CLINICAL REPORT

Percutaneous Peripheral Nerve Stimulation for the Treatment of Chronic Low Back Pain: Two Clinical Case Reports of Sustained Pain Relief

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■ **Abstract:** As the leading cause of disability among U.S. adults, chronic low back pain (LBP) is one of the most prevalent and challenging musculoskeletal conditions. Neuromodulation provides an opportunity to reduce or eliminate the use of opioids to treat chronic LBP, but the cost and invasiveness of existing methods have limited its broad adoption, especially earlier in the treatment continuum. The present case report details the results of a novel method of short-term percutaneous peripheral nerve stimulation (PNS) in 2 subjects with chronic LBP. At the end of the 1-month therapy, stimulation was discontinued and the leads were withdrawn. PNS produced clinically significant improvements in pain (62% average reduction in Brief Pain Inventory Question #5, average pain), and functional outcomes (73% reduction in disability, Oswestry Disability Index; 83% reduction in pain interference, Brief Pain Inventory). Both subjects reduced nonopioid analgesic use by 83%, on average, and the one subject taking opioids ceased using all opioids. The only adverse event was minor skin irritation caused by a topical dressing. The clinically significant improvements were sustained at least 4 months after start of therapy (79% average reduction in pain; both reported minimal disability; 100% reduction in opioids; 74% reduction nonopioids). The results reveal the utility of this novel, short-term approach and its potential as a minimally invasive neuromodulation therapy for use earlier in the treatment continuum to produce sustained pain relief and reduce or eliminate the need for analgesic medications, including opioids, as well as more expensive and invasive surgical or therapeutic alternatives. ■

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INTRODUCTION

Chronic low back pain (LBP) affects approximately 10% of the population and is the leading cause of disability, including reduced activities of daily living and reduced quality of life, among adults in the United States.[1,2] Despite numerous treatment options for individuals with chronic LBP, the need remains for nonopioid and less invasive therapies capable of reducing pain and disability, as analgesics and physical therapy commonly fail to sufficiently eliminate pain long term.[3–11] As a result, patients often resort to interventional or more invasive surgical or neurodestructive therapies, each with their own set of risks and side effects (eg, anesthetic and corticosteroid injections,[12–14] intrathecal therapy,[15,16] ablation,[17,18] spinal cord stimulation,[19–23] surgery[24–27]). Traditional peripheral nerve stimulation (PNS) can be challenging to deliver, have technology limitations, or be associated with high rates of adverse events.[28]

There have been multiple calls[29–32] for the development of a system designed specifically for PNS without the issues of lead migration, fracture or infection, high costs, and invasiveness of existing systems that have been repurposed for PNS. Use of a specifically developed percutaneous coiled lead (MicroLead™; SPR Therapeutics, Cleveland, OH, U.S.A.) with an excellent safety profile[33–38] and fewer complications than other neurostimulation electrodes[39,40] could overcome limitations of previous PNS systems.

The present report investigates the feasibility of reducing chronic LBP and disability using a novel, minimally invasive, short-term percutaneous PNS therapy in 2 subjects who are the first to reach long-term follow-up in an ongoing case series. Previous studies of percutaneous PNS for the treatment for chronic shoulder pain suggested that clinically significant[41–43] pain relief at the end of a short-term therapy can be sustained long term in a majority (≥ 70%) of responders.[34,44–47] Percutaneous PNS may provide similar long-term improvements in chronic LBP, offering an alternative therapeutic option to improve function and quality of life.

METHODS

Percutaneous PNS therapy was evaluated in 2 individuals to explore its feasibility in producing clinically significant improvements in chronic LBP. Subjects were enrolled under an investigational device exemption approved by the U.S. Food and Drug Administration (FDA), and institutional review board (IRB) approval (Quorum IRB, Seattle, WA, U.S.A.) was obtained prior to conducting any research activities. Written informed consent was obtained from each individual prior to participation. At the time of subject participation, the device was investigational; however, the device has since received FDA 510(k) clearance and is indicated for up to 30 days in the back and/or extremities for (1) symptomatic relief of chronic, intractable pain, postsurgical and post-traumatic acute pain; (2) symptomatic relief of post-traumatic pain; and (3) symptomatic relief of postoperative pain.

