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Treatment of Post-Amputation Pain With Peripheral Nerve Stimulation

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Background: Present treatment methods are often unsatisfactory in reducing post-amputation pain. Peripheral nerve stimulation (PNS) could reduce the pain, but it is rarely used because present methods require invasive surgical access and precise placement of the leads in close proximity (≤2 mm) with the nerve.

Methods: The present study investigated the feasibility of delivering PNS to patients with moderate-to-severe post-amputation pain in the lower extremity using a fine-wire lead placed percutaneously under ultrasound guidance a remote distance (0.5–3.0 cm) away from the sciatic and/or femoral nerves.

Results: Fourteen of the 16 subjects who completed in-clinic testing responded to stimulation, reported ≥75% paresthesia coverage, obtained clinically significant pain relief, and proceeded to a two-week home trial with a percutaneous PNS system. Two of the 14 responders had their leads removed early because of accidental dislodgement ($N = 2$), two had temporary discomfort near the lead ($N = 2$), and one had return of post-amputation pain despite stimulation ($N = 1$) and did not complete the home trial. The nine responders who completed the home trial reported reductions in their mean daily worst post-amputation pain ($56 \pm 26\%$, $56 \pm 26\%$, $N = 9$), average residual limb pain ($72 \pm 28\%$, $42 \pm 27\%$, $N = 7$), average phantom limb pain ($81 \pm 28\%$, $47 \pm 48\%$, $N = 7$), residual limb pain interference ($81 \pm 27\%$, $53 \pm 17\%$, $N = 6$), phantom limb pain interference ($83 \pm 31\%$, $56 \pm 46\%$, $N = 7$), and Pain Disability Index ($70 \pm 38\%$, $55 \pm 32\%$, $N = 9$) during the second week of stimulation and four weeks after the end of stimulation, respectively. All nine responders rated their change in quality of life as improved at the end of stimulation and at the end of the four-week follow-up period. Subjects reported minor decreases in the Beck Depression Inventory scores ($43 \pm 51\%$, $32 \pm 57\%$, $N = 9$). Most subjects had no substantial changes other than minor decreases ($N = 3$) in pain medication.

Conclusion: Achievement of significant pain relief and improvements in quality of life with a minimally invasive method of PNS holds promise for providing relief of post-amputation pain.

Keywords: Amputee, electrical stimulation, peripheral nerve stimulation, phantom limb pain, residual limb pain

Conflict of Interest: Richard L. Rauck, MD, Steven P. Cohen, MD, Christopher A. Gilmore, MD, James M. North, MD, and Leonardo Kapural, MD, PhD are consultants to NDI Medical and participated in SPR scientific and clinical advisory board meetings. NDI Medical and SPR Therapeutics have multiple patents and patent applications related to this work.

INTRODUCTION

Amputation can lead to chronic pain, and up to 70–80% of patients have significant pain (1,2). Following amputation, patients may have two types of chronic pain: phantom limb pain (PLP) and/or residual limb pain (RLP). The pain can be extremely debilitating to amputees, significantly decrease their quality of life, increase their risk of depression, and negatively affect their interpersonal relationships and their ability to work (3–5). In amputees with moderate-to-severe pain, it is frequently the pain following amputation rather than the loss of a limb that most impacts the activities of daily living, prevents completion of simple tasks, and correlates most negatively with return to employment (6–8). Poorly treated pain can further impair function by preventing the use of prostheses. Medications are often unsatisfactory in reducing post-amputation pain and have the potential for unwanted side-effects, addiction, or misuse (9–13). The present study investigates the feasibility of reducing post-amputation pain using a novel method of delivering electrical stimulation.

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Disclosures: NDI Medical (the sponsor of this study) and SPR Therapeutics (a subsidiary of NDI Medical) have a commercial interest in the device presented in the study. Richard Rauck, MD, Steven P. Cohen, MD, Christopher A. Gilmore, MD, James M. North, MD, and Leonardo Kapural, MD, PhD are consultants to NDI Medical. Rosemary H. Zang, RN is an employee of SPR Therapeutics. Joseph W. Boggs, PhD and Julie H. Grill, MS are employees of NDI Medical, with equity holdings and stock options.

Electrical stimulation can reduce post-amputation pain when it is delivered via spinal cord stimulation (SCS) (14–18) or peripheral nerve stimulation (PNS) (19–26). SCS can provide pain relief in well-selected amputees, but the number of studies is limited (27) and success rates are variable (14–18,27–30). PNS has the potential to be an effective therapy when the majority of the pain is confined to the distribution of one to two nerves (31,32), such as with lower extremity amputation when the post-amputation pain is limited to the distribution of the sciatic and femoral nerves (20,21,23).

Clinical use of PNS has been limited in part because the only PNS devices with US Food and Drug Administration (FDA) clearance to treat pain are radio-frequency-powered implantable stimulators that are not actively marketed today. Presently, PNS is often delivered with systems that were originally developed for SCS that have been modified for placement on a peripheral nerve for research or off-label use (32–37). These systems often fail in the periphery because of technical complications of lead migration and lead fracture because they are not specifically designed to withstand the mechanical stresses of the periphery (32,38). Using existing systems for PNS typically requires the clinician to be surgically trained to achieve the deep surgical access and precise placement of the lead in direct contact with or in close proximity (≤2 mm) to the nerve (25,32,38–41). Although reimbursement codes exist for PNS, the cost of the time, resources, and infrastructure necessary to perform the precise surgical placement of existing systems combined with the invasiveness of the procedure has reduced enthusiasm for PNS (32). With existing systems, there has been no way to trial the therapy to determine which patients will respond without performing the invasive surgery to place the lead on a major peripheral nerve trunk and then to remove it if the trial is unsuccessful (32). Additionally, there are no randomized controlled clinical trials demonstrating the safety and effectiveness of PNS for the treatment of post-amputation pain, which can itself influence reimbursement decisions and industry investment in developing new technology.

