Review Article

Acute and Chronic Pain Management in Sickle Cell Disease

Abstract

Sickle cell disease is a genetic haemoglobin disorder affecting millions of people worldwide. Pain is one of the most commonly reported complication of sickle cell disease. Pain is further classified into two categories acute pain and chronic pain. Chronic pain is associated with more serious complications. Management of pain has a significant impact on quality of life of sickle cell disease patients. The purpose of this research is to review the available information about acute and chronic pain management in sickle cell disease. The best treatment for both acute and chronic pain requires a customized, varied approach. This approach combines therapeutic, non-pharmacological therapies, as well as integrated therapies as per the specific needs of each patient. Opioids are effectively used in management of the pain of sickle cell disease and their use is supported by literature especially in chronic pain. Methadone, ketamine, and nitrous oxide are also used to manage pain. For the treatment of acute pain, nonsteroidal anti-inflammatory medications, short-acting opioids, and adjuvants are used effectively in clinical practice. Opioids have become the recommended treatment for pain in sickle cell disease, and many chronic pain patients are sustained on opioid therapy for the rest of their lives. However, the distinction between acute and chronic opioid therapy modalities is blurred in sickle cell disease due to the association between recurring acute pain and chronic pain. Limited literature is available regarding management guidelines and therapeutic strategies so more clinical research and trials are needed in future to design and study effective management strategies for both acute and chronic pain.

Keywords: *sickle cell, disease, pain, management, acute, chronic*

Introduction:

Sickle cell disease is a spectrum of hereditary hemoglobinopathies caused by mutations in the -globin chain of haemoglobin that affects about 100,000 people in the United States and over 3 million people globally. Chronic haemolytic anaemia, severe acute, and chronic pain, and end-organ impairment occur over the lifespan in sickle cell disease patients. Sickle cell disease is linked to a higher risk of premature death, with a median death age of 43 years with

an interquartile range of 31.5–55 years. Treatment necessitates early detection, averting complications, and managing end-organ damage (1-3). Sickle cell disease is reported in approximately over a quarter million live births, and the United Nations and the World Health Organization have identified sickle cell disease as a global health crisis that is expected to worsen in the next decades. Sickle cell disease affects 90,000–100,000 people in the United States; 1 in every 365 African American babies is born with the disease, and 1 in every 13 African Americans has sickle cell trait. In the United States and many other developed countries, both sickle cell disease and trait are detected during new-born screening. In West and Central Africa, where up to 18% of people have sickle cell trait and 1–2% of kids are born with sickle cell disease, even more people are impacted; few of these nations provide new-born screening or basic health care. Individuals from the Mediterranean region, the Middle East, Saudi Arabia, India, Asia, and South and Central America are all affected by sickle cell disease. sickle cell disease affects millions of people around the world, but the global prevalence is unknown due to a lack of neonatal screening in many countries (4).

Sickle-cell disease pain can be acute, chronic, or a combination of the two. Acute tissue infarction pain, whether in skeletal or soft tissue, is usually rapid, unpredictable, and intense. It normally stops after the sickle-cell crisis has passed. Chronic pain in sickle cell disease is not only a continuation of the pain caused by vaso-occlusion: it is frequently caused by avascular necrosis of bone at numerous joints, most commonly the hips, shoulders, and ankles. Avascular necrosis, which causes chronic back pain and the well-known 'fish-mouth' appearance on X-rays, is also widespread in the spine. Abdominal pain could be a symptom of a sickle-cell crisis affecting the abdominal viscera, or it could be a surgical emergency like a perforation. Similarly, rheumatoid arthritis, osteoarthritis, and other forms of degenerative joint disease can produce chronic joint pain in patients with sickle cell disease. Acute exacerbations of chronic pain in a person with a previously identified cause of chronic pain, such as hip necrosis, might be caused by new vaso-occlusive events in the same place or movement-induced injury to the injured joint. The emergence of broad painful crises in a person who previously had chronic pain at one or a few anatomical places is a little easier to diagnose and manage (5).

