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A Multicenter, Prospective Trial to Assess the Safety and Performance of the Spinal Modulation Dorsal Root Ganglion Neurostimulator System in the Treatment of Chronic Pain

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Objectives: This multicenter prospective trial was conducted to evaluate the clinical performance of a new neurostimulation system designed to treat chronic pain through the electrical neuromodulation of the dorsal root ganglia (DRG) neurophysiologically associated with painful regions of the limbs and/or trunk.

Materials and Methods: Thirty-two subjects were implanted with a novel neuromodulation device. Pain ratings during stimulation were followed up to six months and compared with baseline ratings. Subjects also completed two separate reversal periods in which stimulation was briefly stopped in order to establish the effects of the intervention.

Results: At all assessments, more than half of subjects reported pain relief of 50% or better. At six months postimplant, average overall pain ratings were 58% lower than baseline ($p < 0.001$), and the proportions of subjects experiencing 50% or more reduction in pain specific to back, leg, and foot regions were 57%, 70%, and 89%, respectively. When stimulation was discontinued for a short time, pain returned to baseline levels. Discrete coverage of hard-to-treat areas was obtained across a variety of anatomical pain distributions. Paresthesia intensity remained stable over time and there was no significant difference in the paresthesia intensity perceived during different body postures/positions (standing up vs. lying down).

Conclusions: Results of this clinical trial demonstrate that neurostimulation of the DRG is a viable neuromodulatory technique for the treatment of chronic pain. Additionally, the capture of discrete painful areas such as the feet combined with stable paresthesia intensities across body positions suggest that this stimulation modality may allow more selective targeting of painful areas and reduce unwanted side-effects observed in traditional spinal cord stimulation (SCS).

Keywords: Chronic pain, dorsal root ganglion (DRG), neuromodulation, spinal cord stimulation (SCS), visual analog scale (VAS)

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Conflict of Interest: Jeff Kramer is an employee of Spinal Modulation, Inc. Liong Liem is a consultant for Philips, Spinal Modulation, St. Jude, Boston Scientific, and Medtronic. Marc Russo is a consultant for Medtronic, St. Jude Medical, Boston Scientific, Nevro Corp., and Mainstay Medical Inc. He has also received teaching honoraria from Medtronic, St. Jude, Boston Scientific, and Nevro Corp. Frank J.P.M. Huygen is a consultant for Spinal Modulation and Grunenthal. He has also received an investigator-initiated study grant from St. Jude Medical. Jean-Pierre Van Buyten is a consultant for Nevro Corp., Medtronic, Mainstay Medical Inc., and Spinal Modulation. Iris Smet is a consultant for Nevro Corp., Medtronic, Mainstay Medical Inc., and Spinal Modulation. Paul Verrills is a consultant and peer-to-peer teacher for Boston Scientific, St. Jude Medical, Medtronic, Spinal Modulation, and Nevro Corp. Robert Levy is a consultant for Bioness Inc., Nevro Corp., Medtronic, Inc., Spinal Modulation, Inc., St. Jude Medical, and Vertos, Inc. He also owns stock options from Bioness, Inc.; Nevro Corp.; Spinal Modulation, Inc.; and Vertos, Inc. Timothy Deer is a consultant for Bioness Inc., St. Jude Medical, Medtronic, Spinal Modulation, and Nevro Corp.

INTRODUCTION

Electricity has been used for the neuromodulation of pain pathways for over a century (1). In the 1960s, development of the gate control theory and pioneering clinical work in spinal cord stimulation (SCS) ushered in the current era of neurostimulation as an accepted pain-treatment modality, particularly for chronic neuropathic pain in which more traditional options often prove ineffective (2,3). Neurostimulation can offer relief for intractable pain conditions which may otherwise negatively impact quality of life and participation in community and social roles, and take a heavy economic toll both in healthcare costs as well as lost productivity (4,5).

SCS is a thoroughly tested and well-described neurostimulation technology; its usage has grown rapidly in the past 40 years and over 27,000 SCS devices are implanted per year in the United States alone (6). Several recent systematic reviews have shown that it is a relatively safe and often an effective treatment option for patients suffering from chronic, intractable pain (7–9). In the largest prospective trial published to date, SCS was found to significantly reduce lower limb pain associated with failed back surgery syndrome (FBSS) relative to a conventional medical management control group over an extended time period (10,11). Similarly, SCS can be effective in the treatment of complex regional pain syndrome (CRPS) (12–14).

Despite its clinical utility for some patients, SCS therapy carries limitations. Twenty percent of subjects trialing an SCS system do not proceed beyond the trial stimulation (15). Overall, the treatment has been found to be a successful long-term solution in approximately 50% of patients that have a successful temporary trial stimulation (7,11,15,16). Failures may be due to difficulty in programming the device to align the stimulation-associated paresthesias with the painful areas of the body, inability to derive the correct combination of pulse width, frequency, and amplitude of the electrical waveform needed to address the individual's pain, or due to device issues such as lead migration. SCS can also be vulnerable to positional or postural effects in which the intensity or location of paresthesias may change when the subject changes his/her body position such as moving from lying to sitting (17). This change is due to shifts in the relative distance between the stimulating electrodes and the dorsal columns through the effects of gravity or physical forces due to epidural lead placement in the highly mobile spine (7,18,19). Additionally, some patients may not tolerate the pins-and-needles sensation of the paresthesias associated with SCS, particularly if these are extraneous and located in nonpainful areas of the body (20). These issues suggest that alternative neuromodulation techniques or targets should be investigated to allow the implanting physician to more properly address challenging pain presentations.