Presently, precise placement of multiple electrode contacts in close proximity to the nerve is required to provide selective stimulation of the target sensory neurons (i.e., types Ia and Ib) that evoke the comfortable sensations (paresthesia) associated with pain relief and avoid activation of the nontarget motor neurons (type alpha) and sensory neurons (types III and IV) that can generate unwanted muscle contractions and painful sensations, respectively (42). It can be particularly challenging to achieve selective stimulation of target fibers in the large diameter nerve trunks of the lower extremity, such as the trunks of the sciatic and femoral nerves. PNS has a historically lower success rate in the lower extremity relative to the upper extremity (21,22,32,42–44), possibly because of the challenge of selectively activating only the target sensory neurons located deep in the center of a larger diameter nerve trunk without activating the nontarget motor neurons (42,45), which can be further complicated by displacement of the electrode contacts relative to their initial precise placement along the nerve during weight-bearing movements of the lower extremity (32,38,42,46,47).

Present solutions to selective activation of target fibers in the lower extremity include surgical dissection of the nerve and placement of multicontact electrodes along the nerve trunk (32,38,42) or more distal placement of the electrodes on the smaller diameter nerve branches (33,39). As an alternative to present approaches, we hypothesized that a single-contact electrode lead placed remote from the nerve trunk would enable selective stimulation of only the target sensory fibers. A method of PNS that does not require surgical access or precise placement of the lead in close proximity to the nerve would be beneficial because it could reduce the barriers to using PNS. Specific advantages could include easier placement, a lower incidence of revision for lead migration, and reduced risk of nerve trauma or infection. The present case series investigated the feasibility of producing comfortable paresthesia coverage and reducing post-amputation pain using leads placed percutaneously under ultrasound guidance at a significant distance (0.5–3.0 cm) from the sciatic and femoral nerves in lower extremity amputees.

The proposed method of intentionally placing a single electrode a significant distance away from the nerve represents a paradigm shift in PNS. Conventional methods have required multiple electrodes to be placed directly on the nerve to deliver selective stimulation within the narrow therapeutic window between the threshold for nontarget fibers and the threshold for target fibers. However, we propose there is an alternate and novel way to activate the target fibers selectively and obtain widespread paresthesia coverage throughout the entire nerve distribution. We propose that the therapeutic window can be widened by using a unique combination of stimulus parameters and electrode positioning.

The present study tested the hypothesis that positioning the electrode a sufficient distance (e.g., 0.5–3.0 cm) away from the nerve could increase the threshold of the nontarget fibers more than it would increase the threshold of the target fibers, which would widen the therapeutic window and enable selective stimulation of the target fibers to produce comfortable paresthesia coverage and pain relief. Data generated in mathematical modeling studies indicate that decreasing the duration of the stimulus pulse (μsec) can desirably increase the difference in stimulus amplitude (mA) thresholds required to activate the nontarget fibers relative to the target fibers, making it easier to activate only the target fibers. Decreasing the stimulus pulse duration increases the stimulus amplitude threshold of the nontarget fibers more than that of the target fibers because the nontarget fibers have smaller diameters than the target fibers (48,49). Mathematical modeling data also indicate that the difference in stimulus amplitude thresholds can be increased further by increasing the distance between the stimulating electrode and the nerve trunk (i.e., placing the lead remote from the nerve trunk) (48,49). The novel combination of a short pulse duration and remote lead placement work together to increase selectively the threshold of the nontarget fibers more than the threshold of the target fibers, which effectively increases the therapeutic window allowing generation of paresthesia coverage and pain relief with a lead placed a sufficient distance (e.g., ≥0.5 cm) away from the nerve. The potential to provide pain relief with a lead inserted percutaneously and remotely from a major peripheral nerve trunk could change the risk–benefit ratio for patients and increase the viability of treating pain with PNS (30). The data from the initial subject in the series were published as a case report (26), and the present study reports the data from the entire series.

METHODS

The study was approved by the FDA under an investigational device exemption, and investigational review board approval was obtained. The research study followed standard good clinical practice guidelines.

The subjects enrolled in the study after providing informed written consent and meeting all eligibility requirements. Inclusion criteria included a well-healed unilateral lower extremity amputation, daily worst RLP, and/or PLP score ≥4 on an 11-point numerical rating scale on the Brief Pain Inventory-Short Form (BPI) Question 3

Table 1. Baseline Demographic and Amputation Information Is Shown for the 16 Subjects Who Completed In-Clinic Testing.

Demographic and amputation information	
Age (years)	
Mean ± Standard Deviation	47 ± 12
Median (range)	49 (23–65)
Gender (*N*)	
Male	14 (88%)
Female	2 (12%)
Ethnicity (*N*)	
Hispanic or Latino	0 (0%)
Not Hispanic or Latino	20 (100%)
Race (*N*)	
African American	4 (25%)
Caucasian	12 (75%)
Time since amputation at enrollment (years)	
Mean ± Standard Deviation	10 ± 12
Median (range)	4 (0.2–33.0)
Level of amputation (*N*)	
Below knee	9 (56%)
Above knee	7 (44%)
Location of amputation (*N*)	
Right leg	10 (63%)
Left leg	6 (37%)
Reason for amputation (*N*)	
Trauma	11 (69%)
Vascular disease or dysfunction	4 (25%)
Cancer	1 (6%)
Residual limb pain (*N*)	12
Time since onset of residual limb pain (years)	
Mean ± Standard Deviation	9 ± 12
Median (range)	3 (0.02–33)
Phantom limb pain (*N*)	14
Time since onset of phantom limb pain (years)	
Mean ± Standard Deviation	9 ± 11
Median (range)	4 (0.2–33)

(BPI3), Beck Depression Inventory-II (BDI-II) score of ≤20, and age ≥18 years. Exclusion criteria included the presence of sepsis, infection, diabetes mellitus type 1 or 2, implanted electronic devices, anticoagulation therapy (aside from aspirin therapy), history of valvular heart disease, previous limb injections within the past six months, pregnancy, any previous allergy to skin contact materials and/or anesthetic agents, and ongoing litigation, pending workers compensation claims, or other secondary gain issues. Baseline demographic and amputation information is provided in Table 1. Subjects were permitted to continue use of all analgesic medications throughout the study and were asked (but not required) not to increase their dosages of these medications above the baseline dosage during the two-week home trial.

