Pain Crises in Sickle Cell Disease: A Clinical Guide to Prevention and Treatment: How to Manage an Acute Pain Crisis in Sickle Cell Disease: Practical Recommendations

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How to Manage an Acute Pain Crisis in Sickle Cell Disease: Practical Recommendations

Oxygen therapy and rapid treatment should be the standard of care for preventing and treating pain in a sickle cell crisis. A pathophysiologic and clinical overview for in-hospital and remote telemedicine situations.

By Sota Omoigui, MD (/author/34894/omoigui)

INTRODUCTION TO SICKLE CELL DISEASE, INFLAMMATION, AND PAIN PATHWAYS

Defining Sickle Cell Disease

Sickle cell disease (SCD) is the consequence of homozygosity for a single amino acid change in the beta-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 beta-0 thalassemia. 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 SCD.1,2

The sickling process causes secondary changes in cell shape, size, cation and water content, and membrane structure that contribute to the impairment of intrinsic cell deformability.3 A loss of deformability causes a rise in blood viscosity. Whole blood viscosity is dependent on the number (and volume) of erythrocytes in the blood, and is thus linearly related to hematocrit.4 Thus, in people with SCD, the rheological defect is partially compensated by a low hematocrit, which moderates the rise in whole-blood viscosity, and by a rise in cardiac output, which increases capillary flow velocity. Sickle cell patients with high blood viscosity usually have more frequent vaso-occlusive crises and impaired oxygen delivery than those with low blood viscosity.5

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, and ultimately,
vascular occlusion

Abnormal sickle-shaped red blood cells disrupt blood flow in capillaries, with the vaso-occlusion leading to distal tissue ischemia and ischemia-reperfusion injury,defined as tissue damage that occurs as the result of the interruption of the blood supply causing hypoxia, followed by resolution and consequent reperfusion of the tissue.6 Cells undergoing cell death mechanisms present cytosolic calcium accumulation, mitochondrial dysfunction, and cell swelling, and release major inflammatory damage-associated molecular patterns (DAMPs), such as ATP, heme, high-mobility group box 1 (HMGB1) and heat shock proteins, which are increased in SCD.

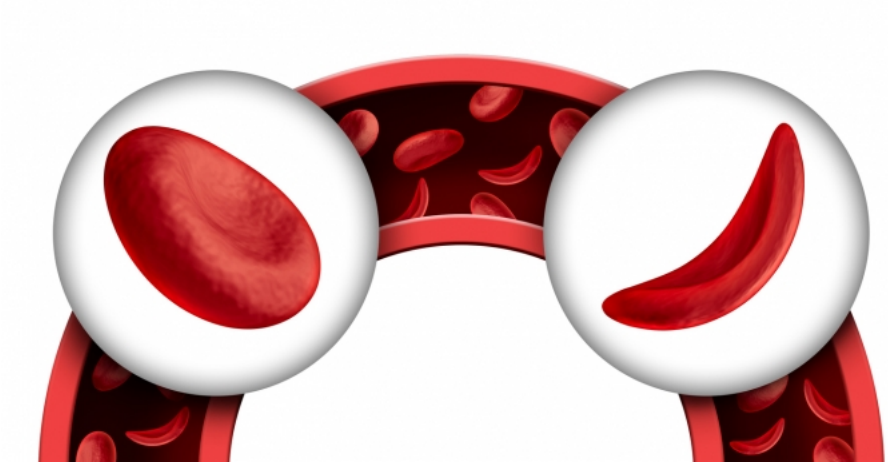
These DAMPs can promote multiple inflammatory pathways, including neutrophil extracellular trap (NET) formation and inflammasome assembly. When blood flow is restored following disruption of vaso-occlusion, the tissue is then reperfused and the damaged tissues are reoxygenated, paradoxically causing further damage, due to the production of reactive oxygen species (ROS) and calcium overload. An effect of ischemia-reperfusion injury may be the activation of invariant natural killer T (iNKT) cells, which can induce pulmonary inflammation by triggering IFN-γ and INF-γ-inducible chemokines.7

Inflammatory Processes in Sickle Cell Disease, Anemia

Sickle cell anemia is fundamentally an inflammatory state, with activation of the endothelium, through proximate effects of ischemia-reperfusion injury, endothelium-derived NO depletion by cell-free hemoglobin, endothelial NOS uncoupling and consumption of L-arginine (the substrate for NOS) by arginase released during hemolysis and interactions/adhesion of sickle RBCs and leukocytes with the vessel wall.Cell-free heme also induces microvascular endothelial barrier dysfunction in the lung by inducing necrotic death.

