

Case Report



The Use of Spinal Cord Neuromodulation in the Management of HIV-Related Polyneuropathy

Nebojsa N Knezevic, MD, PhD^{1,2}, Kenneth D. Candido, MD^{1,2}, Shalini Rana, MD¹,
and Ivana Knezevic, MD¹

From: ¹Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, IL; and ²Department of Anesthesiology, University of Illinois College of Medicine, Chicago, IL
Dr. N. Knezevic is Director of Anesthesiology Research and Clinical Assistant Professor and Dr. Candido is Chairman and Professor with the Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, IL; and the Department of Anesthesiology, University of Illinois College of Medicine, Chicago, IL. Dr. Rana is a Resident, Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, IL; and Dr. I Knezevic is Clinical Research Coordinator, Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, IL

Address Correspondence:
Kenneth D. Candido, MD
Advocate Illinois Masonic Medical Center
Department of Anesthesiology
836 W. Wellington Ave.
Suite 4815
Chicago, IL 60657
E-mail: kdcandido@yahoo.com

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Background: The prevalence of HIV-related neuropathy may rise nationwide as Highly Active Antiretroviral Therapy (HAART) usage and HIV-survival rates increase, resulting in higher referral rates to pain practitioners for analgesic strategies. However, if patients' symptoms are refractory to conservative measures, an advanced interventional approach may be indicated.

Objective: We present 2 cases of successful use of spinal cord neuromodulation in the treatment of HIV-related neuropathy.

Study Design: Case Report

Methods: One patient experienced severe lower extremity burning pain, progressively worsening over the past 6 years. He had trouble ambulating, and pain was refractory to conservative treatments. The other patient suffered from low back pain and distal symmetrical polyneuropathy. A remote lumbar discectomy prior to his development of HIV disease resulted in marked improvement in lumbar spinal pain, but subsequent later development of neuropathic pain remained refractory to different treatment modalities.

Results: Both patients reported more than 90% improvement in pain during the spinal cord stimulator (SCS) trial, which led to permanent SCS implantation with equivalent success rates. One of them was followed up for 3 years, and another one for 14 months before he moved overseas. Both of them reported an improved quality of life, reductions in the use of oral opioid analgesics, and increased ability to participate in daily activities without limitations. Neither patient sustained any infectious complications, lead migration, or required battery changes.

Limitations: Controlled double blinded studies with a higher number of patients are needed to prove efficacy in these patients.

Conclusion: These 2 cases demonstrate that SCS neuromodulation is a safe, viable, and efficacious option for patients whose HIV-related neuropathic type pain is refractory to conventional treatment modalities. Our patients appear to be the first case reports that show a remarkable efficacy of SCS in the management of HIV-related polyneuropathy.

Key words: HIV neuropathy, spinal cord stimulation, lower extremity pain, chronic pain, neuropathic pain

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The prevalence of HIV-related neuropathy will likely rise nationwide as Highly Active Antiretroviral Therapy (HAART) usage and HIV-survival rates increase, resulting in higher referral rates to pain practitioners for analgesic strategies. Due to

the effectiveness of antiretroviral medication and a decline in central nervous system (CNS) opportunistic infection and HIV-related dementia, HIV-associated neuropathies have become the most common neurological disorders associated with AIDS (1). This

also could be due in part to the adverse effects of antiretroviral medications on the peripheral nervous system (1).

Patients with HIV-related polyneuropathy typically present with painful paresthesias (pins and needles), dysesthesias (burning sensation), or numbness in their feet, symmetrical in distribution. The pain may be so severe that patients cannot bear to put on socks or shoes (2). The symptoms may lead to gait difficulties and disturbances of sleep, interfering with daily activities (3). Clinical exam may reveal absent ankle jerk reflexes, decreased vibratory sensation of the feet, intrinsic foot muscle weakness, and decreased pain and temperature sensation in a stocking distribution. There may be minimal neurological signs in some patients with distal symmetrical polyneuropathy, suggesting predominant involvement of small nerve fibers (4,5). Additionally, viral load and CD4+ lymphocyte count have been reported to be predictors of symptomatic distal symmetrical neuropathy (6).