After a detailed medical history and physical examination, subjects were sent home with a diary and asked to record medication usage and worst pain levels every day for the duration of the eight-week study. Following the two-week baseline period, subjects returned to the clinic for lead placement and electrical stimulation testing. The lead was a fine-wire helical coil wound from an insulated seven-strand, type 316L stainless steel wire with a single anchoring barb and electrode contact. The lead was preloaded in a 20-gauge, insulated hypodermic needle introducer. The location of post-amputation pain relative to the distribution of the sciatic and femoral nerves determined whether a lead was placed to stimulate the sciatic and/or femoral nerves. The sciatic nerve was accessed with a posterior approach using the greater trochanter and the ischial tuberosity as landmarks. The femoral nerve was accessed with an anterior approach using the femoral artery and femoral crease as landmarks. The insertion site was cleansed using aseptic technique, and local anesthesia was administered. Intravenous conscious sedation was used during lead placement if requested by the subject ($N = 2$).

Prior to placing the fine-wire lead, a monopolar needle electrode (24 gauge; Jari Electrode Supply, Gilroy, CA, USA) was inserted to within 0.5–3.0 cm of the trunk of a major peripheral nerve (i.e., the femoral nerve trunk and/or the sciatic nerve trunk) to deliver test stimulation under ultrasound guidance (MicroMaxx®, SonoSite, Inc., Bothell, WA, USA) to confirm electrode distance from the nerve trunk. Test stimulation (50–100 Hz, 10–40 μsec, 1–20 mA) was delivered with a battery-powered electrical stimulator (Maxima® II or Rehabilicare® NT2000, Empi, Inc., St. Paul, MN, USA) to confirm that a comfortable paresthesia could be evoked in the region of post-amputation pain without evoking unwanted muscle contractions or uncomfortable sensations. Evoking comfortable paresthesia in the distal regions of post-amputation pain (e.g., in the amputated foot or lower leg) without evoking subcutaneous sensations proximal to the lead (e.g., in the skin over the electrode at the upper thigh or buttock) confirmed that PNS was being delivered successfully to the major peripheral nerve innervating the region of pain without activating subcutaneous afferents in the local region superficial to the electrode. If local subcutaneous sensations were evoked (suggesting the electrode was placed too superficial), the needle electrode was advanced slightly (0.2–0.5 cm) and test stimulation was delivered again. If stimulation evoked unwanted muscle contractions or uncomfortable sensations in the distribution of the nerve trunk (suggesting the electrode was placed too close to the nerve), the needle electrode was withdrawn slightly (0.1–0.2 cm) and test stimulation was delivered again. The process of advancing or withdrawing the needle electrode in small increments, delivering test stimulation, and adjusting stimulus intensity was repeated until comfortable sensations of paresthesia were evoked in the distal regions of post-amputation pain without evoking unwanted sensations or unwanted muscle contractions. Once successful electrode placement was confirmed, the monopolar needle electrode was withdrawn and replaced with the fine-wire lead under ultrasound guidance using the same insertion site and the same approach except that the introducer typically was advanced 0.5–2.0 cm less than the monopolar needle electrode, placing the lead slightly more remote from the nerve.

If correct lead placement was confirmed by evoking a comfortable paresthesia in the painful area without evoking muscle contractions, subjects were qualified to proceed to the two-week home trial with a stimulator (Rehabilicare NT2000). The lead was deployed by withdrawing the needle introducer while maintaining pressure at the skin surface. The lead was coiled outside the skin to create a strain-relief loop, and the exit site was bandaged with waterproof bandages (Tegaderm, 3M, St. Paul, MN, USA). Subjects were instructed regarding the use of the stimulator and care of the bandages before progressing to the home trial. Subjects were scheduled to return to the clinic after the first week of the home trial for bandage change, exit site inspection, and an adjustment in stimulus intensity if needed before progressing to the second week of the home trial. Subjects were scheduled to return after the second week of the home trial for lead removal and again for one-week and four-week post-treatment follow-up visits. Subjects who did not qualify for the home trial exited the study after a telephone