Once activated, the endothelium produces and releases a number of potent inflammatory molecules, including IL-1β, IL-8, IL-6, IL-1α, GM-CSF, plasminogen activator inhibitor (PAI)-1, MCP-1, and RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted), which contribute to the inflammatory milieu in SCD. Activated endothelium also expresses adhesion molecules such as VCAM-1, ICAM-1, E-selectin, and P-selectin, which are important for red cell, leukocyte, and platelet tethering and adhesion. Endothelin-B receptor-mediated signaling in leukocyte adhesion to the endothelium has also been shown in SCD.7

Surrogate markers of endothelial dysfunction and inflammation, including pro-inflammatory cytokines (eg, interleukin [IL]1β, IL6, IL8, tumor necrosis factor [TNF]-α. and interferon [INF]-γ) and markers of endothelial activation (eg, endothelin [ET]-1, adhesion molecules, and selectins), are elevated at baseline and during complications.8



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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 can occur with sickle cell inflammatory processes and crises. (Image: iStock)

In addition to the inflammatory molecules known to be elevated during steady-state in SCD, some of these are further elevated during acute vaso-occlusive episodes (VOEs), including the cytokines CD40L, IL-6, and IL-18, and chemokine IL-8 (CXCL8). The acute phase proteins, substance P, C-reactive protein, and pentraxin-3, and the lipid chemoattractant, leukotriene B4 (LTB4), are also further increased during VOE.

In contrast, alterations in anti-inflammatory molecules may occur in VOE, with IL-10 observed to be significantly decreased in VOE compared to levels in steady-state SCD individuals,9 while IL-4 has been reported as increased in SCD VOE, possibly reflecting shifts in CD4+:CD8+ T cell ratios.7

In the initiation of the acute painful vaso-occlusive episodes that are characteristic of SCD, inflammatory processes act as key components. Complications of the disease including autosplenectomy, acute chest syndrome, pulmonary hypertension, leg ulcers, nephropathy, and stroke. Abnormally high plasma values of IL-6 have been reported in SCD patients at a steady state. Both IL-6 and C reactive protein are elevated during VOC. Median IL-6 level in sputum is dramatically elevated during acute chest syndrome(ACS) compared with non-ACS patients. In patients who had concomitant sputum and plasma collections during ACS, median IL-6 level was > 150-fold higher in sputum (6892 pg/mL) than in plasma (42 pg/mL). Thus massive production of IL-6 in the lungs by activated endothelial cells or other inflammatory cells is involved in ACS pathophysiology, by inducing local inflammation independently of systemic inflammation.10

Acute chest syndrome may show elevated IL6 levels and may be treated with IL6 receptor antibodies such as tocilizumab. Tocilizumab (TCZ) is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R. Dramatic improvement has been reported after tocilizumab administration in a child and an adult patient with SCD and ACS related to SARS-CoV-2.11

Clinical Manifestations and Symptoms of Sickle Cell Disease

Sickle cell disease is characterized by chronic hemolysis resulting in chronic anemia (average Hgb concentration around 8 g/dl) and fatigue. The following SCD symptoms can occur as the result of vascular occlusion and disruption of tissue oxygenation (ie, the sickle cell "crisis":

The Sickle Cell Crisis may include: 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.

Further, hemolysis plays a central role in the pathophysiology, contributing significantly to anemia, jaundice, vasculopathy, nitric oxide deficiency, and inflammation.

Vasculopathy of SCD has been implicated in the development of pulmonary hypertension, stroke, leg ulceration, and priapism, particularly associated with hemolytic severity.12,13

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 7 years.14 In this vulnerable population, sickle cell anemia (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 a stroke).

In patients with SCA, 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.15,16

Pain Pathways in Sickle Cell Anemia: A Brief Review

In 2002, the author published a Law of Pain stating that: "The origin of all pain is inflammation and the inflammatory response."17-19 Inflammation occurs when there is infection or tissue injury. In sickle cell crisis, vaso-occlusion leads to distal tissue ischemia as well as ischemia-reperfusion injury. A variety of inflammatory mediators are generated by tissue and organ injury. These include substances produced by damaged tissue, substances of vascular origin as well as substances released by nerve fibers themselves, sympathetic fibers, and various immune cells.

