PAIN MANAGEMENT IN PATIENTS WITH SICKLE CELL DISEASE - A REVIEW

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ABSTRACT

Pain is defined, by the International Association for the Study of Pain (IASP), as an 'unpleasant sensitive and emotional experience, associated with or described in terms of tissue lesion'. It may be classified as acute or chronic when it becomes a symptom that worsens the quality of life, and thus loses its protective function. Pain may also be considered as chronic when it lasts over 3 to 6 months. Acute painful episodes, are the most common cause for patients with sickle cell disease (SCD) to seek medical attention. The causes of chronic pain are diverse in this population. In a sense, chronic sickle cell pain is a spin off the recurrent acute painful episodes. Pain management in patients with SCD presents unique challenges and opportunities.

Keywords: Pain, sickle cell disease, opioids, NSAID.

INTRODUCTION

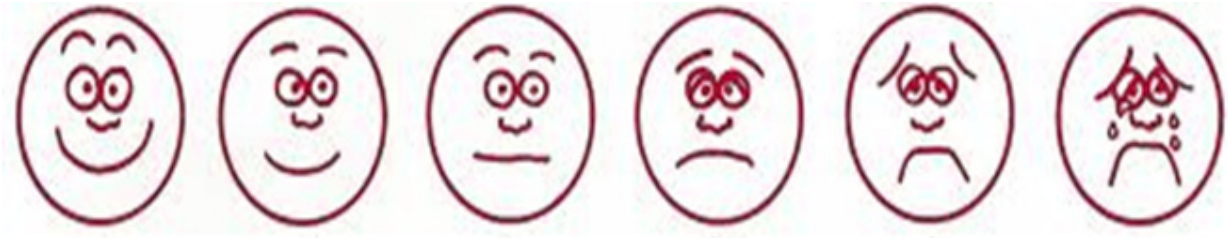
Sickle cell anaemia (SCA), an autosomal recessive disease, results from a valine for glutamic acid substitution at position six of the β-globin gene of haemoglobin (Hb). When the sickle haemoglobin (HbS) molecule is deoxygenated, there is a hydrophobic interaction between this and other haemoglobin molecules that trigger an aggregation into large polymers, resulting in sickle-shaped deformities of the red blood cell (RBC).[1] When RBCs sickle, the common critical manifestations are vaso-occlusive, sequestration, haemolytic, and aplastic crises. Acute, painful episodes are the most common cause for patients with sickle cell disease (SCD) to seek medical attention. While the annual incidence rate of pain episodes increases with age, rates in adults with SCD are underestimated because the majority of such episodes are managed at home. Sickle cell pain syndromes include an unusual triumvirate of acute, chronic and neuropathic pain that occur sequentially or simultaneously with age.

Unlike other diseases associated with chronic pain, sickle cell acute pain manifests itself in infancy and continues to recur throughout the life span. SCD is the most common globin gene disorder: across the world, about 300,000 children are born with it each year.[2,3] The pain of sickle cell crisis is excruciating and, in global terms, a major health problem. No evidence-based guidelines exist for the treatment of SCD-associated acute pain episodes, either in the hospital or at home.

TYPES OF PAIN IN SICKLE CELL DISEASE

Pain caused by sickle cell disease can be acute, chronic or a mixture of the two.[4] The acute pain of tissue infarction, in skeletal or soft tissue, tends to be sudden, unpredictable in onset and intense. Most adults with SCD are aware of their triggers for vaso-occlusive pain episodes and are sensitive to avoiding them. Established precipitants of pain include extremely cold temperatures, change in weather, over-exertion, dehydration, onset of menses, direct or indirect exposure to tobacco smoke, and concomitant exacerbation of co-morbid conditions.[5]

Clinically, acute sickle pain is typically sharp and/or throbbing in nature, of sudden or gradual onset. It may last from hours to weeks in duration. The average duration of an acute painful crisis in adults, based on the length of hospital stay, is about 7 days.[6] Acute sickle cell pain is believed to be secondary to vaso-occlusion by sickled erythrocytes that adhere



0	1	2	3	4	5
No Hurt	Hurts Little Bit	Hurts Little More	Hurts Even More	Hurts Whole Lot	Hurts Worst

Figure 1a. The Wong-Baker faces scale for assessment of intensity of pain in children.
"These faces show how much something can hurt. This face [point to left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face] - it shows very much pain. Point to the face that shows how much you hurt [right now]." "Score the chosen face 0, 1, 2, 3, 4, or 5, counting left to right, so '0' = 'no pain' and '5' = 'very much pain.' Do not use words like 'happy' and 'sad.' This scale is intended to measure how children feel inside, not how their face looks."

