

Sickle Cell Pain Crisis: Clinical Guidelines for the Use of Oxygen

A CASE REVIEW

Oxygen therapy may prevent the vaso-occlusion and disruption of tissue oxygenation that often lead to painful sickle cell disease crises.

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Defining Sickle Cell Disease and Its Economic Burden

Sickle cell disease (SCD) is the consequence of homozygosity for a single amino acid change in the β -globin chain that results in structurally abnormal hemoglobin S, or by compound heterozygosity for hemoglobin S and another β -globin chain abnormality, typically hemoglobin C or β -thalassemia. In addition, α -thalassemia is a modifier of the clinical manifestations of SCD. Hemoglobin SS (HbSS) and HbS beta-0 thalassemia present in a similar clinical manner and are commonly referred to together as sickle cell anemia (SCA), which is the most severe subtype of sickle cell disease.¹

HbSS represents a large proportion of SCD in the Americas, United Kingdom, and certain regions of Africa while higher proportions of hemoglobin SC are observed in Burkina

Faso and hemoglobin S β -thalassemia in Greece and India. As confirmed in the PUSH and Walk-PHaSST studies, HbSS, absence of co-inheriting alpha-thalassemia, and low hemoglobin F levels tend to be associated with more hemolysis, lower hemoglobin oxygen saturations, greater proportions of elevated tricuspid regurgitant jet velocity and brain natriuretic peptide, and increased left ventricular mass index.²

HbS polymerization in SCD results in a very complex cascade of processes that include:

- erythrocyte sickling
- intravascular hemolysis with release of cell-free hemoglobin
- increased adhesion of red cells to the endothelium of blood vessels
- activation of platelets
- production of inflammatory cytokines
- vascular occlusion.

A Brief History of Sickle Cell Disease

Sickle cell disease was first described by Herrick in 1910 in regard to a dental student who presented with pulmonary symptoms. He further described the “peculiar sickle-cell shape” of the red blood cells of the patient.³ In 1927, Hahn and Gillespie suggested that hypoxia caused the sickling of red blood cells by saturating a cell suspension with carbon dioxide to induce shape changes.⁴

In 1930, Scriver and Waugh confirmed this concept by inducing venous stasis in a finger using a rubber band.⁵ The stasis-induced hypoxia increased the proportion of sickle-shaped cells from approximately 15% to more than 95%. Linus Pauling, noting these studies, hypothesized in 1945 that sickle cell anemia might originate from an abnormality in the hemoglobin molecule.⁶ In 1949, Pauling demonstrated the differential migration of sickle versus normal hemoglobin by gel electrophoresis.⁷ Later that year, the autosomal recessive inheritance of the disease was described.⁶ About the same period, Watson, et al, theorized that the presence of fetal hemoglobin (HbF) could explain the longer period necessary for sickling of newborn red blood cells.⁸

Ingram proved thereafter that sickle hemoglobin (HbS) differed from normal hemoglobin A by a single amino acid, with glutamic acid replaced by valine.⁹ Other studies demonstrated the physical properties of HbS and the formation of intracellular polymers upon deoxygenation.¹⁰

Gelation consists of polymerization of hemoglobin S molecules into fibers and the alignment of these fibers to form a crystalline phase. The aligned fibers rigidify the red cell and produce the shape distortion referred to as sickling. Gelation may be induced by deoxygenation of hemoglobin S molecules.

Abnormal sickle-shaped red blood cells disrupt blood flow in capillaries, with the vaso-occlusion leading to distal tissue ischemia, ischemia-reperfusion injury, and concomitant inflammation.¹¹ SCD is characterized by chronic hemolysis resulting in chronic anemia (average Hgb concentration around 8 g/dl) and fatigue. Excruciating pain, hemolysis, acute chest syndrome, bone or joint necrosis, sepsis, stroke, acute cholecystitis, pulmonary hypertension, pulmonary embolus, bone marrow fat embolism, priapism, as well as renal failure, with increased morbidity and mortality, may be a result of vascular occlusion and disruption of tissue oxygenation (ie, the sickle cell “crisis”). Further, hemolysis plays a central role in the pathophysiology, contributing significantly to anemia, jaundice, vasculopathy, nitric oxide defi-

ciency, and inflammation. Vasculopathy of SCD has been implicated in the development of pulmonary hypertension, stroke, leg ulceration, and priapism, particularly associated with hemolytic severity.¹²