The most prevalent sickle cell disease complication is severe intermittent acute pain, which accounts for more than 70% of sickle cell disease patients' acute care visits. Chronic daily discomfort becomes more common as people get older, affecting 30–40% of adolescents and adults with sickle cell disease. Acute pain is caused by vaso-occlusion of sickled red blood

cells, resulting in ischemia-reperfusion damage and tissue infarction, and can occur in one or several anatomic regions. Chronic pain is generally diffuse with neuropathic pain features and can be induced by sensitization of the central and peripheral neural systems. Reports of persistent pain on most days during the preceding 6 months, either in a single place or numerous locations, is a common definition of chronic pain. Chronic pain is also caused by disease complications such as avascular necrosis and leg ulcers (6). In sickle cell disease, the agony of a vaso-occlusive crisis is intense and can be incapacitating. It is the most prevalent and devastating condition that sickle cell disease patients face as children, teenagers, and adults. It is excruciatingly painful, lasts a long time, and is the leading cause of hospitalization among sickle cell disease patients. Severe pain can start as early as 6 months of life and occur at random periods throughout a person's life. The way this pain is addressed has a significant impact on how patients manage pain and life (7). The purpose of this research is to review the available information about acute and chronic pain management in sickle cell disease.

Methodology:

This study is based on a comprehensive literature search conducted on June 3, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about the acute and chronic pain management in sickle cell disease. There were no restrictions on date, language, participant age, or type of publication.

Results and Discussion:

Acute pain is a defining feature of sickle cell disease and the leading cause of hospitalization. Vaso-occlusion damages tissue, releasing a slew of inflammatory mediators that trigger the transmission of painful sensations, culminating in pain perception. There are four stages to the acute sickle cell pain crisis. Each phase is accompanied by changes in the disease's indicators. In roughly 16% of discharged patients, readmission occurs within one week, and in about 50% of discharged patients, readmission occurs within one month. Failure to aggressively manage acute pain can lead to chronic pain syndrome, which can lead to neuropathic pain. The treatment of sickle pain is predominantly pharmaceutical, with opioids

being the most commonly utilized analgesics. Histaminergic, excitatory, dopaminergic, and proserotonergic actions are all side effects of opioids use. Individual differences among individuals are explained by cellular and molecular mechanisms of opioids, which justifies the use of tailored treatment approaches (8).

Strategies for pain management in literature

The management of acute and chronic pain in sickle cell disease patients is a clinical problem. This is because of lack of clinical sickle cell disease pain research and also lack of understanding of the various biochemical variations that exist between acute and chronic pain. These difficulties, taken together, provide impediments to targeted, effective responses. In general, the best therapy for both acute and chronic pain necessitates a customized, interdisciplinary approach. This method includes pharmacological, nonpharmacological, and integrative therapy approaches that are tailored to the specific needs of each patient. There is no such thing as a one-size-fits-all strategy to pain management. This interdisciplinary team in the context of sickle cell disease includes specialists in haematology, pain medicine, psychology and psychiatry, emergency medicine, nursing, and physical therapy, among others (9).

Osunkwo I stated that opioids are critical in the treatment of acute sickle cell disease pain, and there is a lot of evidence to back them up. Flowchart for the management of chronic pain in sickle cell disease is illustrated in **(Figure 1).** Despite the paucity of evidence supporting their utility in the treatment of chronic noncancer pain, opioids are utilized in the management of chronic pain in sickle cell disease. Chronic opioid therapy has many negative effects, such as central sensitization, poor oral health, opioid-induced constipation, sleep problems, cognitive dysfunction, depression, endocrinopathy, tolerance, physiologic opioid dependence, hyperalgesia, and increased overdose- and cardiovascular-related mortality, often outweigh its perceived benefits. Central sensitization is frequently misdiagnosed as increased opioid tolerance, leading to increased opioid dosages in an attempt to alleviate symptoms (10). Carroll reported that in sickle cell disease, both acute crises and chronic pain have few objective pathology correlations, however their mechanisms are unclear. In sickle cell disease, opioids have become the standard of care for severe acute pain, and many patients with chronic pain are kept on opioid therapy for the rest of their lives. Because of the close link between repeated acute pain and chronic pain in sickle cell disease, the boundary

between acute and chronic opioid therapy paradigms is blurred. Furthermore, stigma and fears about addiction plague opioid management for those with sickle cell disease (11).

