COMMENTARY

The Sickle Cell Crisis: A Dilemma in Pain Relief

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Sickle cell anemia is a progressive hemoglobinopathy producing chronic hemolytic anemia, microvascular thrombosis, ischemic pain, tissue infarction, decreased quality of life, and ultimately shortened life expectancy.[1,2] In sickle cell anemia, valine is substituted for glutamic acid in the sixth amino acid of the β-globin chain. In a person who is homozygous, all hemoglobin is of the abnormal HbS type, and repeated episodes of sickling result in a less malleable molecule even at sites of normal atmospheric pressures of oxygen.[3] The hemoglobin variant HbS gene is found throughout Africa, Asia, the Caribbean, the Middle East, and southern Europe.[4,5]

The pain experienced during a sickle cell crisis is the product of sickled, less malleable red blood cells adhering to the vascular endothelium, plugging arterioles and capillaries and ultimately leading to occlusion and infarction.[3,6,7] Nociceptive fibers are stimulated in response to tissue irritation or injury; they can be classified into type A δ fibers, which are thinly myelinated and allow fast conduction, and the unmyelinated and more slowly conducting type C.[8] Hypoxia, acidosis, and the release of chemical mediators of inflammation, such as potassium, adenosine triphosphate, bradykinin, prostaglandins, and substance P, activate and/or sensitize nociceptors.[9] When tissue injury first occurs, the acute pain, which lasts several days to several weeks, is characterized by sympathetic, somatic, and endocrine adaptations along with fluctuations in intensity.[10] If the pain becomes chronic, ie, persisting longer than 3 to 6 months, facilitation of pain pathways could occur, resulting in a heightened response to a variety of painful stimuli.[10-13] Chronic pain is typically accompanied by vegetative signs (sleep disturbance, decreased appetite, weight loss, and diminished libido) and subsequent psychological malady with few identifiable autonomic changes.[10] The vaso-occlusive crisis of sickle cell anemia has been described as progressing through 4 distinct phases: (1) prodrome: symptoms of numbness, aches, and parasthesias that develop in areas subsequently affected by pain and that last up to 2 days, (2) initial infarct: crisis pain that increases gradually and peaks by the second or third day, (3) postinfarct: persistent and severe pain with signs and symptoms of inflammation, and (4) resolution: gradual remission of pain.[4] Nevertheless, much variability remains in the frequency and intensity of painful crises, ranging from painful episodes that readily respond to conservative treatment to chronic persistent pain with acute exacerbations.[12]

The initial management of a sickle cell crisis should be aimed at providing rapid pain control.[13] Once the pain is controlled, treatment guidelines recommend addressing underlying complications, including infection and severe anemia; providing adequate hydration; administering supplemental oxygen; and employing narcotic analgesics for pain relief.[7,13-15] Both the American Academy of Pain Medicine and the American Pain Society promote the use of opioid analgesics for the treatment of moderate to severe sickle cell pain. For sickle cell pain that does not respond to nonopioid analgesics, they endorse the administration of sustained-release opiate preparations, such as morphine sulfate controlled-release tablets, which provide convenient and consistent analgesia.[16] Pain relief also can be effectively achieved with the patient-controlled analgesia system.[17]

ADDICTION VS PSEUDOADDICTION

Addiction is a chronic neurobiological disorder, the presentation and evolution of which are affected by genetic, psychological, and social components. It is characterized by an impaired ability to control drug use and continued use despite recurrent problems related to self-administration.[10,18-20] The incentive-sensitization theory of addiction postulates that craving and relapse are drug-induced neuroadaptations that cause stimuli and their re-presentations to become highly salient or "intensely wanted."[21]

The neurophysiologic model of addiction suggests a pathologic appropriation of reward-related learning processes. The development of long-term associative memory occurs within the nucleus accumbens, prefrontal cortex, amygdala, and the dorsal and ventral striata. These neural circuits receive input from midbrain dopamine neurons; this "reward" is liked or craved, and specific cues that predict its availability are learned.[22] The prefrontal, orbitofrontal, and anterior cingulate cortices are involved in the activation of goal-directed or drug-seeking behavior.[23] In addition, the lateral prefrontal cortex is associated with the impaired inhibitory control observed in people with substance use disorders.[24] Thus, addiction could explain a patient's aberrant, drug-seeking behavior[10]; however, "as needed" dosing schedules, drugs with inadequate potency, and longer than appropriate dosing intervals can also explain exaggerated behaviors that have been referred to as pseudoaddiction.[25]