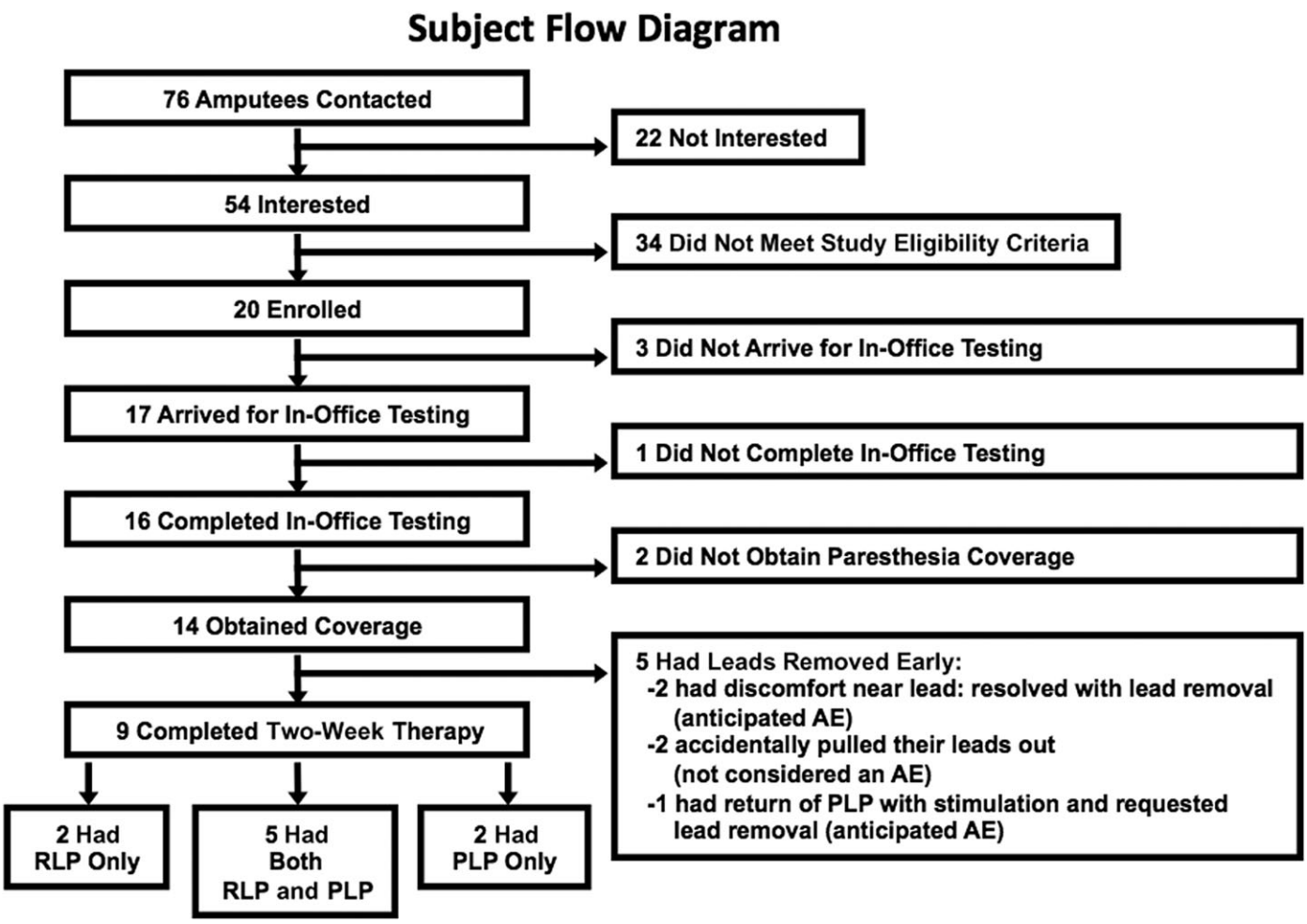

Figure 1. Flow diagram of subject disposition. Of the 16 subjects who completed in-office testing, two subjects did not obtain paresthesia coverage or pain relief. Of the 14 subjects who obtained paresthesia coverage and pain relief, five subjects had their leads removed before the two-week home trial was completed and nine subjects had their leads removed as scheduled after completion of the two-week home trial.

follow-up to assess any potential adverse events (AEs) one to two days following the stimulation testing visit.

Statistical analysis was performed with the Wilcoxon matched-pairs signed-rank test, and *p* values are reported without adjustment, consistent with feasibility study design and the number of subjects.

RESULTS

At the time of enrollment, subjects were between two months and 33 years after amputation with a mean time since amputation of 10 ± 12 years (Table 1). Causes of amputation included trauma, vascular disease or dysfunction, and cancer (Table 1). Of the 20 participants who enrolled, three did not arrive for testing, one did not complete in-clinic testing, and 16 subjects completed in-clinic testing (Fig. 1).

Of the 16 subjects who completed in-clinic testing, two subjects (amputation cause: $N = 2$ vascular disease or dysfunction) verbally reported no paresthesia coverage or pain relief. One of the nonresponders denied any sensation during stimulation, and the other reported stimulation as painful. Fourteen subjects (amputation cause: $N = 11$ trauma, $N = 2$ vascular disease or dysfunction, $N = 1$ cancer) responded to stimulation and obtained paresthesia coverage of the painful area (average percentage coverage of the painful area: 95 ± 8%, range: 75–100%) and clinically meaningful (≥30%) pain relief when the leads were placed approximately 0.5–3.0 cm from the femoral and/or sciatic nerves under ultrasound guidance (Fig. 2). Optimal paresthesia coverage was obtained when the leads were placed approximately 0.5–3.0 cm from the nerve trunk, and increasing the distance greater than 3 cm typically reduced paresthesia coverage. The responders described the sensation of stimulation as tingling ($N = 14$), vibrating ($N = 5$), buzzing ($N = 4$), warm ($N = 3$), tapping ($N = 2$), thumping ($N = 2$), pulsing ($N = 2$), and massaging ($N = 1$). Paresthesia coverage could be obtained without evoking unwanted muscle contractions in all responders, and all responders indicated that sensation was not painful. No AE occurred during in-clinic testing.

Nine of the 14 responders completed the two-week home trial after which the leads were removed. One of the nine accidentally pulled out his lead five days into the home trial, returned to the clinic to have the site inspected and the lead replaced, and completed the home trial. Five subjects did not complete the two-week home trial. Two subjects reported temporary discomfort (an anticipated AE) at the site of the lead following lead placement, which resolved following lead removal. Two subjects accidentally pulled out the leads, which caused temporary discomfort (an anticipated AE) but did not cause tissue damage. Due to concerns of subject