Individuals exhibiting chronic LBP, pain confined to the lumbar region (ie, not radiating to the lower extremities), and lasting long term (≥ 3 months) were enrolled as part of an ongoing case series study. Individuals underwent a baseline examination to determine eligibility and must have had at least 1 month of stable medication history. Eligible subjects recorded their average pain every day in a diary on a 0- to 10-point numeric rating scale (Question #5 of the validated Brief Pain Inventory Short Form; BPI-5). To enroll, subjects must have had a baseline pain score of ≥ 4 (BPI-5). Subjects were not enrolled if they had signs of serious underlying causes of LBP, history of significant trauma to the low back, prior lumbar surgery, injections within 3 months of baseline or radiofrequency ablation within 6 months of baseline (eg, which could damage nerves and limit efficacy of PNS), pending litigation or secondary gain issues, allergy to adhesives, an implanted neurostimulator or pacemaker/defibrillator, or reported a score of ≥ 20 on the Beck Depression Inventory (BDI-II). Due to the feasibility stage of this investigation, specific diagnostic procedures or use of previous LBP therapies was not required for enrollment; however, both patients had failed multiple prior therapies. The 2 case reports presented here represent the first 2 subjects to reach long-term follow-up after completing therapy. Enrollment in the case series study and completion of the follow-up period remain ongoing at this time.

Following a 1-week baseline period, subjects underwent bilateral lead placement prior to beginning therapy. Two 20-gauge introducers, each preloaded with a MicroLead (Figure 1), were inserted, one on each side of the spinous process in the center of the subject's region of greatest pain (L4 for both subjects) with the subject in prone position under sterile conditions.[48] The MicroLead was deployed ~1 to 2 cm posterior to the lamina to target the medial branch of the dorsal primary ramus (~4

to 5 cm under the skin). Lead placement was directed using ultrasound guidance and known anatomical landmarks (eg, spinous process, transverse process, paraspinal muscles). Leads were placed to stimulate the medial branch of the dorsal ramus after the branch exits the intervertebral foramen prior to innervation of the multifidus and facet joints. Successful lead placement relative to the nerve target was confirmed by the ability to evoke comfortable contractions of the lumbar multifidus confirmed by visualization under ultrasound (Figure 2)[49–51] and patient-reported sensations. The introducer needles were then removed and the leads remained in place for the duration of the therapy (1 month). The external portions of the leads were covered with a waterproof dressing and connected to small body-worn stimulators (SPRINT PNS System; SPR Therapeutics). Stimulation parameters were adjusted to stimulate the medial branch of the dorsal ramus, resulting in comfortable activation of the multifidus (frequency = 12 Hz, duty cycle = 50%), and subjects were provided with a customized range of intensities (amplitude = 13 to 20 mA, pulse width = 15 to 130 μs) that they could select from to produce comfortable sensations. Subjects were instructed to use stimulation therapy for 6 hours per day for 1 month. Subjects were encouraged to continue with their normal routine and activities of daily living, but were not allowed to engage in any other treatments for LBP apart from their baseline medications (eg, physical therapy).

Subjects recorded daily pain levels and analgesic medication consumption in weekly diaries and returned to the clinic once per week during the therapy period for assessment of pain, disability, and adverse events. At the end of treatment (EOT), stimulation was discontinued and leads were withdrawn using gentle traction. Subjects returned to the clinic or received phone calls for follow-up visits monthly up to 4 months after start of therapy. Additional validated outcomes of disability (Oswestry Disability Index [ODI][43]), pain interference (BPI-9[52]), patient global impression of change (PGIC), and depression (BDI-II) were assessed from baseline and throughout the follow-up period.

RESULTS

Two subjects (Subject 1 and Subject 2) with chronic pain confined to the lower back participated (Table 1). Two MicroLeads were placed in each subject without complications, as outlined in the Methods section. At-home stimulation was delivered for one continuous 6-hour session each day for the 1-month therapy period, and compliance was monitored with the device. For the duration of the therapy, leads remained in situ without breakage or fracture. Subjects were able to participate in their normal activities of daily living. Subjects reported that stimulation produced comfortable sensations (eg, described as vibrating, tingling, pulsing, or tapping) in the region of their LBP. Weekly inspections of the lead exit sites, queries for changes in sensation, and evaluation of stimulation thresholds for comfortable muscle activation suggest that no lead migrations occurred in these subjects. At the EOT, stimulation was discontinued and the leads were removed intact and without discomfort or complication. The only adverse event was skin irritation in one subject, which was resolved by providing latex-free dressings.

