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Observational Report

Cross Talk: A New Method for Peripheral Nerve Stimulation. An Observational Report with Cadaveric Verification

Frank JE Falco, MD[1,2], Jeffrey Berger, MD[2], Alan Vrable, MD[2], Obi Onyewu, MD[1,2], and Jie Zhu, MD[1,2]

From: [1]Mid Atlantic Spine and Pain Physicians, Newark DE; [2]Temple University Hospital, Temple University Medical School, Philadelphia, PA.

Dr. Falco is Medical Director, Mid Atlantic Spine & Pain Specialists of Newark, DE; Director, Pain Medicine Fellowship Temple University Hospital and Clinical Assistant Professor Temple University Medical School, Philadelphia, PA.
Dr. Berger and Dr. Verable are Pain Medicine Fellows, Temple University Hospital, Philadelphia, PA.
Dr. Onyewu and Dr. Zhu are Attending Physicians, Mid Atlantic Spine & Pain Specialists of Newark, DE; Faculty Members, Pain Medicine Fellowship Temple University Hospital, Philadelphia, PA.

Address correspondence:
Frank Falco, MD
Mid-Atlantic Spine
139 East Chestnut Hill Road
Newark, DE 19713
E- mail: cssmo1@aol.com

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Background: Relief of regional, non-appendicular pain, particularly low back pain, through spinal cord stimulation (SCS) has proven challenging. Recently, peripheral nerve stimulation (PNS), also known as peripheral nerve field stimulation (PNFS) depending on the stimulation area, has demonstrated efficacy for the treatment of well-localized, small areas of pain involving the abdomen, inguinal region, pelvis, face, occipital area, and low back. More widespread application of peripheral nerve stimulation has been limited by its narrow field of coverage in a larger group of patients with diffuse or poorly localized pain.

Objectives: To determine if cross talk (the creation of an electrical circuit and therefore electrical stimulation between separate subcutaneously placed PNS leads [i.e. inter-lead stimulation]) was clinically possible across large painful areas, assess the breadth of stimulation coverage via cross talk, evaluate the clinical efficacy of peripheral nerve stimulation cross talk (PNSCT), and confirm the existence of cross talk across a large area in a cadaveric model.

Study Design: Case series observational report and cadaveric experimentation.

Setting: A private, comprehensive interventional pain management practice with pain medicine fellowship training in the United States.

Methods: Eighteen consecutive patients with non-appendicular, regional pain were included in the study. Data collection for the implanted patients included the presence or absence of stimulation between the PNS leads, stimulation tolerability, stimulation region, lead orientation, lead montage, inter-lead distance, and pain relief from PNSCT compared to PNS without cross talk.

A cadaveric analysis was performed to determine the presence or absence of an electrical circuit with 2 subcutaneously PNS leads to confirm or refute the existence of electrical stimulation from on lead to the other within subcutaneous fat with the leads placed at a significant distance apart from one another.

Results: All 18 patients experienced significant pain relief, reduction of pain medication, and functional improvement. Cadaveric experimentation confirmed the presence of an electrical circuit with PNS leads placed at a distance far apart from one another and verified that inter-lead stimulation (cross talk) does occur in subcutaneous fat over a great distance.

Limitations: This study was limited by its small sample size, and the short-term follow-up after implantation.

Conclusions: The use of the PNSCT technique allows for significant analgesia for large painful areas that have been poorly captured using traditional SCS techniques and not considered as an option with the current application of peripheral nerve stimulation.

Key words: Peripheral nerve stimulation, peripheral nerve field stimulation, cross talk, spinal cord stimulation, neuromodulation, low back pain, failed back surgery syndrome, abdominal pain, neck pain, post herpetic neuralgia, occipital headaches

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Spinal cord stimulation (SCS) uses electrical energy to modulate pain transmission via direct stimulation of the spinal cord to provide safe and effective relief from a variety of painful conditions. Since its introduction by Shealy in 1967 for the treatment of cancer pain, the indications for SCS have expanded to the treatment of pain relating to failed back surgery syndrome (FBSS), radiculopathy, intractable angina, peripheral vascular disease, phantom limb, complex regional pain syndromes types I and II, and peripheral neuropathy (1,2). More recently, SCS has been successfully utilized for the treatment of chronic abdominal pain, mesenteric ischemia, and irritable bowel syndrome (3-5). Compared to re-operation for FBSS, SCS has demonstrated greater efficacy, substantial reductions in health care utilization, and significant long-term cost savings (6-11). Peripheral nerve stimulation techniques of the occipital and the trigeminal nerves have been used for the treatment of headaches and facial pain (12-15). Retrograde, anterograde, and extraforaminal approaches for spinal canal placement of SCS leads have been used for cervical, lumbar, and sacral nerve root stimulation in the treatment of radiculopathy and pelvic pain (12-14).

Although SCS has been an effective treatment option for patients suffering from chronic neuropathic pain of the upper and lower limbs, the use of SCS to treat axial pain including the low back, neck, chest, and abdominal areas has proven far more challenging with unreliable long-term pain relief (3,15). Adequate low back parasthesia coverage typically necessitates midline lower thoracic lead placement to direct electrical current into the deeper spinal cord structures. Electrode placement at higher levels often captures low back pain but is limited by the large width of CSF which can promote stimulation to the dorsal roots leading to uncomfortable, band-like dermatomal stimulation patterns. While stimulation montages often produce favorable parasthesia coverage of axial pain at the time of surgical implantation, long-term relief is unreliable with loss or receding stimulation coverage and perception due to accommodation or changes in the electrical fields within the spinal cord (16,17).

Several case reports have emerged in the literature describing the use of peripheral nerve stimulation (PNS) to provide significant relief from well-localized chronic pain syndromes involving the low back, abdomen, and pelvis (18-24). In these reports, the application of PNS was not being applied to stimulate single identifiable peripheral nerves but rather to generate electrical impulses from the diffuse subcutaneous network of afferent nerves. In those reports where PNS did involve the stimulation of peripheral nerves, the area of stimulation was limited to the distribution of that nerve. A major perceived shortcoming of PNS has been its narrow field of coverage limiting its application to well-localized painful regions (19,22).

In this report, a technique is introduced that allows for stimulation and pain relief of large areas through the use of cross talk between peripherally implanted stimulation leads through clinical application and confirmed by way of cadaveric experimentation.

Methods

The observational report was performed based on the instructions of the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) (23,24). Since the study did not involve any human experimentation and all the patients signed HIPAA compliant informed consent, IRB approval was not required. This observational report also has applied all appropriate precautions with regards to confidentiality, informed consent, and HIPAA compliance. All the precautions were taken to protect patient privacy.

Study Design

Data were collected from patients with chronic pain that had not responded to conservative or surgical treatment and whose pain significantly impacted their quality of life. In addition, an assessment of PNSCT was conducted in a cadaver lab using specific equipment to determine the presence or absence of an electrical circuit with 2 widely separated PNS leads placed subcutaneously in a fresh frozen human cadaver, for the cadaveric portion of the study.

Inclusion Criteria

- No evidence of acute or treatable organic pathology
- An area of pain generally confined to one anatomical region, however the pain could be diffuse and nonspecific within that region
- Failure to respond to conservative treatment including the use of a transcutaneous electrical nerve stimulation (TENS) unit, physical therapy, medication management, interventional procedures, and in some cases, surgical treatment

- Psychiatric / psychological assessment demonstrating no psychological co-morbidities that would be a contraindication for undergo PNS treatment
- PNS implantation

Data Collection

Data were collected to include the presence or absence of stimulation between the PNS leads, stimulation tolerability, stimulation region, lead orientation, lead montage, inter-lead distance, area of stimulation, and pain relief from peripheral nerve stimulation cross talk (PNSCT) compared to PNS without cross talk. Outcome analysis consisted of pain relief from PNSCT, opioid use, and functional improvement.

Data were collected including the measurement of voltage, resistance, and current within a segment of the electrical circuit created by the cross talk between the PNS leads (25-29).

Setting

This study was conducted in a private comprehensive inteventional pain management practice in the United States. Data were collected from August 2008 through April 2009. Cadaveric experimentation was performed at a cadaver laboratory (Vista Labs, Baltimore, MD) on July 30, 2009.

Participants

The patients had a wide variety of chronic pain disorders (with the exception of one patient who had a 2-month history of post herpetic neuralgia) and had failed conservative treatment including oral opioids, therapy, interventional pain procedures, and in several cases, lumbar spine surgery. Many of the patients had multiple sources and areas of chronic pain for years.

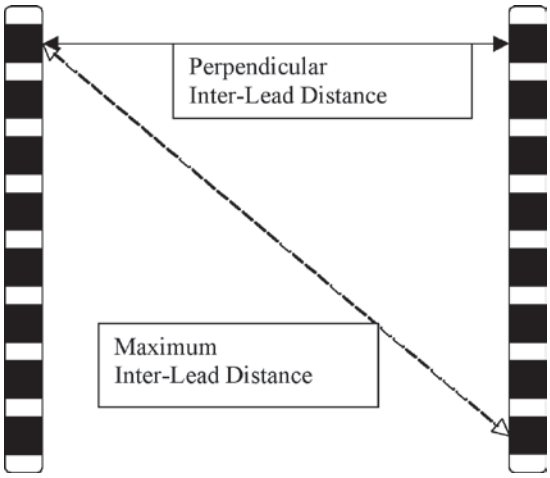
Variables

Several variables were used in this assessment. The most important of these was to determine whether or not it was possible to clinically generate an electrical circuit (cross talk) between 2 or more widely separated subcutaneously placed PNS leads as well as to experimentally confirm the presence or absence of an electrical circuit with PNS cross talk. Other outcomes regarding PNSCT consisted of stimulation tolerability, pain relief from PNSCT compared to PNS without cross talk, the degree of pain relief from PNSCT, decreased opioid use, and functional improvement.

