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Pain Management of Sickle Cell Disease

Samir K. Ballas, MD[a,b,*]

[a]*Cardeza Foundation for Hematologic Research, 1015 Walnut Street, Philadelphia, PA 19107, USA*
[b]*Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA*

Sickle cell disease (SCD) is an inherited disorder of hemoglobin structure that has no established cure in adult patients. Cure has been achieved in selected children with sickle cell anemia using allogeneic bone marrow transplantation [1] or cord blood transplantation [2]. SCD is a quadrumvirate of (1) pain syndromes, (2) anemia and its sequelae, (3) organ failure, including infection, and (4) comorbid conditions. Pain, however, is the insignia of SCD and dominates its clinical picture throughout the life of the patients (Fig. 1). Pain may precipitate or be itself precipitated by the other three components of the quadrumvirate. Moreover, management of sickle cell pain must be within the framework of the disease as a whole and not in isolation. SCD is unlike other pain syndromes where the provider can make decisions on treatment based solely on the pain and its associated behavior. A primary care physician, for example, taking care of a middle-aged patient with job-related low back pain may decide to expel the patient from his or her care if the patient in question demonstrates suspicious drug-seeking behavior. Doing the same with patients who have SCD could be counterproductive. There are anecdotes of patients with SCD who were dismissed from certain programs only to be found dead at home within 24 hours after dismissal or to be admitted to other hospitals with serious complications [3]. Sickle pain could be the prodrome of a serious and potentially fatal complication of SCD in some patients. This article focuses on the pathogenesis and management of acute and chronic sickle cell pain.

CLASSIFICATION OF PAINFUL EPISODES IN SICKLE CELL SYNDROMES

Box 1 lists the major types of pain syndromes in patients with SCD. These are divided into those secondary to the disease itself, those associated with therapy, and those that are due to comorbid conditions. The acute sickle cell painful episode is the insignia of the disease; it is unpredictable in nature and may be

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* Cardeza Foundation for Hematologic Research, 1015 Walnut Street, Philadelphia, PA 19107. *E-mail address:* samir.ballas@jefferson.edu

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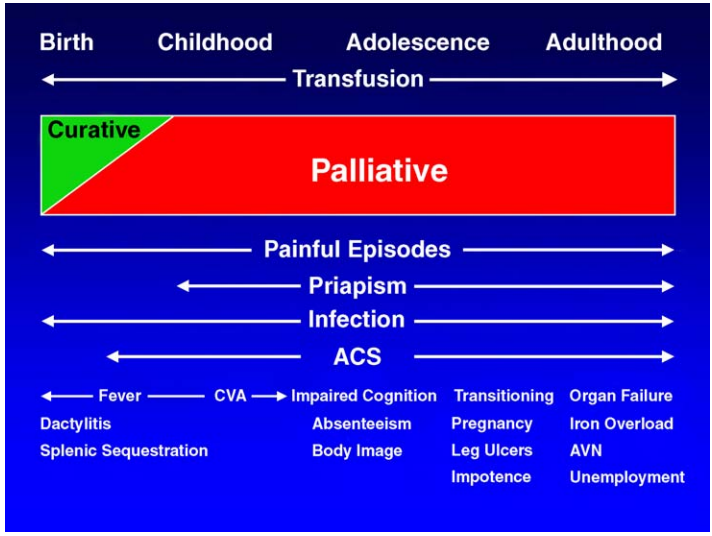

Fig. 1. Sequence of complications of sickle cell anemia from birth through adult life. Cure is possible in selected children. The mainstay of management in most patients is palliative, with pain management being most important. ACS, acute chest syndrome; AVN, avascular necrosis; CVA, cerebrovascular accident. (*Modified from* Ballas SK. Sickle cell disease: current clinical management. Semin Hematol 2001;38(4):308; with permission.)

precipitated by known or unknown factors. Sickle pain may involve any part of the body, and the severity, location, and duration of the pain vary latitudinally among patients and longitudinally in the same individual. The serum concentration of some acute phase reactants may increase in acute painful episodes and interfere with the efficacy of treatment with opioid analgesics [4]. Objective signs are often absent in the patient with a sickle cell crisis, especially within 1 to 2 days of its onset, an absence that engenders problematic attitudes in some care providers treating patients who have sickle pain [5].

