Clinical Note

Spinal Cord Stimulation Relieves Chemotherapy-Induced Pain: A Clinical Case Report
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Abstract
We present two patients with chemotherapy-induced painful neuropathy that had been poorly controlled with medications but successfully treated with spinal cord stimulation (SCS). A trial period of SCS provided effective pain relief in both patients who subsequently underwent permanent stimulator implantation. Psychophysical tests were performed before and after the implantation of trial and permanent stimulators. SCS improved pain scores and facilitated a reduction of medications. Both patients reported improved gait and one of them also reported an increase in leg flexibility. Psychophysical tests demonstrated an improvement in touch and sharpness detection thresholds. In summary, SCS offers a therapeutic option for patients with chemotherapy-induced peripheral neuropathy who have poor pain relief with standard medical treatment. J Pain Symptom Manage 2004;27:72–78. © 2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Spinal cord stimulation, chemotherapy-induced neuropathy, psychophysics, analgesia

Introduction
Electrical spinal cord stimulation (SCS) describes the use of pulsed electrical energy near the spinal cord and adjacent neural structures to control pain. This most commonly involves the implantation of leads in the epidural space to transmit pulsed energy across the spinal cord or near the desired nerve roots. Electrical SCS has been used to treat patients with different types of painful conditions, with varying degrees of success. The method is based on the “gate control” theory, which postulates that activity in large-diameter cutaneous afferents, or Aβ fibers, inhibits transmission of pain signals in small diameter fibers to spinal neurons that project to the brain. Linderoth and Foreman have proposed that the antidromic activation of dorsal column fibers by the SCS may exert an inhibitory effect on the hyperexcitability of wide-dynamic-range neurons once they were sensitized by peripheral nerve injury. Additional spinal and supraspinal structures could
be also involved in the SCS-mediated analgesia, but stimulation of large fibers of the dorsal column and the dorsal horn would play the most important role.4,5 Since the first report of SCS 30 years ago6,7 clinical indications have expanded to include treatment for failed back surgery syndrome, radiculopathy, complex regional pain syndrome, peripheral nerve injury, postherpetic neuralgia, diabetic neuropathy, and ischemic pain due to peripheral vascular disease or angina.1,8-10 Appropriate patients for permanent implant of an SCS should have a diagnosis amenable to this therapy (i.e., neuropathic pain), have failed conservative therapy, and have no significant psychological issues; patients also must have a trial that has demonstrated pain relief.3

SCS is a technically challenging interventional/surgical pain management technique. It involves the careful placement of an electrode array (leads) in the epidural space, a trial period, anchoring the lead(s), positioning and implantation of the internal pulse generator (IPG) or RF receiver, and the tunneling and connection of the connecting wires. First, under fluoroscopy and sterile conditions, a lead is introduced into the epidural space with the standard epidural needle placement. The lead is steered under fluoroscopic imaging into the posterior paramedian epidural space up to the desired anatomic location. Trial stimulation is undertaken to attempt to “cover” the painful area with an electrically-induced paresthesia. If the trial is successful, the IPG/RF unit is generally implanted in the lower abdominal area or in the posterior superior gluteal area. It should be in a location the patient can access with their dominant hand for adjustment of the settings with a remote control unit.

Chemotherapy-induced painful peripheral neuropathy is a complication experienced by patients receiving treatment for many kinds of malignant neoplasms, which occurs at varying frequency and severity depending on the type of drug used, the duration of the regimen, the cumulative dose received, and the presence of comorbidities.11-14 Because pain and motor impairment are the most frequent cause of premature termination of chemotherapy, and the nerve damage may be only partially reversible,9 this complication affects survival in cancer patients and quality of life in cancer survivors. The prime culprits in producing painful neuropathy are the derivatives of platinum compounds, vinca-derived alkaloids, taxols, and suramin. Patients affected by chemotherapy-induced neuropathy have been treated with a wide variety of analgesics including opioids, anti-epileptic drugs, and tricyclic antidepressants, but often without satisfactory relief of pain. Here we present the first report of which we are aware of the successful treatment of chemotherapy-induced neuropathy with spinal cord stimulation and describe the results of quantitative sensory testing before and after the procedure.