The inflammatory mediators activate local pain receptors and nerve terminals and produce hypersensitivity in the area of injury. Activity of the mediators results in the excitation of pain receptors in the skin, ligaments, muscle, nerves, and joints. Excitation of these pain receptors stimulates the specialized nerves eg, C fibers and A-delta fibers that carry pain impulses to the spinal cord and brain. Subsequent to tissue injury, the expression of sodium channels in nerve fibers is altered significantly, thus leading to abnormal excitability in the sensory neurons.

Nerve impulses arriving in the spinal cord stimulate the release of inflammatory protein Substance P. The presence of Substance P and other inflammatory proteins such as calcitonin gene-related peptide (CGRP), neurokinin A, and vasoactive intestinal peptide removes magnesium-induced inhibition and enables excitatory inflammatory proteins such as glutamate and aspartate to activate specialized spinal cord NMDA receptors. This results in magnification of all nerve traffic and pain stimuli that arrive in the spinal cord from the periphery. Constant C-fiber nerve stimulation to transmission pathways in the spinal cord results in even more release of inflammatory mediators, but this time within the spinal cord.

Inflammation causes increased production of the enzyme cyclooxygenase-2 (Cox-2) and 5-lipoxygenase (5-LOX), leading to the release of chemical mediators both in the area of injury and in the spinal cord. Widespread induction of Cox-2 expression in spinal cord neurons and in other regions of the central nervous system elevates inflammatory mediator prostaglandin E2 (PGE2) levels in the cerebrospinal fluid. The major inducer of central Cox-2 upregulation is inflammatory mediator interleukin-1 in the CNS. Abnormal development of sensory-sympathetic connections follows nerve injury and contributes to the hyperalgesia (abnormally severe pain) and allodynia (pain due to normally innocuous stimuli). These abnormal connections between sympathetic and sensory neurons arise in part due to sprouting of sympathetic axons. Research has have shown that sympathetic axons invade spinal cord dorsal root ganglia (DRG) following nerve injury, and activity in the resulting pericellular axonal "baskets" may underlie painful sympathetic-sensory coupling.20

Sympathetic sprouting into the DRG may be stimulated by neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin 4/5 (NT-4/5). The CNS response to pain can keep increasing even though the painful stimulus from the injured tissue remains steady. This "wind-up" phenomenon in deep dorsal neurons can dramatically increase the injured person's sensitivity to the pain.

Local tissue inflammation can also result in pain hypersensitivity in neighboring uninjured tissue (secondary hyperalgesia) by spread and diffusion of the excess inflammatory mediators that have been produced as well as by an increase in nerve excitability in the spinal cord (central sensitization). This can result in a chronic pain syndrome comprising diffuse muscle pain and spasm, joint pain, fever, lethargy, and anorexia.

Thus, persistent afferent neuronal barrage due to failure to timely and adequately treat multiple acute pain crises can result in chronic pain in patients with SCD.

PUBLIC HEALTH ASPECTS OF SICKLE CELL DISEASE, SICKLE CELL ANEMIA INCLUDE:

In the US, SCDoccurs 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.22

Several global agencies, including the UN and World Health Organization, have recognized SCD as a public health issue. 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. According to Odame, in low-income countries these challenges lead to loss of days

from school and work, whichfurther 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.”

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.

SICKLE CELL CRISIS AND PAIN TRIGGERS

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

In patients with SCD, 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,27 performed 5 full-night and 7 daytime studies to examine this further. According to the 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.28 Another study found that low nocturnal oxygen saturation was “highly significantly associated with a higher rate of painful crisis.”29 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,30,31 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%.32

Description of Acute Pain Crisis in Sickle Cell Disease

In a sickle cell pain crisis, pain is initially localized and frequently affects a single joint or the spine. This is the golden moment to interrupt the pain and abort the crisis at home. As pain increases in severity, chest splinting leads to regional hypoventilation, hypoxemia, and increased sickling of the red blood cells. There is a release of adhesion molecules, causing interaction of this rigid, polymerized sickled RBC to the endothelium. The increased adhesion of erythrocytes followed by the formation of heterocellular aggregates physically causes small vessel occlusion and resultant local hypoxia.33

This process triggers a vicious cycle of increased HbS formation and the release of inflammatory mediators and free radicals that contribute to reperfusion injury, increased pain, increased hypoventilation, and increased sickling. Ischemic injury progresses with every passing minute, generating more inflammatory mediators. The pain crisis begins to spread over multiple bones and joints as well as the spine, becoming a full-blown crisis, well before the patient arrives at the emergency room. Intravascular *in situ* sickling in the pulmonary capillaries results in lung infarction and acute chest syndrome.