ACUTE SICKLE CELL PAIN

Acute Sickle Cell Painful Episodes (Crises)

Pathogenesis

The most important pathophysiologic event in sickle cell anemia, which explains most of its clinical manifestations, is vascular occlusion; this may involve both the micro- and macrovasculature [6,7]. The primary process that leads to vascular occlusion is the polymerization of sickle hemoglobin (Hb) on deoxygenation, which in turn results in distortion of the shape of red blood cells (RBC), cellular dehydration, and decreased deformability and stickiness of RBC, which promotes their adhesion to and activation of the vascular endothelium.

Adherence of sickle RBC to vascular endothelium results in intimal hyperplasia in larger vessels, which may lead to vascular occlusion and tissue

Box 1: Classification of painful episodes in sickle cell disease

Pain Secondary to the Disease Itself
- *Acute pain syndromes*
  - Recurrent acute painful episodes (crises)
  - Acute chest syndrome
  - Hepatic crisis
  - Priapism
  - Calculus cholecystitis
  - Hand-foot syndrome[a]
  - Splenic sequestration[a]
- *Chronic pain syndromes*
  - With objective signs
    - Aseptic (avascular) necrosis
    - Arthropathies
    - Leg ulcers
    - Chronic osteomyelitis
  - Without objective signs
    - Intractable chronic pain
- *Neuropathic pain*

Pain Secondary to Therapy
- Withdrawal
- Loose prosthesis (hip or shoulder)
- Postoperative pain

Pain Due to Comorbid Conditions
- Trauma
- Arthritis (septic, degenerative, rheumatoid, collagen disease)
- Peptic ulcer disease
- Other conditions

[a] Occurs in infants and children.

infarction [8,9]. Moreover, recent in vivo studies in transgenic mice suggest that vascular occlusion results in the creation of an inflammatory state [10,11], which in turn contributes to the sensation of pain.

The sequence of pathophysiologic events that lead to the perception of pain in SCD is not well known. It is agreed that tissue ischemia due to vascular occlusion resulting from in situ sickling causes infarctive tissue damage, which

in turn initiates a secondary inflammatory response. The secondary response may enhance sympathetic activity by means of interactions with neuroendocrine pathways and trigger release of norepinephrine. In the setting of tissue injury, this release causes more tissue ischemia, creating a vicious cycle. It is the combination of ischemic tissue damage and secondary inflammatory response that makes the pain of SCD unique in its acuteness and severity. Tissue injury generates several major pain mediators [12–15], including but not limited to interleukin-1, bradykinin, K^+, H^+, histamine, substance P, and calcitonin gene-related peptide (CGRP). Interleukin-1 is an endogenous pyrogen and also upregulates the cyclo-oxygenase gene, leading to synthesis of prostaglandins E_2 and I_2. Bradykinin, K^+, H^+, and histamine activate nociceptive afferent nerve fibers and evoke a pain response. Prostaglandins sensitize peripheral nerve endings and facilitate the transmission of painful stimuli along A-δ and C fibers that reach the cerebral cortex via the spinal cord and the thalamus. Moreover, activated nociceptors release stored substance P, which itself facilitates the transmission of painful stimuli. Bradykinin, substance P, and CGRP also cause vasodilation and extravasation of fluids that can lead to local swelling and tenderness. The pathway for painful stimuli is subject not only to activators, sensitizers, and facilitators but also to inhibitors. Serotonin, enkephalin, β-endorphin, and dynorphin are endogenous central pain inhibitors. Thus, in a given patient, the net outcome of tissue ischemia may be severe or mild pain, depending on the extent of tissue damage and the net balance of pain stimulators versus pain inhibitors. This situation may explain, in part, the considerable variation in the frequency and severity of painful crisis among patients and longitudinally in the same patient.

Clinical picture

The clinical picture of sickle cell pain is protean. Sickle cell pain has unique features. Pathophysiologically, it is nociceptive (ie, secondary to tissue damage). It may be acute or chronic, somatic or visceral, unilateral or bilateral, localized or diffuse and mild, moderate or severe [16]. Typically, acute painful episodes affect long bones and joints, with the low back being the most frequently reported site of pain [17]. Other regions of the body, including the scalp, face, jaw, abdomen, and pelvis, may be involved. A severe acute sickle cell painful episode has been defined as one that requires treatment in a medical facility with parenteral opioids for 4 or more hours [18,19]. The occurrence of three or more such crises indicates that the affected patient has severe SCD. The words most often used to describe sickle pain include "throbbing," "sharp," "dull," "stabbing," and "shooting," in decreasing order of frequency [17].