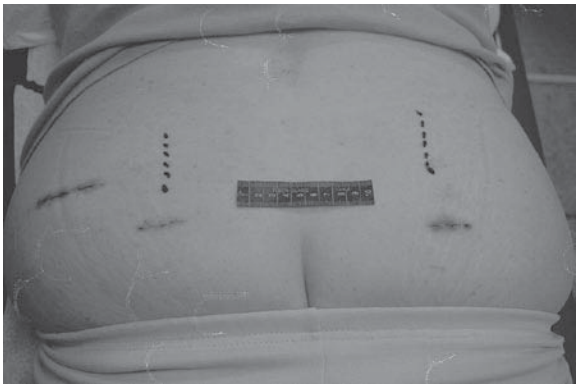
Data Sources / Measurement

The inter-lead distance between the PNS leads was measured along a perpendicular line from each lead as well as the greatest distance between any 2 or more electrodes from opposite leads to determine the maximum inter-lead distance for each patient (Fig. 1A). This was accomplished by marking the skin for each PNS lead from distal electrode to proximal electrode under fluoroscopy and then measuring the inter-lead distance perpendicular to the leads and the maximum inter-lead distance (Fig. 1B). The cross sectional area of stimulation from PNSCT was determined by multiplying the length of the perpendicular inter-lead distance with the length of the stimulating portion of the PNS leads (Fig. 1C). The latter length was calculated from the distal end of the most distal electrode to the proximal end of the most proximal electrode (PNS) (Fig. 1C).

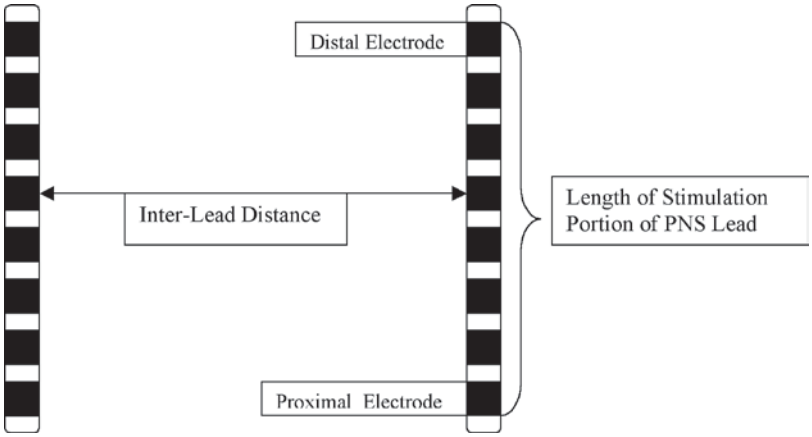
For the PNS octrode leads used in this study (St. Jude Medical Neuromodulation Division) the electrodes were 3 mm in length with 4 mm inter electrode spacing which equaled a total length of 52 mm or 5.2 cm. For the PNS wide spaced quad leads used in this study (St. Jude Medical Neuromodulation Division) the electrodes were 3 mm in length with 11 mm inter electrode spacing between the top and bottom 2 electrodes with 18 mm inter electrode spacing between the second and third electrodes which equaled the same total length of 52 mm or 5.2 cm. Therefore, 5.2 cm was used for the stimulation length of the PNS lead with the perpendicular inter-lead distance to determine the cross sectional stimulation area produced from PNSCT for all implanted patients (Figs. 2). The only exceptions to this method of calculation were the stimulation areas for 2 patients (Fig. 3, Table 1). One was implanted with bilateral vertically "stacked" PNS wide spaced quad leads (Fig. 3A). The PNS stimulation length was determined to be 18.4 cm that took into account the 5.2 cm stimulation length for each quad lead and the 8 cm distance between the distal and proximal electrodes of the "top" and "bottom" PNS leads measured at the time of implantation. The second patient was implanted with a horizontally positioned PNS lead that "criss crossed" with a vertically placed PNS lead (Fig. 3B). The rhomboid area of stimulation was calculated by dividing the rhomboid into 4 right angle triangles and summating the triangular cross sectional areas (Fig. 4).



A. Schematic representation of measuring the inter-lead distance between the PNS leads along a perpendicular line as well as the maximum inter-lead distance.



B. Skin markings for each PNS lead performed under fluoroscopy in order to measure the inter-lead distance perpendicular to the leads and the maximum inter-lead distance.



C. Schematic representation of PNS leads demonstrating the measurements of the inter-lead distance and lead stimulation length to determine the cross sectional area of stimulation from PNS with cross talk.

Fig. 1. *Measurement of interlead distance.*

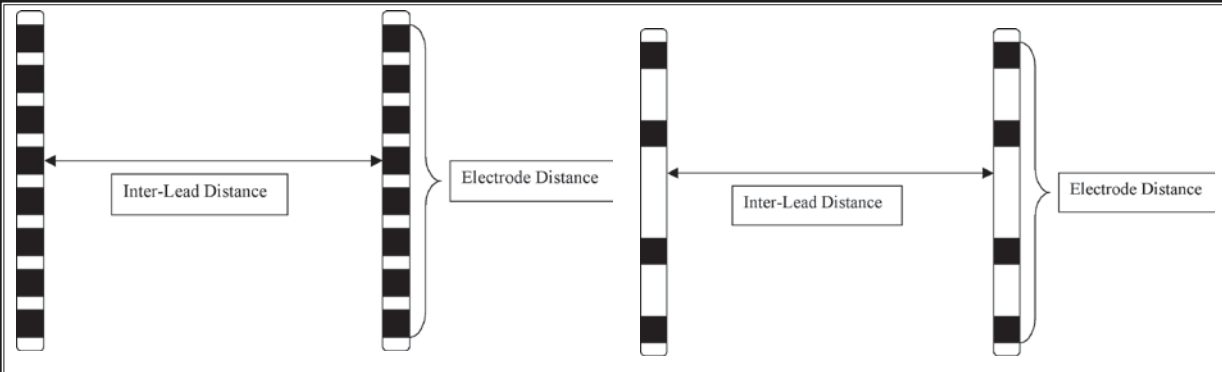


Fig. 2. *Schematic representation for calculating the cross sectional area of the stimulation from PNSCT from octrode and wide base quad leads.*

Table 1. *Mathematics for calculating lead stimulation length for octrode and wide based quad leads as well as bilaterally vertically stacked wide base quad leads in one patient.*

ELECTRODE TO ELECTRODE DISTANCE

Octrodes: Electrodes are 3 mm in length, with 4 mm longitudinal spacing, and 7 mm spacing from the center of one electrode to the next.

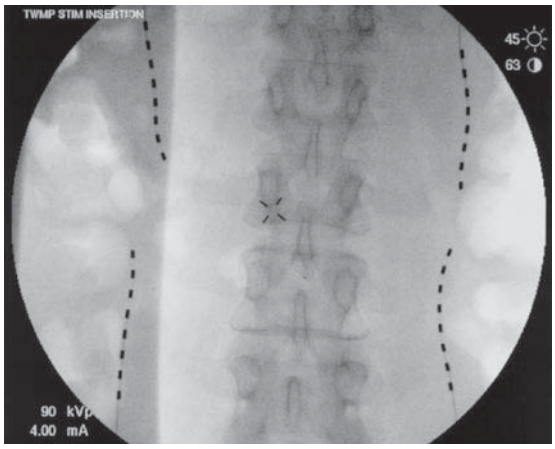
Electrode to Electrode: 3 mm x 8 = 24 mm
4 mm x 7 = 28 mm
Total = 24 mm + 28 mm = 52 mm = 5.2 cm.

Wide Spaced Quads: Electrodes are 3 mm in length with 11 mm longitudinal spacing between top two contacts and bottom two contacts and 18 mm longitudinal spacing between contacts 2 and 3. Center to center spacing between top two contacts and bottom two contacts is 14 mm and center to center spacing between contacts 2 and 3 is 21 mm.

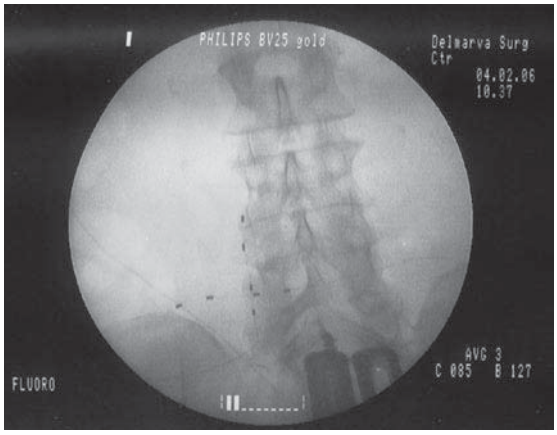
Electrode to Electrode:
Distance for top 2 and bottom 2 electrodes: 3 mm x 2 = 6 mm
Inter-electrode distance = 11 mm
Total = (6 mm + 11 mm) x 2 [for top & bottom] = 34 mm
Distance between 2nd and 3rd electrodes = 18 mm
Total Distance = 18 + 34 = 52 mm = 5.2 cm.