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Pseudoaddiction arises when a patient's pain is inadequately managed, and the response to this undertreatment is used as evidence for the diagnosis of drug addiction.[5,26] Pseudoaddiction is postulated to progress through 3 phases. The cycle begins with "as needed" dosing of inadequate analgesics for the treatment of continuous or frequent pain. Initially, the patient merely requests more pain medication. When these requests are overlooked, the patient then tries to convince the physician of his/her pain by moaning, grimacing, and/or crying. The physician interprets this behavior as aberrant and again refuses the requested dose escalation. Finally, the crisis phase occurs when the patient increases his/her level of bizarre, drug-seeking behavior. The cycle continues, with the patient persistently trying to acquire the drug and the physician consistently refusing to treat the pain, resulting in a lack of trust between the 2 parties, and, ultimately, in the patient being viewed as a drug addict.[27]

Although pseudoaddiction can be distinguished from addiction by the resolution of aberrant behaviors and improvement in functioning when adequate analgesia is achieved,[10,28] the identification of aberrant behaviors in opioid-treated patients can be difficult, particularly in the acute care setting. Behaviors that could indicate a substance use disorder include sale or forgery of prescriptions, theft of drugs, injection of oral formulations, concurrent abuse of alcohol and illicit drugs, repeated escalation of dosage, drug-related deterioration in daily functioning, and repeated resistance to changes in therapy.[29] Risk factors that can assist clinicians in the detection of abuse include a personal or family history of substance abuse, a criminal record, and frequent automobile accidents.[18] Among the screening tools available to evaluate a patient's potential for aberrant drug behavior is the screener and opioid assessment measure for patients with chronic pain (SOAPP).[30] Sickle cellanemia–associated addiction does not result solely from the administration of prescribed narcotics; a number of other factors are likely involved, including genetic predisposition, socioeconomic status, and family dynamics.[31]

The Race Issue

Patients with sickle cell anemia could suffer disproportionately from recurrent painful episodes with inconsistent and inadequate pain control because of socioeconomic factors associated with their minority status.[12,32-34] In a national study by Tamayo-Sarver et al[35] of emergency department visits, disparities in the treatment of migraine headaches, nontraumatic back pain, and ankle fractures with opiate analgesics were associated with patient race and ethnicity. More specifically, African Americans were less likely than white and Hispanic people to be prescribed opioids for conditions with minimal objective findings.[35] In the United States, young African American males with sickle cell anemia require frequent medical interventions for their painful vaso-occlusive episodes.[36,37] Perhaps because of the higher rates of illicit drug use in the wider population of African Americans,[38] these young men arouse more concern about addiction and diversion during the treatment of their pain.[15,36,37,39] The perception and communication of pain and the response to it are influenced by a range of sociocultural factors.[40] Two hypotheses have been advanced to explain why racial and ethnic minorities presenting with pain are less likely to receive appropriate attention in acute care settings.[12] First, minority patients are less likely to have a regular primary care physician and therefore have less access to specialty care (ie, pain management), possibly resulting in more frequent use of the emergency department for routine health care services. Second, racial/ethnic minorities might be less assertive during doctor-patient interactions and thus less effective in the verbal and nonverbal communication of their pain; as a result, physicians might not feel the trust necessary to comfortably prescribe opioid analgesics in acute care settings.

No population-based study has been conducted to examine whether patients with sickle cell anemia are at higher risk for addiction than those of similar racial and socioeconomic background with other nonmalignant chronic pain disorders; nor are there data evaluating risk factors for drug dependence among patients with sickle cell anemia.[28,31,36,40,41] A 2006 national survey showed that 75% of nonmedical users of prescription analgesics were white.[42] Overall, the health care system appears less responsive to the needs of African Ame ricans than white people, as evidenced by the lack of general medical services including cardiac catheterization, renal transplant, and antibiotics.[43,44] These disparities inevitably contribute to the confusion about the true incidence of opioid addiction in the sickle cell population.

The Therapeutic Dilemma

A patient with sickle cell anemia who presents with a vaso-occlusive crisis exemplifies a quandary in pain management: the obligation to relieve suffering without enabling addiction. The most prevalent malady in the emergency department is pain,[45] yet patients with sickle cell anemia who have persistent or recurrent pain that is controlled with opiate analgesics represent a unique challenge.[15,46] In almost all painful conditions, the correlation between objective abnormalities seen on examination or radiologic studies and the patient's report of pain is poor.[47] No reliable biological markers exist to assess the occurrence and severity of a sickle cell crisis.[31] According to Shapiro,[46] "episodes last from hours to weeks followed by a return to baseline; the onset and resolution is sudden or gradual; and the majority of painful episodes have no clear precipitant."