A study by Needleman found that patients with VOC and chest pain have more shallow, rapid breathing than patients with pain elsewhere. Adequate opiate analgesia reduces these differences. The authors stated that pain-associated shallow breathing and maldistribution of ventilation may contribute to the pathogenesis of acute chest syndrome, and these results support the need for adequate pain relief and monitoring of ventilatory patterns during the treatment of VOC.34

Acute Chest Syndrome (ACS) as a Manifestation of SCD

The major acute pulmonary complication of SCD is ACS, and it is a major cause of morbidity and mortality. ACS has been defined as the presence of a new pulmonary infiltrate (involving at least one complete lung segment, not atelectasis) with chest pain, a temperature of > 38.5°C, tachypnea, wheezing, or cough in a patient with SCD.35 Mechanisms that lead to this syndrome include lung infarction, fat emboli from infarcted bone, pulmonary infection, atelectasis from splinting due to thoracic pain during VOC, *in situ* thrombosis, vascular injury due to cell-cell interactions and inflammatory mediators, and thromboemboli.

The National Acute Chest Syndrome Study Group reported on 671 episodes of ACS that were treated in 30 centers. Half of the patients were admitted to the hospital for a reason other than ACS, mostly VOC. Clinical findings of patients with ACS developed in a mean of 2.5 days after hospital admission. Pulmonary infection, caused by 27 different organisms, was present in 36% of episodes, with chlamydia, mycoplasma, and viruses being the three most common pathogens. Fat emboli, with or without infection, were present in 8.8% of patients, pulmonary infarction was inferred in 16% of patients, and in 46% of patients the cause was unknown. Pleural effusions were present in 36% of patients at the time of diagnosis, and in 55% during the hospitalization. Bilobar involvement was typical. Pain was determined to be a prodrome of the ACS, indicating the need to monitor for and try to prevent its development in those admitted to the hospital for VOC.35,36

TREATING PAIN IN SICKLE CELL DISEASE

Standard Treatment of Sickle Cell Pain Crisis

Termination of a sickle cell pain crisis may be achieved with immediate administration of oxygen, intramuscular injection of anti-inflammatory medications such as ketorolac or diclofenac (in the absence of any contraindications), and treatment of pain using a unit dose of a parenteral opioid such as hydromorphone, morphine, pethidine (meperidine), or fentanyl by intramuscular (IM) or subcutaneous (SQ) injection.

A Word About Meperidine

Of note, meperidine is generally not recommended as an analgesic in any condition by US or NICE guidelines due to increased accumulation of active metabolite normeperidine, high levels of which can induce CNS excitation including tremor, myoclonus, and seizures. However, there may be situations where no other opioid is available or where patients cannot tolerate any other opioid. In one study, intravenous patient-controlled analgesia (IV PCA) meperidine hydrochloride was used for post-operative pain relief.

Patients who received less than 10 mg/kg per day of IV PCA meperidine hydrochloride therapy were unlikely to experience central nervous system excitatory adverse effects and maintained adequate analgesia. Based on the dose ranges for symptomatic and asymptomatic patients, 10 mg/kg per day of meperidine, by an IV PCA device, for no longer than 3 days was proposed as a maximum dose and offering a reasonable safety margin in most patients.20 CNS excitation is more likely to occur with high doses of meperidine, prolonged administration of meperidine, decreased excretion of normeperidine in patients with impaired renal function, and increased hepatic metabolism of meperidine in patients receiving medications that induce hepatic enzyme systems.

The sole use of partial opioid agonists such as pentazocine (not available in the US, but still used in Africa), nalbuphine, or buprenorphine is strongly discouraged as these classes of drugs have a ceiling effect and are not indicated in severe pain. However, partial agonists may be combined with full agonists such as hydromorphone or morphine to provide better analgesia with reduced side effects. Oral opioid medications are ineffective in aborting a pain crisis and will result in exacerbation and prolongation of the crisis with subsequent multi-organ damage.

The American Society of Hematology 2020 guidelines panel for management of acute and chronic pain in sickle cell disease, noted two theoretical concerns of rapid treatment and tailored dosing of opioids: rapid pain treatment and higher doses could increase euphoria and the risk of opioid tolerance, and higher opioid dosing could increase perceptions of opioid misuse.However, the panel determined that both theoretical concerns had no supporting evidence and that these concerns should not affect the decision to improve SCD analgesia in the ED.37

The panel noted that rapid treatment of all medical conditions is a general goal of acute care, which is so self-evident that additional evidence may not be needed to support rapid treatment of SCD pain, and that conducting an RCT to further support this recommendation would be unethical. The panel agreed that there is potential for moderate-to-large cost savings associated with reducing the frequency of hospital admissions for SCD pain.