Patient
Bilateral dual wide spaced quads suture 8 cm apart between quad leads: Total Distance = (5.2 cm x 2) + 8 cm = 18.4 m.

The presence or absence of an electrical current and thus cross talk (electrical stimulation between leads) was experimentally conducted with PNS leads first in a saline medium and then later in a fresh frozen human cadaver. The saline experiment was undertaken with a basin of saline (a highly conductive medium), 2 octrode PNS leads, an oscilloscope voltmeter (Tektronix 2232 100 MHz Digital Storage Oscilloscope) to measure voltage, variable resistance box (EICO, Electronic Instrument Company, Inc.) to provide an accurate resistance source, digital multimeter (Ideal Industries, Inc.) to identify which colored wires within the trial connector cable aligned with each electrode in the PNS leads, an MTS programmer/battery source (St. Jude Medical Neuromodulation Division), and RP3 Rapid Programmer (St. Jude Medical Neuromodulation Division) that synchs with the MTS programmer/battery source (Fig. 5). The objectives of the saline experiment were to determine if the experimental set up was capable of measuring voltage, current, and resistance with the PNS leads, and to determine the accuracy of the PNS programmer display of the stimulation parameters current, frequency, and resistance. The same set up was used to measure the same stimulation parameters with the PNS leads placed within the subcutaneous fat of a fresh frozen human cadaver).

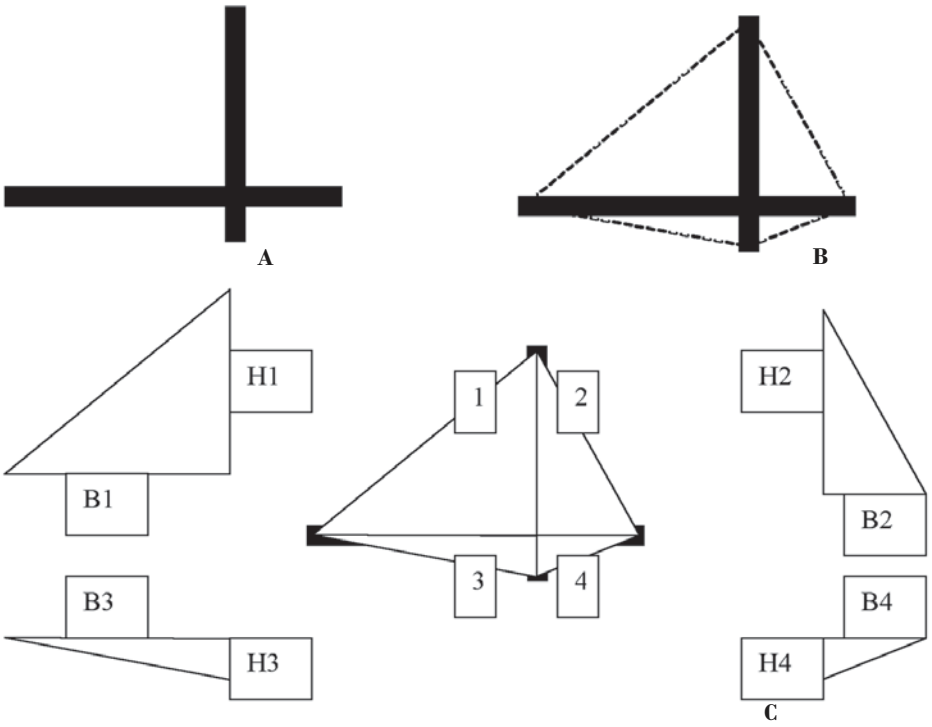


3A. Fluoroscopic x-ray of bilateral vertically stacked octrode PNS leads for the cross talk trial in one patient.



3B. Fluoroscopic x-ray of PNS lead orientation in the second patient after implantation.

Fig. 3. *Illustration of placemetn of "stacked" and "criss-crossed" leads.*



Cross Sectional Area (CSA) = ∑ triangles 1 through 4
CSA right angle triangle = ½ [Height (H) x Base (B)]
CSA = $\sum^{1-4}$ ½ [Height (H) x Base (B)]

CSA = $\sum^{1-4}$ ½ [Height (H) x Base (B)]
CSA = ½ [(H1B1) + (H2B2) + (H3B3) + (H4B4)]
H1 = H2, H3 = H4, B1=B3, B2=B4
CSA = ½ [(H1B1) + (H1B2) + (H3B1) + (H3B2)]
CSA = ½ [H1(B1 + B2) + H3(B1 + B2)]
CSA = ½ [(H1+H3) x (B1 + B2)]
(H1 + H3) = (B1 + B2) = 5.2 cm
CSA = ½ [(5.2 cm) x (5.2cm)]
CSA = 0.5[27.0]
CSA = 13.5 cm²

D

Fig. 4. *Mathematics for calculating the cross sectional area of stimulation for PNSCT in patient 22 after implantation. A. PNS lead orientation. B. Outline of rhomboid area of stimulation divided into 4 right angled triangles. C. Separation of the 4 right angle triangles with the height (H) and base (B) identified as H1 through H4 and B1 through B4. D. Mathematical calculation of the cross sectional area of stimulation for PNSCT in the secon patient.*

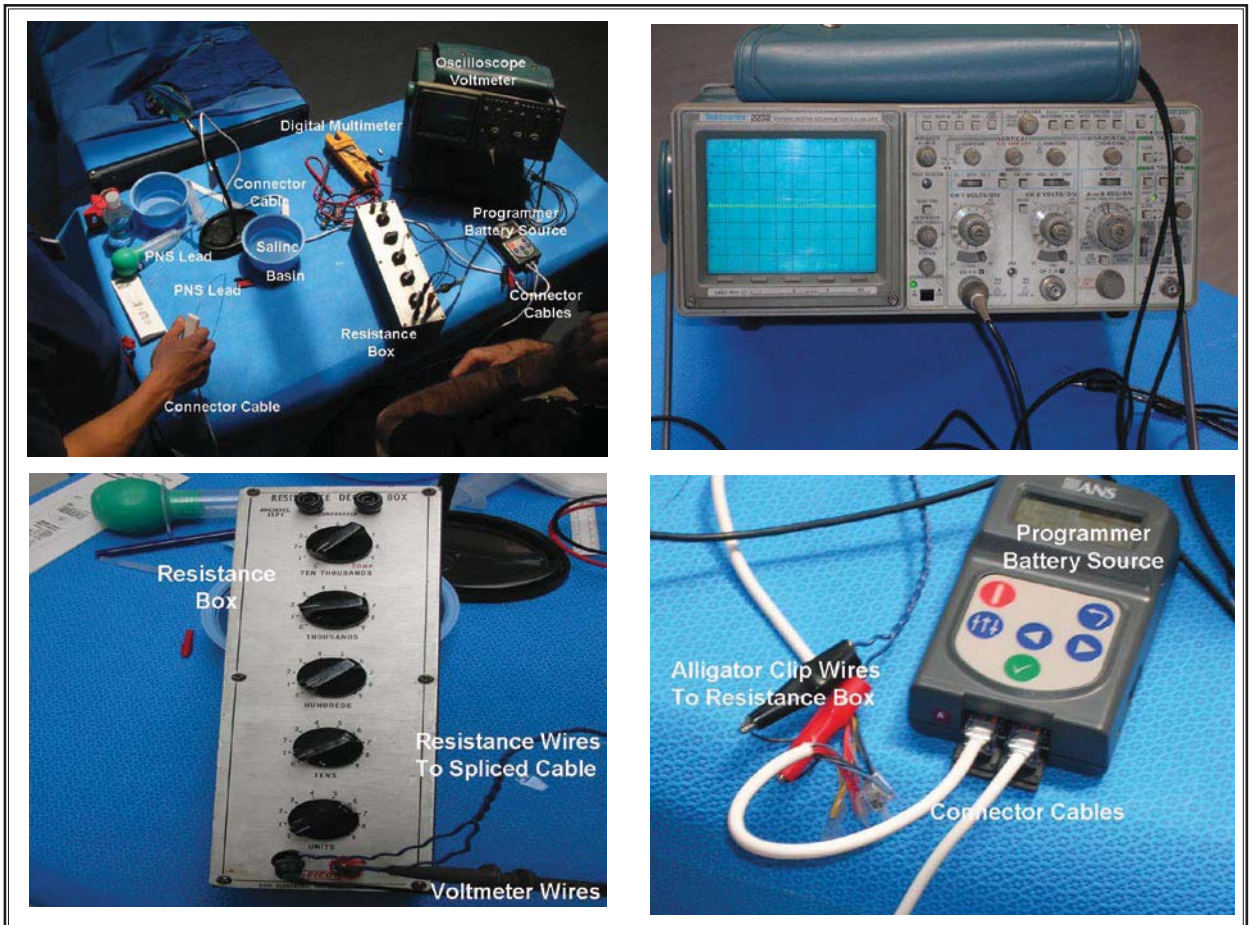


Fig. 5. *Saline PNSCT experiment. A. Set up. B. Oscilloscope voltmeter. C. Resistance box. D. Programmer and spliced cable with brown wire connected to resistance box with alligator clip wires.*

Bias

The goal was to do our best to eliminate any ambiguous data by recording and analyzing most of the data in terms of absolutes that did not involve subtle changes or responses. For example, PNSCT was assessed concretely as either existing or not without any other possible response in between.