Sickle cell disease has a wide range of symptoms and consequences. Appropriate pain management is critical since both acute and chronic pain severely reduce quality of life. The World Health Organization's analgesic ladder, which was established for cancer-related pain, is used to make recommendations for the management of acute painful crises. Basic long-acting opioids and on-demand short-acting opioids can be used to treat chronic pain. Anticonvulsants, antidepressants, and potentially ketamine should be tried if patients display indicators of neuropathic pain (12). To treat acute pain, nonsteroidal anti-inflammatory medications short-acting opioids, and adjuvants are used. Nonsteroidal anti-inflammatory medications are only prescribed to patients with a blood creatinine level of less than 1.0 mg/dL and no proteinuria or albuminuria. Antihistamines, antiemetics, laxatives, antidepressants, and gabapentin, when needed, are among the adjuvants. Patients with sickle cell disease do not have the same problems as the general population when it comes to opiate consumption. An examination of data from the Centres for Disease Control and Prevention revealed that opioid overdose was responsible for less than 1% of deaths among sickle cell disease patients between 1999 and 2013, and that this low rate of mortality did not vary appreciably during the 15-year period (13).

Ballas stated that in the therapy of most sickle cell pain disorders, opioids tend to play a critical role. In the treatment of sickle cell pain, buprenorphine is underutilized. Methadone, ketamine, and nitrous oxide block the transmission of painful sensations through the N-methyl D-aspartate receptor, therefore they can be used to help individuals with severe pain who are not responding to other analgesics. Furthermore, the pharmacokinetics of morphine in sickle cell disease patients differ from those in other pain syndromes. In trials of children with sickle cell disease who were given intravenous morphine during vaso-occlusive crisis, the clearance of morphine was much higher, especially in prepubertal children, than in studies of children with postoperative pain or cancer pain. Similarly, in the steady state, in the absence of painful vaso-occlusive crisis, enhanced morphine clearance was documented in young people age less than 18 years with sickle cell disease (14). Kanjee reported that in 2019, the American Society of Haematology modified its guidelines for the treatment of acute and chronic pain caused by sickle cell disease. Several of the suggestions are conditional, allowing the treating physician to make specific options. These include conditional recommendations for the use of ketamine in the treatment of acute pain and the

commencement and discontinuation of long-term opioid medication in the treatment of chronic pain (15).

Gupta expresses that sickle cell disease pathobiology, peripheral and central sensory processes, and descending neuromodulatory pathways are all targets for new pain treatments in development. Many therapeutic techniques, in particular, have the potential to reduce opioid use and increase analgesia. When compared to treating pain after it has been induced, targeting pain at its source may be the most effective strategy of preventing sickle cell disease suffering. Targeting mast cells with imatinib, Food and drug administration authority-approved medicine, to reduce sickle pathobiology's elicitation of somatosensory processes looks to be a highly promising pharmacotherapeutic technique for preventing and treating sickle cell pain (16). Aich stated that mast cell and microglial activation, neurogenic inflammation, and leukocyte-derived elastase are all immunomodulatory components of acute and chronic sickle pain that can be used to target and prevent pain genesis. Hypoxia and reperfusion injury, oxidative stress, haemolysis, and adhesion molecules are all vascular modulators. Existing pain, on the other hand, need analgesics that do not have an unintended effect on sickle pathobiology. Cannabinoid and nociception receptors, as well as the serotonergic spinothalamic pathway, have recently been identified as analgesic targets. Acupuncture, hypnosis, and perception-based therapies are examples of complementary techniques that have proven analgesic potential. It is difficult to treat sickle cell disease discomfort with a single therapy due to the variability of pain development. Understanding the molecular and cellular entities that influence neural interactions in the sickle microenvironment may help to reduce sickle cell disease discomfort and develop better analgesics (17).