Demographics and Mortality

In children, splenic sequestration of the sickle-shaped red blood cells may result in splenic enlargement, profound anemia, infection due to lack of splenic function, and death before age 8.¹³ In this vulnerable population, SCA is responsible for significant morbidity and mortality. In fact, up to 16% of under-age-5 deaths that occur in West Africa may be attributed to sickle cell anemia.¹⁴ In the United States, among children and adults with SCA (ie, homozygous for sickle hemoglobin), the median age at death was 42 years for males and 48 years for females. Among those with sickle cell-hemoglobin C disease, the median age at death was 60 years for males and 68 years for females.

Among adults with SCD, 18% of the deaths occurred in patients with overt organ failure, predominantly renal, while 33% percent were clinically free of organ failure but died during an acute sickle cell crisis (of note, 78% reported pain, the chest syndrome, or both; 22% had stroke). In patients with SCA, the acute chest syndrome, renal failure, seizures, a baseline white cell count above 15,000 cells per cubic millimeter, and a low level of fetal hemoglobin were associated with an increased risk of early death. In those with SCA, 50% survived beyond the 5th decade. A large proportion of those who died had no overt chronic organ failure but did pass during an acute episode of pain, chest syndrome, or stroke.^{15,16}

An estimated 300,000 children are born each year with SCA, with two thirds of them in Africa.¹⁷ In the US, SCD occurs among about 1 out of every 365 black or African American births, and about 1 out of every 16,300 Hispanic American births. About 1 in 13 Black or African American babies is born with sickle cell trait (SCT). Population estimates range from 104,000 to 138,900 based on birth-cohort disease prevalence, but from 72,000 to 98,000 when corrected for early mortality.¹⁸

Public Health

Therefore, several global agencies, including the UN and World Health Organization, have recognized SCD as a public health issue.^{19,20} Looking at the total cost of care for a population of both children and adults with SCD, nationwide hospitalization costs are substantial, at about a half-billion dollars per year. It is likely that these calculations are a marked underestimate. Extensive emergency room and non-hospitalization-based treatment, as well as other social

costs, must also be considered, making the actual financial burden to society much greater.²¹

According to Odame, in low-income countries, these challenges lead to loss of days off school and work, which further aggravates the socioeconomic constraints on the majority of individuals with the disease. “Thus, improved quality of care would significantly impact patient outcomes, maximizing their educational achievement, and enhancing their socioeconomic productivity.”²² Similarly, in the United States, the medical costs do not begin to capture the economic burden. Many adults with sickle-cell disease are disabled to some degree, and many have varying organ damage, making it difficult for them to work. Family members often wind up as caregivers, with a rippling outward of the economic burden.

Treatment Approaches Targeting Root Causes

Long-term treatment for SCD may include hydroxyurea, which increases production of hemoglobin F, thereby reducing the incidence of sickling. Hydroxyurea has been shown to decrease the rate of painful crises in some patients, related to the size of the HbF treatment response.²³

In November 2019, the FDA approved two transformative treatments for sickle cell disease: Oxbryta and Adakveo. Oxbryta (voxelotor) increases the affinity of hemoglobin for oxygen, resulting in a decreased concentration of deoxygenated sickle hemoglobin, thereby inhibiting polymerization, reducing the amount of red blood cell destruction, and increasing hemoglobin levels.^{24,25} In clinical trials, hemoglobin response occurred as early as two weeks and in some cases returned to near normal levels. Clinical trial findings showed that Oxbryta raised hemoglobin levels in 51% of the 90 patients treated with Oxbryta at a high dose of 1500 mg daily, compared with 6.5% of those on placebo.^{26,27} Hemoglobin levels rose over the 24 weeks to a mean of 9.8 g/dL in the patients given Oxbryta at that high dose, and to 8.9 g/dL in 92 patients treated with a lower 900 mg daily study dose. At high dose, Oxbryta’s use also lowered levels of two established biomarkers of hemolysis: reticulocytes (by 19.9%) and bilirubin (by 29.1%). Oxbryta is administered orally, once daily for patients 12 years and older.