The conventional management of HIV-related polyneuropathy consists of a multimodal type regimen including use of opioids, anticonvulsants, Lidoderm® patches, and capsaicin, all which may offer limited relief. The use of certain opioids for achieving analgesia in patients with HIV-related painful distal sensory polyneuropathy is, in fact, enchainning hypersensitivity for pain and facilitating pro-nociceptive effects (7). With commonly used analgesic monotherapy, at least moderate relief is achieved in about half of patients. Since the etiologies for distal symmetrical polyneuropathy may vary, an advanced interventional approach may be indicated for patients whose symptoms are refractory to conservative measures (8). We present 2 patients whose symptoms were refractory to various treatments. Both patients had outstanding responses to placements of permanent spinal cord stimulator (SCS) systems.

CASE DESCRIPTIONS

Case 1

A 39-year-old man with a past medical history significant for hepatitis C and depression, diagnosed with HIV 6 years previously, presented with burning pain in his limbs. The symptoms had gradually progressed over 4 years. The most severe pain was on the soles of the feet, which increased with walking, standing, and local application of pressure, and was relieved with opioid analgesics and complete rest. He smoked half a pack-

age of cigarettes daily for 15 years. Previously, the patient had used illicit drugs such as cocaine, marijuana, and ecstasy, but had participated in a therapeutic community and was sober for more than 2 years when he presented to us. An electromyogram/nerve conduction velocity (EMG/NCV) performed in his neurologist's office confirmed the diagnosis of predominantly sensory axonal distal neuropathy. He was treated with pregabalin 350 mg daily in divided doses, acetaminophen with codeine 1300/10 mg daily, gabapentin 400 mg twice daily, atrypla (Emtricitabine-Tenofovir-Efavirenz) 600 mg daily, citalopram 20 mg daily, clonazepam 0.5 mg twice daily, and buspirone 20 mg twice daily. He continued to experience pain and requested aggressive interventional therapy to be considered.

Following failure of conventional methods to reduce the patient's neuropathic pain, a trial of dual lead St. Jude's® Medical SCS lead placement under monitored anesthesia care was offered. Intravenous antibiotics (cefazolin 2 g) were given 30 minutes prior to skin preparation. The interlaminar space at L2-3 was identified, and skin wheals were made 4 – 5 cm caudal to it on either side of the dorsal midline. Fourteen gauge, 3.5-inch, Coude-type epidural needles were inserted sequentially under fluoroscopic guidance into the epidural space using the loss-of-resistance to saline technique. Two 8-electrode leads were advanced under continual fluoroscopic monitoring until they were situated with the proximal-most contacts at the cephalad-most margin of the T-10 vertebral body, slightly to the right and then left of the anatomical midline. The epidural needle was withdrawn and gooseneck anchors were sutured over the leads. Stimulation assessment captured the patient's "usual, customary, and daily type of pain" without adventitious stimulation elsewhere. The patient demonstrated intact sensory and motor functions as per pre-surgical evaluations and was taken to the recovery suite. Following the procedure, the patient was prescribed acetaminophen 650 mg 2 tablets every 8 hours for analgesia. The patient tolerated the procedure well without sequelae.

On the third day post-procedure, the patient reported a 90 – 95% improvement in pain and a reduced consumption of oral opioids. A decision was made to proceed with a permanent SCS implant, which was uneventfully undertaken 3 weeks later using 2 leads attached to an implantable pulse generator (IPG) (Fig. 1a, b). The patient was extremely satisfied with the results following permanent SCS placement. He showed 95