to vascular endothelium. Vascular occlusion leads to ischaemia and consequent damage of the tissues supplied by the occluded vessel. Tissue damage creates a state of inflammation with the release of several inflammatory mediators. Each inflammatory mediator, released peripherally after tissue damage, binds to a specific receptor on the neurons of peripheral nerves. These neurons are crowded with multiple receptors for inflammatory mediators and for descending inhibitory pathways from the central nervous system (CNS). This state of affairs of one neuron with multiple receptors implies that inhibition of the transmission of the painful stimulus at the level of the peripheral nerve entails the blocking of all these receptors.[7]

Chronic pain[8] is simply pain that does not go away for 3 or more months. It is usually described as pain that is deep, persistent and there all the time. Chronic sickle cell pain is of two types. The first is due to obvious causes such as leg ulcers and avascular necrosis. The second type is due to persistent or frequently recurrent acute painful episodes that lead to chronic pain syndrome, especially without the proper treatment.

Assessment of Pain

Assessment is the gold standard of effective pain management.[9] It should be conducted before and periodically after the administration of analgaesics. The patient's self-report is the most important factor in the hierarchy of pain management. Other factors in the process of assessment should include the presence or absence of other complications of the disease. The patient's self-report[10] should include multidimensional scales describing intensity, quality, location, distribution, onset, duration, mood, sedation, pain relief, and factors that aggravate or relieve pain. Periodic assessment with rating and categorising of pain will delineate mixed pain syndromes, which may occur as the pain progresses over time.

Four stages of a pain event have been described in adults with SCD: prodromal, initial, established, and resolving. No combination of clinical and laboratory findings exists to determine if an individual is currently in pain.

The intensity of pain can be assessed using any of several available scales,[11,12] such as the visual analogue scale, verbal scale, numerical scale, or Wong-Baker faces scale for children (Figure 1a). Explain to the child that each face is for a person who feels happy because he has no pain or sad because he has some or a lot of pain. Face 0 is very happy because he does not hurt at all. Face 5 on the other hand, hurts as much as you can imagine, although you do not have to be crying to feel this bad. Ask the child to choose the face that best describes how he/she is feeling. The rating scale is recommended for persons aged 3 years and older.

The most common measurement for adults is the Visual Analog Scale (VAS), a continuous line, 100 mm in length, ranging from no pain to severe pain (Figure 1b). When treated in the emergency department (ED), adults with SCD report that a change in the VAS of 13.5 mm is the minimum objective change that relates to a clinically significant subjective change in a vaso-occlusive pain episode.

Other guidelines have used a scale to assess response to therapy (0=none, 1=little, 2=moderate, 3=good, 4=complete).

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.

Management of the Acute Pain Crisis

Pain is a common experience in children beginning as early as 4 to 6 months of age, and dactylitis in infants is an early prognostic indicator for increased risk of complications in children. The failure to address the pain early can have lifelong implications on their health, generating a vicious cycle of fear, avoidance of pain, and poor coping strategies. Unrelieved pain can have more than negative consequences such as missed days of school and other life activities, or fear or mistrust of health care providers, but also can lead to amplified responses to subsequent pain experiences and sensitivity to pain later in life. Frequent typical vaso-occlusive pain may involve limbs, abdominal viscera, ribs, sternum, vertebrae, and sometimes skull bones.[13] Pain episodes can start suddenly, or they may follow an illness along with decreased activity, loss of appetite, and increased jaundice. Painful episodes are associated with early mortality in adults with SCD.

General principles of management[14]

Fluid replacement therapy: Fluid balance should be monitored in all patients. The patient should be encouraged to take oral fluids (60 ml/kg/24 h in adults). If the patient is unable to drink sufficient amounts or is vomiting, intravenous or nasogastric fluids are necessary at a similar rate. Central lines should be avoided unless needed for life-saving.

Oxygen: Oxygen should be given if pulse oximetry shows the oxygen saturation is below the patient's known steady-state level. Some patients have low steady-state oxygen saturations, which appear to be well tolerated without oxygen.

Thromboprophylaxis:[15] Patients with SCD appear to have a hypercoagulable state at baseline and they often have other factors that further increase the risk of venous thromboembolism (VTE) (e.g. indwelling catheter, immobility, infection). For all adults (those >18 years) with SCD who are admitted to the hospital for an acute medical condition, thromboprophylaxis is recommended with low dose of unfractionated heparin (e.g. 5000 units SQ three times a day).

