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Pain Syndromes in Sickle Cell Disease: An Update

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ABSTRACT

Objective. Pain has a critical role in the management of sickle cell disease (SCD). Patients may suffer from several pain syndromes, which may be or not may be associated with other clinical complications, such as anemia, organ failures, and infections.

Design. Data for review were identified by using PubMed to search MEDLINE, limiting the search to abstract/articles in English, Italian, French, and Dutch. The key words *pain*, *sickle cell disease*, *anemia*, *hemoglobin*, *hemoglobinopathy*, *analgesics*, *opioids*, *morphine*, *acetaminophen*, *paracetamol*, *nonsteroidal anti-inflammatory drugs*, *hematology*, and *quality of life* were variously combined in the title, abstract, and key word search list. The abstract database of most hematological congresses and the bibliographies of most relevant articles were also considered.

Results. There are two major types of SCD pain: acute and chronic. Sometimes, mixed and neuropathic pain can be also observed. Acute pain is mostly related to vaso-occlusion. Chronic pain may be due to some SCD complications, such as leg ulcers and avascular necrosis.

Conclusions. Pain management in the SCD setting needs multidisciplinary approaches, given the several syndromes and the pathogenic mechanisms that are likely involved. Pain management is not standardized and often difficult, so that many patients with SCD are still poorly treated. Further efforts to develop care plans and treatment protocols as well as management guidelines are required.

Key Words. Sickle Cell Disease; Pain; Pain Management; Morphine; Hemoglobin

Introduction

Sickle cell disease (SCD) includes a group of genetically inheritable disorders characterized by the substitution of valine for glutamic acid in the sixth position of the β globin [1]. These globin abnormalities lead to profound changes in molecular solubility and instability and the tendency of deoxygenated hemoglobin (Hb) to undergo polymerization [2,3]. SCD may result from compound defects, in which HbS is associated with other abnormal Hbs such as Hb C (SCD-SC) or Hb D (SCD-SD) and HbE (SCD-SE) or with an interacting thalassemia gene, as observed in sickle β-thalassemia (β^s/β^o thal and β^s/β^+thal). The severity of the resulting syndrome depends upon the type of the associated abnormalities. SCD is a systemic multiorgan disease, which includes clinically heterogeneous features ranging from asymptomatic to very aggressive forms [4–6]. Acute pain is the predominant symptom associated with SCD; it is frequently related to vaso-occlusive crisis (VOC), which, in some cases, may be the prodrome of serious and potentially fatal complications, such as the acute splenic sequestration crisis (ASSC) [3], and the acute chest syndrome (ACS) [5]. Other pain syndromes observed in SCD patients may be due to several disease complications, such as leg ulcers, bone and joint disease [7], or nerve disturbances [8]. The long-life course of the illness, combined with frequent hospitalizations for pain and other complications, can contribute significantly to impair psychosocial functioning [9] and to reduce patient's quality of life (QoL) [10]. Pain is the cause of more than 90% of hospital admissions among adult patients with SCD [5,6]. Because of SCD's worldwide distribution as a result of immigration to

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countries with a traditionally low prevalence of SCD [11,12], affected individuals may be treated and monitored not only in specialized centers but also in general hospitals and emergency services [13]. Thus efforts should be made both to develop treatment protocols and management guidelines and to optimize their application in many different health care environments.

Materials and Methods

Data for review were identified by using PubMed to search the MEDLINE, limiting the search to abstract/articles in English, Italian, French, and Dutch. The key words *pain*, *sickle cell disease*, *anemia*, *hemoglobin*, *hemoglobinopathy*, *analgesics*, *opioids*, *morphine*, *acetaminophen*, *paracetamol*, *nonsteroidal anti-inflammatory drugs* (NSAIDs), *hematology*, and *quality of life* (QoL) were variously combined in the title, abstract, and key word search list. The abstract databases of most hematological congresses and the bibliographies of most relevant articles were also reviewed.