Phases and objective signs

Objective signs of a painful crisis, such as fever, leukocytosis, joint effusions, and tenderness, occur in about 50% of patients at initial presentation [5]. During the evolution of the painful crisis, however, objective laboratory signs become evident in most patients, provided that these parameters are determined serially [20]. The acute sickle cell painful episode that requires hospitalization appears to

evolve along four distinct phases: prodromal, initial, established, and resolving [21]. Each phase may be associated with certain clinical and laboratory findings. As the pain of a crisis intensifies, the percentage of dense RBC increases with a concomitant decease in RBC deformability. Some patients develop hyperhemolysis during the evolution of the acute painful episode, with decrease in Hb level and increase in the reticulocyte count [21]. As pain resolves, the pattern is reversed, with a decrease in the number of dense red cells and an increase in RBC deformability [20].

Pain management

Pain is the hallmark of SCD, and the acute sickle cell painful episode (painful crisis) is the most common cause of more than 90% of hospital admissions among adult patients who have SCD [16]. Effective management of sickle cell pain is complex and entails thorough understanding of the issues that are associated with the treatment of pain of an incurable disease on a chronic basis [16,22]. Major prerequisites for an effective and rational management of sickle cell pain pertain to the patient, the pathophysiology of the disease, the pharmacology of analgesics, and the attitude of the health care provider.

A patient is a unique human entity. The more a provider knows the patient, the more effective pain management becomes. Knowledge of the patient should not be limited to age, sex, precise diagnosis, complications, and previous pain management methods. It should also take into consideration the biopsychosocial fabric of the patients' lives, including their level of education, employment status, occupation, family structure, source of income, ethnicity, housing conditions, fears, religion, beliefs, habits, hobbies, and perception of the severity and prognosis of their disease. This approach allows the physician to individualize pain management and avoid unfounded generalizations about patients and their consumption of opioid analgesics. Such generalizations, for instance, may result in oversedation of a patient naïve to opioids or in undertreatment of a patient too tolerant of them.

Sickle cell pain is unique and, like other types of pain, is a complex human experience that is strongly affected not only by pathophysiologic factors but also by psychologic, social, cultural, and spiritual ones. It is, however, consequent to tissue damage generated by the sickling process and occlusion of the microvasculature, as described in the preceding discussion.

An important aspect of effective management of sickle cell pain is the intent of the care provider. Do the providers in question endeavor to treat patients in an empathetic manner by listening to, respecting, and believing them? Or do they stigmatize them as drug addicts demonstrating drug-seeking behavior and thereby justify the expulsion of some patients from their system? Do the providers actively seek management of sickle cell pain, or are they passively forced by the system to which they belong to treat patients in a cursory manner? These are difficult questions to answer and research. The outcome of management of sickle cell pain relies heavily on the ethical principles to which the providers in question subscribe.

Effective management of acute sickle cell pain in the emergency room and hospital may be achieved by following four major sequential stages: (1) assessment, (2) treatment, including choice of the analgesic, the dose, and the route and method of administration, (3) reassessment to evaluate the effectiveness of the treatment stage and implement changes as needed, and (4) adjustment, including titration of the dose of opioid to achieve adequate pain relief, rescue, tapering, and switching to oral medications, driven by the feedback loops of reassessment.

Assessment. Assessment is the cornerstone of effective pain management. It should be conducted before and periodically after the administration of analgesics [16,22–24]. Because pain is subjective in nature, the patient's self-report is the most important factor in the hierarchy of pain management. Assessment relies heavily on the patient's self-report. Other factors in the process of assessment should include the presence or absence of other complications of the disease, such as infection, family members' report, and vital signs, including temperature, blood pressure, pulse, respiratory rate, and pulse oximetry. The patient's self-report should include multidimensional scales describing intensity, quality, location, distribution, onset, duration, mood, sedation, pain relief, and factors that aggravate or relieve pain [22–24].

Initial pain assessment establishes a baseline against which the effectiveness of analgesics in achieving pain relief will be compared. Assessment allows the patient and the treatment team to discuss management strategies and treatment objectives. Periodic assessment with rating and categorizing of pain will delineate multiple pain syndromes, which may occur as the pain progresses over time. Thorough assessment will thus result in intervention and modification of the treatment plan when necessary. Any change in therapy that does not take the patient's self-report into consideration by means of periodic assessment, especially a change in the dose and frequency of administration of analgesics, may be doomed to fail and to create misunderstanding between the patient and provider.