Case Report 1

Subject 1 had nonspecific bilateral LBP for 9 years prior to enrollment. This subject reported an average pain score at baseline of 4.9, despite regular nonsteroidal anti-inflammatory drug use and a history of chiropractic management, massage, and acupuncture for her LBP. Subject 1 experienced a clinically significant reduction[41–43,53,54] in average pain intensity (BPI-5) that was sustained at least 4 months after start of therapy (Figure 3A). At the end of the short-term therapy, Subject 1 reported a 45% reduction in average pain intensity compared with baseline, which was further reduced to a 74% reduction 1 week after EOT. Four months after start of therapy, this subject experienced average pain intensity of 1, a 79% reduction in average pain compared with baseline. Subject 1 also experienced a reduction in worst pain intensity (BPI-3) at the end of the short-term treatment (25%), which was further improved up to 68% reduction in worst pain 1 week after EOT. This subject was taking nonopioid analgesic medications (4,800 mg ibuprofen and 440 mg naproxen per week) at baseline and experienced a substantial reduction in medication usage at EOT (81% reduction, taking 1,000 mg ibuprofen per week), which was sustained 4 months after start of treatment (Figure 3B). Subject 1 had minimal disability measured via the ODI at start of therapy that was maintained within the normal range throughout the therapy and follow-up period (Figure 3C) and was able to continue working. Depression, measured via the BDI-II, was reduced to 0 at EOT (from minimal depression at baseline) and

Table 1. Baseline Characteristics and Results at the End of Short-Term Therapy

	Subject 1	Subject 2
Baseline back pain characteristics and demographic information		
Age (years)	45	41
Sex	Female	Female
Duration of back pain (years)	15	9
Suspected cause of LBP	Unknown (nonspecific)	Discogenic back pain (bulged disc)
Region of back pain (spinous levels)	L1–S1	L2–L5
Lead placement (spinous level)	L4	L4
Baseline medication (average per day from weekly diary)	686 mg ibuprofen, 63 mg naproxen	200 mg tapentadol, 2,400 mg gabapentin, 2 patches of topical diclofenac
Baseline depression (BDI-II)	3	14
Results at EOT (1 month)		
Medications at EOT (average per day from weekly diary)	143 mg ibuprofen	0.9 patches of topical diclofenac
Depression at EOT (BDI-II)	0	0
Patient global impression of change at EOT	Minimally improved	Very much improved
Subject satisfaction survey responses		
"I would recommend this therapy to a friend."	Strongly agree	Strongly agree
"If my back pain returns, I would want to receive stimulation therapy again."	Strongly agree	Strongly agree
"I prefer using stimulation therapy to taking medications."	Strongly agree	Strongly agree
"If it had been available, I would have pursued this therapy earlier in the course of treatment for my LBP."	Strongly agree	Strongly agree
"Compared to previous treatments with neurostimulation, my pain was better managed with this therapy."	Strongly agree	Strongly agree

LBP, low back pain; BDI, Beck Depression Inventory; EOT, end of treatment.

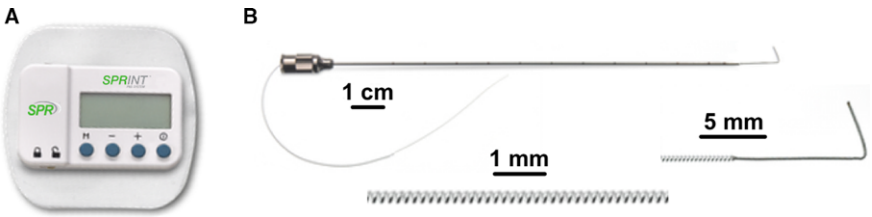

Figure 1. Percutaneous peripheral nerve stimulation (PNS) system for chronic low back pain. PNS was delivered to produce comfortable paraspinal muscle contractions in the region of back pain using body-worn stimulators (A) via SPR's fine-wire, percutaneous MicroLead™ (B) for 1 month. Images used with permission from SPR Therapeutics.

maintained as minimal depression throughout the entire follow-up period. Subject 1 reported improvement in her quality of life at EOT via the PGIC scale ("minimally improved" at EOT when she had a 45% reduction in pain, which later improved to a 79% reduction). In response to a subject satisfaction survey, this subject reported that she strongly agreed to having a preference of using stimulation therapy to taking medications and would want to receive stimulation therapy again if her back pain returned.