Preventing a Sickle Cell Crises

Voxelotor

Voxelotor (Oxbryta) left shifts the hemoglobin oxygen dissociation curve and 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.38,39 Hemoglobin response may occur as early as a few days and in some cases return to near-normal levels.

Clinical trial findings40,41 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. 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. In some patients, hemoglobin may rise as high as 12 g/dl at the high dose.

At high dose, Oxbryta’s use also lowered levels of two established biomarkers of hemolysis: reticulocytes (https://labtestsonline.org/tests/reticulocytes) (by 19.9%) and bilirubin (https://www.uofmhealth.org/health-library/hw3474) (by 29.1%). Oxbryta is administered orally, once daily for patients 12 years and older.

Oxbryta is an effective replacement for blood transfusion to treat anemia in a non-emergent situation as it can raise hemoglobin levels within just a few days.

High dosing of Oxbryta may increase hemoglobin up to 12 g/dl and may be associated with more frequent pain crisis. The dose should be maintained or titrated down to 1500 mg two or three times a week to maintain an optimal hemoglobin concentration of 10 g/dl.

Oxygen

Nocturnal hypoxemia is a prelude to VOC.27-29 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, and concomitant inflammation, resulting in organ damage and other complications with increased morbidity and mortality.Oxygen therapy is a simple yet cost effective way to prevent VOC and its attendant morbidity and mortality.

Prior to sleep or at bedtime, where the oxygen saturation is at or below 90%, and especially in the presence of VOC, triggers such as daytime exertion, shortened duration of sleep, stress, fatigue, exercise, exposure to cold, ingestion of alcohol, airline travel, altitude that exceeds 2,000 feet, infection, and malaria, oxygen should be administered by nasal canula at a rate of 1.5 to 2 liters/minute. This should be delivered by an oxygen cylinder or preferably by a home or portable oxygen concentrator, to maintain an oxygen saturation of > 95%. This can result in a decrease by 85% to 90% in the frequency of nocturnal vaso-occlusive crises.

Upon onset of a crisis, oxygen administration within the first few minutes may reverse the sickling and terminate the crisis. Subsequently, oxygen is no longer preventive but should be part of an abortive protocol.

Oxygen may be obtained from oxygen cylinders or, more conveniently, and with less maintenance, from portable oxygen concentrators such as the SeQual Eclipse, Inogen, Respironics, AirSep, DeVilbiss, and others, which extract oxygen from ambient air.

Oxygen should be provided in continuous flow from a tank or concentrator. Pulse dose oxygen delivery triggered by inspiratory effort does not provide adequate oxygen delivery and should not be used.

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 an FAA certified concentrator such as the SeQual Eclipse.

See also, Dr. Omoigui's prior paper on oxygen guidelines in sickle cell crisis (https://www.practicalpainmanagement.com/pain/other/sickle-cell-pain-crisis-clinical-guidelines-use-oxygen) .

Hydroxyurea

Hydroxyurea 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.42

Recommended Dosing: 15 mg/kg/day to start and increase as needed by 5 mg/kg/day every 12 weeks, if blood counts are within acceptable range; Max dose 35 mg/kg/day.

Adakveo

Crizanlizuman-tmca (Adakveo)is a monoclonal antibody targeted against the P-selectin glycoprotein that is expressed on activated endothelial cells and platelets. It can be considered for use as part of a comprehensive management of a pain crisis.43

Although polymerization of deoxygenated HbS is the primary event in the pathophysiology of sickle cell disease,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.44 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.45

In clinical trials, patients treated with crizanlizuman-tmca experienced fewer healthcare 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 crizanlizuman-tmca 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.46crizanlizuman-tmca is administered, in patients 16 years and older, by IV infusion, over 30 min, at weeks 0, 2, and then every 4 weeks.

Blood Transfusion

Due to the risks of alloimmunization and hemolytic transfusion reaction, the routine use of blood transfusion or chronic transfusion therapy is not recommended for prevention or treatment of VOC or recurrent SCD pain.

