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Peripheral Nerve Stimulation for Intractable Neuropathic Foot Pain in Sickle Cell Disease: A Case Report Introducing a Novel Interventional Approach

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Background: Neuropathic pain is a common yet underrecognized and undertreated issue in patients with sickle cell disease (SCD), often resistant to conventional pharmacologic therapies. Despite their potential benefits, interventional approaches remain underutilized in this population.

Case Report: We report the case of a 70-year-old woman with hemoglobin SCD who developed chronic burning pain in the lower extremity, refractory to opioids and neuropathic agents. Examination revealed marked allodynia, hyperalgesia, and a Douleur Neuropathique-4 questionnaire score of 7, consistent with neuropathic pain. She underwent a 60-day trial of peripheral nerve stimulation (PNS) targeting the common peroneal nerve, resulting in a 59% reduction in pain severity and a 71.4% improvement in functional interference. These benefits were sustained at 12-month follow-up without complications.

Conclusions: Our case highlights the potential of PNS as a safe and effective treatment option to improve pain control and quality of life in patients with refractory SCD-related neuropathic pain.

Key words: Sickle cell disease, neuropathic pain, peripheral nerve stimulation, case report

BACKGROUND

Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by chronic hemolytic anemia, vaso-occlusive episodes, and progressive multiorgan dysfunction (1). Pain in SCD patients, presenting as acute intermittent pain, chronic daily pain, and acute-on-chronic pain, is the most common and debilitating symptom, significantly affecting patients' quality of life (2). Acute pain in SCD has been attributed to vaso-occlusive crises (VOCs), arising from microvascular obstruction by sickled erythrocytes, leading to ischemia and subsequent tissue injury (3). However, many adolescents and adults with SCD also develop chronic pain, which persists beyond acute episodes, and is defined as "ongoing pain present on most days over the past 6 months in either a single location or multiple locations" (2). Recently, growing evidence suggests neuropathic pain, "resulting from a direct consequence of a lesion or disease affecting the somatosensory system" (4), is also prevalent in SCD patients, especially those with chronic pain syndromes (5-7).

An estimated 25% to 40% of SCD patients suffer from neuropathic pain (6), and its pathophysiology in SCD is multifactorial, possibly involving a combination of peripheral and central mechanisms. Peripheral mechanisms, such as vaso-occlusion, ischemia-reperfusion injury, and inflammation, lead to nerve damage and nociceptor sensitization (6,8). Meanwhile, central mechanisms include central sensitization, where repeated nociceptive input from the periphery leads to

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neuroplastic changes, manifesting as heightened pain sensitivity and development of chronic pain (9,10).

Current treatment for SCD-related pain heavily relies on opioids, which are more effective for acute episodes but suboptimal for chronic pain due to less efficacy and many associated risks. For example, chronic opioid therapy is associated with tolerance, physical dependence, and opioid-induced hyperalgesia (2). Moreover, frequent higher opioid demand for acute pain in SCD patients often blurs the difference between legitimate opioid needs and opioid misuse, complicating clinical management and contributing to stigma and undertreatment (11). Pharmacologic treatments, such as anticonvulsants and antidepressants, have shown promising benefits in other types of neuropathic pain; however, their efficacy remains uncertain in managing neuropathic pain phenotypes in SCD (2,12,13).

Peripheral nerve stimulation (PNS) is a minimally invasive neuromodulation technique that delivers electrical impulses to targeted peripheral nerves, thereby modulating both nociceptive and neuropathic pain signaling pathways (14,15). The American Society of Pain and Neuroscience has provided evidence-based clinical guidelines for utilizing PNS to treat a variety of chronic pain conditions, such as peripheral neuropathies, nerve entrapments, failed back surgery syndrome, phantom limb pain, complex regional pain syndrome, postherpetic neuralgia, etc (16). Despite the expanding indications, there is currently no published evidence supporting PNS application for neuropathic pain in SCD patients.

Our case report presents an SCD patient who developed chronic foot neuropathic pain. After exhausting pharmacologic managements without meaningful pain relief, the patient underwent a 60-day percutaneous PNS therapy using the SPRINT® PNS System (SPR Therapeutics, Cleveland, OH), targeting the common peroneal nerve (CPN) at the popliteal fossa. To our knowledge, this is the first report exploring PNS application in SCD-associated neuropathic pain.

CASE REPORT

A 70-year-old African American woman with a longstanding history of hemoglobin SCD, diagnosed at the age of 8, has been followed by the SCD clinic for decades. Since childhood, she has experienced numerous acute pain episodes requiring frequent emergency department visits and hospitalizations, in addition to chronic, widespread baseline pain. She has been on long-term opioid therapy for many years, having trialed multiple opioid regimens. At one point, her regimen included extended-release oxycodone 80 mg orally twice daily and immediate-release oxycodone 20 mg orally every 6 hours as needed (total morphine dose equivalent of 360 mg per day). Despite this, the patient continued to suffer from debilitating neuropathic pain-like symptoms in multiple body regions, including bilateral arms, hands, legs, and feet, which she reported "a constant burning pain." She has no obvious etiology, which can cause peripheral neuropathy, such as diabetes, vitamin B12 deficiency, alcohol use, chemotherapy, HIV infection, etc.

