is estimated that 8% have the sickle cell trait and 0.3% - 1.3% have the disease. With migration and intermarriage, identification of ethnic groups for screening becomes problematic. Since 1990, the state of California has adopted a universal neonatal screening program. In November 2005, the Ontario Government announced universal screening for hemoglobinopathies. Neonatal screening is vitally important, since without early screening, early institution of vaccination and antibiotic prophylaxis, mortality in SCD can be as high as 20% by the age of 3.

PATHOPHYSIOLOGY OF SICKLE CELL DISEASE

Substitution of negatively-charged glutamate for valine, which has no polarity, makes oxygenated HbS unstable and subject to accelerated denaturation and break-

down. Once deoxygenated, HbS is much less soluble than normal adult hemoglobin and forms hydrophobic bonds with adjacent HbS molecules. This aggregation can trigger a polymerization reaction, forming long strands of HbS. These deform the erythrocyte and produce the classic sickle cell morphology. These are the 2 important features of sickle cell hemoglobin: instability and insolubility.[3]

The instability of HbS exposes the red blood cell (RBC) membrane to increased oxidant stress. Free iron and iron-containing compounds disrupt cell membrane ion transport pathways, allowing potassium loss and cellular dehydration. The disruption of the RBC membrane also increases the adherence of RBCs to the vascular endothelium. This, in turn, causes increased shear and oxidant stress on the endothelium. Adhesion molecules found on both RBCs and endothelial cells mediate adherence to the endothelium. The changes in the membrane cause increased RBC fragility and a shortened RBC lifespan (12-17 days vs 120 days). To replace these RBCs, more reticulocytes (immature RBCs) enter the circulation and these reticulocytes have more adhesive proteins on their surface compared with older RBCs.

Sickle cell disease pain or vaso-occlusive crisis (VOC), which is the commonest clinical manifestation of the disease, can occur from 0 to 10 times per patient per year.[5] The classic model for vaso-occlusion is RBCs sickling under the influence of local hypoxia. These rigid cells then pile up and block small blood vessels. In turn, the RBCs upstream become hypoxic and sickle; thus, the situation worsens. However, the pathophysiology is considerably more complex than a simple mechanical blockage of blood vessels (Table 1).

There is evidence of a heightened inflammatory response in SCD and those individuals with higher baseline levels of inflammation are more severely affected. Higher baseline leukocyte counts are predictive of more severe disease in infants,[6] correlating with the development of silent brain infarcts in children and indicating a higher risk for acute chest syndrome (ACS). Other evidence for inflammation as a key component in SCD is the higher level of cytokines and platelet- activating factor found in patients with SCD.

Laboratory research on transgenic sickle cell mice suggests that VOC has features of ischemia-reperfusion injury. After a hypoxic insult, SCD mice demonstrate increased numbers of leukocytes that adhere to the vascular endothelium, with leukocyte extravasation and oxidant production by the vascular endothelial cells.[7] There is also evidence for dysregulation of vascular tone in SCD. Nitric oxide (NO) is an important regulator of vascular tone, endothelial adhesion, and platelet aggregation. Low levels of arginine (an NO precursor) and of NO metabolites have been demonstrated in SCD patients during VOCs. The levels were inversely proportional to estimates of pain severity.[8] NO is consumed by the high concentrations of cell-free ferrous hemoglobin in patients with SCD. Unregulated vasoconstriction contributes to vaso-occlusion,[8] augmenting tissue hypoxia and end-organ damage.[1] It also appears that the coagulation system is activated in SCD.[9]

TABLE 1: Mechanisms involved in the pathophysiology of vaso-occlusive crisis (VOC).

Mechanism	Evidence or associated features
Red blood cell (RBC) sickling under hypoxia	RBC rigidity Mechanical blockage of blood vessels
Increased inflammatory response	Increased cytokines Increased platelet-activating factor
Ischemia-reperfusion injury	Increased leukocytes Leukocyte extravasation
Dysregulation of vascular tone	Nitric oxide (NO) consumption Low arginine and NO metabolite levels