Epidemiology of SCD pain

Several studies have investigated the epidemiological features of pain in SCD. One of the first was performed on a cohort of 3,578 individuals affected with SCD-SS, SCD-S/β^othalassemia, and SCD-S/β^+thalassemia and reported an average pain rate of 0.8, 1.0, and 0.4 crises per person per year, respectively. In the SCD-SS group, 39% of patients had no episodes of pain, and 1% had more than six episodes per year. Moreover, a small number (5.2%) of patients presenting 3–10 episodes per year had 32.9% of all pain crises. Although some pain crises may occur without any apparent precipitating cause, some risk factors, such as increased hematocrit, the presence of α thalassemia, a reduced oxygen saturation of inspired air, cardiac and pulmonary impairments, dehydration, infections, acidosis, and hypothermia, have been associated with high pain rates, while protective effects of high concentrations of HbF have been recognized [14].

In another study, the occurrence of pain was directly correlated with early death [15]; these findings were confirmed by a report claiming that, out of 209 adult patients who died during the study period, 78 percent had pain [16]. The French Study Group on SCD reported that 172 (58%) of 299 patients suffered annually from one or more pain crises [17]. In addition, a comparative analysis on the incidence of pain involving 308 affected individuals showed that 58.6% of men and 56.5% of women with SCD reported pain, which was not statistically different, but that crises occurred more frequently in men with SCD-SS [18]. Regarding the infants with SCD, patients with SCD-SS and SCD-S/β^othalassemic had more pain than those with SCD-S/β^+thalassemia or SCD-SC [19]. In the home setting, 37 children with SCD during 18,377 days experienced 514 distinct pain episodes, which were reported on 2,592 days and 2,326 nights [20].

Some studies have addressed the association of pain with other factors, such as increased body weight and dietary patterns [21]. Moreover, the presence of respiratory symptoms is associated with frequency of pain crisis [22]. Other associations with pain in patients with SCD include windy weather, low humidity [23], and psychological stress [24]. The association of VOC with some gene polymorphisms, such as those for endothelin 1 and endothelial constitutive nitric oxide (NO) synthase, has been recently described in patients with SCD-SS [25].

Chronic pain due to leg ulcers, avascular necrosis, and other degenerative conditions afflicting bones and joints occurs in 5–10% of adult patients [26]. Patients with SCD and α-thalassemia have a higher incidence of avascular necrosis because of their high hematocrit and increased blood viscosity. Headaches are reported in 50–76% of cases [27].

A mechanism of europathic pain maintained centrally by abnormal somatosensory processes and central sensitization is advocated to explain the origin of some painful states of unknown origin [6]; however, no clinical studies have been demonstrated so far to explain the occurrence of these mechanisms in SCD patients, although they are reported in other painful chronic illnesses, such as musculoskeletal [28,29] and peripheral arterial diseases [30].

Classification and Pathophysiology

Most SCD pain syndromes are detailed in Table 1. Acute pain is the hallmark of the disease and is mostly associated with VOC, whose occurrence is related to the HbS polymerization and to the subsequent formation of sickle-shaped erythrocytes. Other recognized contributing factors in the determinism of VOC are endothelial cell activation, erythrocyte and leukocyte adhesion, vasoconstriction, coagulation activation, cellular dehydration, the inflammatory response, reperfu-

Table 1 Pathophysiology of the most common pain syndromes in patients with sickle cell disease

Pain Type	Pain Origin and Syndromes
Nociceptive	
Deep somatic	Vasocclusive crisis, bone marrow infarction, priapism
Superficial somatic	Leg ulcers
Visceral	Infarction of parietal blood vessel of cava viscera (ischemic colitis), appendicitis, pancreatitis, acute splenic sequestration crisis, splenic infarcts, splenic abscess, cholelithiasis, choledocholithiasis peptic ulcers
Neuropathic	
Peripheral neuropathic	Vaso-occlusive crises, neuropathies
Central neuropathic	CNS damage, ictus, central sensitization (?)
Mixed	
Neuropathic + Somatic	Vaso-occlusive crisis
Breakthrough	
Incident (related to the movement)	Vaso-occlusive crisis, skeletal damage
Nonincident pain	Transient flares of pain during stable analgesia