Meanwhile, the patient had been followed by the pain medicine clinic for years and underwent various interventional procedures periodically, including intraarticular knee steroid injections for osteoarthritis and lumbar epidural steroid injections for radiculopathy with positive response. She also engaged regularly with physical therapy and the pain psychology team, participating in cognitive behavioral therapy, mindfulness training, and biofeedback, with limited relief. Due to her uncontrolled neuropathic-like symptoms, adjunctive neuropathic pain medications were also trialed. Gabapentin (up to 3,600 mg per day) was started but then later discontinued due to severe sedation without meaningful pain relief. Pregabalin (up to 400 mg per day) and duloxetine (up to 120 mg per day) were subsequently attempted, which did alleviate other pain areas, but the burning pain in the left leg persisted.

At a follow-up visit in the pain medicine clinic, the patient continued to report persistent burning pain localized to the left anterior shin and dorsal foot areas, while the other part of her burning pain became tolerable with medications. Clinical examination revealed significant allodynia and hyperalgesia in the affected areas, and her Douleur Neuropathique-4 questionnaire score (6) was 7, suggestive of neuropathic pain. Following a thorough discussion between the patient and the pain management team, an ultrasound-guided diagnostic block of the left CPN with 0.5% bupivacaine was performed. The block resulted in approximately 100% pain relief lasting > 24 hours. Given the positive response, a 60-day percutaneous PNS therapy using the SPRINT PNS System, targeting the same nerve, was initiated. Although the lead was placed at the popliteal fossa near the knee, it was positioned parallel to the nerve under real-time ultrasound guidance to avoid crossing the joint and minimize mechanical stress

during joint movement. The patient was monitored with follow-ups every 3 months after the PNS lead was explanted.

She also completed the Brief Pain Inventory before and after PNS therapy. At baseline, her pain severity average score was 5.5, and the pain interference average was 7.0, indicating substantial impact on both pain intensity and daily functioning. At the time of lead explantation, her pain severity score decreased to 2.25, and pain interference dropped to 2.0. These results reflect a 59% reduction in pain severity and a 71.4% improvement in pain interference. Even after 12-month follow-up, she continues reporting consistent, significantly sustained pain relief and rates her overall improvement as "very much improved" on the Patient Global Impression of Change scale (2).

DISCUSSION

Acute pain episodes resulting from VOCs are the hallmark of SCD (17). However, chronic neuropathic pain has recently gained more attention as a prevalent but undertreated condition, potentially arising from both central and peripheral mechanisms (6,10). The efficacy of pharmacologic interventions for managing SCD-related neuropathic pain remains inconclusive and warrants further investigation (7,10,13). The patient exhibited classic features of peripheral neuropathy (including burning, tingling, allodynia, hyperalgesia, and functional impairment), and showed only partial relief with neuropathic pain medications. Despite trials of anticonvulsants and antidepressants, in addition to sustained opioid therapy, her symptoms persisted, resulting in consideration of alternative treatment strategies. Our case highlights the use of PNS as a novel, minimally invasive approach for managing refractory neuropathic pain in an SCD patient. Following a 60-day course of PNS therapy, the patient experienced not only significant pain reduction but also substantial improvements in daily functioning and overall quality of life.

PNS modulates both peripheral and central pain pathways. Given that SCD-related chronic pain involves a combination of peripheral nerve injury, inflammation, and central sensitization, this dual mechanism makes PNS a mechanistically rational option for SCD patients. PNS activates large-diameter, low-threshold Aβ fibers, which inhibit nociceptive transmission from Aδ and C fibers via the gate-control mechanism, thereby reducing pain signal propagation in the dorsal horn of the spinal cord (18). Beyond segmental gating, PNS also reduces inflammation by suppressing local proinflammatory cytokines and neurotransmitter release (18,19), which is especially pertinent in SCD, where neuroinflammation and immune activation contribute to pain chronification (20). Centrally, PNS decreases central sensitization and hyperalgesia by inhibiting wide dynamic range neurons in the dorsal horn and modulating endogenous pain inhibitory pathways, including serotonergic, GABAergic, and glycinergic systems (16,21). Lastly, PNS can also induce longer-term changes in cortical and subcortical pain processing regions, promoting adaptive neuroplasticity (21). Clinical guidelines suggest that PNS modulates inflammatory pathways, autonomic function, and central pain processing, making it a mechanistically rational intervention for neuropathic pain in SCD (16).

SCD patients often present complex clinical challenges due to a wide array of medical comorbidities, including acute pain crises, acute chest syndrome, stroke, nephropathy, retinopathy, avascular necrosis, priapism, leg ulcers, chronic pain, and progressive multiorgan dysfunction (22). The minimally invasive nature of PNS, particularly the 60-day system, makes it an appealing option for this vulnerable population, as it avoids the risks associated with more invasive surgical procedures. While PNS has demonstrated promising efficacy in multiple chronic pain conditions (16), its application in SCD remains novel and underreported. In this case, the patient tolerated stimulation well, with no device-related complications observed, supporting the feasibility and safety of PNS. Successful outcomes with PNS require appropriate patient selection, and ideal candidates typically exhibit well-localized neuropathic pain attributable to a discrete peripheral nerve. In this case, the patient's symptoms followed the distribution of the CPN, and diagnostic nerve blocks resulted in complete pain relief, an encouraging predictor of PNS responsiveness. This case adds to the growing evidence that PNS may be an effective and safe intervention for managing refractory neuropathic pain in patients with SCD.

CONCLUSIONS

Our case highlights PNS as a promising, minimally invasive therapeutic approach for neuropathic pain in SCD, especially when conventional treatments fail. The positive and sustained outcomes in this case suggest that PNS may represent a safe and effective approach to improve pain control and quality of life in patients with refractory SCD-related neuropathic pain. Further studies are needed to validate these findings in larger cohorts.

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