Housed within the bony structure of the bilateral vertebral foramen of each spinal level is the neural structure of the dorsal root ganglion (DRG), a cluster of primary sensory neuron somata enclosed in the dural sheath. These cells transmit sensory information, including nociceptive signals, from distal locations in the body to the dorsal columns of the spinal cord and thence to the rest of the central nervous system (21). Previous reports have implicated the DRG in the development and maintenance of chronic pain (22,23). In animal models, several pathophysiologic changes in the DRG occur, including altered electrophysiological membrane properties (24), changes in the expression of integral membrane proteins (25), and altered gene expression (26). These changes may explain how the DRG can significantly contribute to chronic pain states (22).

In addition to the putative clinical value of DRG stimulation for long-term pain relief, it is possible that this modality may address the issues that make SCS untenable for some patients. Further, because the DRG is encased in bony vertebral structures, it may be possible to mitigate the over- or understimulation artifacts that some SCS patients report occur with certain movements or postures. The relative immobility of the bony vertebral structures surrounding the DRG may also provide some defense against lead migration. The cerebrospinal fluid (CSF) layer interposing the DRG and the lead is smaller than that between the spinal cord and the lead in dorsal column stimulation, and the stimulation targets are presumably located less deep than dorsal column fibers; together, this suggests that the energy requirements of a DRG stimulator will be lower than that of traditional SCS systems (27). The proximity of the leads to the DRG and the lack of CSF that could act as a current sink (28) may also reduce the power demands of the stimulator.

Given the success in treating various pain conditions with electrical neuromodulation techniques and the emerging role of the DRG in the development, maintenance, and treatment of chronic pain, we report on a novel stimulation system to treat chronic pain through electrical neuromodulation of the DRG. The aim of this study is to evaluate the safety and effectiveness of neuromodulation of the DRG in a prospective, open-label, single-arm, internally controlled study across seven clinical sites.

MATERIALS AND METHODS

Subjects

Subjects were recruited from investigators' practices at three European sites and four Australian sites from March 2011 through February 2012. All study elements were ethics committee approved and each subject gave written informed consent prior to beginning any study activities.

To be eligible for the study, subjects were required to be 18 years or older; be diagnosed with chronic, intractable pain in the trunk,

limbs, and/or sacral region for a minimum of six months; have a minimum baseline pain rating of 60 mm on the visual analog scale (VAS; 0 mm indicates no pain and 100 mm indicates the worst possible pain); have failed other treatment modalities (e.g., pharmacological, surgical); have stable pain medication dosage for a minimum of 30 days prior to study enrollment; and have a stable pattern of neurological symptoms.

Exclusion criteria were presence of an escalating or changing pain condition within the month prior to enrollment in the study; pain primarily within a cervical dermatomal distribution; corticosteroid therapy at the intended site of stimulation within the past 30 days; coagulation disorder; diagnosis of a malignancy; radiofrequency treatment of an intended target DRG within the past three months; existing indwelling devices (e.g., urinary catheter); and existing spinal cord stimulators, implantable cardioverter-defibrillators, or pacemakers.

Study Design

After enrollment, subjects underwent a medical history review and brief physical/neurological examination, and then completed baseline clinical assessments including VAS pain ratings for overall pain and specific anatomies (back, leg, foot), quality of life using the EQ-5D-3L (29), psychological disposition using the 30-item Brief Profile of Mood States (POMS), and the impact of pain on daily functions using the Brief Pain Inventory (BPI) through pain severity and pain interference composite scores. Pain severity is the average of worst pain in the last 24 hours, least pain in the last 24 hours, average and current pain scores. Pain interference is the average interference of seven daily functions during the past 24 hours: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

After baseline assessments, subjects were implanted with quadripolar neurostimulation leads (described next) according to standard surgical procedures. The stimulating contacts were placed near relevant DRGs according to the individual's location and distribution of pain (Fig. 1). Stimulation leads were connected to an external neurostimulator, and the device was programmed with combinations of pulse width, amplitude, and frequency that generated the best pain/paresthesia overlap. On an average, the temporary trial phase lasted 9.4 ($\pm$1.0, standard error of the mean [SEM]) days, although the protocol allowed anywhere from 3–30 days. At the end of the trial period, stimulation was discontinued until (and if) the permanent neurostimulation system was implanted.

At the end of the trial period, subjects were asked to name the percentage of pain improvement experienced (in all areas of pain and overall) as a result of neurostimulation of the DRG. Subjects who achieved 50% or greater pain relief in their primary pain area during the trial period completed preimplant pain ratings as a stimulation-off internal control and then received the fully implantable neurostimulator under standard surgical procedure; data for only these subjects were included for analysis in this study. Stimulation was initiated within 24 hours of implantation. Subjects repeated the baseline assessments at one and four weeks postimplant. After the four-week assessment, stimulation was temporarily suspended for approximately one week as another internal control; during this time, subjects had access to pain medication as well as rescue stimulation if needed. A stimulation-off pain assessment was completed at five weeks postimplant and stimulation was resumed. Clinical endpoints were again assessed at two, three, and six months postimplant, although it should be noted that three sites did not collect data for the two-month point. Adverse events were monitored throughout the study. The study design is summarized in Figure 2.