The intensity of pain can be assessed using any of several available scales, such as the visual analogue scale, verbal scale, numerical scale, or Wong-Baker faces scale for children. It is important, however, to stick to one scale and use it routinely, so that both the patient and provider become familiar with it and with its significance to a particular patient. Nociceptive sickle cell pain typically is sharp or throbbing in nature. Pain that is burning, shooting, lancinating, or tingling suggests the presence of a neuropathic component that entails the use of certain adjuvants, to be discussed later [5,22].

Initial pain assessment establishes a baseline against which the effectiveness of analgesics in achieving pain relief is compared. Subsequent assessment may lead to increasing the dose of analgesics to achieve desirable pain relief, tapering the dose of analgesics as the painful episode resolves, and identifying adverse effects of therapy or the emergence of complications of the disease that allow intervention and modification of the treatment plan as needed.

Nonpharmacologic management of pain. Nonpharmacologic management of pain includes cutaneous stimulation (transcutaneous electrical nerve stimulation), heat, cold and vibration, distraction, relaxation, massage, music, guided imagery, self-hypnosis, self-motivation, acupuncture, and biofeedback. Although there are no well-controlled clinical trials of the efficacy of these methods in the management of sickle cell pain, there are many anecdotal reports of their efficacy in pain management.

Pharmacologic management of pain. Pharmacologic management of pain includes three major classes of compounds: nonopioids, opioids, and adjuvants [5,22,23]. A major difference between nonopioids and opioids is that the former have a "ceiling effect," a term that refers to a dose above which there is no additive analgesic effect [25]. Nonopioids include acetaminophen, nonsteroidal anti-inflammatories (NSAIDs), topical agents, tramadol, and corticosteroids.

Acetaminophen has analgesic and antipyretic effects but no anti-inflammatory component [26]. The daily total adult dose must not exceed 4 g in four to six divided doses [27]. High dosages damage the liver and could be fatal. The daily dose should be decreased in the presence of liver disease. The daily dose of combination medications (medications that contain acetaminophen plus an opioid) must be controlled so that the 4-g limit of acetaminophen is met.

NSAIDs (Table 1) include nonselective cyclo-oxygenase (COX) inhibitors and selective and partially selective COX-2 inhibitors [28–30]. NSAIDs have an anti-inflammatory effect in addition to their analgesic and antipyretic potential. They act primarily at the level of nociceptors where pain impulses originate and hence are often referred to as peripherally acting analgesics. They exert their analgesic effect by inhibiting COX enzymes and decreasing the synthesis of prostaglandins [28], thus decreasing or abolishing the sensitization of nociceptors by prostanoids. The traditional nonselective NSAIDs inhibit both the housekeeping COX-1 and the inducible COX-2 enzymes. Selective NSAIDs inhibit only the COX-2 enzyme and spare COX-1, which is needed to produce physiologic levels of prostaglandins.

NSAIDs have potentially serious, systemic adverse effects. They include gastropathy, nephropathy, and hemostatic defects. NSAIDs should not be administered to patients with renal disease or history of peptic ulcer disease. It is advisable not to administer them continuously for more than 5 days to patients with SCD. Moreover, certain NSAIDs are associated with idiosyncratic (non–prostaglandin-mediated) reactions [28]. Most recently reported among these is immune thrombocytopenia resulting from sensitivity to metabolites of naproxen and acetaminophen [31]. The antibodies described were mostly specific to Glyco Protein (GP) IIb/IIIa and less often specific to GP Ib/IX/V. COX-2 inhibitors are associated with significantly fewer gastrointestinal and hemostatic adverse effects [29,30] than the nonselective NSAIDs, but their effect on renal function appears to be the same [32,33]. The concomitant administration of ketorolac with opioids is reported to exert an additional analgesic effect and decrease the quantity of opioids consumed for the treatment of acute painful episodes [34].

Table 1
Nonopioid pharmacologic agents commonly used in the management of pain

Drug (Brand name)	Maximum daily dose (mg)	Half-life (T 1/2, h)
Acetaminophen[a]	4000	1–3
Non-steroidal anti-inflammatory drugs		
Nonselective COX inhibitors		
Salicylates		
Acetylsalicylic acid (aspirin)[a]	4000	4–15
Nonacetylated salicylates		
Salicyl salicylate	3000	4–15
Diflunisal	1500	7–15
Choline magnesium trisalicylate	3000	4–15
Propionic acid derivatives[a]		
Ibuprofen[a]	3200	2
Naproxen[a,b]	1500	13
Fenoprofen	3200	2
Ketoprofen[a,b]	300	2
Flurbiprofen	300	3–4
Acetic acid derivatives		
Indomethacin[b]	200	3–11
Ketorolac orally	40	3–11
Ketorolac intramuscular/intravenous	120	3–8
Sulindac	400	16
Tolmetin	1800	1–2
Diclofenac[b]	150	2
Etodolac[b]	1000	7.3
Nabumetone	2000	22.5–30
Anthranilic acid derivatives		
Mefenamic acid	1000	2–4
Meclofenamate	400	2–3
Oxicams		
Piroxicam	20	30–86
Selective COX-2 inhibitors		
Celecoxib	400	11–12
Partially selective COX-2 inhibitors		
Meloxicam	15	15–20