Methods

Appropriate patients were identified through the Pain Management Service at the University of Texas-M. D. Anderson Cancer Center. Patients were screened for their willingness to undergo a trial of SCS associated with quantitative sensory testing. Informed consent was obtained. The protocol was approved by the institutional internal review board.

Before the temporary stimulator trial, patients were tested in order to determine baseline thresholds in each of three psychophysical tests. The time required for each testing session was approximately 1 hour. The test was performed in a quiet room with the patients seated comfortably with eyes closed. Three sites were tested: 1) painful area: the area of ongoing pain; 2) border area: a zone of sensory disturbance adjoining but outside the painful area; and 3) normal area: the area reported by the patient as “normal.”

Touch Detection Thresholds

Touch detection thresholds (TTs) were determined using the up/down method of Dixon15 with von Frey monofilaments. Starting with a 0.05 g force monofilament, each filament was applied for approximately 1 sec. If the subject failed to detect the stimulus, then the next higher force von Frey monofilament was applied. When the subject detected the presence of the stimulus, the next lower von Frey was administered. The up/down test sequence continued until three successful detections were recorded. If there was no detection to the highest force von Frey monofilament, then the detection threshold was assigned the maximum value tested (90 g).
Sharpness Detection Threshold (SDT)

Sharpness detection was determined using a weighted blunt needle. The tip of a 30 gauge needle (200 µm diameter) was filed to produce a flat, cylindrical end. Brass weights of known mass were fitted to the Luer connection of the needle, the entire assembly was placed inside a 10 cc syringe so that the needle came out of the tip of the syringe and the assembly moved freely within the syringe. When the needle is applied to the skin surface, a reliable and consistent force is applied. Three forces were used: 10, 20 and 40 g. Each stimulus was applied for about 1 sec, 10 times within each area of interest in a pseudorandom order, with an inter-stimulus interval of 10–20 seconds. When a stimulus was perceived, subjects chose from 4 words to describe the sensation: touch, pressure, sharp, and pain. The threshold for each sensation was defined as the lowest weight force needed to evoke each sensation in 1 or more of the 10 trials.

Heat Pain Threshold and Cold Pain Threshold (HP)/(CP)

The threshold for heat pain was determined using the Marstok technique. Starting at a baseline temperature of 35°C for 3 sec, the heat stimulus was increased in a ramp of 0.85°C/sec. Subjects were instructed to signal when the stimulus was perceived as warm, hot, and then painful or when the cutoff temperature of 51.5°C was reached. No correction was made for reaction time artifact. If a subject failed to reach all thresholds before the cutoff temperature, then 51.5°C was recorded for each. The threshold for cold detection was determined in a similar manner, except that the base temperature was started at 30°C, decreasing at a rate of 0.85°C/sec to a 5°C cut off temperature.

Pain Intensity Rating

Patients were asked to report the intensity of their ongoing pain at the time of each testing session as well as to rate their daily maximum pain by drawing a line on a 10-cm visual analog scale.

Results

Patient 1

A 65-year-old, right-handed, white man with a history of arterial hypertension and a primary melanoma in the right elbow, Clark’s level 4, was treated with interleukin-2. Bilateral constant pain developed in his lower extremities following 4 weeks of treatment (Figure 1A). The patient described the pain as “burning, numb, sharp, and dull” and as being the worst in the toes. These symptoms severely limited his daily functions and quality of life. Over the 5 months leading up to seeking the SCS, the patient had been unsuccessfully tried on several medications, alone and in combination, including morphine controlled-release 30 mg three times daily, methadone up to 10 mg three times daily, hydrocodone (5 mg once or twice a day), oral transmucosal fentanyl citrate 200 µg (for breakthrough pain), gabapentin up to 3600 mg per day, and tiagabine up to 36 mg per day. The patient had inadequate analgesia despite these medications. The patient’s pain score at the first interview was 4.5 (out of 10) before surgery while on daily medications. The patient’s maximum pain rating was measured as 9.3 (out of 10). At the time of the baseline psychophysical assessment and SCS trial, the patient was taking morphine controlled-release 30 mg three times daily, morphine immediate-release 15 to 30 mg three times daily, and gabapentin 800 mg three times daily. The dual lead stimulation trial was considered successful with a pain reduction of more than 90% (VAS with SCS 0.2/10). Optimal effect of the SCS for this patient was obtained at the L1 level. He was free of any pain for 4 days after removal of the trial SCS, but then his pain returned to the pre-SCS level. One week later, the patient was implanted with a permanent dual lead SCS device, with the leads centered over the L1 level. (Genesis, ANS, Inc, Plano, TX).