Adakveo (crizanlizumab-tmca) is a monoclonal antibody targeted against the P-selectin glycoprotein that is expressed on activated endothelial cells and platelets.²⁸ Although polymerization of deoxygenated HbS is the primary event in the pathophysiology of SCD, vaso-occlusion is caused by the adhesion of sickle erythrocytes and leukocytes to the endothelium, which results in vascular obstruction and tissue ischemia. The degree of sickle erythrocyte adhesion correlates with vaso-occlusion and increased severity of disease.²⁹

P-selectin that is expressed on the surface of the endothelium mediates abnormal rolling and static adhesion of sickle erythrocytes to the vessel surface in vitro. Translocation of endothelial P-selectin to the cell surface results in the prompt adhesion of sickle erythrocytes to vessels and the development of vascular occlusion in transgenic mice with sickle cell disease.³⁰ In clinical trials, patients treated with Adakveo experienced fewer health care visits for vaso-occlusive crisis annually (median annual rate of 1.63 visits), compared to patients who received a placebo (median annual rate of 2.98 visits). In addition, 36% of patients who received Adakveo did not experience vaso-occlusive crisis during the study, and it delayed the time that patients first experienced vaso-occlusive crisis after starting treatment from 1.4 months to 4.1 months.³¹ Adakveo is administered, in patients 16 years and older, by IV infusion, over 30 minutes, at weeks 0, 2, and then every 4 weeks.

Curative Therapies

Curative therapies for SCD may include:

- hematopoietic stem cell transplantation (allogenic, related matched, allogenic unrelated donor, and haploidentical)
- genomic therapies using lentiviral vectors for gene therapy and gene editing, or
- reprogrammed stem cells.

These therapies are largely in use, with some gene therapies undergoing clinical trials. Costs and availability of these new therapies, however, limit their global application, even in high-income countries.

Preventing a Crisis

The focus after confirming SCD is on prevention and reducing crisis frequency. Preventive *crisis* approaches may include:

- oxygen therapy during sleep
- prophylactic administration of penicillin in childhood
- avoiding temperature extremes
- good hydration
- antimalaria prophylaxis
- pain medication
- folic acid supplementation
- regular blood transfusion combined with iron-chelation therapy where indicated
- prop open doors and/or windows to improve indoor air circulation during sleep.

Oxygen as a Treatment: What the Literature States

At the time of this writing, a PubMed search did not reveal any articles that have evaluated the use of oxygen to

prevent sickle cell crisis. Yet, it is well established in the literature that nocturnal hypoxemia is a prelude to vaso-occlusive crisis (VOC).³²⁻³⁴ Vascular occlusion and disruption of tissue oxygenation are a prequel to excruciating pain, chest splinting with further hypoxemia, acute chest syndrome, hemolysis, distal tissue ischemia, ischemia-reperfusion injury, concomitant inflammation, resulting in organ damage and other complications with increased morbidity and mortality. The author believes that oxygen therapy is a simple yet cost-effective way to prevent VOC and its attendant morbidity and mortality.