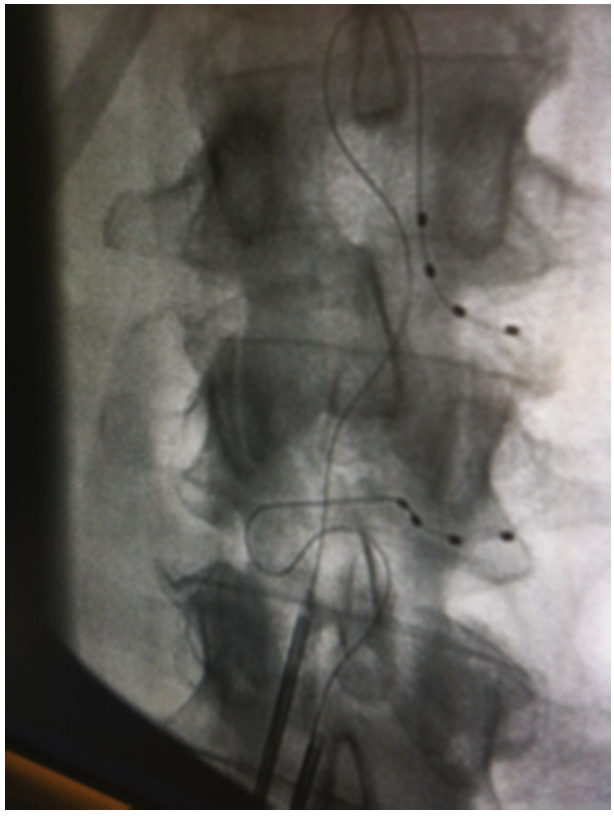

Figure 1. Fluoroscopic image of leads placed near the DRG. Notice that the second most distal contact in each lead is underneath the pedicle. DRG, dorsal root ganglia.

The primary objective of the study was to evaluate the adverse event rate and paresthesia generation, whereas the secondary objectives include pain relief as measured by VAS, quality of life as measured with the EQ-5D questionnaire, mood as measured by the POMS, and physical functioning as measured with the BPI.

Determining Paresthesia Intensity

Testing took place in the clinic at the postimplantation programming session, zero to one day after the surgical procedure. A VAS for paresthesia (0 = no feeling and 10 = very intense) was used to determine the effect of body position on stimulation intensity. Subjects were asked to stand upright and, after adjusting the amplitude of stimulation in their preferred program to a comfortable level, to rate the perceived intensity of the paresthesia. Subjects then lay supine on an examination table without changing the stimulation parameters, and again rated their paresthesia intensity. The paresthesia intensity rating scale was validated during the clinical trial. The results of the validation are currently being drafted as a separate manuscript.

Device Description and Implantation Technique

The Spinal Modulation Axium neurostimulator system is comprised of a stimulator device (an external trial neurostimulator [TNS] is used for the trial period, followed by an implanted neurostimulator [INS] if successful), up to four quadripolar percutaneous leads and wireless patient- and clinician-programmer devices. Both TNS and INS are constant voltage devices.

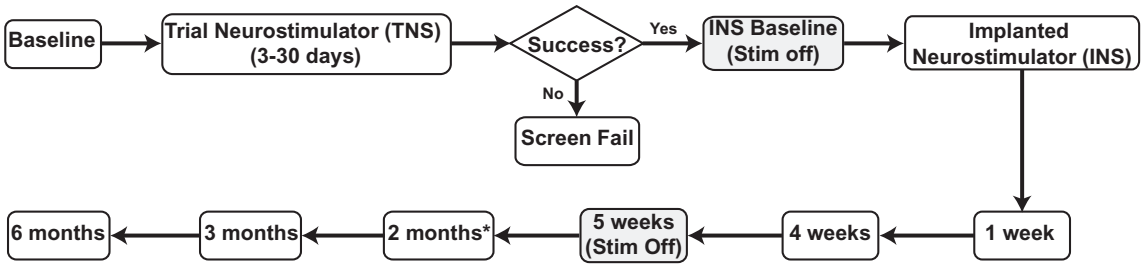

Figure 2. Schematic of the study design. *Two-month data were not collected by three sites.

Under monitored anesthesia care, leads are placed via an epidural approach, with access gained using the loss-of-resistance technique standard for this type of intervention. Leads are advanced in an anterograde fashion and then are steered into the intervertebral foramen near the DRG under fluoroscopic guidance. Appropriate lead position is determined through intraoperative device programming to confirm paresthesia overlap with the painful regions. If pain–paresthesia overlap is not achieved through programming, the leads are repositioned under fluoroscopy and programmed again. The DRG is in a consistent location anatomically, thus lead position can accurately reflect the ability to stimulate the ganglion. Also, because cell bodies are present in the ganglion and not in the nerve root, coupled with the fact that many membrane alterations occur in the parykaria of primary sensory neurons and not nerve roots, there are electrophysiological difference between these structures. In part, the ability to steer an electric field around a ganglion provides an enhanced ability to provide acute and specific sub-dermatomal coverage compared with a nerve root. And although prior investigators had tried DRG stimulation, limitations were realized in both the methodology of lead placement and also ability to provide desired stimulation therapy. The technology utilized in the current study provides differences in both the lead delivery methods and also the ability to provide stimulation to the DRG compared with the older technology utilized in prior studies. For the trial period of up to 30 days, either trial or implant leads may be used. If trial leads are used, they are removed and replaced with implant leads at the end of a successful trial. If implant leads are used, disposable lead extensions are also employed to allow the leads to remain in place at the end of the trial period. Measures intended to limit lead migration, such as strain relief loops and use of lead anchors, are used. Stimulation programming is based on patient feedback; stimulation amplitude can be adjusted by the patient at any time.