Stimulation-induced paresthesia with the SCS implant was described as bilateral from his buttock to his knees in the first 24 hours and then it expanded bilaterally to his feet and was maintained consistently. Final parameter settings for the stimulator were a frequency of 22 Hz, a pulse width of 286 µsec, and an amplitude of between 0–2 V and cycles with time on for 15 sec and time off for 15 sec (Figure 1B). Twenty-four hours after the permanent stimulator was implanted, the patient reported a VAS score of (1.5/10) and 96 hours after implantation, it was reduced to 0. The patient also reported an improved gait and flexibility of his
Fig. 1. The diagrams show the area of sensory disturbance, pain, and the stimulation-induced zone of paresthesia in Patient 1. The dark gray area in 1A shows the area of pain, while the light gray stippled area shows the border region next to the painful area. The dotted area in Figure 1B shows the area of stimulation-induced paresthesia as described by the patient 96 hours after implantation of the permanent SCS. The skin areas used for testing are indicated with arrows. TT = touch threshold; SDT = sharpness detection threshold; % = percentage of sharpness perception reported by the patient.

legs. Psychophysical testing showed that the patient’s touch detection had improved. At baseline, the patient was unable to detect the strongest filament (90 g) but 4 days after the implantation his touch threshold improved to 60 g in the glabrous painful and normal area. The patient’s sharpness detection improved somewhat as well. At baseline, he detected 50% and 60% of all stimulations with the 40 g needle in both the border and “normal” area, and 96 hours following the stimulator implantation this detection improved to 80% for both tested areas.

Four months after the implant, the patient reports continued good pain relief (VAS 2/10) using the stimulator 6–12 hours per day. His medications have been reduced to oxycodone 5 mg 3–4 times daily (Table 1).

**Patient 2**
A 46-year-old, white man, right-handed, with a history of Ewing sarcoma located on the right infraclavicular area had pain that started in his lower extremities after two weeks of chemotherapy with vincristine. The pain characteristics were reported as “burning, numb, dull, spreading, itching and electric” and were worst on the toes (Figure 2A). The highest intensity of pain experienced by the patient was 8.8/10 (VAS) and was 4.6/10 (VAS) at the time of baseline

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*Morphine equivalent daily dose*
psychophysical testing while on daily medications. He had been unresponsive to amitriptyline (25 mg/day), tizanidine (16 mg/day), oxycodone (up to 240 mg/day), gabapentin (up to 1200 mg/day) and zonisamide (200 mg/day). At the time of the trial stimulation, he was receiving methadone 15 mg three times daily and hydromorphone (4 mg) for breakthrough pain (up to 5 doses/day).

Six hours after surgery for the temporary stimulator with the leads centered on T11, the stimulation-induced paresthesia was reported to cover most of the painful areas, with better coverage in his left foot. The dual lead stimulation trial was considered successful as pain ratings were reduced to 0/10. This effect dissipated with removal of the trial SCS such that the pain ratings returned to baseline levels by day 3 after the trial SCS. Three weeks later, the patient was implanted with a permanent dual lead SCS device (Genesis, ANS, Inc, Plano, TX), with the leads centered over T11. Two weeks after, the area covered by the stimulation-induced paresthesia had changed to the lateral area of his legs and his ankle (Figure 2B). The parameter settings were frequency at 80 Hz, pulse width 500 µsec, and amplitude between 0–4 V. Six hours after the permanent SCS implantation the patient’s pain rating had improved to a VAS of 2.4/10. Two weeks after implantation, he reported a “slight improvement” in his pain (VAS 3.6) but was enthusiastic about his improved gait and flexibility of his legs as well as the return of the “normal” sensations in his legs and feet. Three months after the implant, the patient reported continued good pain relief (VAS 3) using the stimulator 18 hours per day. His medications are now reduced to oxycodone controlled-release 80 mg three times per day and amitriptyline 25 mg once daily (Table 1).