CNS = central nervous system.

sion injury, and impaired blood flow due to reduced NO bioavailability [31]. Hb changes and oxidant damage of the red blood cells (RBC) membrane by reactive Hb by-products result in increasing K-Cl cotransport leading to K^+ and water loss, Ca^{2+} accumulation, Gardos channels (Ca^{2+}-activated K^+ export) activation, and further dehydration. Moreover, sickle RBC adherence to vascular endothelium may lead to vascular occlusion and tissue infarction, which in turn initiates a secondary inflammatory response, creating a vicious cycle. Indeed, several inflammatory mediators, such as interleukin-1, bradykinin, histamine, substance P, and prostaglandins (PGs) E2 and I2 activate nociceptive afferent nerve fibers and promote vasodilatation and extravasations of fluids that can lead to local swelling and tenderness [32]. In addition, PGs 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. This pain, reflecting both tissue death and secondary inflammatory responses, is categorized as deeply somatic; given its acuteness and severity, it represents the insignia of this disease [6]. The etiology and the patophysiology of most common chronic pain syndromes [6–8,26] observed in SCD patients are reported in Table 1.

Clinical Features

VOC-related pain may involve any part of the body, and its severity, location, and duration may vary within groups of patients and within each individual. Moreover, the frequency and severity of each pain crisis may change as a person grows from childhood to adulthood, with the break point being the late teens. The frequency of the painful crises denotes the gravity of the sickling disorder; three or more crises annually indicate severe disease [6].

In a study of 192 children with SCD, 21 of which presented 41 episodes of acute pain, the most commonly affected bones were the humerus (38%), tibia (23%), and femur (19%). Tenderness, swelling, impaired joint motion, local heat, and erythema were the prominent clinical findings other than pain [33]. In most cases, pain gradually disappears over a period of hours to days with symptomatic management. However, the infarction may occasionally involve extensive portions of vascular bed resulting in bone marrow (BM) necrosis [34]. BM necrotic particle embolisms represent a recognized provocative factor for the development of ACS [3,35] and fat embolism syndrome, which are the main life-threatening complications of SCD. Among the chronic pain syndromes, avascular necrosis is associated with deep somatic pain, often complicated by incident pain. Abdominal pain is common during crises. Its pathogenesis is not fully understood, and it may represent a diagnostic challenge, mimicking a wide spectrum of surgical emergencies. The careful evaluation and the differential diagnosis of pain, excluding other potential mimicking conditions such as BM infarction and vertebral body's necrosis, ASSC [36], hepatobiliary disorders, ischemic colitis, pancreatitis and other gastrointestinal illnesses, are essential to avoid unnecessary surgical intervention [37].

Prevention of Pain

The prevention of SCD pain should be a part of a comprehensive approach to SCD. Precipitating factors, such as dehydration, infections, diuretics, altitude, acidosis, and hypoxia, should be avoided. Folic acid supplements as well as treatment of medical and surgical complications should be provided. The HbS value should be maintained lower than 30%, and HbF levels, which are inversely related to the occurrence of pain, should increase [5,38].

Pharmacological attempts to induce HbF production with hydroxyurea (HU) [39] should be carried out in adult patients, in whom even small increments in its concentration may positively

affect pain [40]. However, while HU therapy for adult patients with SCD is a well-established indication [41], its use in infants and children should be cautious and require close monitoring in light of the demonstrated acquired genetic mutations induced by this drug [42]. However, some recent studies report long-term sustained efficacy and safety of HU therapy in this setting [43,44].