There are no objective measurements of pain severity, and analgaesia should be titrated against the patient's reported pain, as recorded on a pain chart.

Initial management should be aimed at providing rapid pain control.[16] Analgaesia should then be maintained with long-acting oral or parenteral analgaesia, with provision for bolus analgaesia if breakthrough pain occurs. The choice of analgaesia will depend on how far along the 'analgaesic ladder' the patient has already progressed, and treatment

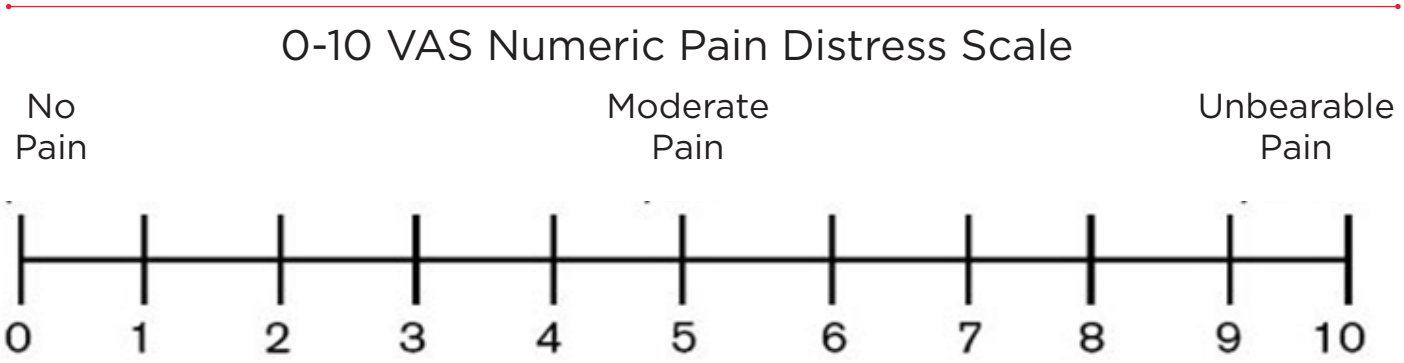


Figure 1b. The Visual Analog Scale (VAS) for pain measurement in adults.

The 0 to 10 pain scale is commonly and successfully used with hospitalised and nursing home patients, even those with mild to moderate dementia. The scale is often displayed as a line numbered from 0 to 10. This scale asks the person in pain to assign a number, from 0 to 10, to the severity of their pain. It is important to properly instruct the person in how to rate their pain. 0 means you have no pain at all. 10 means the worst possible pain you can image. The values on the pain scale correspond to pain levels as follows:

1 – 3 = mild pain
4 – 6 = moderate pain
7 – 10 = severe pain

should generally start with the next step. Once pain is controlled, the underlying cause should be assessed more comprehensively.

Paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Paracetamol (acetaminophen)[17] is an analgaesic and antipyretic with little anti-inflammatory effect, whose exact mode of action is currently unknown. It is the most widely used drug for pain relief. In order of increasing effectiveness, paracetamol can be administered rectally, orally and intravenously. Paracetamol, at therapeutic doses, rarely results in adverse effects and, unlike NSAIDs, does not cause gastrointestinal ulceration or bleeding.

NSAIDs[17,18] are analgaesic, anti-inflammatory, antiplatelet, and antipyretic. They exert their analgaesic effect by reducing the production of prostaglandins responsible for pain and inflammation. NSAIDs achieve this by inhibiting the enzyme COX-2, which is essential in the synthesis of prostaglandins. NSAIDs vary in whether they selectively inhibit COX-2. Non-selective NSAIDs, such as ibuprofen and diclofenac, inhibit not only COX-2 but also cyclo-oxygenase 1 (COX-1). COX-1 is involved in the synthesis of prostaglandins that have a role in the maintenance and protection of the gastrointestinal (GI) tract, platelet adhesion, and renal function. Non-selective NSAIDs are therefore associated with adverse GI effects, renal toxicity, prolonged bleeding time, bronchospasm and oedaema.

One complication of SCD is nephropathy—characterised by proteinurea, ranging from microalbuminuria to massive excretion (with nephrotic syndrome). The nephropathy can be worsened by NSAIDs, so treatment with these agents should be stopped after a week at the most. NSAIDs can be used to control mild to moderate pain and may have an additive role in combination with opioids for severe pain. The doses and frequency of treatment should be monitored every 3 to 6 months in chronic users.