Study Size

A small sample size was considered appropriate to detect that effect, based on previous interventional pain management studies (30-32).

Statistical Methods

Range and means were determined for age, pain intensity, pain relief, pain duration, PNSCT maximum inter-lead distance, and stimulation cross sectional area. Percentages were listed for gender, stimulation tolerability, applicability to different body regions, and the difference between pain relief from PNSCT compared to PNS without cross talk. Opioid use reduction attributed to PNSCT was quantified by patient accounts of dosage, frequency, schedule, and percent reduction of their opioid medications. The range, mean, and statistical significance of the numeric rating scale (NRS) for pain and the ODI were determined using the paired t test comparing results prior to and after PNS implantation with the application of cross talk.

Results

Participants

There were 28 consecutive patients chosen based on non-appendicular pain, pain intensity, and reduced function to participate in this study. All the patients underwent a PNSCT trial and 26 had a positive response with greater than 50% pain relief (Fig. 6).

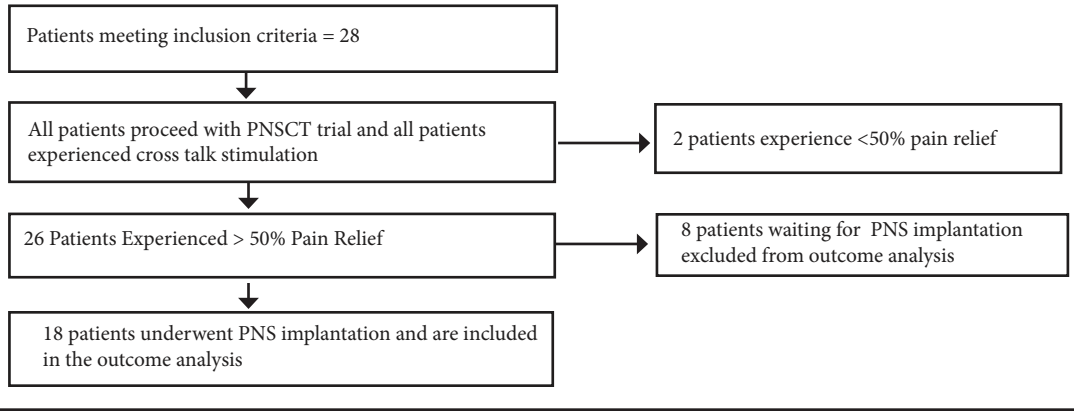


Fig. 6. *Flow diagram of the patients in the study.*

Descriptive Data

There were 13 women and 5 men who made up the 18 patients in the final data collection and analysis of this study. The age range of the participants spanned from 29 to 82 years old with a mean age of 56 years. The duration of pain for these patients ranged from 2 months to 35 years prior to the PNSCT trial with an average period of 8.4 years. The chronic areas of pain treated with PNSCT consisted of intractable headaches and pain involving the neck, mid back, low back, and abdominal areas with one patient suffering from acute post herpetic neuralgia involving the right thorax region. Three patients suffered from purely neuropathic pain, 5 solely had nociceptive pain, and the remaining 10 patients had mixed pain. Fourteen of the 18 patients had used a TENS unit(s) during their course of treatment prior to PNSCT and none of them had received any significant pain relief. Eight patients had a history of having undergone one or more surgical spine procedures collectively including a lumbar IDET procedure (1), one lumbar laminectomy/discectomy (2), more than one lumbar laminectomy/discectomy (2), one lumbar fusion (3), more than one lumbar fusion (3), and a thoracic kyphoplasty (1). Another patient had history of gastric bypass, laparoscopy, cholecystectomy, and lysis of adhesions. The follow-up time post PNS surgical implantation for these patients ranged from 5 weeks to 6 months with an average time of 3 months.

Outcome Data

All 18 consecutive participants experienced cross talk stimulation that covered their entire area of pain. None of the patients during the PNSCT trial had any difficulty with tolerating the cross talk. They continued to experience cross talk stimulation without any issues regarding stimulation tolerability. Fourteen of the 18 surgically implanted patients had TENS unit therapy at some point in the care prior to their PNSCT trial and implantation. All 14 of those patients failed to benefit from TENS therapy but responded to PNS cross talk and experienced better pain relief with PNS cross talk compared to PNS lead stimulation without cross talk.

Different montage sequences were used for the implanted patients to create PNS cross talk (Fig. 7). The leads for the PNSCT were positioned apart and parallel to one another either in a vertical or horizontal position with the exception of patient 22 where the horizontal lead crossed over and was perpendicular to the vertical lead (Fig. 3B). The inter-lead distance varied from 5.5 cm to 34.25 cm with an average distance of 19.2 cm. The diagonal inter-lead distance spanned from 5.5 cm to 38.4 cm with a mean distance of 20.9 cm. The cross sectional area of stimulation created by PNSCT ranged from 13.5 cm^2 to 377.2 cm^2 with a mean area of 114 cm^2.

All 18 patients experienced a reduction in their NRS pain scores from PNS cross talk. The NRS pain level for the 18 patients prior to implantation varied from 10 to 7 with an average intensity level of 9.1 and a standard deviation of 1.05 (Fig. 8A). The NRS pain level after implantation varied from 0 to 3 with an average of 1.2 and a standard deviation of 1.03 (Fig. 8A). There was a statistically significant 7.9 point reduction in the mean NRS pain score after PNS implantation with cross talk

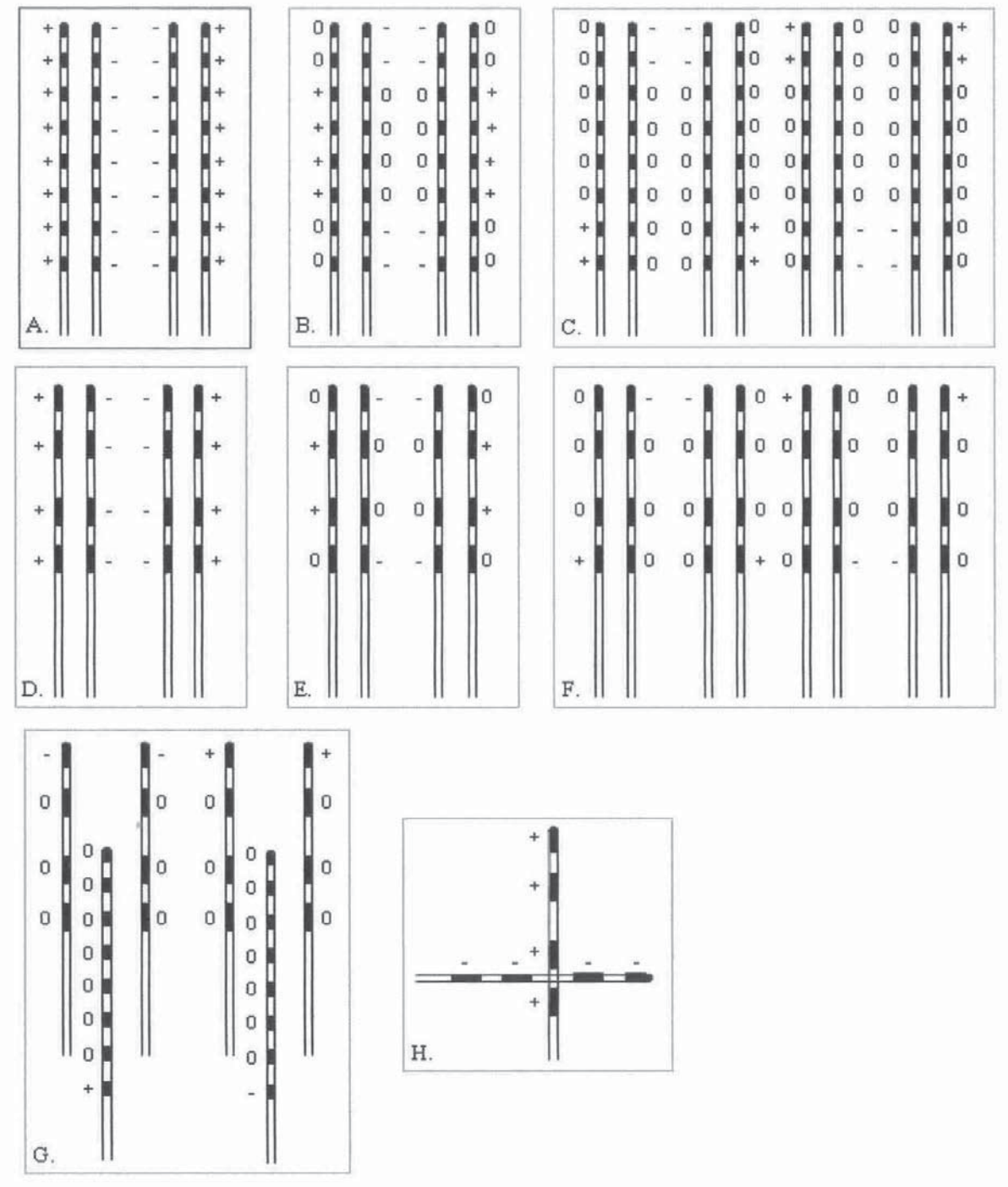
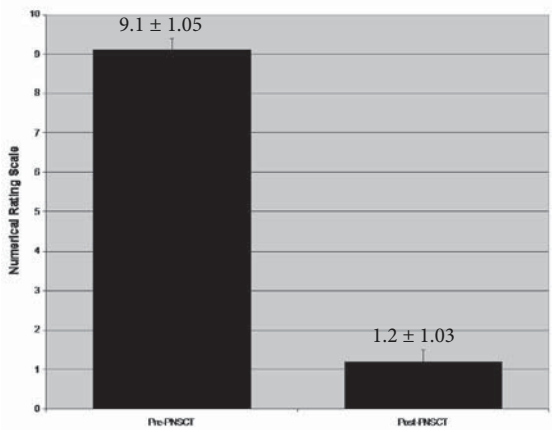
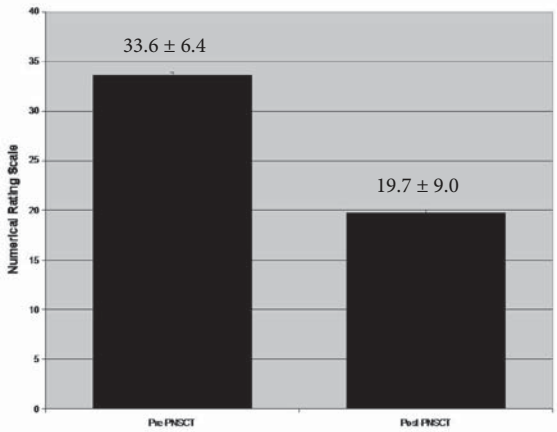