Data Management and Analysis

ISO 14155 guidelines were adhered to during data collection. Data were gathered on preprinted case report forms by site staff. Data quality and compliance with study procedures and regulatory requirements were confirmed at regular monitoring visits. Safety endpoints were expressed as the cumulative frequency of adverse events (AEs) related to the device and/or the procedure throughout the study. Clinical endpoints were analyzed using SPSS V20 (IBM, Armonk, NY, USA) through descriptive statistics and two-tailed paired *t*-tests (with the exception of the paresthesia ratings in different positions, which used unpaired *t*-tests) with significance levels set at $p = 0.05$. All data are presented as average $\pm$ SEM. With the exception of the end of the trial period, the percentage of pain relief at all time points is expressed as the mean of the subjects' baseline-to-follow-up pain reduction percentage. Hypothesis testing for pain ratings compares baseline VAS scores against scores at all follow-up time points for overall pain, and at six months postimplant for pain specific to back, legs, and feet.

This report represents a six-month interim analysis of prospective results. As with any interim analysis of an ongoing study, the later follow-up time points in this report have fewer subjects than at baseline; this artifact is not an indication of study attrition.

RESULTS

Patient Demographics and Baseline Characteristics

Of the 51 individuals screened, 39 reported greater than 50% improvement in pain relief at the end of TNS while 12 subjects failed the trial (76.5% success rate). Thirty-two subjects received the INS (women = 17, men= 15). The mean age of the men was 58.9 ($\pm$8.9) years while the women had a mean age of 46.9 ($\pm$12.5) years. All subjects had chronic pain of neuropathic origin of varying etiologies. The most common pain diagnoses were CRPS and FBSS. Subjects experienced pain located in the back, leg, and foot; many subjects experienced pain in more than one region. A number of subjects experienced pain in other diverse anatomical regions; owing to the small samples across heterogeneous locations, these "other" locations were not analyzed. The distribution of subjects across diagnoses and pain locations is listed in Table 1.

Seven of the 39 subjects with >50% pain reduction at the end of TNS did not proceed to the INS stage. Two subjects had not indicated any reason for refusing the implant. One subject's pain had not recurred since TNS and hence refused any further intervention. Another subject, with 100% pain relief in one foot but none in the other, also did not receive the INS. One subject was withdrawn by the investigator while two more subjects withdrew from the study (atrial fibrillation and infection).

Lead Placement

Surgeons used implant leads during the TNS procedure for 22 of the 32 subjects who received an INS; in the other 10 subjects, the temporary trial leads were removed and replaced with implant leads during the INS procedure. Although the neurostimulation system could accommodate up to four leads, the majority of INS subjects ($N = 21$) were implanted with two leads while five subjects were implanted with only one lead. The average stimulation settings for all the implanted leads were: pulse width—362 msec, amplitude—907 μA, and frequency—46 Hz.

Safety

A total of 70 events (9 severe adverse events [SAEs] and 61 AEs) were reported in 24 subjects. No SAEs were definitely related to the

Table 1. Breakdown of Subject Diagnoses and Painful Regions.

Diagnosis	Numbers of subjects with pain in specific regions				
	N	Back	Leg	Foot	Other regions
Complex regional pain syndrome	9	0	7	7	5
Failed back surgery syndrome	8	7	7	0	2
Postsurgery pain	5	3	2	2	4
Radicular pain	2	0	2	1	0
Lumbar stenosis	2	0	2	0	1
Disc-related pain	4	1	3	3	1
Others (peripheral nerve damage and pain after postvascular stenting)	2	0	3	1	1
Totals	32	11	26	14	14

Table 2. List of Adverse Events (AEs) and Severe Adverse Events (SAEs) with Percentage of Occurrence Listed in Parentheses.

Biologic AEs and SAEs		Device AEs and SAEs	
Description of the AE/SAE	Frequency	Description of the AE/SAE	Frequency
Infection	7 (10.0)	Uncomfortable stimulation	3 (4.1)
Cerebrospinal fluid leak or associated headache	6 (8.6)	Temporary cessation of stimulation	3 (4.1)
Inflammation	6 (8.6)		
Inadequate pain relief	4 (5.7)		
Flu-like symptoms/cough	4 (5.7)		
New injury/condition	5 (7.1)		
Temporary motor stimulation	8 (11.4)		
Other (unspecified)	8 (11.4)		

study device. SAEs include: infection (3 events in 3 subjects), CSF hygroma, loss of paresthesia coverage, prolonged hospital stay, inflammation, temporary cessation of stimulation and ataxia (1 event each). All events were resolved and no clinical sequelae were reported. Further data collection is warranted to look for any delayed onset AE. Three SAEs were possibly related to the device (37.5%) and five were not related to the device (62.5%). A relationship of one SAE to the device has not been established. The majority of the SAEs were severe (55.6%). Thirty (49.2%) of the AEs were not related to the device. Most of the AEs (45 or 73.7%) were either mild or moderate while 16 (26.2%) of the AEs were deemed severe. The most common AEs (>3% occurrence) are listed in Table 2. Two lead revisions were performed in two different subjects for the following reasons: lead migration and loss of stimulation. Five devices were explanted (due to infection: 3; lack of efficacy: 1; subject noncompliance: 1) and one device was switched off (and the subject withdrawn from the study) before the six-month follow-up period.

