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Improvement in Neuropathic Pain, Proprioception, and Gait Stability after Spinal Cord Stimulator Implantation for Chemotherapy-Induced Peripheral Neuropathy

Mihir M. Kamdar, MD[1], Lathan W. McCall, MD[1], Ashley M. Saba, DPT[2], and Brian J. Wainger MD, PhD[1,3]

Background: We present a patient with gait instability and pain due to chemotherapy-induced peripheral neuropathy (CIPN) who experienced marked improvement in motor function, proprioception, and pain following placement of a spinal cord stimulator (SCS).

Case Report: A 62-year-old woman underwent placement of a permanent SCS after failing conservative therapy to manage her severe CIPN. Preoperatively, she reported significant gait instability in addition to her pain, typically suffering 10 falls per month. Postoperatively, she experienced a pronounced reduction in her pain level from 8 of 10 to 2 of 10 and in her number of falls from 10 to 0 per month. Furthermore, we formally assessed gait speed and function, Timed Up and Go (TUG) testing, postural control, and lower extremity function before and after SCS placement, and we found a profound improvement in all measurements.

Conclusions: For patients with CIPN, SCS devices represent an increasingly viable treatment option. Our patient demonstrated significant improvements in not only pain, but also surprisingly in her motor function and gait stability with SCS therapy. This case highlights a potential additional benefit of neuromodulation in patients suffering from CIPN.

Key words: Balance, cancer pain, chemotherapy-induced peripheral neuropathy, gait speed, neuromodulation, neuropathic pain, paresthesia, proprioception, spinal cord stimulation

BACKGROUND

Chemotherapy-induced peripheral neuropathy (CIPN) affects between 30% to 40% of cancer patients and is dose-limiting in as many as 60% to 80% of cancer treatment regimens (1). It can cause significant neuropathic pain and gait instability, both of which negatively impact the quality of life of cancer patients. CIPN is often refractory to pharmacologic therapies, with only duloxetine demonstrating moderate benefit in randomized clinical trials, although many other drugs are used off-label (2). With the population of cancer survivors in the United States expected to increase to 18 million by 2022, the incidence of CIPN is likely to increase. As such, novel and more effective strategies are needed to longitudinally manage CIPN (3).

SCS has been demonstrated to provide effective analgesia in a variety of neuropathic pain conditions, including postlaminectomy failed back syndrome and complex regional pain syndrome (4,5). We present a patient with CIPN who experienced a remarkable reduction in not only pain but also falls and motor debility following SCS implantation. This case merits discussion

From: [1]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA; [2]Department of Physical Therapy, Massachusetts General Hospital, Boston, MA; [3]Department of Neurology, Massachusetts General Hospital, Boston, MA

Corresponding Author: Mihir Kamdar, MD, E-mail: mkamdar@mgh.harvard.edu
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as it demonstrates the wider applicability that SCS could have for CIPN patients and the potential for SCS to improve not only pain but also objective functional outcomes in patients with CIPN.

CASE

The patient provided consent for her case to be presented in this report.

A 62-year-old woman with a past medical history of MSH-2 related Lynch syndrome (HNPCC 1), hyperlipidemia, and cecal adenocarcinoma status post total colectomy first presented to our clinic on September 18, 2017 for evaluation and management of painful chemotherapy-induced peripheral neuropathy. She did not have a history of diabetes or other known neurologic syndromes. She initially developed peripheral neuropathy following a course of 9 of 12 planned cycles of folinic acid, fluorouracil, and oxaliplatin chemotherapy (FOLFOX) for cecal adenocarcinoma, completed on April 1, 2015. Her chemotherapy was truncated at 9 of 12 cycles due to worsening neuropathy resulting in severe pain and gait imbalance.

The pain was in a stocking-glove distribution, beginning in the feet and hands and radiating proximally to the ankles and wrists, respectively. She described a tearing pain in her extremities, and, as with many CIPN patients, her symptoms were worse in the lower extremities. Additionally, she described a constant electric hum as well as episodic burning sensations in the hands and feet. She also complained of numbness and tingling in her fingers and feet. She underwent electromyography on July 1, 2015 which demonstrated a polyneuropathy with distal degeneration of sensory axons in the hands and feet. The pain significantly affected her ability to perform activities of daily living, such as cooking and gardening. She was unable to stand on cold tiles in her bare feet. The pain even affected her ability to hold her husband's hand.