The addition of erythropoietin is suggested to allow more aggressive HU dosing in patients with high risk for SCD [45]. The benefits provided by others HbF-inducing agents, such as arginine butyrate, are reported in some children with SCD [46]. Sickle cell dehydration and the role of the Gardos channels represent other major targets of prevention of VOC by possibly blocking them by increasing the abnormally low erythrocyte magnesium (Mg) content of sickle erythrocytes [47,48]. Thus, oral Mg pidolate has been provided favorable results in clinical trials [49]. Other Gardos channel inhibitors, such as clotrimazole [50] and ICA-17043 [51], are under study.

The efficacy of chronic transfusions in reducing debilitating pain, although reported on the basis of empirical experience [6], has not be proven in controlled studies.

At present, no controlled trials have demonstrated that the above-mentioned agents modify the clinical disease course of SCD in patients [52].

Diagnosis and Assessment of Pain

The cornerstones of pain management are the recognition, the diagnosis, and the assessment of pain intensity. Patient report is the primary source for assessment [53], except in infants where behavioral observations are used. Therefore, the intensity of pain can be assessed by using any of several available scales, such as the visual analog scale, verbal scale, numerical scale, or Wong–Baker faces scale for children [54,55]. Pain assessment and treatment should be a part of a comprehensive SCD management, given the close relationships that link contributing and precipitating factors of pain with the other three main pathologic features of SCD [6], such as anemia, infections, and organ damage, such as ACS [56].

Pain Management

A pain crisis in SCD, due to its association with pathology, is an emergency that should be promptly evaluated and vigorously managed to achieve pain relief as soon as possible. Patients should be regularly monitored for analgesic effectiveness, complications of SCD, and hypoxia. Treatment should rely on bed rest, fluid hydration, administration of analgesics according to the pain intensity [57], and complementary and nonpharmacological measures [58]. Oxygen inhalation has no effect on the duration of pain [59,60] and may involve complications [61]. Although high doses of methylprednisolone decrease the duration of severe pain, this drug has a limited role due to the rebound attacks after therapy is discontinued [62]. NO is under investigation as an antisickling agent for its vasodilatation properties. Indeed, it regulates blood vessel tone, endothelial adhesion, and the severity of ischemia-reperfusion injury and anemia; breathed NO reduces the tendency of HbS to polymerize and may be beneficial for VOC [63]. Intravenous (IV) poloxamer 188 significantly reduced total analgesic use and pain intensity in patients with SCD-related pain [64]. However, taken together, the effects of the potentially sickle-modifying agents are very limited and require further research.

Pharmacological Approaches and Strategies

Pharmacological pain management relies on analgesics and should be aimed at providing rapid pain control, which should be then maintained with long-acting oral or parenteral agents, with provision of supplementary doses if breakthrough pain occurs. Regimens to treat sickle pain include nonopioids, opioids, and adjuvant agents [65]. Management of mild to moderate pain should rely on NSAIDs or paracetamol, unless there is a contraindication. If mild to moderate pain persists, an opioid can be added. Treatment of persistent or moderate to severe pain relies on opioids. The combination of nonopioid analgesics with opioids allows lower doses of the latter (balanced analgesia).

Nonopioid Analgesics

This class of nonsedating analgesic drugs includes NSAIDs and paracetamol. The former are provided of anti-inflammatory, analgesic, and antipyretic properties. They act primarily on nociceptors, where pain impulses originate, by inhibiting the synthesis of PGs, thus decreasing or abolishing the sensitization of nociceptors by prostanoids. The traditional nonselective NSAIDs inhibit both the housekeeping cyclo-oxygenase (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 PGs [6]. Indeed, the inhibition of PGs by NSAIDs may lead to several side effects, such as hemostatis, congestive heart failure, acute renal failure, nephrotic syndrome, and gastropathy. Therefore, stronger NSAIDs are reserved for older children with severe pain. Moreover, given the borderline renal function frequently found in adults with SCD, the use of NSAIDs can be a matter of debate. Aspirin should be avoided due to a risk of Reye's syndrome in febrile children. In the presence of these contraindications, NSAIDs should be avoided and replaced with other drugs.