Abbreviation: COX, cyclo-oxygenase.
[a] Available over the counter.
[b] Available in delayed/extended release forms.

On September 30, 2004, Merck voluntarily withdrew Rofecoxib from worldwide use. This decision was based on a study that was designed to detect benefits of Rofecoxib (25 mg) in preventing recurrence of cancerous polyps over 3 years. Two thousand six hundred patients enrolled (62% males, 40 to 60 years old, 16% on aspirin). After 18 months, the patients taking Rofecoxib had significantly higher incidence of cardiovascular disease compared with those taking a placebo. This finding made all other coxib inhibitors suspect of causing cardiac problems. It is therefore recommended to monitor patients taking COX-2 inhibitors carefully, with special attention to cardiac and renal functions.

Tramadol [35] is a synthetic, centrally acting analgesic that is not chemically related to opioids. It acts as a weak agonist with preferential affinity to the μ-receptors. Moreover, it inhibits neuronal reuptake of both serotonin and norepinephrine and stimulates the release of serotonin. Thus, it has functional properties of an opioid and an antidepressant. This drug received an initial enthusiastic reception based on the perception that it was not associated with clinically significant respiratory depression or addiction potential; this enthusiasm waned after reports indicated that seizures may be an adverse effect and that abuse potential is increasing. Currently, tramadol is not a scheduled drug. It appears to be as effective as acetaminophen with codeine, with the added advantage of a tricyclic antidepressant–like effect. Tramadol may be administered by the oral or parenteral route, and it is available in slow-release form. Only the oral form is currently approved for marketing in the United States. Anecdotally, tramadol appears to be effective in the management of mild or moderately severe pain in some patients with sickle cell anemia.

Opioid analgesics [36] have fewer systemic adverse effects than NSAIDs, but their use in SCD is associated with many myths about drug-seeking behavior and addiction. Four major classes of opioids exist: agonists, partial agonists, mixed agonists-antagonists, and antagonists (Box 2).

Traditionally, opioid antagonists have been regarded as having no analgesic effect, and their use is primarily limited to counteracting the depressive effects of opioid agonists. Recently, however [37], there have been reports showing that small doses of antagonists in combination with agonists appear to enhance the analgesic effect and to prevent or delay tolerance to opioid agonists. Should this approach be proved by controlled trials, it would be a novel tool in the management of pain.

Opioid agonists are most often used in the management of sickle cell pain, especially in adults. They decrease or modify the perception of pain at the level of the central nervous system. They exert their effect by binding to μ-, κ-, and, to a lesser extent, δ-receptors [36]. Opioid agonists can be administered by several routes (eg, orally, subcutaneously, intramuscularly, intravenously, transdermally) and methods, including continuous intravenous drip, patient-controlled analgesia pump, and intermittent injection. Meperidine, morphine, and hydromorphone are the major opioid analgesics used in the treatment of severe pain in the emergency department and hospital. Controlled-released opioids, such as controlled-release (CR) oxycodone and morphine CR, are useful in the management of chronic pain and in combination with short-acting opioids for breakthrough pain. Fentanyl is available in parenteral, transdermal, and transmucosal formulations. Methadone is a true long-acting opioid that can be used in combination with short-acting opioids in selected patients.

Adverse effects of opioid analgesics include itching, nausea, vomiting, sedation, and respiratory depression. Seizures may be associated with opioids, especially with the prolonged use of meperidine and the consequent accumulation of its major metabolite, normeperidine, in some patients. The effects of meperidine and normeperidine on seizure induction are more pronounced in the

Box 2: Classification of opioids

Opioid Agonists

- Codeine
- Hydrocodone and dihydrocodeine
- Oxycodone
- Morphine
- Meperidine
- Hydromorphone
- Levorphanol
- Oxymorphone
- Methadone
- Fentanyl
  - Parenteral formulation
  - Transdermal patch
  - Transmucosal lozenge

Partial Agonists

- Buprenorphine

Mixed Agonists-Antagonists

- Pentazocine
- Nalbuphine
- Butorphanol

Antagonists

- Naloxone
- Nalmefene
- Naltrexone

presence of renal disease. Tolerance and physical dependence occur in some patients, but addiction is rare [5]. Methadone may be associated with prolongation of the QTc interval [38].