Psychophysical tests showed improved touch detection in the pain area after SCS implantation. His touch threshold in the painful area improved from 60 g at baseline to 23 g at 6 hours and 9.12 g at 14 days after implantation, respectively. Touch detection improved in the

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**Fig. 2.** The diagrams show the area of sensory disturbance, pain, and the stimulation-induced zone of paresthesia in Patient 2. The dark gray area in 2A shows the area of pain, while the light gray stippled area shows the border region next to the painful area. The dotted area in Figure 2B shows the area of stimulation-induced paresthesia as described by the patient 10 days after implantation of the permanent SCS. TT = touch threshold; SDT = sharpness detection threshold; HP = heat pain threshold; CP = cold pain threshold; % = percentage of sharpness perception reported by the patient.
border and normal area as well. Before implantation he was unable to detect even the strongest filament (90 g) at either site; however, 6 hours after surgery his threshold had improved to 90 g in the border area and 23 g in the normal area. Touch detection improved further by 14 days after the permanent stimulator was implanted in both the border and normal areas to detection thresholds of 12.7 and 9.12 g, respectively. At these two sites (border and normal), sharpness detection improved as well. At baseline, the patient was unable to detect any pinpricks, but 14 days later reported feeling 80% of the pricks in the border area and 40% in the normal area to 40 g stimulation. There were no changes in sharpness detection in the painful area. The baseline heat pain thresholds were 44.7°C for the painful area and 41.3°C and 37.2°C for the border and the normal area, respectively. The patient did not report cold pain at the lowest temperature tested in the painful and the border areas but the cold pain threshold in the normal area was 13.9°C. There were no changes in the thermal thresholds in the tested areas after the SCS.

Discussion

Chemotherapy-induced neuropathy is a common adverse effect observed in patients who receive treatment for a wide variety of malignant neoplasms. Most commonly, symptoms are exclusively sensory; some patients also have motor and/or autonomic dysfunction. Sensory symptoms are often symmetrical and described as dysesthetic numbness, electric-shock, tingling and painful burning in a glove-and-stocking distribution. Holland et al. studied 362 patients and reported that 57% of them complained of paresthesias. Most cases resolve after several months but the pain becomes a chronic problem in a significant fraction. Among the drugs that can induce this type of neuropathy, the taxane-derivates, vincristine and cisplatin, have the highest rate of incidence. There are two remarkable aspects in the patients reported here. First, both patients reported pain relief of more than 50% after SCS. This suggests SCS may be an effective treatment for patients with medically refractory chemotherapy-induced pain. Previous studies have shown that a successful SCS trial stimulation was correlated with better long-term results after the permanent stimulator implantation, and in the present report, both patients had good responses to the trials. Both patients were receiving opioid and non-opioid medications with only partial pain relief. In both cases, the patients decreased their daily requirements of pain medications following SCS. The mechanism of this effect is unclear. Several mechanisms have been suggested. Direct suppression of spinal cell hyperactivity has been proposed by different authors as one mechanism. Excitatory and inhibitory amino acid activities in spinal cord are affected by the stimulation of the dorsal horn, dorsal root, and the dorsal column, and activation of supraspinal structures and their descending pain controlling pathways are another pain-limiting mechanism that might be affected by SCS.

The second major finding is that the patients’ performance on the psychophysical tests showed improvement in the level of perception to touch and sharpness detection. This type of effect was previously noted by Meyerson et al. in animals. Both patients had very high touch thresholds typical of demyelinating neuropathies such as chronic inflammatory demyelinating neuropathy and hereditary neuropathy. Both subjects reported improved gait and one of them also reported an increase in leg flexibility, which could be related to an improvement in proprioception. It has been suggested that improvement in gait and in flexibility could be an indirect beneficial effect related to the suppression of the neuropathic pain. Decrease (improvement) in touch thresholds would enhance the sensory motor feedback from the foot to the central motor neurons that might contribute to improvement of gait dynamics. The physiological basis for this improvement is unclear.

In summary, this is the first report of patients with medically intractable chemotherapy-induced pain who were treated successfully with SCS. Due to the small number of patients and other variables, such as medication use and a possible placebo response, more clinical research is needed to validate the findings and determine the feasibility of SCS as a long-term treatment for chemotherapy-induced neuropathy.
References