According to an editorial hypothesis by Eaton (1976), et al, *“The capillary transit time is of the order of 1 second, and saturation of the cellular hemoglobin on leaving the capillary is less than 75%. The cell remains in the venous return at relatively constant saturation for varying lengths of time, averaging about 15 seconds, before reaching the lungs where it is rapidly reoxygenated. Oxygenation in the lungs produces complete intracellular degelation, and because of the high arterial PH, the hemoglobin remains ungelled until the cell reaches the capillary. From the time the cell enters the capillary the oxygen saturation decreases continuously. As a result, the solubility of the intracellular hemoglobin continuously decreases, the supersaturation ratio increases, and the delay time for sickling decreases. If the delay time becomes shorter than the time required for the cell to escape the capillary, sickling will occur inside the capillary, with the possibility of vaso-occlusion. On the other hand, the delay time may not become so short, and the cell will reach the venous system before sickling has begun....”*

“Such crises occur as a result of sickling within capillaries and consequent blockage of the microcirculation by the rigidified cells.... Thus, a crisis occurs when the delay times are shortened enough or the capillary transit times lengthened enough to increase significantly this probability. Acidosis, dehydration, and fever, as well as oxygen deprivation, which reduce markedly the delay time, have been implicated as factors that can precipitate a crisis. Tissue damage is more likely in organs where the delay times are short, or where the capillary transit times are long.... In contrast, myocardial damage from infarction is infrequent, even though the capillary oxygen tension is low, presumably because of the rapid blood flow in the coronary circulation.”³⁵

Eaton, et al, further stated: *“The rates of oxygen binding and dissociation are so fast (milliseconds) that the fractional saturation of normal Hb during the ~1-second duration of blood flow through the microcirculation is determined only by the oxygen pressure.”³⁶*

Vaso-occlusive Crisis and Triggers

SCD is characterized by chronic hemolytic anemia as well as recurrent and extremely painful VOC, the latter of which

may lead to acute chest syndrome, avascular necrosis, and organ damage. The VOC phenomenon is considered to occur as the result of capillary blockade at low oxygen saturations, followed by an activation of inflammation and adhesion phenomena further increasing the damage. These painful crises often require medical attention and hospitalization.

Pathophysiological triggers that may contribute to VOC include: hypoxia, daytime exertion, waking up earlier with a shortened duration of sleep, daytime exertion, stress, fatigue, exercise, exposure to cold, ingestion of alcohol, airline travel, altitude that exceeds 2,000 ft, infection, malaria, or pregnancy.

In patients with sickle cell disease, VOC tends to occur most often at night, due to the relative hypoxia as a result of varying degrees of sleep apnea, or due to a trigger the patient may have been exposed to during the day. During sleep, minimum oxygen saturation is significantly lower. Castele, et al, performed 5 full-night and 7 daytime studies to examine this further.³² According to the reported findings: *“For all patients the mean (+/- SEM) of the median oxygenation values was 93.3% +/- 0.4% during wakefulness and 91.4% +/- 0.8% during sleep. During wakefulness the lowest saturation was 90% +/- 0.5%; during sleep there was a fall in the lowest oxygen saturation to 86.5% +/- 0.9%. In all patients a fall in oxygen saturation was associated with a decrease in respiratory depth without a change in respiratory frequency.”*

- This nocturnal hypoxemia is a prelude to VOC. Another study found that low nocturnal oxygen saturation was “highly significantly associated with a higher rate of painful crisis.” Other triggers of crises that involve varying degrees of tissue hypoxia may include exercise, fatigue, infection, and exposure to cold. Exposure to cold results in vasoconstriction and delayed transit time, which can trigger a crisis.
- Subsequent to commercial airline flights, patients with SCD are known to experience complications such as bone pain, splenic infarction, osteonecrosis (avascular necrosis) of the hip, and, in some cases, prolonged crisis resulting in death (anecdotal report). These complications have been linked to prolonged oxygen desaturation at high altitudes, with oxygen saturations measured as low as 77%.³³⁻³⁹

Prevention — Use of Oxygen

Despite the crucial role that hypoxia plays in the pathophysiology of red blood cell sickling and VOC, there has been no published article in the medical literature to the author’s knowledge on the use of oxygen to prevent and manage

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sickle cell crisis, thereby preventing organ damage.

In the past decade, the advent of battery-powered portable oxygen concentrators, which generate oxygen from ambient air, has freed people from a need to have sources to supply and refill oxygen cylinders.