In addition to pain, her CIPN syndrome included motor and proprioceptive deficiencies resulting in gait instability and frequent falls. She could not utilize assistive devices because of severe neuropathy in her hands, so she had to lean against walls to prevent falls. She reported approximately 10 falls per month, with multiple "close calls" daily. Physical therapy evaluation prior to the procedure noted significant gait and balance dysfunction primarily due to sensory impairment. Specifically, the therapist noted significantly impaired gait speed and function, Timed Up and Go (TUG) testing, postural control, and lower extremity function (Table 1).

She previously trialed neuropathic medications including gabapentin, duloxetine, pregabalin, oxcarbazepine, and amitriptyline at therapeutic doses and for significant duration. She had received oxycodone for a separate surgical procedure as well as oxycodone extended release from a prior pain clinic, and she reported that these medications had no effect in controlling her neuropathic pain. She remained on high-dose gabapentin, oxcarbazepine, and amitriptyline, though with only mild relief of her pain. She underwent physical therapy, including desensitization and gait training modalities, without significant improvement.

As her persistent pain and disability were refractory to conservative therapies, a trial of SCS was discussed. After passing a requisite psychological screening, the patient underwent a SCS trial on August 13, 2018 to target her lower extremity pain. During the trial, 2 percutaneous 8-electrode Vectris Surescan MRI - Conditional SCS leads (Medtronic, Minneapolis, MN) were positioned in the epidural space with tips of the leads at the base of the T8 vertebral body and the T8/T9 interspace. Paresthesia-mapping confirmed good coverage of the areas of her lower-extremity pain.

On August 20, 2018, she presented for follow-up evaluation reporting a significant reduction in her pain on the visual analog scale (VAS) from 8 of 10 to 2 of 10 with SCS therapy. She also noted a striking improvement in stability while ambulating, and as a result noted a significant improvement in global function and activity. This was corroborated by her husband who observed these functional improvements during the trial. Within a few days after removal of the temporary leads, the patient reported a return of her pain and gait disturbance.

On September 26, 2018, she underwent placement of a permanent SCS. In the operating room, 2 Medtronic Vectris Surescan MRI-Conditional epidural SCS leads were threaded in the epidural space again to the base of the T8 vertebral body and the T8/T9 interspace (Fig. 1). Paresthesia mapping again elicited coverage of the areas of lower extremity pain. A Medtronic Intellis neurostimulator internal pulse generator (IPG) (Medtronic, Minneapolis, MN) was implanted subcutaneously in the left gluteal region. The procedure was successfully performed without complication and the patient had an uneventful recovery.

She returned to the clinic on October 4, 2018 (postoperative day 12) and again reported significant

Table 1. Physical therapy assessments before and after spinal cord stimulator placement.

Assessment	Pre-SCS (9/11/18)	Post-SCS Placement (12/4/18)	Age/Gender Matched Norm	Minimal Detectable Change/Minimal Clinically Important Difference (MDC/MCID)
Gait Speed	1.0 m/s	1.33 m/s	1.24 m/s	MCID: 0.13 m/s
Functional Gait	7/30 points	22/30 points	27.1 +/- 2.3 (SD)	MCID: 4 points
Timed Up and Go	9.16 s	7.73 s	8.0 s	N/A
6-Minute Walk Test	356 m	499.8 m	538 m	MDC: 58.21 m MCID: 50 m
Postural Control - Romberg, Firm Surface (Eyes Open / Eyes Closed)	30 s moderate sway / 2 s maximal sway	30 s average sway / 28 s mild sway	N/A	N/A
Activities-Specific Balance Confidence Scale	46.25% confident	94% confident	79.9% confident	N/A

subjective improvement in her pain and gait stability with stimulation. She utilizes classic "tonic" stimulation during the daytime, which she turns down at night to subthreshold. For purposes of reproducibility, we are utilizing the 3- anode, 4+ cathode with programming settings of a pulse width of 360, rate of 60, intensity of 6.5, and stimulating approximately over the bottom half of the T9 vertebral body.

By December 3, 2018, 10 weeks postoperatively, she reported continued improvement in her pain symptoms and an average VAS score of 2 of 10 in her feet. Over the next several visits (2/11/2019, 4/8/2019), she continued to report remarkable benefit from the stimulator in terms of pain, allodynia, function, and gait stability.

Postoperatively, she was able to walk barefoot on cold surfaces, which she was not able to do previously, and she tolerated a pedicure for the first time in years. Surprisingly, she also denied any falls since the device had been implanted. During this time, she was able to titrate down her preprocedure gabapentin dose from 4,200 mg total daily to 2,400 mg daily without an increase in her pain levels. She was also able to titrate off of amitriptyline. At our most recent follow-up more than 2 years post implantation on November 30, 2020, she continues to report an average VAS score of 2 of 10 in her feet and continues to do well on gabapentin 2400 mg daily and oxcarbazepine 600 mg 3 times daily.