Red blood cell (RBC) alloimmunization occurs in approximately 30% of transfused sickle cell disease patients compared to 2% to 5% of all transfusion recipients.47 Among SCD patients transfused with RBCs matched only for ABO and D antigens, the rate of alloimmunization to non-ABO RBC antigens is much higher than for other transfused patient populations, ranging from 18% to 37%.48-50 This is due to the differences in RBC antigen expression frequencies between the mostly Caucasian donor base and the mostly African-American SCD patients.

In SCD patients, many partial D, C, and e antigens are described, and importantly, the resulting antibodies are associated with delayed hemolytic transfusion reaction (DHTR) cases. Such allo-immunized patients should be transfused with antigen-negative units (D-negative RBCs for a partial D patient).51,52 One of the common alloantibodies made by SCD patients is against the Rh antigen E. In recent years, phenotypic matching protocols are now the standard of care for SCD patients in order to prevent RBC alloimmunization. Such protocols include matching for C, E, and K1 even for non-allo-immunized patients, to extended antigen matching for Fy, Jk, and Ss blood groups in patients who have made one or more alloantibodies.

DHTR, as a result of allo-immunization against transfused blood cells, is a dreaded complication of transfusion.53 In the severest cases, hyperhemolysis, defined by the destruction of both transfused and autologous RBCs, occurs and may be life-threatening.

Blood transfusion may be indicated where all other measures have failed and for reasons other than pain (eg, stroke, silent stroke, abnormal transcranial Doppler ultrasound, or pregnancy).

Where indicated, blood transfusion aims to increase the oxygen-carrying capacity of blood and to decrease the proportion of sickle hemoglobin (HbS) relative to hemoglobin A (HbA). In the acute situation, simple transfusion will increase oxygen-carrying capacity but with a risk of hyperviscosity if the Hb is increased to significantly over the patient's baseline. Therefore, the target Hb should be 10 g/dL in patients with homozygous HbS (HbSS).54 Exchange transfusion has the advantage of both increasing oxygen-carrying capacity and reducing HbS percentage.

Other Preventive Measures

prophylactic administration of penicillin in childhood (vaccine)

avoiding temperature extremes

good hydration

antimalaria prophylaxis

Actively Treating a Sickle Cell Pain Crisis

When a sickle cell crisis presents, time is of the essence to interrupt the pain, terminate the neuro-inflammatory cascade, and prevent organ damage. In the author's view, it is cruel and inhuman punishment for patients to suffer excruciating ischemic pain for the 1- to 2- hour or longer amount of time to get to the nearest hospital emergency room and be administered the first analgesic dose. Pain is more than just a symptom but is indicative of vaso-occlusion, ischemia, and multi-organ damage.

Thus, the author urges that sickle cell crisis be treated no less emergently than myocardial infarction. The longer the interval to treatment, the greater the ischemic organ damage, the greater the amplification of the neuro-inflammatory cascade, and the more protracted the crisis becomes. The 2020 guidelines for the management of acute and chronic pain by the American Society of Hematologists recommend assessment and administration of analgesia within 1 hour of arrival to the ER.37 Taking into consideration the time for transportation to the hospital, this is too long. It is important to realize that a sickle cell pain crisis represents much more than severe excruciating pain. It represents an inflammatory storm, ongoing ischemia, and multi-organ damage.

The following sections address treatment recommendations whether the patient is at home with remote monitoring by a clinician or clinical team, or in the hospital.

RECOMMENDATIONS FOR MANAGING A SICKLE CELL CRISIS REMOTELY, AT THE PATIENT'S HOME

Management of sickle cell crisis requires immediate termination; as noted, the longer the crisis goes on, the greater the ischemia, inflammatory storm, and multi-organ damage. 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 for days to weeks to control the crisis.

In-Home Care Payments Expanded/Coverage Expanded

Fortunately, in the US, regulatory actions by the Centers for Medicare and Medicaid Services (CMS) were enacted in November 2020 to pay for hospital care outside of traditional inpatient sites. The policy update will reimburse hospitals to provide in-home, hospital-level telehealth care for patients with acute conditions. The policies expand CMS's Hospital Without Walls program, established by federal mandate

in March 2020. The Acute Hospital Care At Home (https://www.cms.gov/files/document/covid-hospitals.pdf) program targets patients with any of more than 60 acute conditions (sickle cell disease is not on the list at the time of this writing) and who would otherwise require inpatient admission.