Traditional medical management has little effect on chronic pain relief because the majority of treatments are aimed at resolving or preventing acute crises. Selective serotonin reuptake inhibitors medication has been the only pharmacological treatment that has consistently showed effectiveness for chronic pain control. Nonpharmacological treatments have shown modest benefit in treating chronic pain in these patients, with cognitive behavioural therapy showing the most promise in patients with anxiety or depression. Chronic pain has also been relieved by stem cell transplantation and genetic therapy, although the criteria for these treatments are unclear and need to be researched further. Existing evidence shows that treating concurrent psychological problems appropriately enhances patient quality of life. To further understand techniques of chronic pain management in sickle cell disease, more large

randomized controlled research are needed (18). Acute and chronic pain are the most common complication of sickle cell disease however being a prevalent issue literature is lacking regarding the clinical studies more research in future is needed to study the effects of various management strategies for pain to develop more efficient guidelines and recommendations regarding pain management in sickle cell disease.

Conclusion:

Pain management in sickle cell disease patients has a significant impact on their quality of life. Given the multiple symptoms and pathologic pathways that are likely involved, pain management in the sickle cell disease scenario necessitates interdisciplinary approaches. Since pain management is not standardized and might be challenging, chance of mistreatment prevails. More research is needed to design care plans, treatment regimens, and management recommendations.

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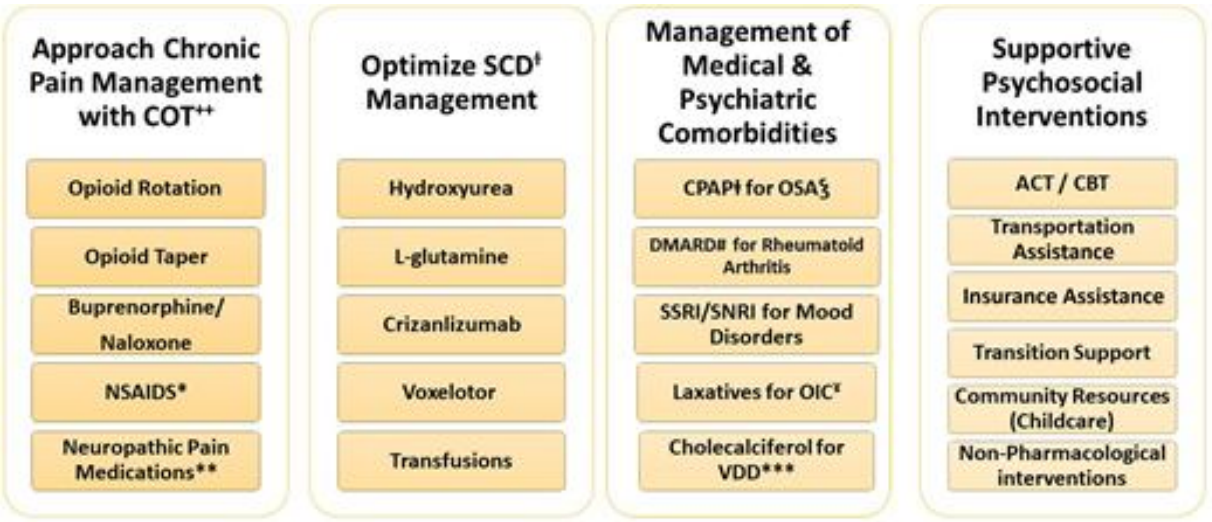

++ Chronic Opioid Therapy; * Nonsteroidal anti-inflammatory drugs; ** Neuropathic Pain Medication e.g. Gabapentinoids, Tricyclic antidepressants, SSRIs and SNRIs; ǂ sickle cell disease, ǂ continuous positive airway pressure; ʒ obstructive sleep apnea; # disease modifying autoimmune drug; ɤ opioid induced constipation; *** Vitamin D deficiency

Figure 1: Management of pain in sickle cell disease patients