Opioid treatment

Opioids are used for severe pain in SCD.[19] The choice of an opioid, its dose, and route of administration should be individualised, based on past history and experience. No one opioid constitutes a panacea for all patients. The general trend today is to avoid the use of meperidine and to administer opioids orally for mild pain and intravenously or subcutaneously for severe pain, and avoid the intramuscular route if possible.

Opioid agonists produce their effect by binding into μ receptors. It is the L-isomers of opioids that exert their analgaesic activity. The binding affinity or strength with which a drug binds to its receptors varies considerably among opioids, with fentanyl, for example, having a higher binding affinity than morphine. The binding affinity of opioids seems to correlate well with their analgaesic potency.

Morphine

Morphine[19,21] is a strong μ-opioid agonist and the gold standard for the treatment of acute sickle cell painful crisis. It may be administered by any route and is available in both immediate and extended release formulation. Morphine is highly histaminergic and is often associated with pruritus that may be severe. Other recently reported side-effects of morphine include increased risk of acute chest syndrome in patients with SCD and acceleration of renal injury, especially in combination with NSAIDs.

The standard dosing[22] interval for morphine injections and rapid release preparations is 4-6 hours, but some individuals become so tolerant to opioids that doses are needed 2-hourly.

Pethidine

Pethidine[23] is short-acting with poor bioavailability and is metabolised to norpethidine, which is a renally-excreted cerebral irritant, causing dysphoria, clonus and seizures. It is usually given by repeated, high-dose intramuscular injections and has resulted in severe muscle damage. Pethidine should only be used in exceptional circumstances when there is a severe allergy to morphine and diamorphine (heroin). Continuous infusions[24] of pethidine should be avoided and it should not be used for more than 48 hours, or at doses greater than 600 mg/24 hours (American Pain Society, 1999). After 48 hours, the pethidine should be stopped and an alternative opiate used if necessary.

There should be no weaning of opioids[25] in the first 24 hours of a hospital admission unless there are signs of respiratory depression, increased lethargy, or other side effects associated with excessive amounts of opioids. Opioids should be weaned by decreasing the dose about 10% to 20% at a time, rather than by increasing the interval between doses. Conversion to oral pain medication should occur

when the intravenous dose is roughly equivalent to home doses of oral medications.

Management of Chronic Pain in Sickle Cell Disease

Management of the chronic underlying pain, requires a multifaceted approach to ensure patient adherence to treatment and adequate management of symptoms. The principles of treating chronic pain are different than those of acute pain. The goal of managing acute pain is to heel the acute injury or precipitating factors. The goal of treating chronic pain is to restore function. Once chronic pain sets in it is joined by other maladies that enhance its chronicity. These include depression, anxiety, suffering, despair, insomnia, loneliness, helplessness, and dependence on pain medications.

Oral opiates such as methadone, morphine, codeine, oxycodone, and hydroxycodone provide alternatives for outpatient treatment and pain management for patients discharged from the hospital.[26] Although these drugs are administered routinely to patients with SCD, their efficacy and safety have not been evaluated for treatment of acute pain crisis. These drugs are given as an oral analgaesic for treatment of mild-to-moderate pain at home, as transitional therapy between hospital treatment and home management, or for management of chronic pain.

Medications that can alter the perception of pain in the spinothalamic tract include opioids, serotonin norepinephrine reuptake inhibitors (SNRIs),[27] and tricyclic antidepressants.[28] The SNRIs duloxetine and milnacipran have indications for chronic pain although not for sickle cell pain. No tricyclics are FDA approved for chronic pain, though they are routinely used for this purpose as an adjunct to non-pharmacologic therapy for chronic neuropathic pain.

Paradoxically, the chronic administration of opioid analgaesics to treat pain may lead to similar confusion by also contributing to or causing pain.[29] Increased sensitivity to pain may be observed in any clinical setting where recurrent acute or chronic pain occurs. This is often erroneously attributed to either more disease-related pain, or to aberrant drug-seeking or addictive behaviors. There are basic steps to be taken when opioid neurotoxicity exists. First, recognise the syndrome; delirium, agitation, or restlessness may make the patient seem to be irrational or to be exaggerating the pain. This usually offends opioids which are frequently used to immediately-release (morphine, hydromorphone oxycodone) opioids, or very high doses of sustained release formulations of morphine, hydromorphone, and oxycodone.