Case Report 2

Subject 2 presented with lumbar degenerative disk disease and reported having chronic bilateral LBP for 15 years prior to enrollment. This subject reported an average pain at baseline of 4.7, despite regular use of opioid and nonopioid analgesic medications and previous use of physical therapy, massage, and surface electrical stimulation. Subject 2 experienced a clinically significant reduction[41–43,53,54] in average pain intensity (BPI-5) with treatment that was sustained through the 4-month follow-up period (Figure 3A). At each time point after short-term therapy through 4 months after start of therapy, Subject 2 reported an average pain intensity of 1, a 79% reduction in average pain compared with baseline. Subject 2 also reported an 85% reduction in worst pain intensity (BPI-3) for the entire duration of the follow-up period, 4 months after start of treatment. At baseline, this subject was using both opioid and nonopioid analgesic medications for her LBP (1,400 mg tapentadol, 16,800 mg gabapentin, and 14 patches of topical diclofenac per week). With treatment, this subject eliminated the use of all opioid analgesics

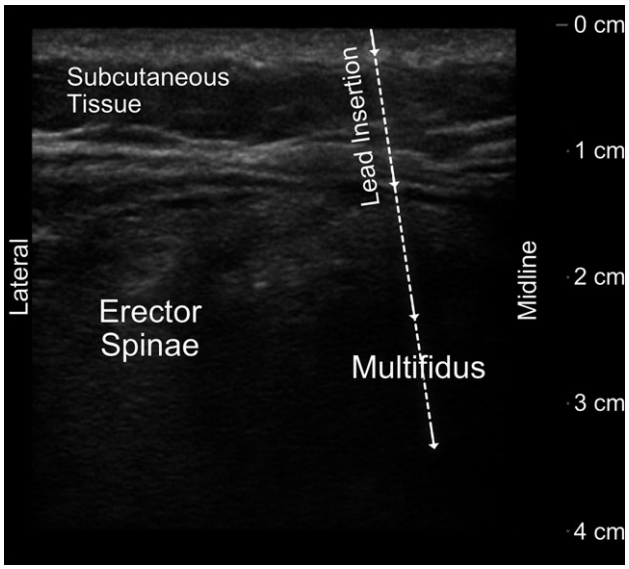

Figure 2. Ultrasound image of lumbar paraspinal musculature during lead placement procedure. Percutaneous (bilateral) leads were placed under ultrasound guidance to target lumbar dorsal ramus nerves and generate multifidus muscle contractions.

throughout the entire 4-month follow-up period and experienced a substantial reduction in nonopioid analgesic medications (using only 6 patches of diclofenac per week, 85% reduction nonopioids, at EOT; Figure 3B). Subject 2 had severe disability at baseline and experienced a clinically significant improvement (≥ 10 points ODI[43,55,56]) and had only minimal disability (ie, within the normal range) at EOT that was sustained for at least 4 months after start of therapy (Figure 3C). Pain interference on physical functioning and daily activities (Question #9 of the validated Brief Pain Inventory Short Form; BPI-9[52]) was also reduced with treatment and sustained at least 4 months after start of therapy (Figure 3D; 83% reduction at EOT, 87% reduction at 4 months after start of therapy). Subject 2 had mild depression (via BDI-II) at baseline, which was reduced to 0 by EOT. This subject rated her change in quality of life with therapy as "very much improved" via the PGIC scale. In response to the subject satisfaction survey, Subject 2 reported that she strongly agreed to having a preference of using stimulation therapy to taking medications and would want to receive stimulation therapy again if her back pain returned.

DISCUSSION

The results of the first 2 cases in this ongoing case series highlight the potential utility of this approach and suggest that short-term percutaneous PNS of the medial branch of the dorsal ramus may reduce or eliminate the need for analgesics and provide long-lasting reductions in pain and disability for individuals with chronic LBP. Two subjects with a history of chronic (ie, average of 12 years) LBP received the percutaneous PNS therapy. Stimulation produced successful activation of the medial branch of the dorsal ramus, as evidenced by multifidus contractions visualized with ultrasound. In these subjects, the short-term (1-month) stimulation therapy produced clinically significant reductions in average back pain intensity by the EOT. Further, these reductions in average back pain intensity were sustained at least 4 months after the start of the short-term therapy. Four months after start of therapy, both subjects experienced a highly clinically significant reduction in average pain (79%) compared with baseline and substantial reductions in analgesic medication usage. Therefore, in addition to short-term improvements in back pain intensity, the temporary percutaneous PNS therapy shows promise in producing long-term improvements in pain.