Remote Monitoring during a Sickle Cell Crisis

With the advent of remote home monitoring that was accelerated by the COVID-19 pandemic, patients with SCD at home, with the right equipment, can have most pain crises treated safely using video or remote monitoring (telemedicine) combined with Bluetooth-enabled smart phones, home Wi-Fi, and compatible tetherless sensors. Vital signs (oxygen saturation, continuous respiratory rate, pulse rate, blood pressure, perfusion index, and continuous body temperature) can be transmitted securely to hospitals or healthcare facilities. An example of a remote home monitoring system is the Masimo Safety Net.55,56

Training and Set-Up

According to CMS, acute conditions, such as asthma, congestive heart failure, pneumonia, and COPD, can be treated appropriately and safely in home settings with proper monitoring and treatment protocols. A similar protocol should be used in the treatment of sickle cell pain crisis. An in-person physician evaluation is required prior to starting care at home. A registered nurse should evaluate the patient once daily in person or remotely, and two in-person visits should occur daily by either RNs or mobile integrated health paramedics, based on the patient's plan and hospital policies.56

Sickle cell anemia patients should be trained along with their relatives or caregivers. They should have available at home the following equipment set up to enable safe and timely administration of the opioid and anti-inflammatory medications.

Oxygen cylinder or oxygen concentrator

Equipment for on site or remote vital sign monitoring including oxygen saturation, temperature, respiratory rate, blood pressure

Intranasal naloxone

Remote video for monitoring by the physician or monitoring station

Unit dose of a parenteral opioid that the patient has tolerated before

Unit dose of a parenteral NSAID that the patient has tolerated before

Dispensing unit doses of opioids with remote video and vital sign monitoring should mitigate concerns of patient abuse, misuse, and addiction. Such unit doses are refilled after utilization and post-pain crisis evaluation.

Medications for in-Home Care

Opioids

Medications such as morphine, fentanyl, hydromorphone, and pethidine produce pain relief by binding and activating specialized opioid receptors at the site of tissue injury and in the substantia gelatinosa of the spinal cord. Once activated, the opioid receptors inhibit the release of inflammatory mediators such as bradykinin at site of tissue injury and Substance P from pain transmitting C nerve fibers. The pain receptors that were previously excited are now suppressed. There is also suppression of the signal traffic in the specialized nerves, eg, C fibers and A-delta fibers that carry pain impulses to the spinal cord and brain. Morphine and other opioids also alter emotional processing of painful input by acting on opioid receptors in the limbic and cortical area of the brain. In addition, morphine and other opioids have additional anti-inflammatory effects.17,18,57

Patients and their relatives or caregivers should have a unit dose of these opioid medications on hand, similar to an auto-injector EpiPen, and be trained in administration of these medications by the IM or SQ route, at home. They should also be trained in the use of a reversal agent such as intra-nasal naloxone. Patients should self administer these medications, as long as they live with a relative or caregiver who can assist, monitor them, enable remote monitoring and communicate by video with the healthcare team.

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 be set up with video and/or remote monitoring equipment and 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 an opioid overdose. Should a unit dose of the parenteral medication fail to stop the crisis, the patient should be advised to proceed to a medical setting. Based on the author's clinical experience, when such measures are instituted at home within the first 15 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 will provide inadequate analgesia and may transform a crisis that should last minutes into one that may last weeks and result in multi-organ damage.

NSAIDs

The 2020 ASH guideline panel *suggests* a short course (5 to 7 days) of NSAIDs in addition to opioids for acute pain management.37 Non-steroidal anti-inflammatories, such as parenteral ketorolac, inhibit the enzyme cyclooxygenase and therefore decrease prostaglandin synthesis. Prostaglandins are inflammatory mediators that are released during allergic and inflammatory processes. Phospholipase A2 enzyme, which is present in cell membranes, is stimulated or activated by tissue injury or microbial products. Activation of phospholipase A2 causes the release of arachidonic acid from the cell membrane phospholipid. From here there are two reaction pathways that are catalyzed by the enzymes cyclooxygenase and lipoxygenase. The cyclooxygenase enzyme pathway results in the formation of inflammatory mediator prostaglandins and thromboxane.The potential risks associated with NSAID use in acute SCD pain include nephrotoxicity, gastrointestinal disorders, and bleeding.

Antihistamines

Stimulation of H1 receptors via a PKC/MAPK/MEK158 signaling pathway has recently been shown to elicit release of the key pro-inflammatory cytokines IL-1β59 and IL-660 with subsequent regulation of nerve growth factor61 release from astrocytes.62 Histamine is a key mediator in the processing of nociceptive information, acting in an antinociceptive manner in the CNS while, conversely, in a nociceptive manner in the PNS.63 In the PNS, histamine is released in response to tissue injury/damage, and, through the sensitization of polymodal nociceptors resulting in increased firing rates, it contributes to the generation of pain hypersensitivity. In neuropathic pain, histamine released in the periphery by mast cells has been shown to play an important role in the development of hypersensitivity following nerve injury.64

Parenteral or oral antihistamines may mitigate the histamine release effects of morphine, modulate neuropathic pain, act as an analgesic adjuvant, as well as decrease adhesion of sickle erythrocytes.