On formal postoperative physical therapy gait and stability assessments, she demonstrated a significant improvement in every tested objective category compared to her pre-SCS implant performance (Table 1). Her Timed Up and Go test, which has intra- and interrater reliability > 95% in back pain patients (7), improved to 7.73 seconds, a value superior to age-matched norms.

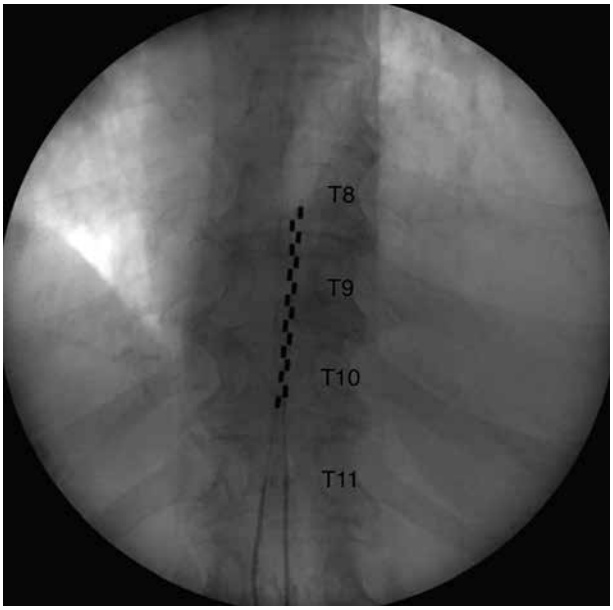

Fig. 1. Lead placement.

Additionally, her gait speed increased to 1.33 m/s, which is also faster than age-matched norms. Finally, her activities-specific balance confidence scale improved from 46.25% to 94%, which no longer classifies her as a high fall risk. On physical exam, her sensory exam was largely unchanged, however, with continued absence of pinprick sensation below the mid shins and severe loss of vibration sense in her foot.

DISCUSSION

As noted, chemotherapy-induced peripheral neuropathy (CIPN) occurs in a large percentage of patients undergoing treatment for cancer. Its prevalence demands

attention with increasing numbers of patients entering survivorship in the setting of improved oncologic therapies and surveillance (8). Spinal cord stimulators are commonly used for the treatment of refractory-pain conditions including postlaminectomy syndrome, radicular pain, and complex regional pain syndrome (4,5). Cases have shown SCS effectively controlling intractable neuropathic cancer pain (9); however, a Cochrane review of the use of SCS in the treatment of cancer-related pain noted that the lack of randomized controlled trials "left the question of effectiveness unanswered" and found a high risk of bias throughout the available studies (10).

Patients with CIPN also often suffer significant gait disturbance and disability presumably due to a combination of proprioceptive and motor effects. In some studies, nearly 20% of patients with neuropathy suffer from falls, the risk of which increases with increasing dose of chemotherapeutic drugs (11,12). A prior report has described a patient with subjective improvement in gait following SCS implantation (13). Recently, cases of improvement in motor function following combined dorsal and ventral SCS implantation in patients with paraplegia have been described, thus hinting at an unappreciated potential of SCS (14). Here, we present objective improvement of nearly every measured category of functional ability and gait on formal assessment following SCS therapy.

Although the reduction in pain was substantial for our patient, it did not seem to fully explain the improvement in motor function and reduction in falls. Recent studies have shed light on the specific cell populations and circuits that may gate pain signals (15,16). However, gating of other modalities, such as itch, also occurs through similar feedback mechanisms exerted by distinct interneuron populations (17). Thus, one potential interpretation of our finding is that A-fiber-mediated proprioceptive information is itself gated by nociceptive circuits, and thus reduction in pain through epidural stimulation led to enhanced transmission of the proprioceptive afferent signals critical for gait and balance. Dissection of the cellular mechanisms of such a process will await more detailed clinical and mechanistic studies.

CONCLUSION

In this report, we present a case of improved pain, gait, and frequency of falls in a patient with CIPN, following implantation of a permanent SCS. Our case demonstrates the multimodal potential of SCS for patients with CIPN. Though the objective functional improvements were nonblinded, they do suggest additional possible advantages of this SCS beyond pain control in patients with CIPN that merit further exploration. Controlled studies in this population are lacking but are warranted to assess for clinical efficacy of this intervention in patients with CIPN. In addition to analgesic analysis, future studies should also include formal independent assessments of sensory and motor function pre- and post implantation. The quality of such studies – and indeed others involving SCS for other conditions – will ultimately depend on true double-blinding, with posthoc confirmation by patient surveys that unblinding has not occurred.

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