As a group, opioid analgesics have no ceiling effect (with the possible exception of codeine); hence the only limiting factor on their dose is adverse effects. Severe sedation and respiratory depression are the most important adverse effects. Hospitalized patients receiving opioid analgesics on a regular basis should be monitored for their respiratory rate and sedation level. A respiratory rate of less than ten per minute or severe sedation justifies skipping, decreasing, or delaying the dose or discontinuing the opioid in question until the depressive effects disappear. Opioid analgesics should be used carefully in patients with

impaired ventilation, asthma, increased intracranial pressure, and liver failure. The dosage of meperidine and morphine should be adjusted in the presence of renal failure. Moreover, morphine is the most histaminergic of all opioids [39], and histamine release may trigger bronchospasm or initiate allergic reactions. The presence of acetaminophen in combination with codeine or oxycodone limits the daily dose that may be safely used so that the maximum allowable dose of acetaminophen is not exceeded. The use of meperidine in conjunction with monoamine oxidase inhibitors may cause a severe adverse reaction characterized by excitation, hyperpyrexia, convulsions, and death [40]. The coadministration of antipsychotics with meperidine may cause neuromuscular disorders, including akathisia, dystonia, tardive dyskinesia, and neuroleptic malignant syndrome [41].

Adjuvants include antihistamines, antidepressants, benzodiazpines, and anticonvulsants. These are heterogeneous compounds that potentiate the analgesic effect of opioids, ameliorate their side effects, and have their own mild analgesic effect. The most commonly used adjuvants in the management of sickle cell pain are listed in Box 3. The role of selective serotonin reuptake inhibitors in sickle cell anemia is not clear at present. Adjuvants must be used with care, and patients should be monitored carefully when receiving them. Adjuvants also have adverse effects, some of which precipitate or worsen manifestations of sickle cell anemia [5].

Acute painful episodes of mild or moderate severity are usually treated at home using a combination of nonpharmacologic and pharmacologic modalities. Home treatment of pain usually follows the three-step analgesic ladder proposed by the World Health Organization [42]. Mild pain is treated with nonpharmacologic agents alone or in combination with a nonopioid. More severe pain entails the addition of an opioid with or without an adjuvant. Data from the Multi-center Study of Hydroxyurea (MSH) [18,19] in sickle cell anemia showed that oxycodone/acetaminophen formulation was the opioid most often used for the home treatment of pain [43]. However, this report preceded the advent of the new formulations of opioids, such as oxycodone CR. Whether oxycodone/acetaminophen continues to be the first choice in this scenario of pain management remains to be seen.

Severe acute sickle cell painful episodes are usually treated in a medical facility using parenteral analgesics. A mark of progress in this area is the advent of day hospitals where patients are promptly evaluated by a team of experts in the management of sickle cell pain, without the delay that is common in hospital emergency rooms [44]. Available data in the literature show that management of patients with severe acute painful episodes in such facilities, especially those that operate on a 24-hour basis, reduces the frequency of hospital admissions. These findings should encourage other metropolitan hospitals in cities with large populations of African Americans to follow suit by establishing acute care facilities specifically designed for patients who have sickle cell disease. The establishment of such facilities nationwide may, in turn, verify the cost-saving potential of this approach to health care.

Box 3: Adjuvants commonly used in the management of sickle cell pain

Antihistamines

- Hydroxyzine
- Diphenhydramine

Benzodiazepines

- Diazepam
- Alprazolam

Tricyclic Antidepressants

- Amitriptyline
- Nortriptyline
- Doxepin

Anticonvulsants

- Phenytoin
- Carbamazepine
- Gabapentin
- Topiramate
- Clonazepam

Phenothiazines

- Prochlorperazine
- Promethazine

Data from the MSH showed that the parenteral opioid most often used in the management of acute sickle cell painful episodes in the emergency department or hospital was meperidine [43]. Since this report from 1996, there have been anecdotal reports from many hospitals of switching to opioids other than meperidine, but detailed studies to confirm this transition are not yet available.