Improvements in functional outcomes were also seen in these 2 subjects. Both subjects experienced at least a 50% reduction in disability (ODI) at EOT, including 1 subject who had severe disability at baseline, and had scores in the normal (minimal disability)[56] range throughout the entire follow-up period. In addition to reducing disability, stimulation also reduced the interference of pain on activities of daily living and physical functioning[52] (BPI-9) by 83% at EOT in Subject 2, which was sustained 4 months after start of therapy. These meaningful improvements in physical functioning were substantiated by the improvements reported by subjects' response for PGIC in quality of life, further revealing the potential of the short-term stimulation therapy to impact disability and function, in addition to pain.

Additional evidence of the long-term impact on pain produced by this short-term percutaneous PNS therapy can be found in the reduction of analgesic medication usage by both subjects. Both subjects reported substantial reductions in medication usage at EOT, an average 83% reduction in nonopioid usage ($n = 2$). One subject eliminated opioid consumption ($n = 1$). Four months after start of therapy, these subjects had sustained reductions in opioid and nonopioid analgesic medication usage (100% and 74%, respectively). These results demonstrate the feasibility of using this novel short-term percutaneous PNS therapy as an alternative to analgesic

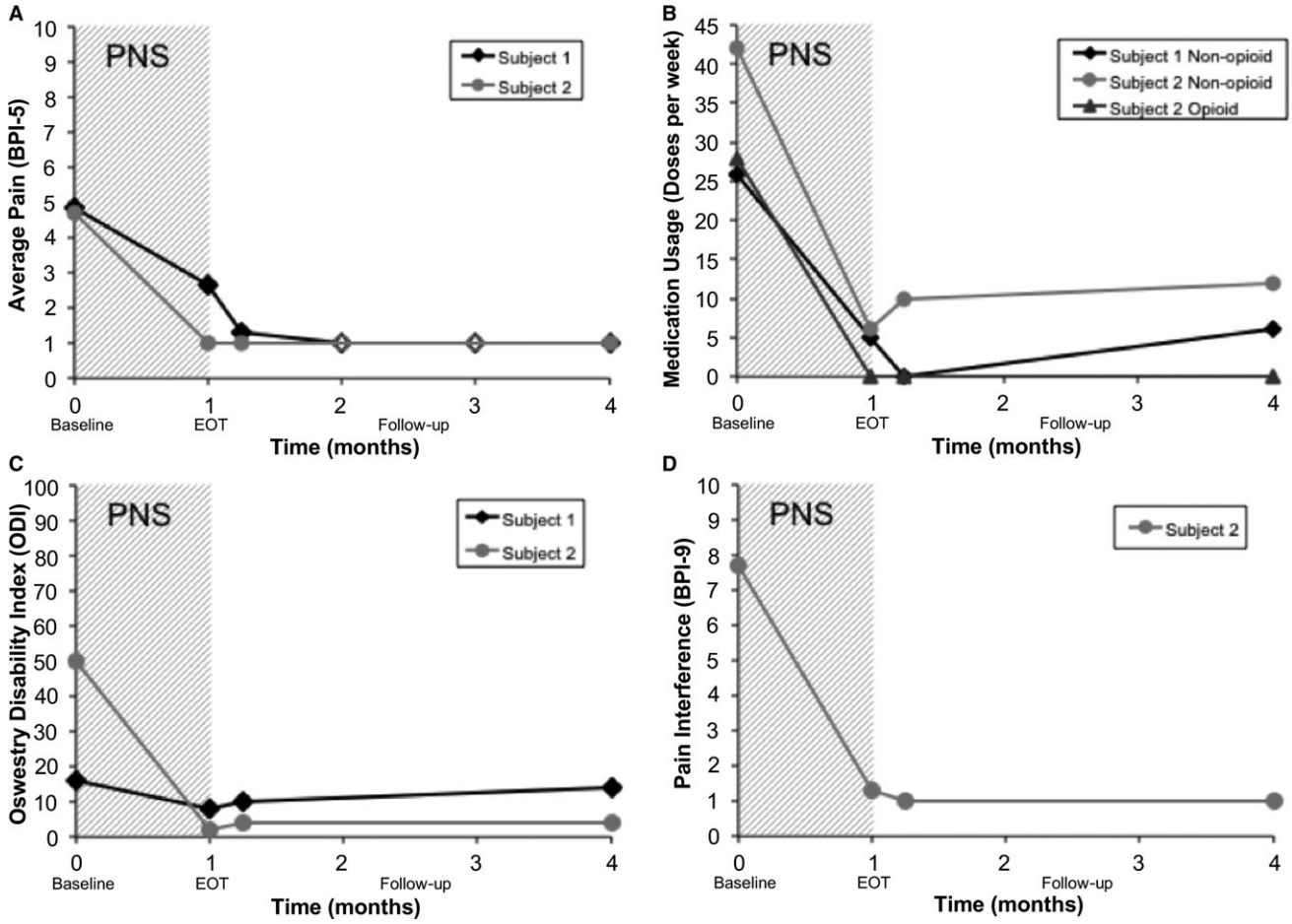

Figure 3. Changes in chronic low back pain, medication usage, disability, and pain interference over time with peripheral nerve stimulation (PNS) therapy. (A) Both subjects experienced clinically significant reductions in average pain intensity (Question #5 of the validated Brief Pain Inventory Short Form; BPI-5) that were sustained for at least 4 months after start of therapy. Subject 1 had a 45% reduction in pain at the end of treatment (EOT) that increased to a 79% reduction at 4 months after start of therapy. Subject 2 had a 79% reduction in pain at EOT that was sustained 4 months after start of therapy. Solid markers represent weekly diary average pain scores and empty markers at 2 and 3 months represent pain scores obtained via phone call administration of BPI-5. (B) With PNS, Subject 1 had an 81% reduction in use of all analgesic medications for back pain (ie, taking nonsteroidal anti-inflammatory drugs) compared with baseline at EOT and a 100% reduction in nonopioid medication usage 1 week after EOT. Subject 2 had a 100% reduction in opioid medication usage that was sustained at least 4 months after start of therapy. Subject 2 also had an 86% reduction in nonopioid usage at EOT and a 71% reduction in