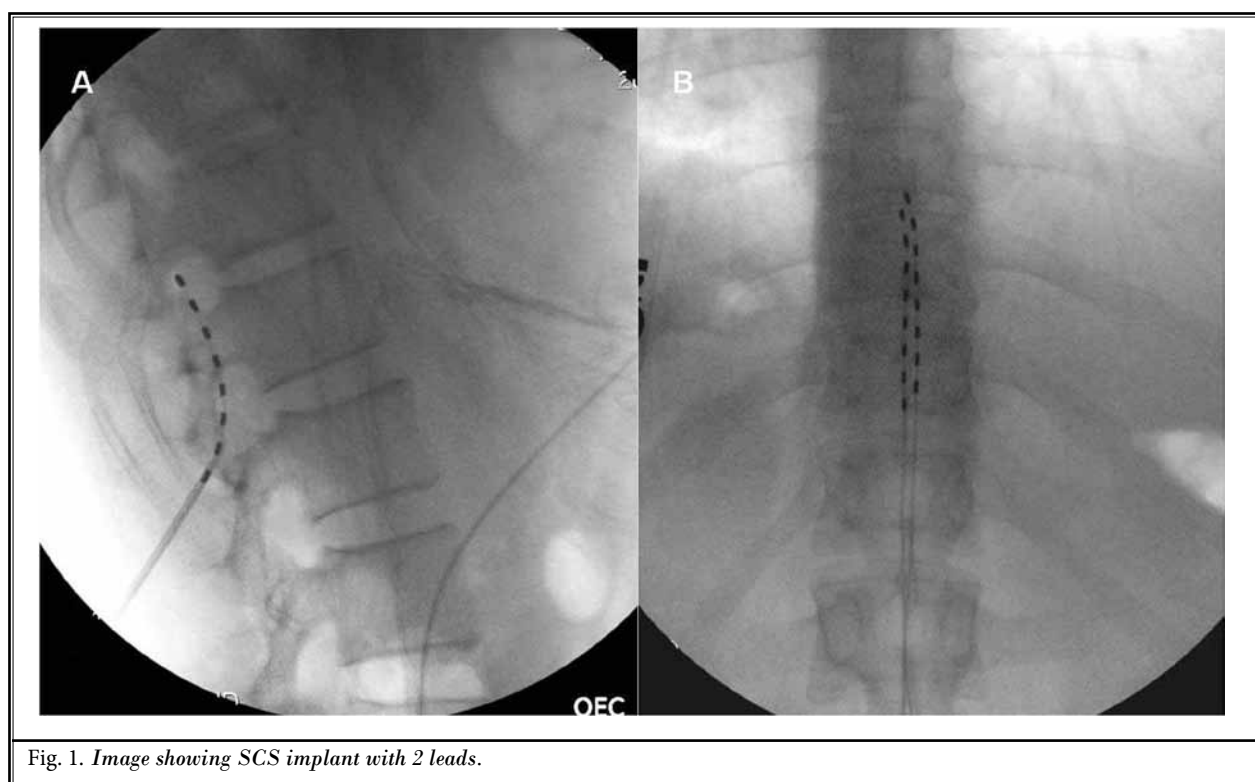


Fig. 1. Image showing SCS implant with 2 leads.

– 100% improvement in pain and did not require any adjuvant analgesic medications whatsoever. Improvement in pain control, quality of life, and functionality were evaluated by several questionnaires (Table 1). He followed-up for the past 3 years since the placement of the implanted SCS, and has been able to perform his daily activities without restrictions or limitations, including finding a job and returning to full duty work as a waiter. He suffered no complications such as infections (either deep or superficial), lead migration, and required no significant changes in programming of the pulse generator. His programming is shown in Table 2.

Case 2

A 46-year-old man presented with hyperalgesia, allodynia, and aching pain that was radiating to both lower limbs, associated with tingling and painful numbness. He was diagnosed with HIV polyneuropathy 6 years previously by his neurologist. He also suffered from bipolar disorder, chronic bronchitis, and hypertension. Magnetic resonance imaging (MRI) showed mild narrowing of the neural foramina at L4-5 and L5-S1 from a remote injury. He underwent a lumbar discectomy remotely at age 22 (before contracting HIV) and reported marked improvement in lumbar axial spinal pain. However, the

symptoms of a distal symmetrical polyneuropathy developed long after surgery, and the neurological exam showed decreased sensation to pain, temperature, and vibration below the knee, and reduced Achilles tendon reflexes bilaterally. His pain worsened to the extent that it started affecting his sleep as well. He was prescribed hydrocodone/APAP (7.5/325) every 4 hours plus oxycodone 15 mg every 6 hours for his chronic pain. He had been treated with efavirenz 600 mg daily, lisinopril 10 mg daily, bupropion 300 mg daily, and alprazolam 1 mg every 4 hours.

An informed consent was obtained for a trial of dual lead St. Jude's® Medical SCS trial placement under monitored anesthesia care. Intravenous cefazolin was given 30 minutes prior to skin preparation for antibiotic prophylaxis. A skin wheal was raised to the left of the dorsal midline approximately 5 cm inferior and lateral to the left of the L2-L3 intervertebral space, using bupivacaine 0.5% with epinephrine 1:200,000, 8 mL via a 25-gauge 1.5-inch needle. A 14-gauge 3.5-inch Tuohy-type epidural needle was atraumatically inserted under fluoroscopic guidance.

Lateral imaging demonstrated that the lead was indeed in the dorsal part of the epidural space. A small incision was made immediately inferior to the first

Table 1. Pain measures and quality of life at baseline (prior to spinal cord stimulator at baseline and after 6 and 12 months post-spinal cord stimulator implantation); whereas the first number represent the Case 1 and the second one the Case 2.