Effectiveness: Overall Pain

At baseline, the 32 subjects rated their overall pain as 77.6 mm (± 2.1) out of a possible 100 mm. With the TNS, the 32 subjects' average pain rating dropped to 26.1 mm (± 3.4), a 66.1% decrease and significantly lower than baseline ($p < 0.001$). Stimulation was discontinued at the end of the trial phase until the permanent neurostimulation system was implanted. During this one-week (minimum) stimulation-off period, the average pain rating rebounded to 74.0 mm (± 3.0), which was statistically indistinguishable from baseline levels ($p > 0.05$).

One week after receiving the permanent INS, the 32 subjects reported that their average overall pain was reduced to 34.9 mm (± 4.3). This represented an average 55.1% (± 5.5%) decrease from baseline ($p < 0.001$) and 50% or more pain relief for 53.1% of subjects. At four weeks postimplant, average pain was 36.6 mm (± 4.6) across 32 subjects, a decrease of 52.7% relative to baseline ($p < 0.001$). There were 62.5% of subjects that achieved 50% or better pain relief at this time point. Stimulation was temporarily suspended after the four-week assessment in order to verify intrasubject effectiveness; after a week without stimulation, subjects reported that their overall pain returned to near-baseline levels: 68.4 mm (±4.6; $p = 0.05$). Stimulation was then restored. At two months postimplant ($N = 22$), the average overall reported pain was 39.5 mm (±6.6; $p < 0.001$), which was an average of 50.7% (±8.0%) decrease from baseline pain; 59.1% of subjects reported at least 50% pain relief. At three months postimplant ($N = 30$), the average overall pain rating was 38.4 mm (±5.7; $p < 0.001$), a 50.8% (±7.0%) decrease from baseline and pain relief of 50% or more for 60.0% of subjects. At six months postimplant, 25 subjects reported pain of 33.5 mm (±6.0; $p < 0.001$), a 56.3% decrease from baseline. There were 52.0% of subjects that had 50% or better pain relief at this time point. These data are depicted in Figure 3.

Pain relief was also assessed in specific regions: the back, legs, and feet. Not all subjects had pain in all of these regions. Back pain was reduced by 16.7% relative to the back-specific baseline at one week postimplant, by 45.9% at four weeks, by 49.7% at three months, and by 58.1% at six months. Relative to the leg-specific baseline, leg pain was reduced by 69.5% at one week postimplant, 68.6% at four weeks postimplant, by 72.4% at three months, and by 69.3% at six months. For the foot, pain was reduced relative to the foot-specific baseline by 78.5% at one week postimplant, by 58.6% at four weeks, by 67.8% at three months, and by 84.5% at six months (Fig. 4). The percentage of subjects with >50% improvement in their VAS is listed in Table 3.

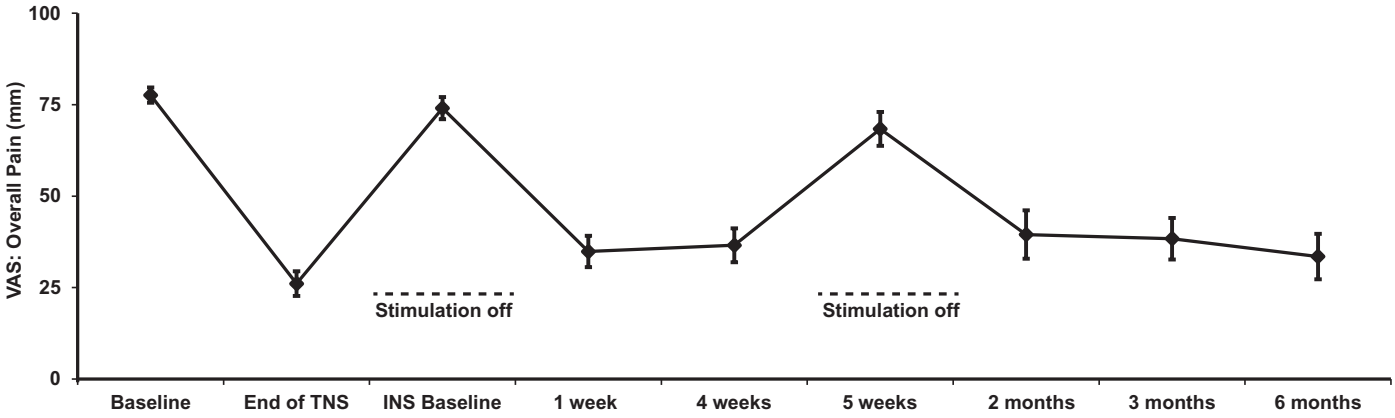

Figure 3. Overall pain ratings at baseline are reduced with DRG neurostimulation and rebound to preimplant levels when stimulation was discontinued for one-week periods. Data points represent mean ± SEM. DRG, dorsal root ganglia; SEM, standard error of the mean.

Paresthesia: Steerability and Positional Stability

Stimulation was selective and highly steerable, resulting in discrete paresthesia coverage in difficult-to-treat anatomies. Steerability of paresthesia was demonstrated through overlapping pain–paresthesia maps (see representative subject data in Fig. 5). A total of 23 subjects were assessed at six-month postimplant for stability of paresthesia intensity across body positions. Paresthesia intensity ratings were 4.0 ± 0.5 and 3.8 ± 0.5 for supine and upright positions, respectively. Paresthesia intensity ratings for the two positions were statistically indistinguishable ($p > 0.05$).

Effectiveness: Quality of Life, Mood, and Function

Change in quality of life, as measured by EQ-5D-3L VAS, was assessed on a 100-mm scale with a rating of 100 corresponding to best imaginable health. At baseline, the self-rated score was 47.0 mm (± 3.8). After one week of stimulation with the INS, the score increased to 64.1 mm (± 3.6; $p < 0.05$) (Fig. 6). The score remained significantly higher at all follow-up time points ($ps<0.05$). The number of subjects that reported problems at baseline in five different EQ-5D-3L subscales decreased significantly for mobility, usual activities, and pain-discomfort domains ($ps<0.05$) (Fig. 7a).