Fig. 7. *PNSCT stimulation montages for the 18 patients that underwent implantation labeled from A to H which correlate with Table 3 where the montages are listed for each implanted patient.*



A. NSR mean pain level for all 18 patients prior to and after PNSCT implantation.



B. ODI mean level for a subset of patients with chronic low back pain prior to and after PNSCT implantation.

Fig 8. *Illustration of outcome parameters.*

(two-tailed *P* value < 0.0001). Ten of the implanted patients (56%) experienced pain levels of 1 or less, and 16 of the patients (89%) had pain levels of 2 or less in the painful areas targeted by PNS cross talk. Pain medication usage dropped in all 18 patients with 7 of the 18 (39%) no longer taking any pain medication at all for their pain targeted by PNSCT and 2 of the 7 not taking any pain medication at all. Eight of the 18 patients (44%) were taking 50% or less pain medication for their pain treated by PNSCT. Three patients either stopped or reduced their breakthrough pain medication.

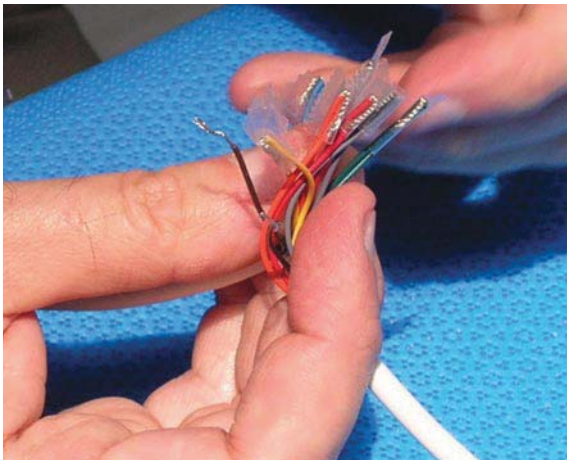
All 18 patients experienced some level of functional improvement. Only 2 of the 18 patients had one area of chronic pain that was treated with PNSCT whereas the other 16 were implanted to treat the most significant of several areas of chronic pain. Therefore, the other 16 still continued to have chronic pain at some level. Nevertheless, overall every patient did improve functionally.

There were 7 patients with chronic low back pain who completed the ODI prior to and after the PNS implantation. The ODI prior to PNSCT for the 7 patients ranged from 28 to 44 with an average of 33.6 and a standard deviation of 6.4 (Fig. 8B). The ODI after implantation varied from 5 to 32 with an average of 19.7 and a standard deviation of 9.0.

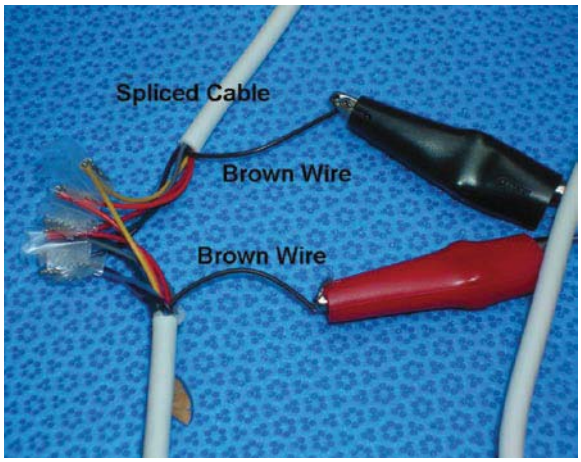
Adverse Events

There were 3 patients that experienced lead migration after implantation which required revisions. One patient underwent a PNS implant for treatment of chronic abdominal pain and the battery would flip over within the abdominal subcutaneous pocket. She in turn would manipulate the battery when she changed her stimulation patterns. This led to a "fishing rod" effect wherein the PNS lead was "reeled" into the pocket. Despite the fact that one PNS lead was "wound up" within the pocket, she continued to experience cross talk with effective control of her abdominal pain. The revision in her case consisted of securing the battery in the pocket to prevent if from flipping and the PNS lead in the pocket was left alone. She continued to experience good abdominal pain relief from the cross talk after the revision. The patient experienced a burning sensation from the left lumbar PNS lead but otherwise continued to have complete low back pain relief from the PNSCT. The left PNS lead was repositioned deeper in the subcutaneous tissues and the burning resolved allowing her to wean off all of her pain medications. She continued to get great pain relief from the cross talk.

Another patient was implanted with a PNS system for treatment of her thoracic pain from a T8 compression fracture that did not benefit from a kyphoplasty procedure. She had a great response to the cross talk with good pain relief. Unfortunately the top transverse lead migrated and the proximal electrode ended up within the titanium anchor (Cinch Anchor, St. Jude Medical Neuromodulation Division) and when the PNS system was in use this led to a severe painful electrical



A. Spliced colored wires for individual PNS lead electrodes.



B. Spliced brown wire (electrode 5) attached to the variable resistance box via alligator clip wires

Fig. 9. *Illustration of splitting wires for saline experiment.*

sensation. There were no side effects from the shocks other than the severe pain. The PNS lead was repositioned and the titanium anchor was replaced with a traditional silicone long anchor (St. Jude Medical Neuromodulation Division) and thereafter the patient did well with good pain relief.

Saline and Cadaveric Study

The results from the saline study were based on the experiment conducted in the following manner. The resistance box was first calibrated for accuracy. The 8 electrodes for each PNS lead and their corresponding colored wire was identified on the basis of conductivity using the digital multimeter (Table 2). One of the trial connector cables was spliced in order to expose and also splice the colored wires for the 8 electrodes (Fig. 9A). The spliced brown wire (electrode 5) was chosen at random and the ends were attached to the variable resistance box via alligator clip wires (Fig. 9B). Electrode 5 from both of the PNS leads was used for stimulation with one designated as a cathode and the other as an anode. The current measured within the brown wire reflects the current flowing at any point throughout the PNS electrical circuit. The wires from the oscilloscope voltmeter were attached to the resistance box in order to measure any voltage drop across the resistance box. The 2 PNS octrode leads were then attached to the portable PNS programmer/battery source with individual trial cable connectors (one of which was the spliced cable) and the leads were separated from each other and placed into the basin containing saline solution.

Table 2. *The eight electrodes for each PNS lead and corresponding colored wire listed in order from distal to proximal electrode.*

PNS Lead Electrode	Wire Color
1	purple
2	gray
3	red
4	blue
5	brown
6	green
7	orange
8	yellow

The PNS programmer was then turned on and the fifth electrode of the PNS lead connected to the spliced cable was designated as an anode (positive polarity) and the fifth electrode of the other PNS lead as a cathode (negative polarity). The current was set at 1.6 milliamperes with a frequency of 30 hertz and a pulse width of 500 milliseconds using the programmer. The resistance from the resistance box was set at 1,000 ohms. Then, the voltmeter was turned on to determine whether or not there was a measurable voltage. The

existence of a voltage drop across the measured segment would undeniably confirm the existence of an electrical circuit based on Ohm's law. When the voltmeter was turned on it did record a voltage drop of 1.6 volts thus establishing the existence of an electrical circuit. The validation of an electrical current within this experimental PNS system verified that current was flowing within the entire circuit including from one PNS lead to the other and therefore confirmed that there definitely was cross talk between the PNS leads in the saline solution.