	Baseline	6 months	12 months
PCS (Pain Catastrophizing Scale)* (on 0 – 52 scale)	35/47	11/21	6/17
Pain Disability Index* (on 0 – 70 scale)	41/46	19/25	11/18
NPSI (Neuropathic Pain Symptom Inventory)* (on 0 – 100% scale)	77/85	33/51	13/23
SF-MPQ-2 (Short-form McGill Pain Questionnaire)* (on 0 – 10 scale)	4.23/9.20	2.08/7.39	1.19/3.91
Continuous pain	3.50/9.66	2.07/6.83	2.01/3.66
Intermittent pain	2.07/ 8.33	1.20/ 8.16	0.2/3
Neuropathic pain	8.83/ 9.33	4.33/ 6.33	2.55/4
Affective descriptors	2.50/ 9.5	0.75/8.25	0/3.5
SF-36 (Short-form Quality of Life Questionnaire)# (on 0 – 100 scale)			
Physical function	10/10	50/30	75/65
Role limitation due to physical health	10/25	30/25	55/ 62.5
Role limitation due to emotional problems	80/25	100/16.6	100/66.6
Energy/fatigue	60/43.75	70/37.5	75/43.75
Emotional well-being	82.5/45	90/35	95/50
Social health	12.5/12. 5	55/50	80/62.5
Pain	12.5/0	62.5/22.5	60/57. 5
General health	65/35	70/35	85/45

*in all pain measures (PCS, Pain Disability Index, and SF-MPQ-2) lower scores mean better pain outcome

#in quality of life SF-36 outcome higher score mean bet

Table 2. SCS programming used by patients.

Patient	Program	Area	Freq (Hz)	PW (US)	Polarities	Perception (mA)	Comfort (mA)	Max Tol (mA)
#1	2	BL lower extremities	60	300	0000 ++-0 0000 0000	6.50	9.20	11.90
#1	3	BL lower extremities	60	400	000+ 0-00 0000 0000	4.40	7.10	9.80
#1	4	BL lower extremities	90	400	000+ 0-00 0000 0000	4.40	7.10	9.80
#2	6	BL lower extremities	90	500	0++-0000 00000000	4.90	11.60	20.60
#2	3	BL lower extremities	90	212	00000+-0 00000000	8.40	13.0	17.60
#2	7	BL lower extremities	90	312	00000000 000-0+00	7.10	11.10	15.10

needle and a 14-gauge 3.5-inch Coude type epidural needle was advanced into the epidural space using the loss-of-resistance to saline technique. A second 60-cm long lead was advanced until its proximal contact was seated at the midpoint of the T9 vertebra, slightly to the right of the first lead, with both in an approximate anatomical midline location. The epidural needles were then removed and gooseneck anchors were used to se-

cure the leads to fascia. The patient tolerated the procedure well and demonstrated intact sensory and motor functioning, as per pre-procedure. The trial period lasted 6 days with the patient reporting 95% analgesic benefit, after which the patient agreed to proceed to permanent implantation 2 weeks after discontinuation of the trial leads (Fig. 2 a, b). This was undertaken 2 weeks after discontinuation of the trial leads.