The combination of individual dimension scores of the EQ-5D-3L can be converted into a single index value for health status that can be used in the clinical and economic evaluation of health care (30,31). Index values were calculated based on general population valuation surveys that used time trade-off (The Netherlands) (32) or VAS (Belgium) (33) methods in the countries where the trials were conducted. Index values for the general population in Australia were not available and hence not included in the calculations. The EQ-5D index values at baseline and at six months for the subjects included in the analysis were 0.289 ± 0.054 ($N = 20$) and 0.725 ± 0.066 ($N = 15$), respectively. The increase in the index value was statistically significant ($p < 0.001$) (Fig. 7b).

Mood disturbance was self-reported with the POMS. Mean ratings on the tension, vigor, and fatigue subscales, as well as the total mood disturbance score, were statistically significantly improved at six months relative to baseline ($ps<0.05$; Table 4).

Pain interference (average of seven domains) as described by the BPI improved from 6.6 (±0.4) at baseline to 4.1 (±0.5) ($p < 0.001$), and maintained this level through six months postimplant, when the average rating was 3.8 (± 0.6; $p < 0.001$). Pain severity (composite score) was rated at 6.9 (±0.2) at baseline. At one week postimplant, pain severity decreased to 4.3 (±0.4; $p < 0.001$). This reduction in pain was maintained through six months postimplant, when the average pain severity was 3.9 (± 0.6) at ($p < 0.001$; Table 5).

DISCUSSION

A prospective, open-label clinical trial with an internally controlled reversal design was conducted across seven clinical sites to characterize the performance of a neurostimulation system designed for stimulation of the DRG for management of chronic pain. Conjectural differentiators of the DRG neurostimulation system relative to traditional SCS systems include selective stimulation or paresthesia coverage in the dermatomes, lack of postural effects, ability to drive paresthesia to areas that are typically difficult to treat using SCS (e.g., foot), and lower therapeutic power demands. The device demonstrated physical stability with lead migration of 3% (2 leads out of 67), which is well below the rate of migration for SCS with percutaneous leads placed over the dorsal columns, which have been reported at 13.2% in a literature review of 51 studies (7), and at 23% in a prospective study of implant techniques and reprogramming compared against radiographic evidence (34). Similar to previously reported values (7,35), one subject reported uncomfortable stimulation, a usually transitory issue associated with developing an effective program for the individual. However, it should be noted that other neuromodulation systems using dorsal column stimulation elicited uncomfortable paresthesias, which could presume some dorsal root/DRG involvement (36).

At all active stimulation time points through six months postimplantation, the average pain relief across subjects was at least 50% as measured on the VAS. Differences between baseline pain and stimulation-on pain were statistically significant. The reduction in pain was also clinically significant; stimulation-induced absolute reductions in VAS were 40–50 mm, while the minimum clinically important difference in VAS for back and leg pain has been estimated at approximately 20–30 mm (37,38). The reduction of pain as measured by the BPI slightly differed in absolute values from the VAS results reported here, as may be expected when using multiple instruments with different psychometric properties (39), but showed the same patterns of pain relief.

DRG stimulation was effective for the pain associated with CRPS and FBSS, as well as for pain localized to the back, legs, and feet. The