At the author’s pain clinic in California, over the past 15 years, oxygen by nasal canula, prior to sleep or at bedtime, has been prescribed to 20 patients with SCD with a resultant decrease by 85% to 90% in the frequency of their VOCs. This oxygen therapy has been simple but transformed their lives, according to patient reports. There has been not a single patient who applied oxygen at bedtime who woke up in a crisis. Patients who did experience a crisis were those who forgot to apply oxygen in the presence of another vaso-occlusive trigger (eg, daytime exertion) or patients with an underlying infection. Other patients had daytime crises as a result of exposure to triggers such as cold, dehydration, infection, etc. In the author’s clinical experience, upon onset of a crisis, oxygen administration after the first few minutes is no longer preventive but may be part of an abortive protocol.

The author recommends that oxygen be administered by nasal canula at a rate of 1.5 to 2 liters/minute, delivered by a home or portable oxygen concentrator, to maintain an oxygen saturation of > 95%. Oxygen should also be administered for the duration of any airline flight.

Oxygen may be obtained from oxygen cylinders or, more conveniently, and with less maintenance, portable oxygen concentrators such as the SeQual Eclipse, Inogen, Respironics, AirSep, and others, that extract oxygen from ambient air. Oxygen should be provided in continuous flow from a tank or concentrator. In the author’s experience, pulse dose oxygen delivery triggered by inspiratory effort does not provide adequate oxygen delivery and should not be used.

It is the author’s opinion that, as a matter of public policy, commercial airlines should be mandated to provide medical oxygen to passengers who require it. Continuous flow oxygen could be provided from a piped oxygen supply, an FAA-approved oxygen tank, or concentrator. Concentrators that only provide pulse dose oxygen delivery triggered by inspiratory effort do not provide adequate oxygen delivery for commercial airline travel are not recommended.

Management — Oxygen and Parenteral NSAIDs and Opioids Management at Home

Management of sickle cell crisis requires immediate termination; the longer the crisis goes on, the greater the potential organ damage and inflammation resulting from ischemia. Prolonged severe pain crises perpetuate a vicious cycle with chest-splinting from pain, increased hypoxia leading to increased vaso-occlusion, increased inflammation, and increased pain. Once a patient enters a full-blown crisis, administration of oxygen alone will not abort it, and if the pain crisis is not controlled within the first 30 minutes, it will progress and the patient will require hospitalization.

In the author’s clinical experience, termination of a sickle cell pain crisis should be achieved at home within the first 15 to 30 minutes of the onset of the crisis. This may be done by immediate administration of oxygen, intramuscular injection of anti-inflammatory medications such as the NSAID ketorolac (in the absence of any contraindications), and treatment and elimination of pain using parenteral opioids such as hydromorphone, morphine, or fentanyl by intramuscular (IM) or subcutaneous (SQ) injection.

Patients and their relatives or caregivers should have these medications on hand similar to an EpiPen and be trained in the administration of these medications by the IM or SQ route, at home as well as the use of a reversal agent such as intra-nasal naloxone. Patients may self-administer these medications as long as they live with a relative or caregiver who can monitor them.

The patient with their caregiver/family should be dispensed a unit dose of the anti-inflammatory and opioid medication that the patient has previously received and tolerated in a monitored medical setting. For example, if a patient has previously tolerated 1 mg Dilaudid (hydromorphone) and 60 mg ketorolac, in a medical setting, then 1 mg Dilaudid unit dose in addition to 60 mg ketorolac in a separate syringe, could be provided to the patient. The family should also be taught to use low-cost finger pulse oximeters with alarm to monitor the patient and be provided with and taught to administer naloxone nasal spray for reversal of any opioid overdose. Should a unit dose of the parenteral medi-

cation fail to stop the crisis, the patient should be advised to proceed to a medical setting. When such measures are instituted at home within the first 15 to 30 minutes of a crisis, the crisis is likely to end and hospitalization may be avoided in the vast majority of patients.