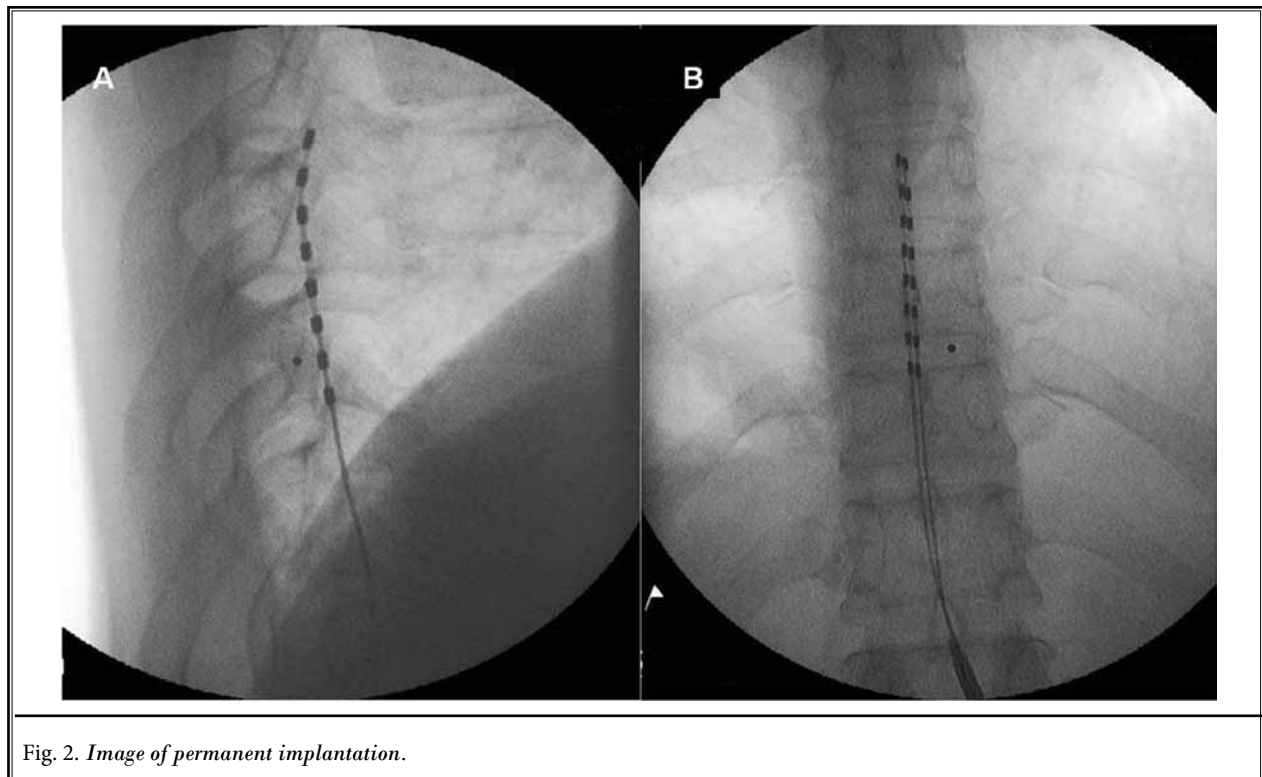


Fig. 2. Image of permanent implantation.

The patient demonstrated outstanding pain relief for one year following the permanent SCS placement and he was weaned off oral opioids. He requested pulse generator site revision for cosmetic reasons one year later, which was performed without any complications. Over the next 14 months, he was > 90% improved and had sustained no apparent adverse sequelae from the use of the SCS, but was lost to follow-up when he moved to England to be closer to his family. His programming is shown in Table 2, and his improvement in pain, quality of life, and functionality in Table 1. However, limited data from 2 cases did not allow interpretable statistical analysis.

Discussion

HIV polyneuropathy may be caused by several distinct etiologies including direct HIV-induced nerve damage, complications of opportunistic pathogens (e.g., cytomegalovirus infection), and toxic neuropathy from HAART. The classification of HIV-associated neuropathies can be determined based on when they evolve with regard to the HIV disease stage and the implementation of therapies used to combat the disease (9). Distal symmetrical poly neuropathy (DSP) represents a neurologic complication of HIV infection (10). The most

disabling feature of DSP is pain, which may be either spontaneous or evoked. DSP occurs in over one-third of HIV-infected patients (3).

The nerve damage can occur by direct or indirect mechanisms. The viral envelope glycoprotein gp120 subunit directly invades the peripheral nerve and the dorsal root ganglion, resulting in neurotoxicity (11,12). Immunopathogenic factors such as macrophage infiltration of the peripheral nerves and dorsal root ganglion may result in indirect neurotoxicity (13). Neuropathy related to antiretroviral exposure is likely due to mitochondrial toxicity (8). The dideoxynucleoside drugs inhibit mitochondrial DNA synthesis by interfering with mitochondrial gamma DNA polymerase. Toxic neuropathy from dideoxynucleoside antiretroviral agents is clinically indistinguishable from HIV DSP (5). Cessation of the dideoxynucleoside antiretroviral drug may cause intensification of symptoms for 6 – 8 weeks post withdrawal, termed “the coasting period” (14). Certain opioid analgesics may “fuel the fire” of HIV enhanced hypersensitivity due to up regulation of specific chemokine receptors (e.g., CXCR4) which is crucial for HIV-associated pain sensations (7).

Numerous studies have indicated that the under-

recognition and under-treatment of neuropathic pain in HIV-infected patients is common. Breitbart et al (15) reported more than 80% of patients presenting to a clinic devoted to AIDS-related pain were receiving inadequate analgesia. Barriers to optimal pain management include patient factors (i.e., reluctance to report pain), provider factors (i.e., fear of addiction and maladaptive pattern of substance misuse), and health care system factors (i.e., multiple prescriptions, regulatory oversight) (16-18).