Next, the actual current flowing through the circuit was calculated using Ohm's law from the measured voltage and resistance set by the resistance box (Fig. 10). The calculated current (the actual current within the PNS electrical circuit) was also the same as the displayed current on the programmer. This confirmed that the delivered current was accurately reflected by the programmer. Lastly, the total resistance (impedance) was measured using the programmer which was determined to be 1,070 ohms. Therefore, the resistance of the saline solution was 70 ohms since the resistance box was set at 1,000 ohms (Fig. 10).

The cadaver study was conducted in the same manner as in the saline study. A fresh frozen human cadaver was used during this part of the study in order to simulate the subcutaneous fat environment where the PNS leads were placed for the trial and implantation portions of the prospective observational study. The same set up was used in the cadaver study that was used in the saline study with the octrode PNS

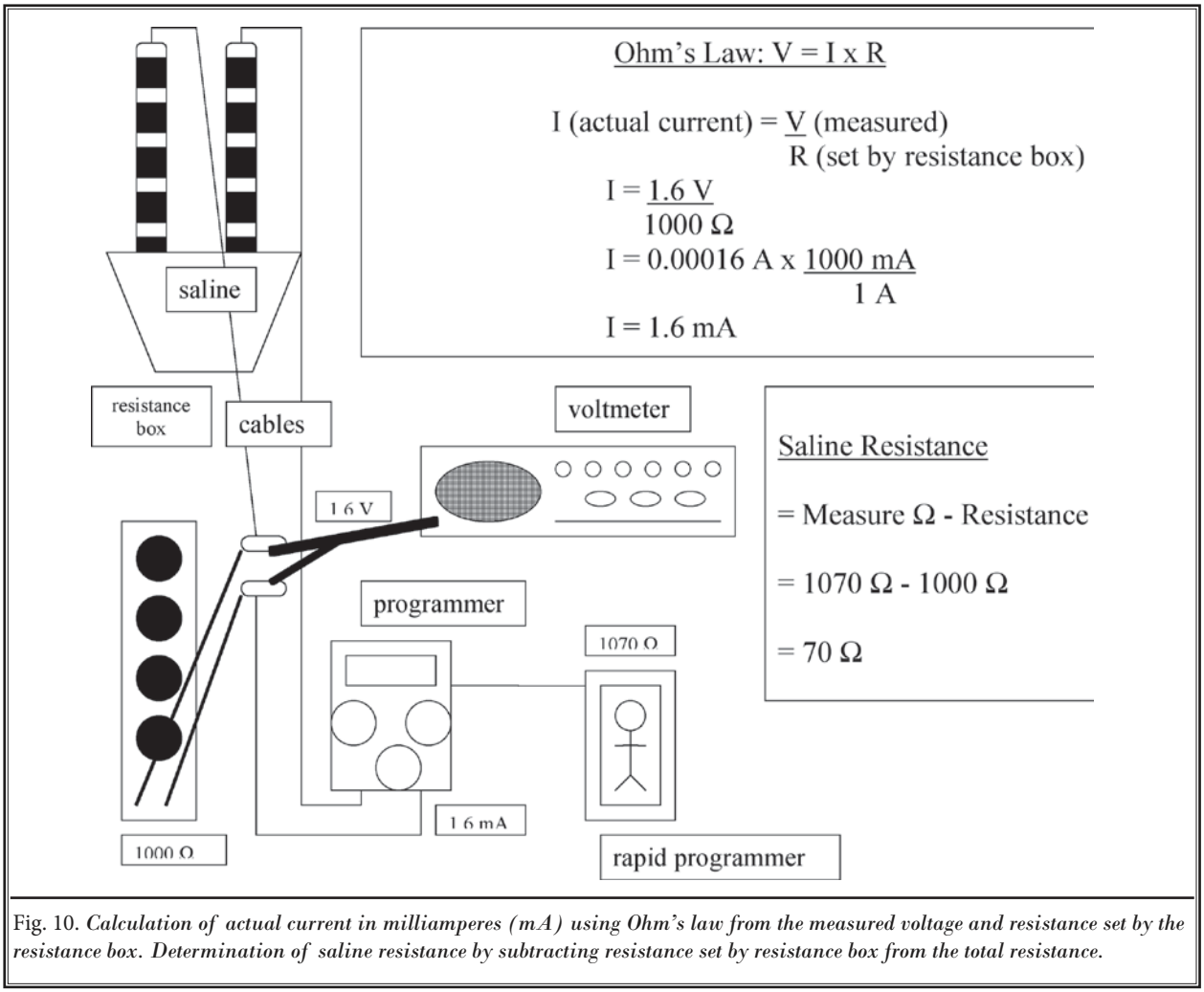


Fig. 10. *Calculation of actual current in milliamperes (mA) using Ohm's law from the measured voltage and resistance set by the resistance box. Determination of saline resistance by subtracting resistance set by resistance box from the total resistance.*

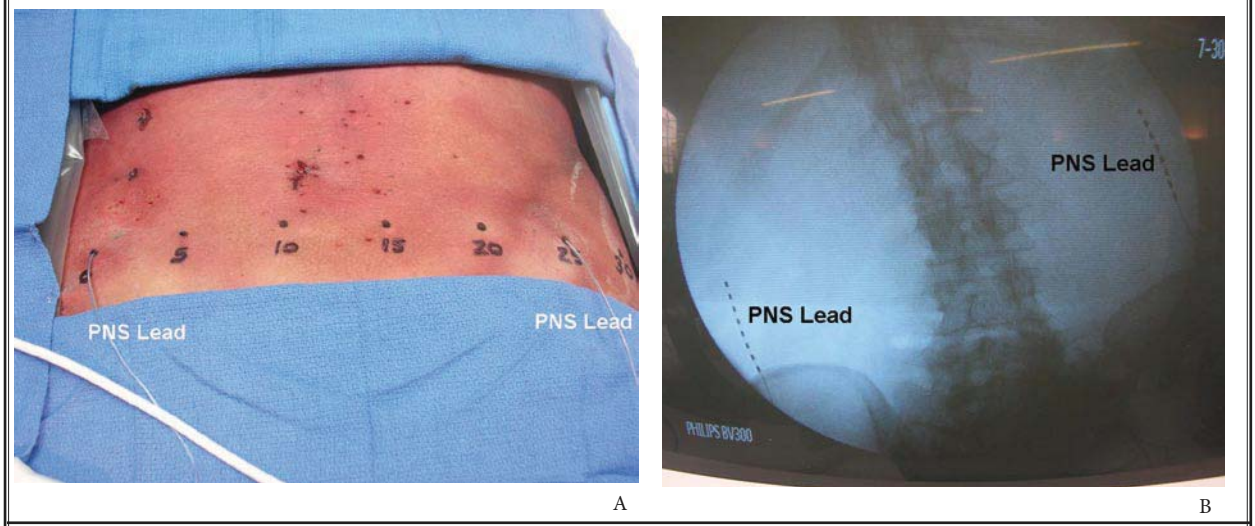


Fig. 11. *Cadaveric experiment PNS lead placement. A. PNS leads placed into the subcutaneous layer of cadaver at a distance of 25 centimeters. B. Fluoroscopic visualization PNS leads in cadaver.*

leads now positioned in the lumbar spine area within the subcutaneous fat layer. The PNS leads were thoroughly rinsed with water and wiped dry prior to being placed into the cadaver to remove any salt residue from the saline study. The PNS leads were placed into the subcutaneous layer of the cadaver under fluoroscopic visualization parallel to one another and at an inter-lead distance of 25 centimeters (Fig. 11).

The programmer was turned on using the same fifth electrode of each PNS lead with the same polarity as in the saline study. The current was set at 2.2 milliamperes with a frequency of 30 hertz and a pulse width of 500 milliseconds using the programmer. The resistance from the resistance box was set at 1,000 ohms. The voltmeter was turned on and a voltage drop of 2.2 volts was observed which established the existence of an electrical circuit within the cadaver. This observation of the voltage drop undeniably established the existence of an electrical circuit within the PNS system based on Ohm's law and therefore verified that current was indeed flowing within the entire circuit including from one PNS lead to the other. This result confirmed that there definitely was cross talk, electrical communication, and therefore stimulation between the PNS leads within the subcutaneous fat layer of the cadaver. The total resistance measured by the programmer was 4,531 ohms making the subcutaneous fat resistance 3,531 ohms (Fig. 12).

The PNS leads were programmed so that the fifth electrode polarities alternated simultaneous to create alternating current from one lead to the other. The same voltage drop was seen with the alternating current that was seen with the direct current.

The polarity of the fifth electrode in both PNS leads was changed to designate an anode in both PNS leads and later changed to a cathode in both leads. As expected, the measured voltage drop was zero in both scenarios indicating the lack of any current and therefore no electrical circuit.

Discussion

This study is the first of its kind that we are aware of that has demonstrated the clinical application of cross talk with peripheral nerve stimulation and, as opposed to traditional PNS use, that it can be used for the treatment of large painful areas. In addition, this paper has validated through scientific testing that cross talk does exist and therefore confirms the clinical results.