Note: Reliance on oral analgesic medication alone to abort a crisis at home may transform a crisis that should last minutes into one that may last weeks and result in more organ damage.

Management in the Medical Setting

Should the crisis fail to resolve or there are additional complications, including fever, chills, shortness of breath, increased redness of the urine signifying hemolysis, chest or abdominal pain, the patient should be advised to seek immediate medical attention. In the medical clinic or hospital, the patient should be evaluated for causes of pain other than a VOC. If the VOC pain is atypical, the medical team should evaluate for other possible etiologies of pain. A history and physical examination and diagnostic tests should be performed. These should include a complete blood count (CBC) with differential, reticulocyte count, serial CBC, chest x-ray or CT scan, and in patients with a temperature > 101.3°F (38.5°C), blood culture and urine culture where urinary tract infection is suspected, and blood smears for malarial parasites, where malaria is suspected.⁴⁰

Pain and inflammation control by the parenteral route in combination with oxygen therapy must be rapidly initiated within the first 30 minutes. Guidelines for Pain Control as published by the National Heart, Lung and Blood Institute (NHLBI) 2014 report on "Evidence Based Management of Sickle Cell Disease" include the following:⁴⁰⁻⁴²

- Calculate the parenteral (IV or SC) opioid dose based on total daily short-acting opioid dose currently being taken at home to manage the VOC.
- Administer parenteral opioids using the subcutaneous route when intravenous access is difficult.
- Reassess pain and re-administer opioids, if necessary, for continued severe pain every 15 to 30 minutes until pain is under control per patient report.
- Maintain or consider escalation of the dose by 25% until pain is controlled.
- Reassess after each dose for pain relief and side effects.

Additional recommendations from NHLBI:

- To reduce the risk of acute chest syndrome in adults and children hospitalized for a VOC, encourage use of incentive spirometry while awake.
- In euvoletic adults and children with SCD and a VOC who are unable to drink fluids, provide intrave-

nous hydration at no more than maintenance rate to avoid over-hydration.

- In adults and children with SCD and a VOC being treated with opioids, monitor for excessive sedation by measuring sedation with an objective sedation scale and oxygenation levels.
- Gradually titrate down parenteral opioids as VOC resolves.
- In adults and children with SCD and a VOC, do not administer a blood transfusion unless there are other indications for transfusion, such as:
 - simple transfusion for symptomatic ACS combined with a decreased Hb of 1g/dl below the baseline
 - exchange transfusion for symptomatic severe ACS (as defined by an oxygen saturation less than 90% despite supplemental oxygen)
 - simple transfusion for acute splenic sequestration plus severe anemia
 - simple or exchange blood transfusion for stroke

Subsequent treatment in patients with fever should include intravenous antibiotics that provide coverage against community acquired pneumonia and gram-negative enteric organisms, treatment for malaria as indicated, as well as simple or exchange blood transfusion where indicated. Assess patients whose hemoglobin concentration is 2 g/dL or more below their baseline (or less than 6 g/dL when the baseline is unknown) for acute splenic sequestration, an aplastic episode, a delayed hemolytic transfusion reaction, ACS, and infection. Manage aplastic events with immediate red blood cell transfusion aimed at restoring the hemoglobin to a safe (not necessarily baseline) value. Isolation of hospitalized patients (droplet precautions) is required to prevent spread of the parvovirus B19 to pregnant women and others with SCD or compromised immunity. In people with hypovolemia due to severe acute splenic sequestration, immediately provide IV fluid resuscitation.

Discussion and Conclusion

In the author's clinical experience with SCD patients, there is no other treatment that is widely available or comparable to oxygen and its ability to rapidly transform lives. The cost of just one hospitalization may be equivalent to the price of a home or portable oxygen concentrator. Costs of concentrators vary from \$500 for a basic home concentrator unit to \$2,500 for flight-certified portable concentrator inclusive of batteries.