An early sign may be clonus, which can be seen while the patient is asleep, before it becomes clinically overt. Allodynia and hyperalgaesia cause the pain to occur all over and do not follow a reasonable distribution. Rapidly increasing the opioid makes the pain worse. Second, discontinue the offending opioid and rotate to another drug. Third, add additional non-opioid adjunctive medications. Fourth, begin hydration to clear opioid metabolites. Fifth, consider benzodiazepines to decrease neuromuscular irritability but avoid sedation.

Transdermal fentanyl[30,31] patches are effective in chronic pain. These patches are easy to administer and contain multi-day dosage, but stable plasma levels may not be reached for 12 hours after application. The main disadvantages of the patches are that analgaesia is slow in onset and difficult to titrate against response, and that a residual depot is left after removal of the patch. We have used fentanyl patches successfully in a few patients in the later stages of admission for acute sickle cell crisis and have discharged the patients with them to take home. Fentanyl is released at a nearly constant rate from the transdermal matrix system into the skin, where it accumulates; this results in a depot of fentanyl in the outer layer of skin. Fentanyl is absorbed into systemic circulation from the depot. This results in a gradual increase in serum concentration over the first 12-24 hours, followed by fairly constant concentrations for the remainder of the dosing interval.

Methadone[32]

Methadone is a synthetic potent-opioid agonist. It has a long half-life (at least 36 hours) but a short duration of analgaesic effect (4 to 6 hours). It is associated with cardiotoxicity due to prolongation of the QTc interval with arrhythmia that could be fatal. It is associated with mortality more than any other opioid. Other medications such as antibiotics and antidepressants contribute to its cardiotoxic effect, and their use with methadone should be avoided or monitored carefully, although, methadone is an excellent analgaesic that is useful in treating chronic pain.

Cannabis[33,34]

Cannabis contains a mixture of phytocannabinoids whose synthetic congeners have been extensively investigated in the laboratory for their effects on pain sensation.

The hypothesis is that vaporised cannabis can induce dose-dependent antinociceptive changes in spontaneous and evoked pain in subjects with neuropathic pain. The second hypothesis is that the higher dose employed induces a greater degree of antinociception that is not independent of differences in mood, cognition, and psychomotor performance. Finally, it is hypothesised that an interaction with time will occur such that antinociception will outlast changes in cognitive impairment and psychomotor performance.

Psychological interventions

According to the cognitive-behavioural model,[35] an individual's interpretation of external events and bodily sensations directly affects their emotional reaction to these events and subsequent behaviour. Every cognitive behavioural approach starts by identifying and modifying unhelpful thinking patterns that are believed to increase distress. Dichotomous thinking, catastrophisation, and overgeneralisation are considered dysfunctional cognitive patterns because they typically arise from limited information and do not entirely reflect reality.[36]

Cognitive-behavioural interventions are an important part of a multimodal approach to pain management. They help the patient obtain a sense of control and develop coping skills to deal with the disease and its symptoms.[37] Guidelines by a National Institutes of Health assessment panel suggest integration of pharmacologic and behavioural approaches for treatment of pain and insomnia. Other studies suggest that behavioural interventions targeted to specific symptoms, such as pain and fatigue, can significantly reduce symptom burden and improve the quality of life for patients with chronic pain.

Non-pharmacological therapies

Non-pharmacological methods used in pain management can be classified in different ways. Meditation, progressive relaxation, dreaming, rhythmic respiration, biofeedback, therapeutic touching, transcutaneous electrical nerve stimulation (TENS), hypnosis, musical therapy, acupressure and treatments are just some of them. Acupuncture[38] is accepted as a scientific treatment method that provides the body to restore its balance by means of stimulating some special points on the body with needles. Mechanism of action for the acupuncture could not be completely understood until now. Chiropractics[39] is the neck-pulling movement used in treatment of the disorders in connective tissues and musculoskeletal system which consists of muscles, joints, bones, tendon, cartilage and ligaments. It is focused on the connection between body structure and the functions of the neural system, and manipulation of bones and joints to regain the health.

CONCLUSION

The act of taking care demands an overload of attention and intense dedication, especially as the healthcare team has to ensure that patients and their families have the conditions to reorganise their lives physically and emotionally. Ineffective pain control prior to discharge may also contribute to high early revisit rates. It is concluded that opioid dose requirements vary widely in patients with uncomplicated vaso-occlusive crisis and often exceed guideline recommendations.

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