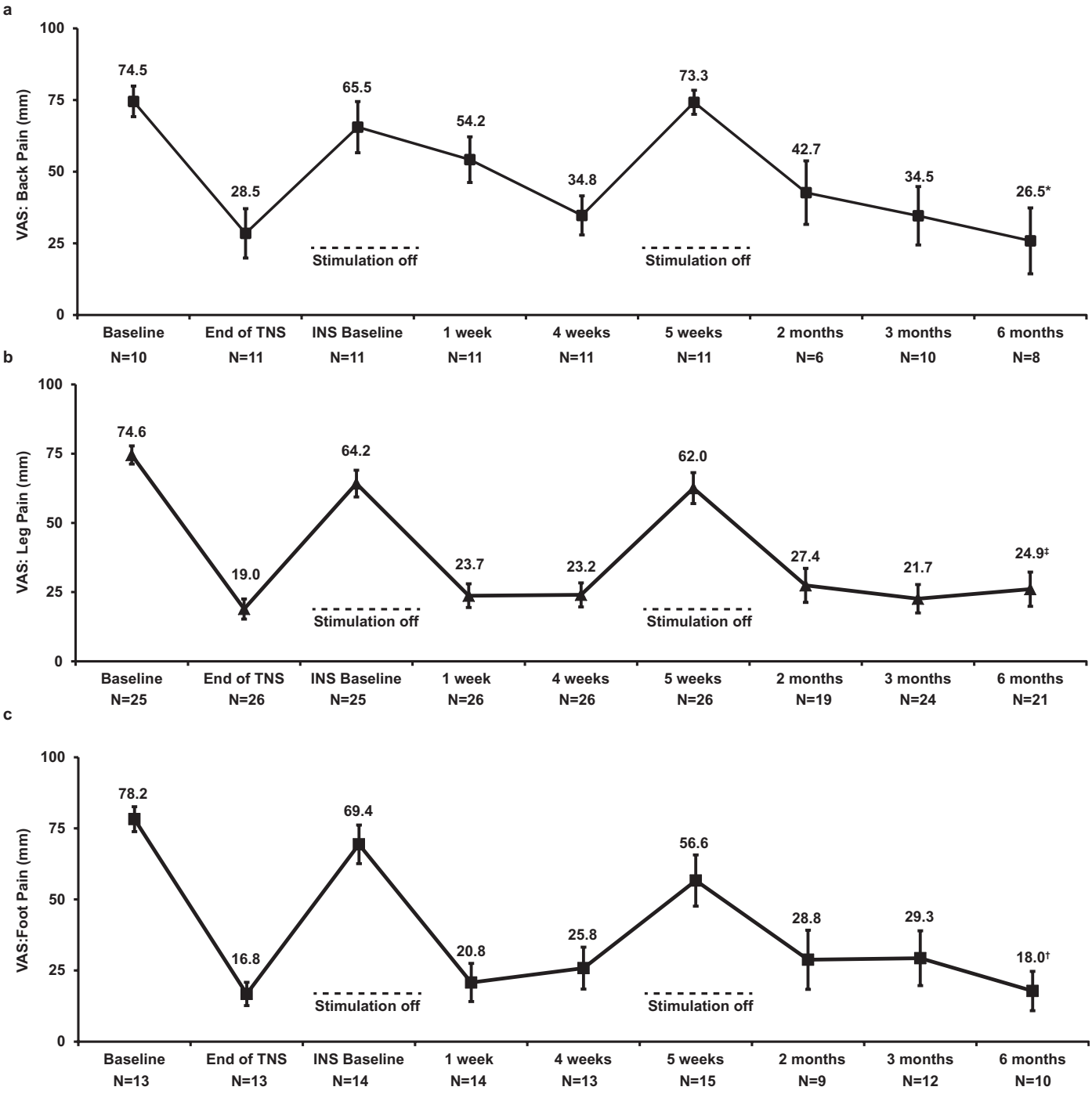

Figure 4. Pain ratings associated with (a) back, (b) legs, and (c) feet are reduced with DRG neurostimulation. Data points represent mean ± SEM. *$p < 0.05$, ‡$p < 0.001$, †$p < 0.005$. DRG, dorsal root ganglia; SEM, standard error of the mean.

magnitude of pain relief in this study exceeded that reported in the largest controlled trial of SCS to date. Data from the PROCESS study describe that 50–60% of FBSS subjects achieved 50% or better leg pain relief through six months of SCS therapy (11); in this study, approximately 75% of clients reported this level of pain relief. PROCESS reported reduction in back pain from approximately 55 mm at baseline to approximately 40 mm at 4, 12, and 24-week follow-ups (11); despite higher baseline back pain, subjects in this study reported reductions of 25–30 mm at the same time points. However, significant methodological differences exist between the PROCESS randomized controlled trial and this open-label study which make direct comparisons of outcomes problematic. For instance, the PROCESS study's intent-to-treat analysis included all randomized subjects while this study excluded screen failures and explanted/switched-off subjects from analysis and may therefore emphasize the relative contribution of the positive outcomes. Recent observational and cohort studies of SCS for a variety of indications have reported overall pain relief (relative to baseline) of 68% (40,41), 52% (42), and 45% (43). A systematic review that included analysis of case studies reported that approximately 62% of SCS patients