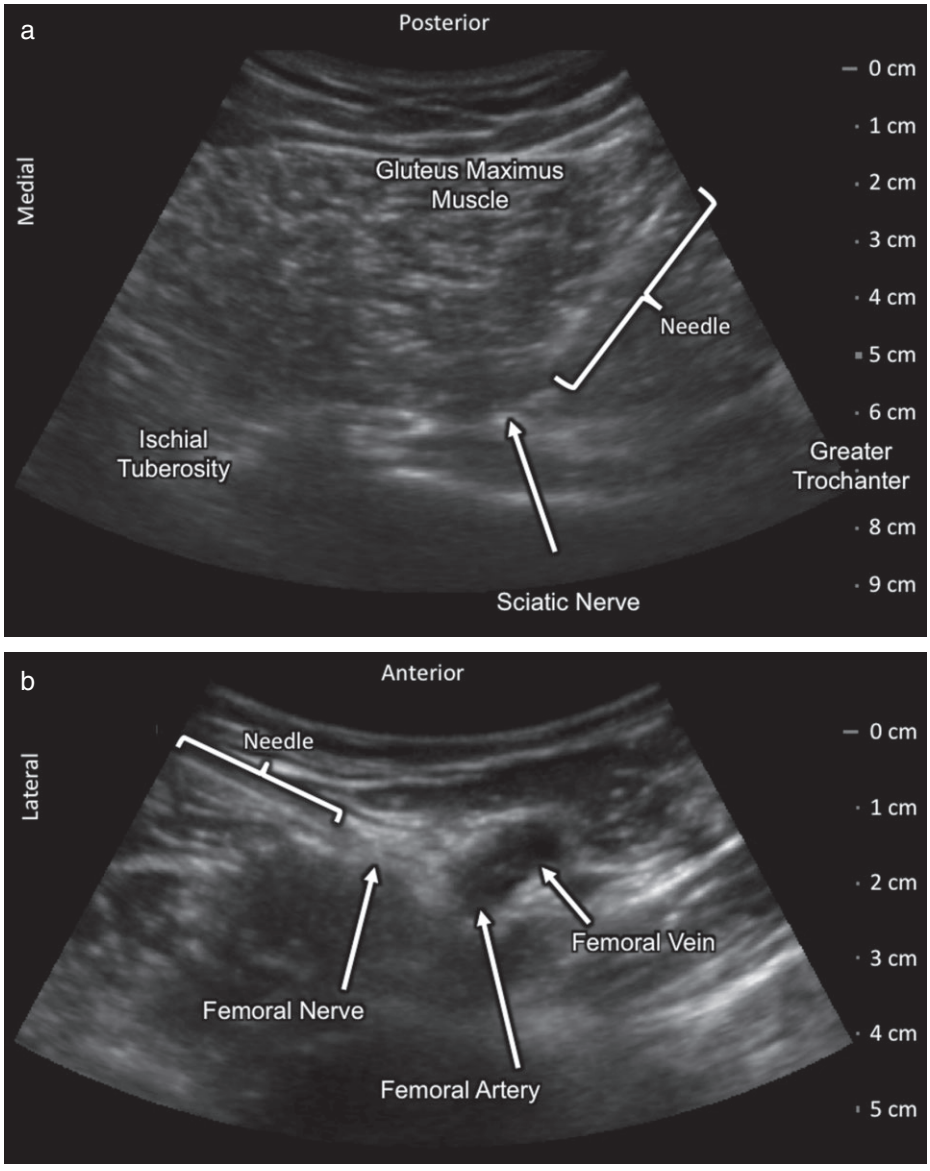

Figure 2. Ultrasound images are shown for sciatic (a) and femoral (b) lead placement.

noncompliance, the leads were not replaced. One subject reported the return of PLP during the first night of the home trial and requested lead removal. Subjects who did not complete the home trial were permitted to not complete efficacy-related assessments to reduce their burden of continued participation and encourage them to continue to complete safety-related assessments regarding AEs for the remainder of their participation in the study. Of the nine responders who completed the home trial, five responders reported both RLP and PLP at baseline, two responders reported only RLP at baseline, and another two responders reported only PLP at baseline. The results of the nine responders who completed the home trial are summarized below.

In their daily diaries, subjects reported a reduction of their mean worst daily post-amputation pain (BPI3) in the second week of stimulation ($56 \pm 26\%$ [$p < 0.005$, $N = 9$]) and in the fourth week of follow-up after the end of stimulation ($56 \pm 26\%$ [$p < 0.005$]) that was statistically significant relative to baseline (Fig. 3). Eight of the nine subjects (89%) reported clinically significant (≥30%) relief during the second week of stimulation, and seven subjects (78%) reported clinically significant relief during the fourth week of follow-up.

Relative to baseline, subjects also reported decreases in average pain (BPI5), pain interference (BPI9), and Pain Disability Index (PDI) scores in the second week of stimulation and in the fourth week of follow-up after the end of stimulation (Figs. 4–6). There were small nonsignificant decreases in depression scores (BDI-II) (Fig. 7). All subjects reported improvement in their quality of life with the assessment of the patient global impression of change in the second week of stimulation and in the fourth week of follow-up after the end of stimulation, and many subjects reported they were either "much improved" or "very much improved" (Table 2).

Analgesic medication usage was assessed in diaries at baseline and throughout the study period. Most subjects had no substantial changes in medication affecting pain except for two subjects who stopped taking acetaminophen and nonsteroidal anti-inflammatory medications during stimulation and one subject who reduced tramadol consumption approximately 50% during fourth week of follow-up.

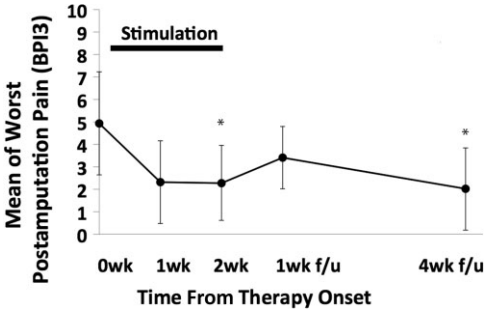

Figure 3. Changes are shown in the mean worst daily post-amputation pain (Brief Pain Inventory-Short Form Question 3) that was most intense during the two-week baseline period for the nine subjects who completed the home trial. Five subjects reported residual limb pain and four subjects reported phantom limb pain as their most intense post-amputation pain in their baseline diaries. Relative to baseline, subjects reported pain relief in the second week of stimulation (56 ± 26% [$p < 0.005$, $N = 9$], range: 22–100%) and in the fourth week of follow-up after the end of stimulation and lead removal (56 ± 26% [$p < 0.005$], range: 25–93%). Eight subjects (89%) reported ≥30% pain relief during the second week of stimulation and seven subjects (78%) reported ≥30% pain relief during the fourth week of follow-up.