Vascular occlusion and disruption of tissue oxygenation can result in severe pain, acute chest syndrome, avascular necrosis, and organ damage. The most frequent occurrence

PRACTICAL TAKEAWAYS

- Sickle cell disease is characterized by chronic hemolysis, resulting in chronic anemia and fatigue; it can cause severe pain, acute chest syndrome, avascular necrosis, and organ damage.
- Sickle cell crises can be triggered by daytime exertion, shortened duration of sleep, stress, fatigue, exercise, exposure to cold, ingestion of alcohol, airline travel, altitude that exceeds 2,000 ft, infection, and malaria.
- Oxygen therapy, delivered during sleep and/or during air travel, may help to prevent a sickle cell crisis, especially after the patient has been exposed to a VOC trigger. A continuous flow oxygen at a rate of 1.5 to 2 liters per minute is advised to maintain oxygen saturation > 95%.
- Sickle cell crises may be managed at home if treatment is provided in the first 15 to 30 minutes and should include immediate administration of oxygen, intramuscular injection of anti-inflammatory medications such as ketorolac, and treatment and elimination of pain using parenteral opioids such as intramuscular or subcutaneous injection of hydromorphone, fentanyl, or morphine.

of painful crisis is during sleep when there is a decrease in oxygen saturation. Prevention of most episodes of sickle cell crisis, and thus organ damage, may be rapidly achieved by administration of oxygen at bedtime or prior to sleep. Oxygen should be administered prior to sleep when the individual is exposed to a trigger.

The author recommends that oxygen therapy should be considered as the standard of care and public health policy should be directed to providing oxygen therapy to all individuals with sickle cell disease. •

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Dr. Omoigui holds US patents for the process of continuous non-invasive hemometry (measurement of hemoglobin) and the audio-capnometer monitor.

**The treatment recommendations made throughout are based on the author's clinical experience unless noted otherwise.*

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SCD OVERVIEW CONTINUED FROM PAGE 28

function. “We know that both peripheral and central sensitivity occurs in SCD. But it’s hard to show exactly what’s going on,” said Dr. Curtis. “We can’t prove with this study that central sensitization is causing pain in SCD, but it’s worth looking at in future studies.”

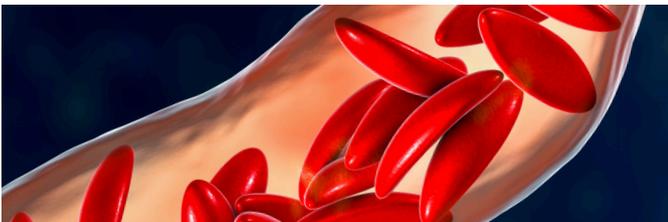
Emotional Components

It’s also important to note that participating patients with neuropathic pain also reported more anxiety and sleep difficulties. Dr. Curtis reinforced that, “with pain, the emotional component is important—memories of pain, how pain affects daily life, and so on... People with central sensitization have more depression and anxiety. And anxiety makes pain worse.” This creates a feedback loop than can be difficult to break. Frequent hospitalization and other factors can also add to the burden of the disease, whether SCD or another chronic pain condition.

Overall, said Dr. Curtis, “If we can show what’s causing the pain, it will be easier to make treatment decisions. If a patient has signs of neuropathic pain, don’t let the fact that the patient is being treated for nociceptive pain stop you from using treatments for neuropathic pain as well.” She also stressed the importance of ensuring that patients’ mental health issues are being addressed as, like many chronic pain conditions, “SCD is really a biopsychosocial disease.” •

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 RESEARCH INSIGHTS

What about L-glutamine for SCD Crises?

Reported by Avery Hurt

As shared in the case report herein, there is not much evidence available regarding therapies that may help to slow or interfere with the natural progression of a sickle cell crisis, which is the most common reason for hospitalization of patients with sickle cell disease (SCD). Hydroxyurea has been used for many years to reduce the frequency of such crises and, until recently, was the only medication shown to improve VOC in patients with the sickle cell anemia (SCA) subtype of SCD.^{2,3} In 2017, FDA approved L-glutamine (Endari) for patients ages 5 years and older to reduce severe complications in other genotypes of SCD as well.