VASO-OCCLUSIVE CRISIS: CLINICAL PRESENTATION

In early childhood, the first painful crisis may take the form of dactylitis or hand-foot syndrome. It presents as an acute onset of painful symmetrical swelling of the hands and feet, associated with fever, anemia, leukocytosis, and typical X-ray findings.[10] Half of all SCD-SS and SCD-SC patients will have a painful crisis by the age of 5 years and 7 years, respectively. In children who present with hand-foot syndrome, 25% will have another episode within 6 months.[11] The prognosis worsens with earlier presentation. Dactylitis before the age of 6 months identifies those children who go on to have severe complications of SCD (ACS, stroke, and death).[12]

In Jamaican cohort studies, painful crises most commonly affected patients between the ages of 15 to 29 yr., with both sexes affected equally. Pain affected the lumbar spine in 49%, the abdomen in 32%, the femurs in 30%, and the knees in 21%. Abdominal crises were associated with abdominal distension in one-third of patients and with referred rib pain in 26% of cases. Fever was often present, even in the absence of an identifiable infection.[13]

Factors often cited by patients as precipitating a crisis were skin cooling, emotional stress, physical exertion, and pregnancy.[13] A cohort study of 95 children demonstrated that nocturnal desaturation, as measured by pulse oximetry, was positively associated with frequent, painful VOCs.[14]

During a crisis, the pain may change location from one day to the next. There may be tenderness, swelling, and erythema or there may be few, if any,

objective findings on physical examination. History and physical examination should be directed at eliminating other pain syndromes. Patients with SCD are susceptible to a variety of pain states including ACS, osteomyelitis, avascular necrosis of the femoral or humeral head, collapsed vertebrae, splenic infarction, splenic sequestration, cholecystitis, cholelithiasis, sickle hepatopathy, priapism, and delayed hemolytic transfusion reaction.[1,15]

PREVENTION OF VASO-OCCLUSIVE EPISODES:

Hydroxyurea

Patients with SCD who also have hereditary persistence of fetal hemoglobin (HbF) are "protected" against episodes of sickle cell pain. Increased HbF interferes with HbS polymerization by diminishing the contact between adjacent HbS molecules. Hydroxyurea, which can induce the production of HbF, was tested as a therapeutic agent in SCD, with dramatic results. However, the decrease in episodes of sickle cell pain with hydroxyurea actually occurs before a detectable increase in HbF, suggesting other mechanisms of action. Three hypotheses for this early benefit have been suggested:

- hydroxyurea has been shown to improve RBC rheology, by increasing intracellular potassium and decreasing cellular dehydration;
- hydroxyurea decreases neutrophil counts;
- hydroxyurea affects nitric oxide metabolism; ingestion causes detectable levels of nitrosylhemoglobin within 30 minutes.[16]

Transfusion

In the Stroke Prevention Trial (STOP), children with abnormal intracranial Doppler study results were either observed or transfused regularly. Transfusions reduced the risk of stroke, ACS, and pain episodes.[17] Unfortunately, chronic transfusion therapy is associated with other complications such as alloimmunization and iron overload; therefore, it is not usually indicated for prevention of VOCs alone.

Cromolyn sodium

In a single-blind, crossover study in 17 patients using hydroxyurea pills and the mast cell stabilizer, chromolyn sodium as a nasal spray, each of the active drugs reduced the number of painful crises, but using both drugs together was even more effective.[18]

REASONS FOR FAILURE OF PAIN MANAGEMENT

There is fairly uniform agreement that the pain of an acute VOC is difficult to treat and is often not well-managed.[15] The majority of published studies are either retrospective, not randomized, or descriptive only. A recent Cochrane review found only 9 randomized controlled trials. Even these studies tended to be small, with poor allocation concealment. No treatment studied to date is capable of totally relieving acute sickle cell pain in all patients.[19]

The pain of a VOC involves activation of multiple inflammatory pathways. Subjectively, patients who suffer this pain describe it as extremely disagreeable. Some patients choose adjectives such as aching, pounding, beating, deep and sickening, and describe high levels of pain intensity.[20] Often patients who present with a VOC have waited for several days and have tried weaker analgesics (eg, acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], codeine). In a study of 263 admissions of children aged 5-19 years the onset of pain was, on average 4.5 days prior to their admission to hospital.[21]