Patients with chronic sickle cell pain and those with frequent acute painful episodes are best managed with a combination of long-acting opioids and a short-acting opioid for breakthrough pain. Again, anecdotal reports suggest that this approach decreases the frequency of admissions to the emergency department or hospital, but data to confirm this finding are not available to date. Oxycodone CR appears to be unique in that it has both an immediate analgesic effect and a delayed long-acting one. These properties have made oxycodone CR popular among drug abusers who have learned to remove the mesh and release a high dose of pure oxycodone that has an immediate "euphoric" effect [45].

Care providers should exert caution in prescribing oxycodone CR and other opioids and should keep records of assessment and plans of management for their patients.

Measures to reduce the morbidity and mortality of sickle cell anemia include prophylactic penicillin therapy (or a macrolide when there is sensitivity to penicillin) in infants and children [46] and hydroxyurea in adults [18,19]. Patients who responded to hydroxyurea experienced significant reduction in the incidence of acute painful episodes, acute chest syndrome, transfusion requirement, and mortality [18,19,47]. The beneficial effects of hydroxyurea are thought to be due to its induction of Hb F production. Any increase in Hb F level appears to have a salutary effect on the clinical picture of sickle cell anemia.

CHRONIC SICKLE CELL PAIN

Chronic pain, in simple terms, is pain that does not go away. Some investigators define it as pain that persists for 3 or more months. The major feature of chronic pain is that it has no useful biologic function. Acute pain, or eudynia, has biologic usefulness in that it alerts the patient to noxious events and elicits flight and fight mechanisms that activate the sympathetic nervous system. Chronic pain, or maldynia, has no biologic usefulness. It becomes a disease in its own right with no activation of the sympathetic system. Having chronic pain is a daunting experience. Emotional distress and behavioral dysfunction are major components of chronic pain syndromes. Such pain disrupts the mind-over-body interaction so that the body, rather than the mind, becomes the operator. Chronic pain induces changes in the brain that culminate in physical deconditioning, pain behaviors, altered mood, irritability, depression, anxiety, sleep disturbance, loss of interest in sex, family stress, financial concerns, decreased self-esteem, frequent visits to health care providers, heavy use of analgesic medications, and fear.

There are two types of chronic sickle cell pain (see Box 1): chronic pain due to obvious pathology (avascular necrosis and leg ulcers) and intractable pain with no obvious signs.

Chronic Pain with Obvious Pathology

Leg ulcers

Leg ulceration [48,49] is a painful and sometimes disabling complication of sickle cell anemia that occurs in 5% to 10% of adult patients. Severe pain may necessitate the use of opioid analgesics. Leg ulcers are more common in men and older patients and less common in patients with α-gene deletion, high total Hb level, or high levels of Hb F. Treatment of leg ulcers includes wound care using wet to dry dressings soaked in saline or Burrow's solution. With good localized treatment, many ulcers heal within a few months. Leg ulcers that persist beyond 6 months may require blood transfusion or skin grafting, although results of the latter treatment have been disappointing. Because leg ulcers may recur after minimal trauma, wearing pressure stockings may appear to be an

effective preventive measure. Principles of management of leg ulcers include education, protection, infection control, debridement, and compression bandages. The efficacy of blood transfusion or exchange transfusion, hyperbaric oxygen, and skin grafting is anecdotal. Recent advances in management include the use of platelet-derived growth factor, prepared either autologously (Procuren) or by recombinant technology (Regranex). The use of newly described semipermeable polymenic membrane dressing may promote healing.

Avascular necrosis

Avascular necrosis [50–53] (also called ischemic necrosis or osteonecrosis) is the most commonly observed complication of SCD in adults. Although it tends to be most severe and disabling in the hip area, it is a generalized bone disorder in that the femoral and humeral heads and the vertebral bodies may be equally affected. The limited terminal arterial blood supply and the paucity of collateral circulation make these three areas especially vulnerable to sickling and subsequent bone damage. Patients with sickle cell anemia and α-gene deletion have a higher incidence of avascular necrosis, because their high hematocrit increases blood viscosity and thus enhances microvasculopathy in the aforementioned anatomic sites. Treatment of avascular necrosis is symptomatic and includes providing nonopioid or opioid analgesics in the early stages of the illness; advanced forms of the disease require total joint replacement. Core decompression appears to be effective in the management of avascular necrosis if performed during its early stages.