Among NSAIDs, ketorolac has an equivalent analgesic activity to morphine in acute pain setting; moreover, the concomitant administration with opioids exerts an additional analgesic effect [38] so it may be added to opioids if they provide inadequate analgesia. It has been used to treat SCD pain crisis with favorable results [66]. However, due to potential renal toxicity, the current recommendation is that ketorolac should not be used for longer than 5 days in a month.

Paracetamol exerts analgesic and antipyretic but not anti-inflammatory effects. Indeed, it does not inhibit peripheral PGs and therefore appears to have a safer profile than NSAIDs. Moreover, there is considerable evidence of an additional central analgesic effect by inhibition of the liquoral PG synthesis, the nociceptive signal transmission in the spinal cord, and the activation of descending serotonergic pathways [67]. It can be administered by different routes, included IV preparations, providing a more rapid onset of analgesia than the oral route [68].

Although specific controlled trials regarding paracetamol use in patients with SCD are lacking, it is widely used as a single agent as an alternative to opioids in SCD [69]. In addition, its association with the latter results in enhanced analgesia and an "opioid-sparing" effect [6,70,71]. However, its use in the presence of hepatic impairment requires caution.

Opioids

Opioid analgesics are the drugs of choice to treat severe pain. Their functional effects are derived from their complex and individual interactions with opioid receptors. Therefore, each opioid can be classified according to its receptor profile as agonist, partial agonist, and agonist-antagonist; moreover, based on their analgesic potency, they are distinguished as weak or strong opioids [72]. Morphine is a full μ receptor agonist with which all other drugs' bioavailability and relative potency should be compared [73]. It remains the drug of choice to achieve a prompt analgesia in patients with SCD [6,74]. Diamorphine (heroin), being highly soluble, produces rapid analgesia and has been successfully employed in the setting of SCD pain [75], although the routine clinical use is unique to the United Kingdom [76]. Among full μ-agonists, strong opioids, hydromorphone [77], and oxycodone [78] have been reported as effective in the setting of acute SCD pain [79]. Fentanyl is rarely used by IV route outside of the anesthesia setting but has become popular for transdermal (TD) administration [80]. This preparation is best suited for patients with stable pain in whom the 24-hour opioid requirement has already been determined. An oral transmucosal fentanyl citrate preparation, recently marketed for breakthrough pain management in patients with cancer and as preemptive analgesia for diagnostic procedures, has been reported as a useful tool in the setting of SCD pain [78,79], although the clinical experience is very limited. Lastly, methadone has been successfully applied as maintenance therapy in outpatients with SCD [78].

The most used weak opioids acting prevalently on μ receptors are codeine and tramadol. Codeine is often used together with paracetamol in fixed-dose for mild to moderate pain. Tramadol is an atypical analgesic acting at the central level, with relatively weak μ receptor affinity. It inhibits serotonin and norepinephrine reuptake in the raphe nucleus, enhancing inhibitory effects on pain transmission [72] and thus is helpful in neuropathic pain [81]. The overall incidence of tramadol-related adverse effects is lower than other opioids. In particular, at analgesic doses, it seems to cause little or no respiratory depression [82], although its use in patients with renal failure requires careful attention [83]. This drug is easily manageable and can be proposed as an alternative for patients not suitable for NSAIDs or for stronger opioids, either as a single agent or in association with ketorolac [38]. Recently, IV tramadol (0.25 mg/kg) combined with nonopioids has been reported as effective to relieve moderate to severe pain in a pediatric SCD crisis; so, this agent can be recommended before using morphine in this setting [84].

Meperidine is widely used in SCD. However, its metabolite normeperidine has a long half-life (15–40 hours) and can be accumulated, causing some side effects (e.g., tremors, myoclonus, seizures and delirium); moreover, it has some inotropic negative effects and could have potentially fatal

interaction with monoamine oxidase inhibitors [85]. Therefore, its use should be avoided or limited in otherwise healthy patients when other options are not available.