The 2 major findings in this study were that all 28 participants during the trial period and all those who were implanted after the trial period experienced cross talk (electrical stimulation between the PNS leads regardless of how large the area of pain), and that the existence of cross talk was verified through cadaveric experimentation. In addition, all 18 patients

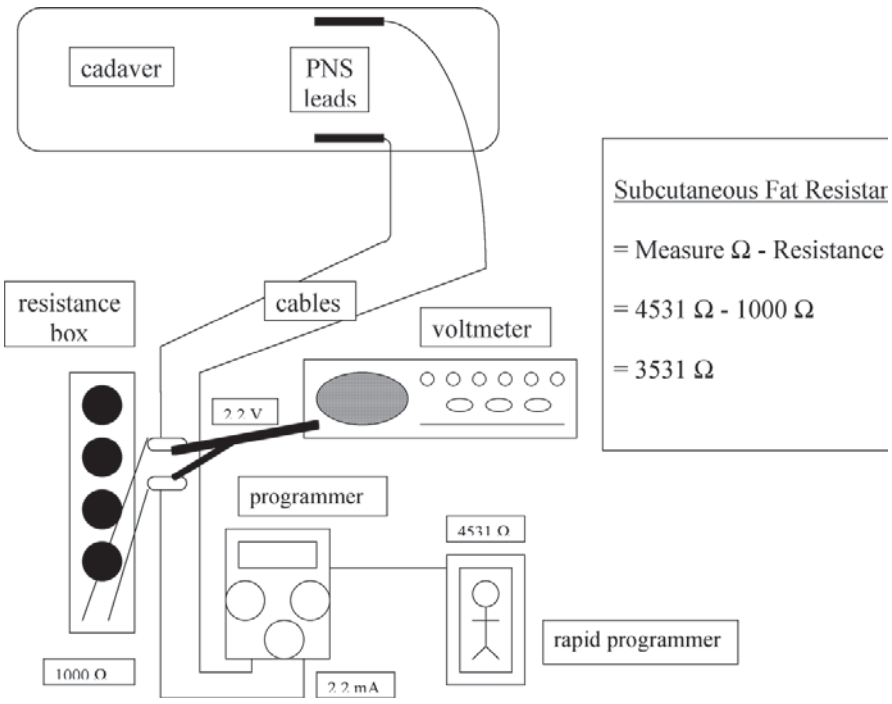


Fig. 12. *Determination of cadaveric subcutaneous fat resistance by subtracting resistance set by resistance box from the total resistance.*

that underwent PNS implantation continued to experience cross talk stimulation and pain relief regardless of age, gender, pain duration, pain type (nociceptive versus neuropathic versus mixed), pain location, size of pain distribution, or previous treatment whether conservative or surgical. Large areas of pain including axial low back pain were treated with PNSCT cross talk. All patients were able to reduce the use of their pain medications to some degree that varied from reducing breakthrough medication to stopping of all of their pain medications. Implanted patients experienced a statistically significant reduction in their pain measured by the NRS. A subset of low back pain patients who completed the ODI Questionnaire had a statistically significant improvement in function where they either dropped to lower levels of disability by category or within the same category of disability. All the patients provided statements reflecting functional improvement to one degree or another.

Previous authors and industrial engineers have opined that it is impossible for cross talk to work. That the effects of cross talk are due to larger overlapping fields of stimulation generated by bipolar intra-lead stimulation where there is no communication between the leads. This is just not the case. By making one entire lead an anode and the other lead a cathode (with single or multiple electrodes), it is impossible to have an intra-lead electrical circuit, i.e. an electrical circuit within each lead. Therefore, the anions (electrons) have no option but to flow from one lead (the cathode (negatively charged electrode) [repels anions {electrons (negatively charged particles)}]) to the other lead (anode (positively charged electrode) [attracts anions {electrons}]), that creates an electrical circuit resulting in clinical stimulation between the leads, i.e. cross talk. This was confirmed during the cadaveric study.

There is no flow of anions (electrons) within the same lead without a cathode and an anode. In fact, trying to program a single PNS or SCS lead without a cathode and anode will lead to an error reading due to the lack of a complete circuit and no stimulation. The same is true for inter-lead cross talk. If one lead is programmed as a cathode or an anode in an attempt to create cross talk without the other lead having the opposite polarity this too will lead to an error reading

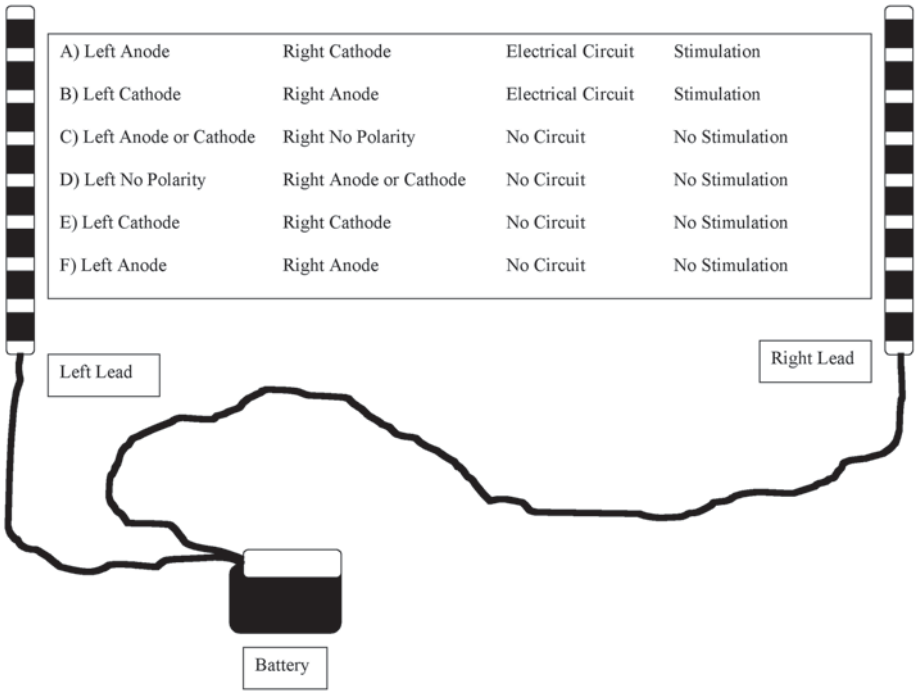


Fig. 13. *PNSCT inter-lead programming scenarios that will and will not create a complete circuit and subsequent stimulation.*

and no stimulation due to the lack of a complete circuit (Fig. 13). This too was confirmed by the cadaveric study. In addition, there would be no electrical circuit and therefore no stimulation or cross talk if one of the PNS leads has no designated polarity regardless of the polarity of the other lead.

The inter-lead stimulation montages presented in Fig. 17 are variations of having one cathode and one anode in 2 lead implants and at least one cathode and one anode in 3 lead implants. The variations in the number of cathodes (negative electrodes) in one lead and anodes (positive electrodes) in the other lead will clinically create different resultant stimulation vectors that influence the direction and magnitude of stimulation. This provides for flexibility in programming inter-lead stimulation (cross talk) when it is necessary to "steer" and modify the intensity of the stimulation in order to achieve the optimal degree of pain relief.

The fact that patients experience stimulation across the entire region of pain from one lead to the other with the different types of PNS cathode to anode lead montages is consistent with the findings from the cadaveric study that confirmed that there is cross talk, i.e. an inter-lead circuit from one lead to the other. The stimulation sensation (the generated stimulation field) associated with PNSCT travels from the anode (positively charged electrode) in one lead to the cathode (negatively charged electrode) in the other PNS lead (Fig. 14) that is opposite to the flow of electrons from the cathode (negatively charged electrode) to the anode (positive charged electron) in opposite leads. To bring "balance" to this stimulation sensation, simultaneous stimulation sets (different lead montages) are programmed wherein the PNS leads switch polarity from anode to cathode configurations and create overlapping and opposite directions of stimulation (alternating current) such that the patient will experience a homogenous distribution of stimulation in the area between the leads that is even and comfortable. Patients have consistently commented that this method of stimulation provides better pain relief than single direction (direct current) inter-lead stimulation.

The subcutaneous fat is the medium in which PNS leads are implanted and where the inter-lead

stimulation, cross talk, takes place. Although fat is a poor conductor of electricity, conduction does take place within fat and it is 100 to 1,000 times more conductive than skin but a factor of 7 times slower than muscle (33).The placement of PNS leads subcutaneously within the fat layer provides a greater conductive medium than skin but slower than muscle. The cadaveric testing in this study proved that an electrical circuit and thus electrical stimulation can be and is created with subcutaneous fat despite the high resistance of fat and with PNS leads separated from each other by a significant distance. This also was observed during the clinical aspect of this study where large distances and areas of the body were subjected to PNSCT with stimulation created within the subcutaneous fat layer.