nonopioids that was sustained at least 4 months after start of therapy. (C) PNS therapy produced reductions in disability, as measured by the validated Oswestry Disability Index (ODI). Subject 2 started with severe disability and both subjects had minimal disability (ODI < 20) within the normal range at EOT that was maintained up to 4 months after start of therapy. (D) PNS therapy produced reductions in pain interference on daily functioning (Question #9 of the Brief Pain Inventory Short Form, BPI-9). Subject 2 had a clinically significant 83% reduction in pain interference on daily activities and function at EOT that was maintained at least 4 months after start of treatment (87%). BPI-9 data were not collected for Subject 1.

medications, which could significantly reduce opioid and NSAID consumption. Further, PNS may also reduce the need for use of destructive or irreversible therapies (eg, lumbar radiofrequency ablation, which destroys signal transduction in nerves that are reversibly activated in PNS). The subjects' responses to the subject satisfaction survey (see Table 1) confirm their preference toward this percutaneous PNS therapy, as both subjects strongly agreed to preferring using stimulation therapy to taking medications and previous treatments with neurostimulation.

The present findings are consistent with an earlier report of percutaneous PNS in 2 subjects with chronic LBP. In these subjects, clinically significant pain relief was achieved with 6 weeks of treatment and sustained long term after therapy.[57,58] These subjects reported an increase in activity levels and improved function that were sustained at least 8 months,[57] leading to the

initiation of the ongoing case series study to better evaluate the feasibility of percutaneous PNS for LBP. Percutaneous PNS in other musculoskeletal pain conditions (eg, chronic shoulder pain) has been shown to produce substantial reductions in chronic pain and improvements in function long term.[34,44–47,59–61] A hypothesis for the prolonged analgesic effects produced by this therapy is the modulation of central sensitization.[62] Specifically, afferent input from muscle spindles and the Golgi tendon organ during comfortable muscle contractions may cause the normalization or partial reversal of membrane excitability and synaptic efficacy of neurons and circuits in nociceptive pathways. Such a mechanism may explain not only the pain reduction, but also the maintenance of this effect after completion of treatment. Work continues to fully explore this carryover effect.[60,63] Additionally, future directions for this work include a publication describing the results from the full cohort of subjects after enrollment is complete in this case series.