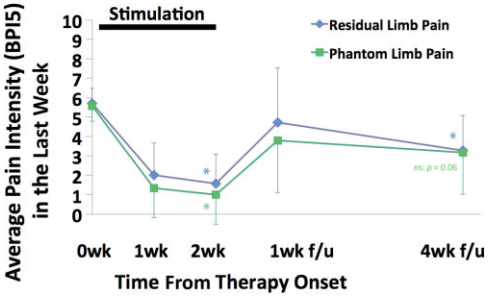

Figure 4. Relative to baseline, subjects reported decreases in average pain (Brief Pain Inventory-Short Form Question 5) in the second week of stimulation (RLP: 72 ± 28% [$p < 0.02$, $N = 7$], PLP: 81 ± 28% [$p < 0.02$, $N = 7$]) and in the fourth week of follow-up after the end of stimulation (RLP: 42 ± 27% [$p < 0.02$], PLP: 47 ± 48% [$p = 0.06$]). Of the nine subjects included in this analysis, five subjects reported both RLP and PLP at baseline, two subjects reported only RLP, and two subjects reported only PLP. PLP, phantom limb pain; RLP, residual limb pain.

DISCUSSION

This case series describes how PNS generated clinically significant relief of post-amputation pain using a fine-wire lead placed percutaneously under ultrasound guidance a remote distance away from the femoral and sciatic nerves. These data suggest that it is feasible to provide pain relief with a novel PNS system that does not require surgery to access the nerve.

Most (14 of 16) subjects responded to stimulation with comfortable paresthesia coverage of the painful area and pain relief. Paresthesia coverage is known to correlate with the potential for long-term pain relief (15), and the successful paresthesia coverage of the majority of the painful area (95 ± 8%) suggests that extending the duration of the therapy has the potential to extend the duration of pain relief, which will be investigated in future studies. It is unclear why two subjects failed to obtain paresthesia coverage, but it may have been related to their history of vascular disease or dysfunction in the residual limb, cortical reorganization, or lead placement. Overall, 100% of the amputees with amputations caused by trauma ($N = 11$ of 11) or cancer ($N = 1$ of 1) responded to stimulation,

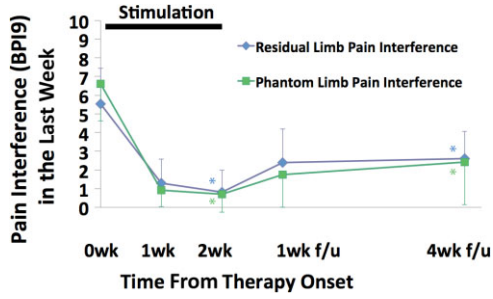

Figure 5. Relative to baseline, subjects reported decreases in pain interference (Brief Pain Inventory-Short Form Question 9) in the second week of stimulation (residual limb pain interference: 81 ± 27% [$p < 0.05$, $N = 6$], phantom limb pain interference: 83 ± 31% [$p < 0.02$, $N = 7$]) and in the fourth week of follow-up after the end of stimulation (residual limb pain interference: 53 ± 17% [$p < 0.05$], phantom limb pain interference: 56 ± 46% [$p < 0.05$]).

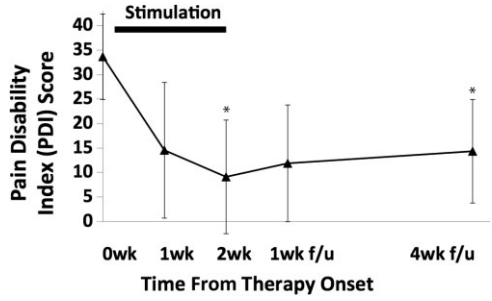

Figure 6. Relative to baseline, subjects reported decreases in Pain Disability Index (PDI) scores in the second week of stimulation (25 ± 16 points [70 ± 38%] [$p < 0.01$, $N = 9$]) and in the fourth week of follow-up after the end of stimulation (19 ± 14 points [55 ± 32%] [$p < 0.005$]). Seven subjects (78%) reported a clinically significant (≥10 points) improvement in their PDI during the second week of stimulation and six subjects (67%) reported a clinically significant improvement in their PDI during the fourth week of follow-up.

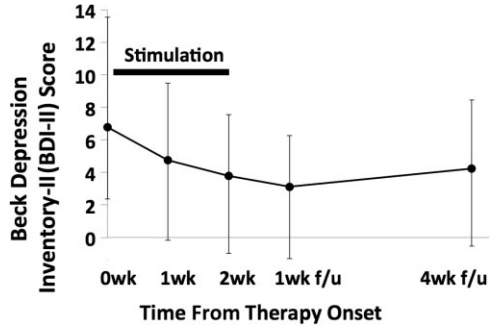

Figure 7. Relative to baseline, subjects reported minor decreases in Beck Depression Inventory scores in the second week of stimulation (43 ± 51% [$p = 0.06$, $N = 9$]) and in the fourth week of follow-up after the end of stimulation (32 ± 57% [$p > 0.10$]).

and 50% ($N = 2$ of 4) of the amputees with vascular disease or dysfunction responded to stimulation. Other than the cause of amputation, the baseline characteristics were similar across subjects. Baseline characteristics were also similar across the nine responders who completed the two-week home trial and the five responders who did not, with the exception of the baseline BDI-II scores, which were slightly lower in the subjects who completed the home trial (7 ± 4) compared with those who did not (14 ± 7) ($p = 0.06$).