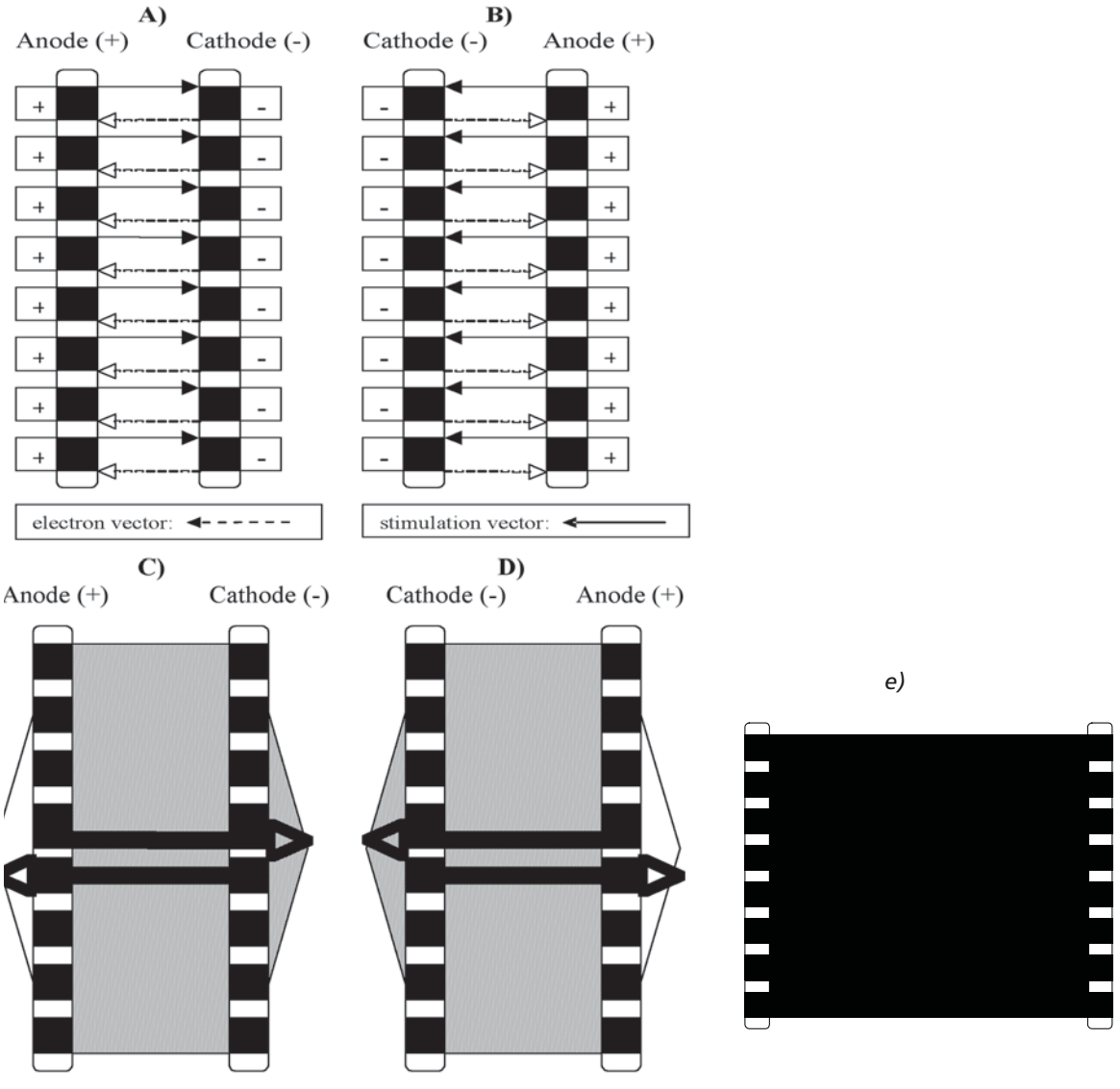


Fig. 4. *PNSCT alternating current stimulation through simultaneous stimulation sets to produce inter-lead cross talk stimulation between PNS leads. A. PNS cathode to anode individual electron and anode to cathode stimulation vectors. B. Reversal of PNS cathode to anode individual electron and anode to cathode stimulation vectors. C. PNS cathode to anode resultant electron and anode to cathode stimulation vectors. D. Reversal of PNS cathode to anode resultant electron and anode to cathode stimulation vectors. E. PNS inter-lead (cross talk) stimulation.*

In the cadaveric testing direct current was used to create the circuit between the PNS leads. The ability to cross talk might be enhanced due to the creation of an alternating current with simultaneous stimulation sets. One parameter associated with alternating current is impedance. The impedance of a substance is the resistance to electricity that is dependant on the frequency such that the resistance is changed according to the frequency (33). We have noticed during the clinical aspect of this study that using a lower frequency enhances the inter-lead cross talk stimulation which again might possibly be due to a drop in resistance to stimulation at the lower frequency. This possible explanation for the mechanism of action could also explain PNS cross talk across more than one stimulation medium. For example, inter-lead stimulation was accomplished between 2 subcutaneous lumbar leads and one sacral canal lead in patient 4 where he felt stimulation within the boundaries of the implanted 3 leads.

Another significant observation in this study with PNSCT is the vast topographical area of pain that can be stimulated with this technique. The largest area of stimulation with PNS cross talk in this study was 377.2 cm^2 equivalent to 78.1 square inches (Fig. 3A). Our experience has been thus far that we have not encountered at this point in time an area of pain that cannot be covered with PNSCT.

The complexity of inter-lead stimulation associated with PNS cross talk distinguishes it from TENS unit therapy. PNSCT is capable of bypassing skin resistance, utilizes alternating current, and can cover large areas of continuous stimulation. These characteristics along with the significant pain relief experienced by all of the PNSCT patients who failed to benefit from TENS units, sets PNSCT apart from TENS unit therapy as a unique and different treatment modality.

This study also demonstrates that PNSCT might be an answer to the "Achilles heel" of spinal cord stimulation (SCS) which is its inability to either treat axial pain or sustain axial pain relief over time. PNSCT can complement SCS when low back pain coverage is difficult to obtain or recedes over time with SCS.

PNSCT was able to cover large areas of pain, and also provided significant pain relief with the reduction of pain medications and improvement in patient function. There was a significant reduction in disability in the subset of patients with back pain assessed by the ODI Questionnaire. More then half decreased their level of disability by one category and the others made significant progress with their category of disability. These outcomes are similar to other studies in Interventional Pain Management (33-43).

Although we now know that cross talk exists with PNS between 2 subcutaneously placed PNS leads by means of creating an electrical circuit, what we don't know is how it generates a neuromodulation effect on pain. There might be a modulation effect during the transmission phase of the pain pathway at the dorsal horn by stimulating the peripheral myelinated mechanical, vibratory, or postural receptors along the lines of the gate control theory (22). Or, pain relief from PNSCT might be due to the prevention of PNS from the stimulation effect that covers larger areas of pain that modify or prevent the release of neuropeptides from injured nerves to nearby nerves during the transduction phase of the pain pathway (22). These are only speculations as to the mechanism of action for PNSCT which as in case of SCS and PNS are not fully understood at this time.

There were several limitations of this study. First there was a small sample size of only 18 patients that were implanted to assess outcome measures. That being said the small number of patients does not refute the results of certain outcome measures. Namely, the existence of cross talk, the distance and area of stimulation accomplished with PNSCT, the statistically significant reduction in pain, and the statistically significant functional improvement in the subset of patients measured by the ODI Questionnaire. The small number of patients in this study has no bearing on the results of the cadaveric experiment that validated the existence of cross talk. The lack of a larger patient population does limit the power of the results due to such a small number.

The last limitation of this study was the short follow-up period that extended out to 6 months with an average of 3 months. This certainly has no bearing on the fact that PNS cross talk does exist and provides pain coverage over large areas of pain, but does raise several issues. Will PNSCT continue to provide stimulation over longer periods of time? Will PNSCT stimulation coverage diminish or recede over time? Will the PNSCT inter-lead stimulation continue? Will the degree of pain relief and functional improvement from PNSCT last? These are all important questions that will need to be answered to determine whether or not PNSCT will provide long-term results or not and if PNSCT is a pain relieving modality of merit that will perform over the passage of time.

The results of this observational and cadaveric study are profound in a number of ways. The study is important in that it now establishes without any doubt that PNSCT does exist which was confirmed in the cadaveric experiment. This confirmation validates the clinical observations of PNSCT within the patients in this study. Despite the limitations of this study the clinical results are certainly encouraging for PNSCT in that this application of PNS provides stimulation over large areas of pain that either cannot be covered by SCS or recedes over time with SCS. This study also demonstrates that PNSCT can provide significant pain relief in patients who have otherwise failed all other forms of treatment, including surgery; reduce or eliminate the need for pain medications; and increase functional activity. These observations regarding clinical improvement with PNSCT should be interpreted with caution due to the small sample size and short-term follow up. Lastly, this study shows that PNSCT is not a panacea for the treatment of regional or axial pain. Not everyone responded to the trial even though they all experienced cross talk stimulation. This again underscores the importance of trialing patients for PNSCT just like SCS before making a decision on whether or not to proceed with implantation.

Conclusion

This study demonstrates and documents that PNS cross talk — the creation of an electrical circuit with inter-lead communication and therefore stimulation from one lead to another despite large distances between them — exists and provides relief of a variety of pain disorders. The results of this study are very encouraging for the treatment of chronic regional and axial pain. Nevertheless, PNS with or without cross talk at this point in time should not be considered as a first line therapy for chronic pain. Rather, it should be reserved for those patients that have failed conventional care both conservative and surgical or in those where surgery is not an option after the failure of other therapeutic options.

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