Currently there are no FDA-approved pharmacological agents recognized for the treatment of neuropathic pain in HIV-related DSP (19), and combination or multimodal therapy is often required to manage symptoms. Available agents include non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) (i.e., ibuprofen) and acetaminophen. For moderate to severe pain (4/10 – 10/10), opioid analgesic combinations (i.e., hydrocodone, oxycodone) may be employed. Antiepileptics such as gabapentin, lamotrigine, carbamazepine, and phenytoin have also been widely used in various forms of painful peripheral neuropathy of diverse etiologies (20). A randomized, double-blind, placebo-controlled study in which a total of 302 patients (151 pregabalin, 151 placebo) were examined, showed that while pregabalin was well tolerated, it was not superior to placebo in the treatment of painful HIV-related polyneuropathy (21). In a multicenter, randomized, double-blind, placebo-controlled study, lamotrigine was initiated at 25 mg per day and was slowly titrated to 300 mg over 7 weeks. However, only 29 patients (20 placebo, 9 lamotrigine) completed the full 14 weeks. The results showed that pain scores at baseline were not significantly different; however, there was a reduction in average pain from baseline to 14 weeks in the lamotrigine group (22).

SCS has been used successfully in conditions such as failed back surgery syndrome associated with ongoing radicular pain, complex regional pain syndrome, neuropathic pain secondary to peripheral nerve damage, ischemic pain associated with peripheral vascular disease, refractory angina pectoris, and traumatic/post irradiation brachial plexopathy. There are several neuropathic pain conditions that have not been formally studied in which patients have responded favorably to SCS including post-amputation pain, intercostal neuralgia, and pain associated with spinal cord damage (23). Several contraindications for the use of SCS include psychological unsuitabil-

ity, bleeding disorders/ongoing anticoagulant therapy, systemic or local sepsis, presence of a demand pacemaker/implanted defibrillator, and immunosuppression (24). In HIV-neuropathy refractory to a pharmacologic multimodal therapy, SCS should be considered a viable treatment option early in the decision-making process. Cameron (24) identified 51 studies with a combined population of 2,972 patients wherein SCS was demonstrated to be a safe and effective treatment for a variety of chronic neuropathic conditions. However, an overall complication rate of 36% was noted with the use of SCS (24).

Similar to HIV neuropathy, diabetic and chemotherapy-induced neuropathy are small fiber neuropathies (25). Small fiber neuropathies, either in diabetes, HIV, or post chemotherapy, have lower response rates to conventional pain treatments than do other forms of neuropathic pain (26).

In our 2 referenced cases, both patients reported more than 90% improvement in pain during the SCS trial, followed by permanent SCS implantation wherein both reported an equivalent analgesic benefit associated with an improved quality of life, reductions in the use of oral opioid analgesics, and both were able to participate in daily activities without limitations.

SCS was also shown to have positive effects in patients with diabetic neuropathy through several observational studies as well as one recently published randomized controlled clinical trial (27). A multicenter clinical trial with 36 patients with painful diabetic peripheral neuropathy was conducted where 22 patients were assigned to receive SCS as well as the best medical treatment (BMT), and 14 were followed being on the BMT only. Treatment success was noted in 59% of the SCS group and in only 7% in BMT only group. Pain relief and sleep were significantly better in the SCS group as well (27).

Patients that developed chemotherapy-induced neuropathy, which can happen even years after they underwent treatment for malignant neoplasia (28), often do not respond satisfactorily to treatments using opioids or antidepressants (29). There are only 3 cases that reported success of SCS treatment in chemotherapy-induced neuropathy (30,31). However, future randomized studies of the use of SCS implantation in small fiber neuropathies, especially HIV-induced and chemotherapy-induced neuropathies are needed to provide sufficient proof of the role of SCS in managing pain in these patients.

CONCLUSION

To our knowledge, these are the first 2 case reports establishing the long-term efficacy of SCS in the management of HIV-related polyneuropathy wherein pain proved refractory to conventional pharmacologic treatment modalities. SCS has the advantage of minimizing the use of opioids in patients who are already utilizing polypharmaceutical analgesic regimens, thereby reducing the risk of drug-drug interactions. It also minimizes problems related to compliance more commonly seen in this group of patients. However, among the considerations and limitations to the use of SCS in the HIV population with polyneuropathy include their CD4 counts (immunosuppression) which could potentially increase

their susceptibility to infections, and therefore demand that extreme caution be implemented while considering the use of SCS.

Disclaimer

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Conflict of interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

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