Percutaneous PNS provides a novel method to provide a short-term neurostimulation therapy for the treatment of pain. Conventionally, traditional PNS has required neurosurgical placement of a paddle-type electrode in intimate proximity to the targeted peripheral nerve, and as such, therapy access to interventional pain management physicians has been quite limited, except for its use in the management of occipital neuralgia.[64] PNS applications in the low back have been plagued by high rates of adverse events (eg, 21 lead migrations occurred in 13 subjects implanted with traditional spinal cord stimulation leads[28]), highlighting the value of the present percutaneous open-coiled lead (MicroLead), which was specifically developed for use in temporary percutaneous therapy and has an excellent safety profile[33–38] and fewer complications than other neurostimulation electrodes.[39,40] This PNS therapy, which involves stimulation of a specific peripheral nerve (medial branch of dorsal ramus) to generate pain relief within the distribution of that nerve, is not to be confused with peripheral nerve field stimulation (PNFS). PNFS involves the placement of leads in the subcutaneous tissues (eg, 1 to 1.5 cm below the skin,[65] compared with ~4 to 5 cm below the skin in this study) to stimulate nonspecific sensory nerve endings and tissue. PNFS generates sensations in a subcutaneous region adjacent to the electrode and cannot generate sensations aligned within the distribution of a specific peripheral nerve because it does not target a single nerve. In contrast, the present report describes the use of PNS to selectively stimulate nerve fibers of the medial branch of the dorsal ramus to generate muscle activation and comfortable sensations to produce pain relief within the distribution of this nerve. The present findings suggest that this short-term percutaneous PNS therapy offers significant advantages as a minimally invasive, short-term therapy with the potential to reduce pain and improve disability long term.

CONCLUSION

This work suggests the feasibility of using percutaneous PNS as a short-term back pain therapy with the potential to produce improvements in pain and disability, leading to improvements in function and quality of life. The outcomes of this therapy, sustained over a 4-month period in 2 subjects, demonstrate the feasibility of percutaneous PNS for the long-term treatment of LBP. In these 2 subjects, the magnitude of improvements in pain, disability, and analgesic medication usage following percutaneous PNS demonstrates its potential as a valuable pain management modality. Its potential in other types of pain, such as chronic joint and musculoskeletal pain, neuropathic pain, and postsurgical pain, has been reported elsewhere,[34,39,44,45,57,66] demonstrating similarly impressive and significant improvements in pain and function. This therapy has the potential to shift the paradigm in the management of chronic pain, offering a minimally invasive treatment with the potential to bring the benefits of an effective neuromodulation therapy to patients earlier in the treatment continuum.

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AUTHORSHIP ROLES

L.K. and C.G. oversaw subject participation and performed lead placements. J.C., R.R., S.C., and M.S. consulted on therapy design and interpretation of the results. A.W., M.M., and J.B. oversaw therapy design and implementation, and completed data analysis and article preparation.

DEVICE STATUS

An investigational percutaneous peripheral nerve stimulation system (SPR Therapeutics) including a percutaneous lead and small body-worn stimulator was used during this clinical study. The peripheral nerve stimulation systems were provided by SPR Therapeutics. At the time, the study was performed and the device was investigational; however, the SPRINT PNS device has since received FDA 510(k) clearance and is indicated for up to 30 days in the back and/or extremities for (1) symptomatic relief of chronic, intractable pain, postsurgical and post-traumatic acute pain; (2) symptomatic relief of post-traumatic pain; and (3) symptomatic relief of postoperative pain. The system is not intended to treat pain in the craniofacial region.

CONFLICT OF INTEREST

SPR Therapeutics, LLC (the sponsor of this study), has a commercial interest in the device presented in this case report. Leonardo Kapural, MD, PhD, Christopher A. Gilmore, MD, Richard L. Rauck, MD, Steven P. Cohen, MD, and Michael F. Saulino, MD, PhD, are consultants to SPR Therapeutics. John Chae, MD, is the Chief Medical Advisor for SPR Therapeutics. Amorn Wongsarnpigoon, PhD, Meredith McGee, PhD, and Joseph Boggs, PhD, are employees of SPR Therapeutics. John Chae, MD, Michael Saulino, MD, PhD, Amorn Wongsarnpigoon, PhD, Meredith McGee, PhD, and Joseph Boggs, PhD, are listed as inventors on issued or pending patents. John Chae, MD, and Joseph Boggs, PhD, have ownership interest in SPR Therapeutics.

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