Mast cells have a very large repertoire of receptors, including cytokine receptors, for responding to microenvironment inflammatory signals.65 Consequently, inflammation may contribute to mast cell activation (MCA) in SCD, leading to histamine release in plasma. Histamine may be a factor of SCD pathophysiology because it efficiently promotes adhesion of sickle erythrocytes by stimulating endothelial histamine H2 and H4 receptors and by inducing P-selectin expression and release of von Willebrand factor.66 Histamine level was elevated in 18% of patients in steady state and in 61% during VOC. Median histamine level was significantly higher during VOC than in steady state (24.1 [7.0–45.0] vs 9.6 [6.2–14.4] nmol/l, $P < 0.0001$). These results suggest a role of mast cell activation in SCD pathophysiology.67 There may be additive sedative and analgesic effects when antihistamines are combined with opioids, and dose adjustment may be necessary.

Steroids

Steroids should not be used in the treatment of a pain crisis except when appropriate for the treatment of other medical indications such as asthma.49

RECOMMENDATIONS FOR THE MANAGEMENT OF A SICKLE CELL CRISIS IN THE HOSPITAL OR HEALTHCARE FACILITY

Should the pain 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 proceed to the hospital and 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.68

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, Expert Panel Report, 2014 Evidence-Based Management of Sickle Cell Disease and incorporating the ASH 2020 Guidelines, include the following:69,70

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. The ASH guideline panel *suggests* tailored opioid dosing based on consideration of baseline opioid therapy and prior effective therapy37

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.

Opioid sparing medication such as sub-anesthetic ketamine 5 mg to 7.5 mg SQ/IM/IV (children 0.1 mg/kg) may be utilized to decrease the amount of opioids required as well as decrease the side effects, while providing effective pain control. (*Author's Note:*ASH dosing recommendation for ketamine infusion for pain is weight-based at 0.1 mg/kg to 0.3 mg/kg/hour with a max of 1 mg/kg/hour. The author has found the higher limit to be too high and administers ketamine daily for pain procedures to adults using single hourly doses of 5 mg to 7.5 mg (0.1-0.15 mls) with good results.)

To reduce the risk of acute chest syndrome in adults and children hospitalized for a VOC, encourage use of incentive spirometry every 1 to 2 hours, while awake.

In euvolemic adults and children with SCD and a VOC who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over-hydration. Except where there is clinically significant dehydration, IV fluids should be administered cautiously as there is risk of harm in patients with cardiopulmonary compromise.

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; and 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, anaplastic episode, a delayed hemolytic transfusion reaction, ACS, and infection.

Clinicians can 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 the 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.

EMERGING OPTIONS FOR SICKLE CELL DISEASE

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, as well as 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.

DISCUSSION AND CONCLUSION

In the author's clinical experience with sickle cell disease, quick and early termination of a pain crisis is the most effective way to abort the inflammatory cascade and prevent suffering, morbidity, and multi-organ damage. The cost of just one or several hospitalizations and the cost of long-term disability will be thousands of times the price of oxygen, opioid and anti-inflammatory medications, administered in-home, with hospital-level telehealth care.

Oxygen therapy at home or during airline flights, and rapid treatment of a pain (multi-organ damage) crisis with video or remote home monitoring should be considered as the standard of care and public health policy should be directed to providing oxygen therapy, at-home medications, and remote monitoring to all individuals with SCD.

PRACTICAL TAKEAWAYS

A major cause of morbidity, prolonged hospitalization, multi-organ damage, and mortality is delayed time to treatment of a sickle cell pain crisis.

Sickle cell disease is characterized by chronic hemolysis, an inflammatory cascade, 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,71 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. 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.*

Oxygen therapy at home, during airline flights, and rapid treatment of a pain (multi-organ damage) crisis with video and/or remote home monitoring should be considered as the standard of care and public health policy should be directed to providing continuous flow oxygen therapy both at home and on commercial airlines, at home medications (parenteral opioids and NSAIDs) and remote monitoring to all individuals with SCD.

**Based on author's clinical experience.*

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