Pharmacokinetic factors

Animal and clinical research suggest that pharmacokinetics of opioid drugs may be modified in SCD patients, with some individuals tolerating high doses of opioids without adequate pain relief. In a retrospective review of patients who used patient-controlled analgesia (PCA) with morphine for post-operative pain after laparoscopic cholecystectomy, SCD patients had a total consumption of morphine more than double that of nonSCD patients. The SCD patients had higher visual analogue pain scores (VAS) at 24 hr after surgery, used more adjuvant analgesics, and continued using PCA pumps longer.[22]

Dampier et al measured morphine clearance in 18 patients with SCD and found a wide range of values (from 6.2 to 59.1 mL/min/kg). Clearance decreased with increasing age and those patients with adverse side effects from opioids were those with the lowest clearance values.[23] In sickle cell transgenic mice, metabolism of morphine is increased by hepatic microsomes.[24]

Racial bias

Studies in the United States demonstrated that being Black or Hispanic is a risk factor for undertreatment of pain, whether that pain is caused by fractures, surgery, or cancer. Therefore, a patient who presents at a hospital, with pain due to a disease that is almost exclusively limited to one of these ethnic groups may receive inadequate care.[25]

Fear of addiction

Physician and nurse attitudes can contribute to the difficulties experienced by SCD patients in obtaining adequate pain relief. In one study, 53% of emergency room physicians and 23% of hematologists thought that > 20% of SCD patients were addicted to opioids. In fact, the real incidence of opioid addiction is only 0.2% - 2%. Another study reported that up to 63% of nurses believe that drug addiction frequently develops among SCD patients.[26] The prevalence of substance abuse is higher in health professionals than in SCD patients.[27]

Communication difficulties

Given previous experience with pain episodes and poor pain relief in the past, some SCD patients become demanding or express definite preferences for a particular opioid or dose of opioid. This leads to conflict with personnel and is often taken as proof of drug addiction.[26]

Systemic problems

Many authors have reported on the inadequacy of SCD pain management in hospital emergency departments. Problems include prolonged waiting before evaluation, disbelief by hospital personnel unfamiliar with SCD pain, and inadequate doses of drugs.[28] To alleviate these problems, several centres have set up day hospitals for SCD patients. They have demonstrated that with timely, aggressive treatment of VOCs, it is possible to dramatically reduce the time from presentation to acceptable pain relief, reduce the number of hospital admissions for VOC and, if hospitalization is necessary, reduce its duration.[29,30]

Probably, the most important part of the American Pain Society's *Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease*, is the emphasis on evaluation, both of the patient's pain *as reported by the patient* and of the patient's response to analgesics. In the acute episode, a simple measure of pain intensity such as the VAS should be chosen and used before pharmacological intervention, at peak effect, and at frequent intervals. In children, a VAS appropriate for age such as the Wong-Baker Faces rating scale or the Oucher Scale should be used.[15]

History, physical examination, and laboratory tests should be directed at eliminating medical complications that require a specific treatment. Parents of SCD children or the patients themselves can often say if the current episode of pain is typical for them or not. Initial management should aim for rapid relief of pain. There is no "one size fits all" recipe for the treatment of sickle cell pain. The choice of medications and the initial doses will be determined by what the patient has been taking at home, patient age and weight, what has previously been successful, and any known target organ damage (eg, renal or hepatic insufficiency). For example, if the patient has been taking acetaminophen at home, the same dosage can be continued and an opioid (eg, morphine intravenous [IV] 0.1 mg/kg), added. Intramuscular (IM) injections are avoided because of unpredictable absorption. In children, an IM injection can be as disturbing as the pain it is intended to treat. If a child learns that a report of pain will lead to an IM injection, he/she may deny the presence of pain. If a patient has been taking an opioid by mouth at home, without relief, then the first dose IV should be adjusted upward. If venous access is a problem, a subcutaneous port such as an Insufflon® can be used or the opioid can be given by mouth with an appropriate dose adjustment to compensate for the first pass effect in the liver. If a patient has had previous problems with morphine side effects, another opioid should be used. In general, mixed agonist-antagonists and partial agonists are not recommended for SCD pain. Meperidine is also contraindicated because of the risk of normeperidine accumulation with repeated doses. The half-life of meperidine is 3 hr, while the half-life of normeperidine, a central nervous system (CNS) stimulant, is 18 hr. The metabolite will accumulate, even in patients with normal renal function. Seizures occur in 1% to 12% of patients with SCD taking meperidine.[31]

A patient should be evaluated for pain relief and sedation 20 min after the first dose. If the patient is still suffering and not sedated, a second dose of opioid should be given, with a re-evaluation 20 min later. If the pain is >5 on the VAS, a third dose can be given.