Intractable Chronic Pain Without Obvious Pathology

This is the worst scenario of chronic sickle cell pain. It is not associated with obvious signs. The only complaint is the patient's self-report of pain that does not go away. Often it is difficult to distinguish a persistent acute painful episode from a chronic pain syndrome. The distinction, however, may not be relevant, because the outcome and treatment are eventually the same or show considerable overlap. Worse still is a patient who is chronic pain, is maintained on high-dose oral opioids, and develops an acute painful episode over and above the chronic pain syndrome: a situation where the dose of opioids must increase to phenomenal levels to achieve pain relief. The pathophysiology of intractable chronic pain is unknown. It appears to result from "central sensitization": a situation where repeated and frequent pain stimuli lower the pain threshold to the degree that ambient innocuous events cause severe pain. It is unknown at which point this occurs or which are the factors that may transform an acute painful episode into a chronic pain syndrome. Surgery, a severe acute painful episode, and severe emotional stresses are some of the proposed causes [15].

Management of chronic sickle cell pain must be multidisciplinary. Leg ulcers necessitate the input of wound care centers, whereas avascular necrosis entails the involvement of orthopedics, physical therapy, rehabilitation, and rheumatology. Intractable pain (central sensitization) dictates the use of nonpharmacologic approaches, of adjuvants, and inevitably, in sickle cell chronic pain, of long-acting or CR opioids with short-acting opioids for breakthrough pain.

NEUROPATHIC PAIN

Neuropathic pain is characterized by sensations of burning, tingling, shooting, lacinating, and numbness. These symptoms may occur in the presence or absence of obvious central or peripheral nerve injury. The mechanism of neuropathic pain presumably involves aberrant somatosensory processing in the central or peripheral nervous system. Sickle cell pain could have a neuropathic component [54,55]. A thorough history and physical examination are essential to determining whether sickle cell pain is associated with a neuropathic component. Mental nerve necropathy [56,57], trigeminal neuralgia [58], acute proximal median mononeuropathy [59], entrapment neuropathy [54], and acute demyelinating polyneuropathy have [54] been described in SCD.

Management of neuropathic pain involves anticonvulsants (see Box 3). Gabapentin appears to be the anticonvulsant that is generally used for this complication.

SPECIFIC RECOMMENDATIONS FOR THE READER

- Recognize that sickle cell pain is protean in nature. Although the acute sickle cell painful episode is the hallmark of the disease, other types of pain are often present. Thus sickle cell pain may be acute, subacute, chronic with objective signs, or chronic without obvious signs. Moreover, the pain could be somatic or visual, nociceptive or neuropathic, localized or diffuse, unilateral or bilateral, and moderate or severe.
- The first step in the management of sickle cell pain is assessment to identify the factors, if any, that precipitated the painful episode. Thorough assessment will also identify the type of pain a patient has and thus make it possible to implement the appropriate plan of management.
- A key component of the process of assessment is believing the patient. Patients who have SCD are the authorities on their pain, and their self-reports must be taken seriously.
- In managing sickle cell pain, consider both the nonpharmacologic and pharmacologic approaches to pain control. Details of these approaches were discussed earlier.
- Recognize that the goal of pain management is to achieve adequate pain relief. The use of nonopioids, opioids, and adjuvants together is more effective in achieving adequate pain relief.
- Be aware that some patients who have SCD suffer from intractable chronic pain without obvious pathologic conditions. Management of these patients requires patience, compassion, regular follow-up, and the use of a multidisciplinary approach.

SUMMARY

The clinical manifestations of SCD fall into four major categories: (1) pain, (2) anemia and its sequelae, (3) organ failure, including infection, and (4) comorbid conditions.

Advances in the pathogenesis of SCD focused on the sequence of events that occur between polymerization of deoxyhemoglobin S and vaso-occlusion. Cel-

lular dehydration, inflammatory response, and reperfusion injury appear to be important pathophysiologic mechanisms.

Management of SCD continues to be primarily palliative in nature, including supportive, symptomatic, and preventive approaches to therapy. There are three major types of sickle cell pain: acute, chronic, and neuropathic pain. The acute painful episode is the insignia of the disease and the most common cause of hospitalization. Its management entails the use of nonpharmacologic and pharmacologic modalities. Pain management should follow certain principles that include an assessment stage, treatment stage, reassessment stage, and adjustment stage. Chronic sickle cell pain may be due to certain complications of the disease, such as leg ulcers and avascular necrosis; intractable chronic pain may be due to central sensitization. Management of chronic pain should take a multidisciplinary approach.

The ultimate goals of management of sickle cell pain should be pain relief, improved physical functioning, reduced psychosocial distress, and improved quality of life.

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