Table 2. To Assess the Patient Global Impression of Change (PGIC), Subjects Were Asked "Since Beginning Stimulation Therapy, How Would You Rate the Change (If Any) in Your Quality of Life (Activity Limitations, Symptoms, Emotions) Related to Your Painful Condition?" on a 7-Point Categorical Scale Ranging From "Very Much Worse" (Rank = –3) to "No Change" (Rank = 0) to "Very Much Improved" (Rank = +3). Subjects Reported Improvement During the Second Week of Stimulation and the Fourth Week of Follow-up After the End of Stimulation. Many Subjects Reported They Were Either "Much Improved" or "Very Much Improved" in the Second Week of Stimulation (89% of Subjects) and in the Fourth Week of Follow-up (56% of Subjects).

Subject	First week of stimulation	Second week of stimulation	First week of follow-up	Fourth week of follow-up
A-01	Much improved	Very much improved	Much improved	Minimally improved
A-04	Minimally improved	Much improved	Minimally improved	Minimally improved
A-09	Minimally improved	Much improved	Not collected	Much improved
A-10	Not collected	Much improved	Much improved	Very much improved
A-11	Much improved	Very much improved	Minimally worse	Minimally improved
A-14	Much improved	Much improved	Much worse	Much improved
A-15	Minimally improved	Minimally improved	Minimally improved	Minimally improved
A-17	Very much improved	Very much improved	Very much improved	Very much improved
A-20	Much improved	Much improved	Minimally improved	Much improved

The nine responders who completed the home trial reported substantial reductions in their daily diaries for mean worst post-amputation pain at the end of the two-week stimulation trial and at the end of the four-week follow-up period after cessation of stimulation. The pain relief reported in the daily diary was accompanied by commensurate improvements in average RLP, average PLP, RLP interference, PLP interference, PDI scores, and the patient global impression of change at the end of stimulation and the four-week follow-up period.

The present method of PNS is distinct from peripheral nerve field stimulation or subcutaneous stimulation in which the lead is placed in the region of pain to activate nearby nerve branches and provide pain relief to the local surrounding area (50–52). In the present study, the lead was placed outside of the area of pain to activate the major peripheral nerve trunks (i.e., the femoral and sciatic nerve trunks) and provide relief to distal areas of pain in the residual and phantom limbs. Thus, paresthesia and pain relief were provided to the distal areas of pain without evoking paresthesia in the local subcutaneous tissue near the lead.

Gate control theory as proposed by Melzack and Wall may explain how activation of large myelinated nerve fibers by PNS can inhibit transmission of pain signals from the spinal cord to higher centers in the central nervous system to decrease the perception of pain (53–55). The inhibition of nociceptive activity in central pain pathways such as the spinothalamic tract is the most commonly cited mechanism of PNS-induced pain relief (22,35,55,56).

PLP is considered to be analogous to a central pain phenomenon (57,58). Previous studies suggest PLP is related to the plastic changes that can occur throughout the central nervous system at multiple levels, including reorganization at the level of the cortex, thalamus, brain stem, and spinal cord (57–61). It may be possible for PLP to be modulated by input at the spinal or peripheral level (13,57). It has been suggested that loss of peripheral sensations such as proprioception may increase PLP (57,62–64), and it is possible that the addition of comfortable sensations, such as the paresthesia induced by PNS, may decrease PLP.

The present study complements previous studies evaluating SCS (14–18) and PNS (19–26) that indicate electrical stimulation has the potential to provide significant pain relief when stimulation generates >50% paresthesia coverage of the painful region (15). In the present study, responders reported ≥75% paresthesia coverage and 56 ± 26% relief of mean worst post-amputation pain during the two-week trial and at the end of the four-week follow-up period, suggesting a carryover effect following the end of stimulation. These data indicate that further investigation is warranted to determine if long-term relief can be provided by either a short-term percutaneous therapy or an implantable version of the present therapy.

PNS offers the potential to deliver therapeutic stimulation to the nerve innervating the region of pain and limit the distribution of paresthesia to the area in which it is needed (31). However, PNS is seldom used to treat post-amputation pain because there are no data from clinical trials and available PNS systems can be technically challenging to place in close proximity to the nerve (25,31,32,40,65). Traditionally, electrical stimulation of a large peripheral nerve trunk, such as the sciatic or femoral nerve, has required surgical access and dissection to place a cuff-, paddle-, or plate-style lead in intimate contact with the nerve (19–25,32). However, recent studies have shown that cylindrical leads can be placed percutaneously in close proximity (≤2 mm) to the nerve under ultrasound guidance (39–41). The present study builds on this foundation by demonstrating that a lead can be placed percutaneously a remote distance (0.5–3.0 cm) away from the nerve and still elicit significant paresthesia coverage and pain relief.

Limitations of the study included the short duration of therapy (two weeks) and follow-up (four weeks), the lack of a placebo or other comparator group, and the case series study design. Additional limitations of the study included the variation of responses across individuals in the PDI and BDI-II scores. For example, although the majority of subjects reported clinically significant improvement in their PDI scores at both the end of stimulation and at the end of follow-up, future studies with larger sample sizes are needed to determine how these results relate to the general population.

Future studies are needed to confirm these results in additional patients with a randomized, placebo-controlled trial that utilizes a longer duration of therapy and a longer follow-up period that will allow better assessment of any potential carryover effect. The prototype system tested in the present case series has been developed into a skin-mounted percutaneous PNS system specifically designed for use in the periphery. The PNS system will be tested in a multicenter double-blinded randomized controlled trial under an FDA-approved investigational device exemption to address these issues and determine the safety and effectiveness of treating post-amputation pain with PNS (Fig. 8). The ability to generate significant pain relief both during and after therapy with a lead inserted percutaneously and remote from the target nerve trunk holds promise for providing relief of post-amputation pain.