There is no evidence that giving supplemental oxygen reduces the intensity or duration of the VOC; therefore, oxygen should be reserved for patients who are hypoxemic.[32] If a patient is dehydrated and unable to take fluids by mouth, IV fluids should be given. Since repeated renal infarctions can cause hyposthenuria, dehydration should be avoided in SCD patients, but there is no proof that giving IV fluids in excess of maintenance requirements shortens the duration of the VOC.[2]

SHOULD THE PATIENT BE ADMITTED TO HOSPITAL?

If the pain crisis does not "break,"after several appropriate doses of a strong opioid plus adjuvant drugs, admission to hospital will probably be required. Essentially, two methods of opioid dosing are suggested:

- IV opioids on a *fixed schedule* (usually q2h), with additional "rescue" doses of 25%-50% of the regular dose q1h as needed;
- IV opioids using a PCA pump, but the patient should first be titrated to pain relief, as described above.

There is no firm evidence that one method is superior to the other, if attention is paid to the patient's response and appropriate adjustments are made as necessary. In some patients, a combination of continuous infusion and intermittent boluses may be appropriate.

In addition to the opioid drugs, adjuvant analgesics (acetaminophen, NSAIDs) should be continued. Medications to counteract the side effects of opioids are necessary. The patient should be prescribed a laxative, an antihistamine, and an antiemetic. Because patients who present with rib or thoracic spine pain are at increased risk of developing ACS, incentive spirometry should be prescribed q2h while awake and oxygen saturation should be evaluated regularly.[33] Finally, because SCD pain can disappear as mysteriously as it appears, clinicians must be prepared to rapidly taper medications when the acute episode begins to wane.

DISCHARGE HOME

With the advent of the SCD day hospital, some patients who would have previously been admitted can be safely sent home. Adult patients, in particular, may wish to avoid a prolonged absence from work. If discharge to home is chosen, a prescription for an oral opioid equivalent to the dose that relieved the pain in the day centre or emergency department, plus NSAIDs or acetaminophen as appropriate, should be given. Proper follow up should be organized.

OTHER MODALITIES

Anti-inflammatory drugs

With the current understanding of the inflammatory basis of sickle cell pain, it is not surprising that both steroids and NSAIDs have been used to treat VOC pain. A study published in the *New England Journal of Medicine* in 1994 reported a significant difference in the duration of the painful episode with high-dose methylprednisolone. Unfortunately, there was a higher relapse rate in the steroid-treated children.[34]

Ketorolac has also been tested. Some studies demonstrate no difference in morphine consumption, while others do. It appears that ketorolac has a role, if the patient has not previously been taking anti-inflammatory drugs at home. Further, it may be more effective in the context of a crisis involving fewer pain sites.[35] Ketorolac is not recommended for > 5 days of continuous use and, as with all NSAIDs, it should be used with caution if renal function is diminished.

Nitric oxide

Nitric oxide (NO) has been used therapeutically to treat patients with respiratory failure caused by ACS. Since sickling occurs only when HbS is deoxygenated, decreasing the partial pressure of oxygen at which hemoglobin is 50% saturated with oxygen (p50) of HbS would be beneficial. Head et al demonstrated that the p50 of HbA is not changed by breathing NO 80 ppm for 45 minutes, but the p50 of HbS is decreased by 4.6 ±2.0 mm Hg.[36] A preliminary study of NO inhalation vs placebo for 4 hr in 20 patients with VOC was promising.[8]

Epidural

If there is poor pain control despite high-dose opioids and, especially, if there is excessive sedation, placement of an epidural is an option. One retrospective case series of 9 patients revealed favourable results.[37] There is also a case report of the successful use of an epidural for priapism in the context of an ongoing VOC.[38] Both these papers dealt with the pediatric age group, but the method should, if anything, be easier to implement in the adult setting.

CONCLUSION

In spite of new insights into the pathophysiology of sickle cell pain and some promising new preventive measures, patients with sickle cell disease still suffer from VOC and need aggressive, timely, individualized treatment with old-fashioned opioids.

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