Buprenorphine is a partial agonist provided with some interesting properties, although no study has reported its use for SCD pain so far. However, it may be an alternative agent, thanks to various application routes, long action, and renal-independent metabolism. Butorphanol is chemically related to buprenorphine, and its use has been compared with morphine in patients with who presented with pain crisis. No differences between the two therapies have been found with respect to pain or relief of pain scores and side effects for which they were are equally effective in the treatment of SCD crisis pain [86].

Mixed agonist/antagonist opioids provide analgesia by acting predominantly at κ receptors; therefore, they unlikely induce respiratory depression so that they can be usefully employed to approach acute pain. Among these agents, nalbuphine has been reported as an alternative to morphine in SCD setting. Indeed, after parenteral administration, it provides effective analgesia without remarkable circulatory and respiratory adverse effects. Moreover, like other agonist/antagonist analgesic drugs, the potential abuse of nalbuphine seems relatively low [87].

Treatment of painful episodes in SCD by opioids may sometimes give rise to concerns about analgesic misuse. In this view, distinguishing addiction from pseudoaddiction may have a critical role in pain management. Indeed, drug seeking caused by analgesic is a nonpain-related syndrome and is due to pscyhologic dependence. Conversely, the term *pseudoaddiction* describes the patient's anticipatory requirement of a dose due to fear of pain, and patients experiencing this fear is due to undertreatment [88,89].

Other concerns about opioids are related to their employment in patients at risk of ACS. Indeed, morphine has been associated with respiratory deterioration eliciting a decrease in oxygen saturation and inducing histamine release. Thus, it could be a potential contributing factor for the development of ACS [90,91]. However, pain may inhibit the thoracic excursion, predisposing to ACS development; therefore, pain relief has to be achieved as soon as possible, after a careful selection of the agents to be administered. In a patient with a previous history of or presenting ACS, pain management should be based on nonopioids eventually associated with partial μ agonist, as tramadol, according to the principles of the balanced and multimodal analgesia, or with agents acting preponderantly on κ receptors, as nalbuphine.

Management Principles

Optimal pain management should include the careful monitoring of the patient and the prevention and the treatment of side effects [92]. The drug selection and the choice of administration route are a critical step in pain management and should follow some basic and easy principles, above all related to the patient's compliance and to the urgency to achieve analgesia. The treatment algorithm, adopted by us, is shown in Table 2.

Although the oral route is optimal for most patients, alternative methods of administration, as

Table 2 Pain management for SCD patients

Treatment Based on Pain Intensity*		
Score 1–4 (MILD Pain)	Score 5–7 (Moderate Pain)	Score 8–10 (Severe Pain)
Paracetamol (PAM)† 20 mg/kg (the first dose can be 40 mg/kg/6 hours)	PAM* 20 mg/kg (the first dose can be 40 mg/kg/6 hours) associated with oral or parenteral tramadol (50–100 mg/6 hours)	PAM* 20 mg/kg (the first dose can be 40 mg/Kg/6 hours) associated with oral morphine (5–10 mg/6 hours) or oxycodone (5–10 mg/6 hours). In case of pain emergency, the IV route should be preferred, adapting the opioid dosage according to the conversion tables.
In patients unsuitable for PAM (liver failure), ibuprofen‡ (10 mg/kg/8 hours) can be used.	In patients unsuitable for tramadol, this agent can be replaced by oxycodone (5 mg/6 hours)	In patients at risk of ACS and/or unsuitable for strong opioids, morphine or oxycodone should be replaced with ketorolac eventually associated with tramadol.