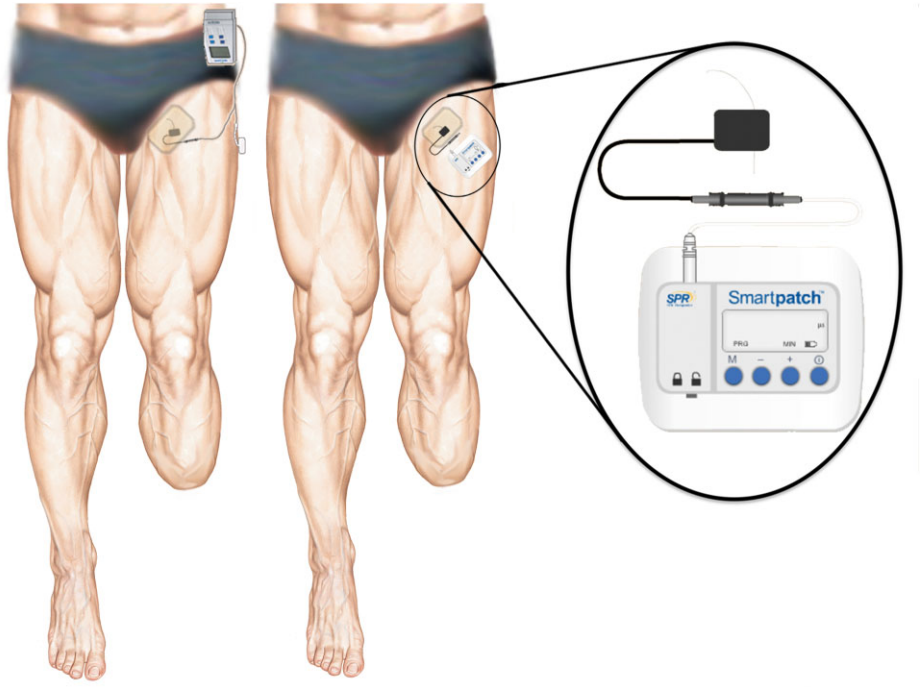

Figure 8. The present study evaluated the feasibility of reducing post-amputation pain with a percutaneous electrical stimulation system prototype consisting of an external stimulator connected by a cable to a fine-wire lead and a surface return electrode, and the percutaneous exit site was covered by a transparent waterproof bandage (Tegaderm, 3M, St. Paul, MN, USA) (Left). The study supported development from the prototype into the SMARTPATCH® Peripheral Nerve Stimulation System (SPR Therapeutics, Cleveland, OH): a skin-mounted electrical stimulator, percutaneous lead, and small adhesive pad that contains the power source for the system and serves as the surface return electrode (Right), which will be tested in a multicenter double-blinded randomized controlled trial under US Food and Drug Administration-approved investigational device exemption to determine the safety and effectiveness of treating post-amputation pain with peripheral nerve stimulation. Both the prototype and the SMARTPATCH system are investigational devices limited to investigational use only.

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Device status: Investigational percutaneous peripheral nerve stimulator systems (NDI Medical) including percutaneous fine-wire leads and commercially available external stimulators (Maxima® II and Rehabilicare® NT2000, Empi, Inc., St. Paul, MN, USA) were used during this clinical study. The peripheral nerve stimulation systems were provided by NDI Medical.

Authorship Statement

Authors Rauck, Kapural, Cohen, Zang, Grill, and Boggs assisted in the designing of the clinical trial. Authors Rauck, Gilmore, and North conducted the study, including patient recruitment and data collection. All authors participated in data analysis, interpretation, and review. Authors Boggs and Zang prepared the manuscript draft with important intellectual input from authors Rauck, Kapural, Cohen, North, and Grill. Authors Rauck, Kapural, Gilmore, North, Zang, and Boggs had complete access to the study data. All authors approved the final manuscript.

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COMMENTS

This is a very interesting and well-documented study. I am puzzled by the authors' ability to obtain excellent stimulation of a complex structure such as the sciatic nerve without even having the lead on the nerve. My experience with about 30 sciatic nerve stimulation implants is that many times, even with a multi-column paddle lead placed on the nerve itself, it is difficult to obtain paresthesias in all the distribution of the nerve. At times the lead has to be repositioned a few times in the OR. Maybe patients with amputation have a different physiology or different expectations. I also find it unusual that a cylindrical lead (with a circumferential electrical field) most likely embedded in or near the muscle(s) and at a few centimeters from a major nerve would not cause unwanted muscle contractions.

In any case, I do not have any personal experience with the technique presented by the authors and I have no reason to doubt their results. This approach seems to be a breakthrough in the management of severe amputation pain. Long-term studies in a multicenter environment will be necessary to assess the true potential of this approach.

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Peripheral nerve stimulation via percutaneous electrode placement techniques is re-emerging as a treatment modality adjunct or alternative to spinal cord stimulation which avoids the need for extensive surgical dissection. Modern warfare, as well as disease is producing a relative epidemic of extremity amputations which can lead to refractory phantom limb pain. This novel percutaneous approach holds promise in providing a safe, reproducible, and effective means of controlling this and other painful conditions.

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PNS is a fascinating area in neuromodulation, and any scientific contribution to the field is commendable. Development of new devices, specifically designed for the peripheral nerves, might improve outcomes and safety, and popularize peripheral stimulation for treatment of various neuropathic disorders. This study tested a newly designed single-contact lead which may simplify the procedure and should provide reliable and lasting paresthesia coverage and pain relief. The article is introducing a groundbreaking concept of deliberately placing the cathode remote from the target nerve and selective activation of sensory fibers by a short-duration stimulus. Moreover, the beneficial effect lasted at least three weeks after the device was removed. Nine of the originally included sixteen patients (56%) achieved a reduction of pain and pain interference. The outcomes are favorably comparable with more traditional surgical lead placement. As a matter of fact the results are so intriguing that I cannot help but to quote Carl Sagan: "Extraordinary claims require extraordinary evidence". It is conceivable that the next step will include development of a new IPG designed to work with the described lead and conduction of a larger clinical study. Hopefully this future study will include a sufficient number of patients, long-term follow up and objective clinically meaningful endpoints.

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Comments not included in the Early View version of this paper.