Physicians vary in their ability to cope with or relate to patients in pain,[48] and patients differ in their ability to withstand it.[31]

The clinical approach to sickle cell anemia is further confounded by the provision of medical services. Because patients with sickle cell anemia are often forced to obtain treatment of their chronic illness in acute care settings, they learn that they must convince the physicians of their pain if they are to receive appropriate treatment.[31,49] For example, 63% of surveyed nurses who cared for patients with sickle cell anemia thought addiction was common among them.[50] In another study, 53% of emergency department physicians believed 1 in 5 of their sickle cell patients had a substance use disorder, whereas only 23% of hematologists shared this belief.[51]

The fear of creating or perpetuating addiction or being deceived by a patient often causes health care professionals to prescribe subtherapeutic dosages of opioids.[10,25,52,53] In a landmark study that examined the effect of physicians' untoward fear of contributing to addiction on their prescribing patterns, Marks and Sachar[25] postulated that prescribing euphoria-inducing drugs evokes puritanical and emotional counterreactions. They documented misconceptions about therapeutic dose ranges of meperidine and an overestimation of the dangers of addiction to meperidine; these misconceptions led to hospitalized patients receiving inadequate treatment for severe pain.

Current criteria for substance use disorders were originally formulated using a population of substance-dependent patients without medical problems, making it difficult for clinicians to use them to differentiate between patients with sickle cell anemia who are in pain and drug-dependent patients.[54,55] Because physiologic dependence and tolerance are well-known consequences of long-term opioid administration, they are not necessarily indicative of addiction[24,56] and cannot be the sole basis for defining substance use disorders.[19] According to Lussier and Pappagallo,[18] "It appears that a biological vulnerability is necessary for addiction to develop and there is no scientific evidence that addiction in pain patients treated with opiates is purely iatrogenic or drug-induced."

The available evidence suggests that the prevalence of drug addiction among patients with sickle cell anemia is no higher than in the overall US population.[49,57] According to Martin and Moore,[31] the incidence among patients with sickle cell disease ranges from 0.2% to 2.0%. Using non–pain-related symptoms (analgesics used in the absence of pain, or in attempts to alter mood, achieve euphoria, or reduce stress other than pain), another study measured the extent to which patients with sickle cell disease were dependent on prescribed narcotics. The results showed that only 2% of the sample met *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* criteria for substance dependence.[26]

IMPLICATIONS

Sickle cell anemia is a well-described, genetically determined hemoglobinopathy. Its painful crises are thought to result from transient episodes of microvascular congestion, tissue ischemia, and the release of inflammatory mediators. The pain associated with such episodes can be excruciating. Addiction is a complex, multifactorial illness that emanates from pathophysiologic adaptations in the dopaminergic pathways of the brain after excessive use of the substance.

Sickle cell crises are undoubtedly difficult to manage; however, clinicians can treat sickle cell pain without contributing to narcotic addiction. If objective evidence points to a substance abuse disorder in these patients, that disorder can be addressed once the acute crisis has subsided.

An impartial and individualized approach to the assessment and management of patients with sickle cell crises will avoid mislabeling them as addicts. Substance use disorder criteria can be used to identify true opioid-dependent patients. The distinction between the patient in sickle cell crisis who needs aggressive pain treatment and the addict can best be made collaboratively by a multidisciplinary team including specialists in hematology, pain management, addiction medicine, and psychiatry.

Experience treating patients in pain is certainly advantageous, but nothing can replace a detailed medical (including mental illness and drug use), family, and social history and a thorough examination together with collateral information. When possible, the patient's treatment plan should include opioids, with the understanding that the patient agrees to use a single physician and pharmacy and that the physician agrees to monitor improvements in daily activities and pain symptoms as well as adverse drug reactions and abuse during regularly scheduled follow-up appointments. Physicians should then educate their patients about the benefits of opioid use and the possible risks of long-term use.

Although it is unknown whether the treatment of sickle cell pain with opioid analgesics predisposes patients to future drug addiction, the available data suggest that the risk of iatrogenic addiction is quite low. The ethics of medicine mandate that physicians relieve a patient's suffering and deliver care equally to all people in need. When encountering patients in pain, specifically those in sickle cell crisis, physicians should consider the confounding variables of pseudoaddiction, treatment setting, personal biases, and fear, as well as be aware of the lack of evidence-based data regarding this issue. Finally, physicians should be able to extrapolate the elements illustrated in this paper to other situations in which personal bias and treatment guidelines could collide.

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