To determine the state of the evidence for the use of L-glutamine in the prevention of vaso-occlusive crisis (VOC) and associated pain in patients with SCD, researchers from the University of Buffalo in New York conducted a systematic review.¹ After elimination of studies that did not meet inclusion criteria, only three trials remained, each under the same lead author.²⁻⁴

In the first,² patients treated with L-glutamine exhibited an increase in levels of the pyridine nucleotides, NAD⁺ and its reduced form NADH, which are thought to be involved in regulating and preventing oxidative damage in red blood cells. Significant improvements were also noted in “subjective clinical outcomes” such as energy levels and levels of chronic pain. However, this 1998 pilot was a non-randomized, single center study and included only 7 patients. The second study,³ published in 2014, compared L-glutamine to placebo in reduction of sickle cell pain crises. This study was a randomized, double-blind, placebo controlled multicenter study. It found a non-significant reduction in the number of pain crises compared with placebo. However, it did show a significant reduction in hospitalizations among the patients treated with L-glutamine. The third,⁴ a randomized, double-blind, placebo controlled, multicenter, 48-week trial, was published in 2018. It examined the effects of L-glutamine in reducing the incidence of pain crises in SCD patients, ultimately demonstrating a significant reduction in pain crises among patients receiving L-glutamine.

Overall, the reviewers concluded that there is a lack of high-quality evidence to support the use of L-glutamine for reduction in the frequency of VOC pain episodes. Nonetheless, the evidence that does exist, they argued, supports continued use of the medication as an option to help reduce pain crises and related hospitalizations, especially among those patients those unable to utilize hydroxyurea or in addition to hydroxyurea.

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New Strategies in Treating Pediatric SCD

Reported by Elizabeth Michaelson Monaghan

In a 5-year study of more than 200 children SCD, “simple and likely reproducible” interventions lowered pain, hospital admissions, length of hospital stays, and readmission rates at Yale New Haven Children’s Hospital among patients experiencing VOC.⁵ The researchers established multiple quality improvement initiatives, including, order sets for hospital admissions in patients’ medical records; daily schedules and guidelines for hospitalized patients; patient education on non-drug pain management strategies, SCD, and coping techniques; and individual home action plans for pain management, which were also available in patients’ records.

Originally, results were disappointing: “After the first year of interventions, our analyses pre- and post-interventions showed no change in admissions or hospital days,” co-author Farzana Pashankar, MD, MRCP, associate professor of pediatrics at Yale School of Medicine, told *PPM*. “This was a surprise, and it made us go back to the drawing board.”

After further analyses, “We found that a small subgroup of patients (only 6% of the total cohort)” were admitted to the hospital four or more times a year. These high-use patients “accounted for almost 61% of total admissions and hospital days,” Dr. Pashankar explained. Identified key risk factors were older age and underlying mental health conditions.

High-use patients began receiving extra support, which included pain plan reviews and updates every 1 to 2 months, as well as information about and prescriptions for hydroxyurea. High-use patients also met with a social worker or psychologist at every visit, during which biofeedback techniques for relaxation and pain management were taught. The team also continuously monitored and supported the cohort to identify patients at risk of becoming high risk, and introduced a pain order set in the pediatric emergency department.

By the time the study concluded, the percentage of SCD patients with VOC admitted to the hospital dropped from 25.4 to 13.3; number of hospital admissions decreased by nearly 55%, and the total number of days that patients spent in the hospital plummeted from 59.6 to 23.2 days a month, a 61% decrease. Length of hospital stays declined from nearly 5 to just under 4 days, on average. And within 19 months of program’s start, the 30-day readmission rate had dipped from 33.9 to 19.4%. Finally, the number of high-use patients more than halved, from 6% to less than 3%. Dr. Pashankar’s team is now looking to see if ER visits among the group decreased as well.

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