* In addition to pharmacotherapy and regardless of pain intensity, alternative/complementary approaches to pain management, such as biomechanical (massage, trigger point pressure) and psychological interventions (relaxation techniques, coping strategies, mood-enhancement strategies, and so on) should be offered.
† Paracetamol (PAM) should be used with caution in patients with liver impairment. ‡ Ketorolac and other NSAIDs should be avoided in patients with borderline renal function or failure and used with caution in patients at high risk of acute chest syndrome.
ACS = acute chest syndrome; NSAID = nonsteroidal anti-inflammatory drug; SCD = sickle cell disease; IV = intravenous.

sublingual, rectal, subcutaneous (SC), IV, and TD, can be used. The intramuscular route is generally discouraged because of erratic absorption and pain. Invasive neuraxial opioid delivery is very rarely performed in patients with SCD [93], although this should be considered in selected circumstances, such as a pregnant women with SCD whose labor is superimposed on pain crisis. The IV route is the fastest way to achieve analgesia in patients having a rapidly escalating or otherwise uncontrolled pain [94].

Patient-controlled analgesia (PCA) devices provide on-demand boluses, eventually associated with continuous infusion (CI) opioids in selected circumstances. This modality of administration may therefore be an interesting alternative as patients can titrate themselves the appropriate dose of opioid until an adequate analgesia is obtained.

In a recently published controlled study, PCA resulted in pain relief at a much lower morphine consumption, and, therefore, it should considered as the first choice in morphine administration [95]. Whatever route is used, the administration of opioids requires knowledge of potency compared with morphine and of bioavailability of the chosen route and a careful titration in each patient [72]. Moreover, once stable analgesia has been achieved, further rescue doses of a fast onset and short-acting opioid should be provided. IV morphine at a dose equivalent to 20% of the oral dosage has been proposed as an inexpensive, safe, and effective option in patients with cancer experiencing pain exacerbations, while a supplemental oral administration of immediate release (IR) morphine solution may not be optimal, given the slow onset of effects [94].

When an opioid is started, an antiemetic (e.g., haloperidol) should be supplied due to the frequency of nausea and vomiting. Moreover, because of the high rate of constipation among patients who receive opioids for 3 or more days, a scheduled bowel regimen (i.e., senna + docusate) should be prescribed. In case of unexpected adverse effects, current recommendations highlight the need for careful evaluation to distinguish them from comorbidity, dehydration, or drug interactions. The dose reduction and the addition of an adjuvant agent are recommended in these circumstances. If side effects persist in patients with chronic SCD pain who should continue to receive opioids, the rotation to another agent according to the equivalency conversion doses should be considered.

The treatment of neuropathic painful states may favorably include tricyclic antidepressants or anticonvulsants [95]. Gabapentin and pregabalin are currently the anticonvulsants of choice, although no data are available in the SCD setting.

Nonpharmacological Approaches

An effective role for some nonpharmacological measures approaches in the management both for chronic both acute pain has been reported. Chronic-pain treatment in SCD, as in all pain diseases, should be multidisciplinary: leg ulcers necessitate the input of wound care centers, whereas avascular necrosis entails the involvement of orthopedics, physical therapy, rehabilitation, and rheumatologists. According to the recommendations of the American Pain Society, pharmacological treatments for SCD should be complimented by psychological, behavioral, and physical modalities [58]. A significant effect of massage on pain score, tension/mood score, and activities of daily living has been reported [96]. Moreover, massage and relaxation were found to reduce the sensory and affective dimensions of pain in adults with SCD [97]. In addition, a recently published study found that many parents of children with SCD use a number of alternative/complementary approaches to pain management in addition to pharmacotherapy, including massage as well as self-prayer and relaxation [98]. Lastly, training in cognitive coping skills in order to enhance pain-coping strategies and to alter pain perception has been reported as effective to negative thinking and lower pain ratings in patients with SCD [99–101]; these findings have recently been outlined by a report claiming with the role of psychosocial variables, such as optimism [102], as important determining factors of pain behavior of patients with SCD.

Conclusions

Pain may be not only the major symptom related to VOC but also the warning sign of life-threatening complications, so that the assessment of a SCD patient with pain should include the overall evaluation of the state of the disease. Pain management continues to be primarily palliative in nature [103]. The treatment of SCD is currently primarily driven by clinical experience and patient preference, given the paucity of controlled randomized trials to guide decision-making. More research is needed.

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