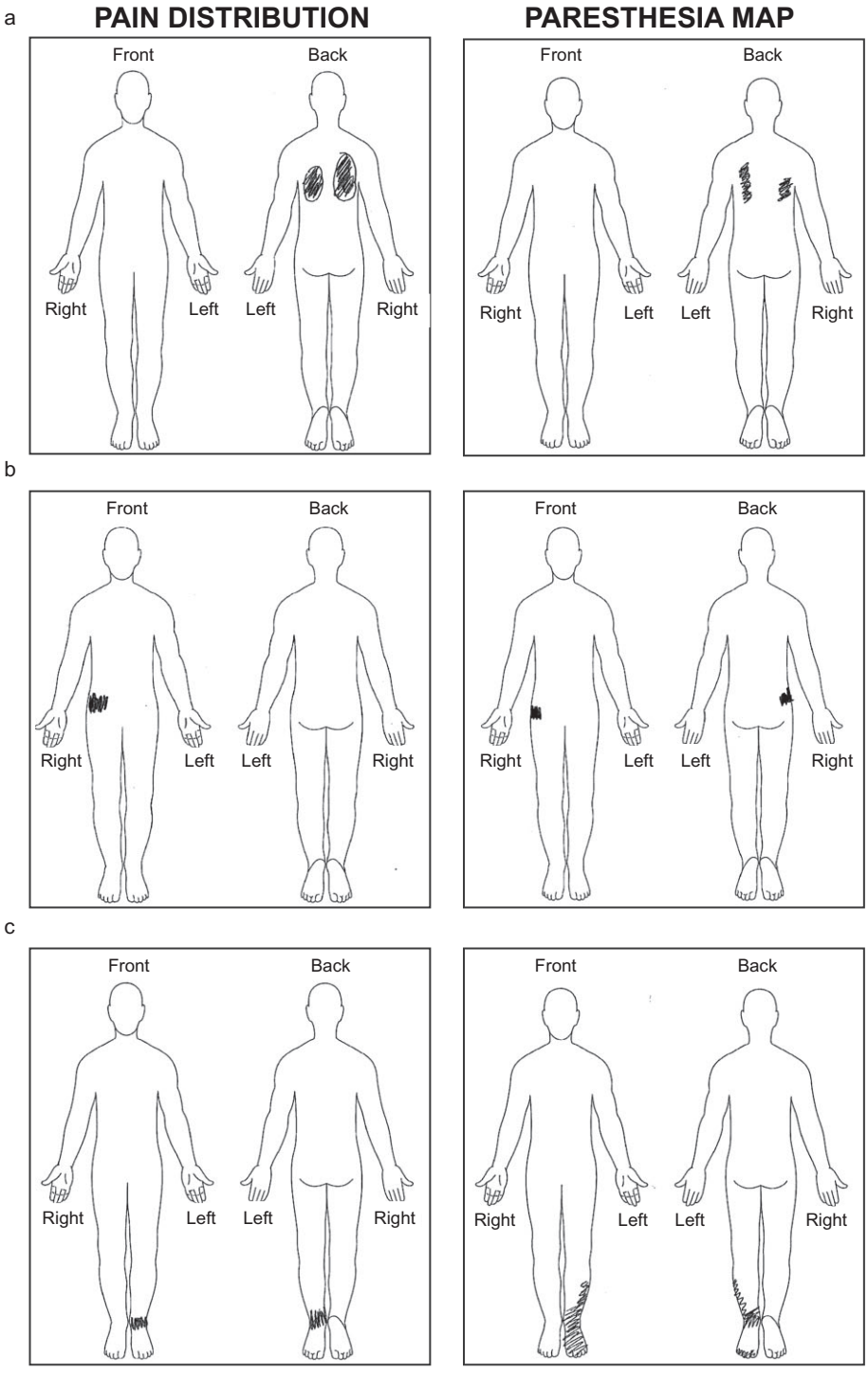

Figure 5. Pain distribution (left column) and paresthesia map (right column) for three representative subjects (a, b, c) in the study. Note the overlap of pain–paresthesia and the discrete coverage possible with the electrical neuromodulation of the DRG. DRG, dorsal root ganglia.

achieve 50% or better pain relief (8), although it was noted that due to heterogeneous design and methodologies, there is some difficulty in generalizing across this open-label knowledge base. Against these reports, the clinical results of DRG stimulation are promising.

The relief of foot pain is of special interest in this study. Reports of nonvascular neuropathic foot pain relief via SCS are few and small (12,44–46), likely because foot coverage with traditional SCS systems are unable to cover discrete painful regions in the foot without generating extensive extraneous paresthesias or motor side-effects. Additionally, the pain relief afforded to the feet by SCS is typically limited. In this study, approximately 90% of subjects with foot pain reported at least 50% foot pain relief, and the average pain relief was more than 80%. Importantly, the stimulation was able to cover the painful areas without generating large unwanted areas of paresthesia. Furthermore, significant positional effects of stimulation were not noted; paresthesia intensity subjects reported much

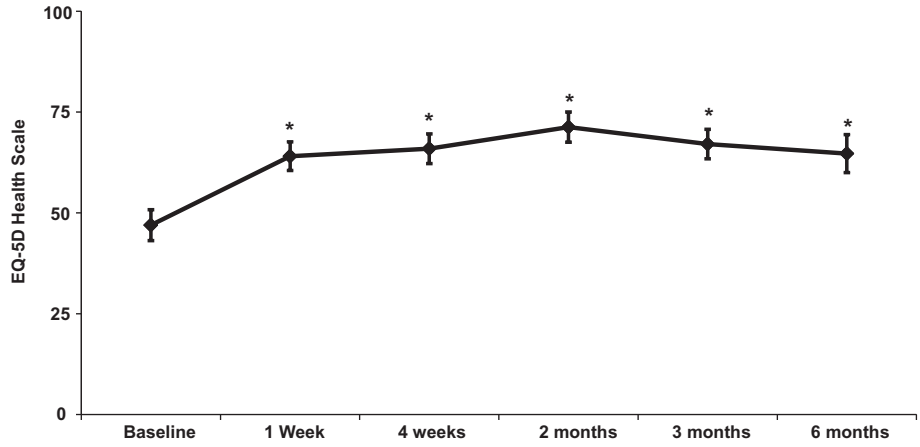

Figure 6. Subjects' mean self-rated health index as reported on the EQ-5D-3L VAS of overall health increased over time, representing a subjective improvement in health. Data points represent mean ± SEM (*$p < 0.05$). SEM, standard error of the mean; VAS , visual analog scale.

Table 3. Percentage of Subjects With >50% Improvement in Their VAS for Back, Leg, and Foot Pain.

	One week	Four weeks	Three months	Six months
Back pain	20.0	50.0	55.6	57.1
Leg pain*	76.0	76.0	78.3	70.0
Foot pain*	84.6	83.3	81.8	88.9

At baseline, number of subjects with back, leg, and foot pain were 11, 25, and 13, respectively.
*Leg pain and back pain VAS at baseline for one subject could not be obtained.
VAS, visual analog scale.

Table 4. Scores of Profile of Mood States (POMS) Subscale and Total Scores at Baseline and After 6 Months, Demonstrating an Improvement in Mood That Was Statistically Significant Across Multiple Domains.

POMS Subscale	Baseline ($N = 32$)	Six months ($N = 24$)
Tension	6.3 ± 0.7	4.2 ± 1.0*
Depression	5.3 ± 0.8	3.3 ± 1.2
Anger	6.1 ± 0.9	3.6 ± 1.1
Vigor	5.9 ± 0.9	8.5 ± 1.0*
Fatigue	11.7 ± 0.9	6.9 ± 1.4*
Confusion	4.1 ± 0.5	4.3 ± 0.7
Total mood disturbance score	27.5 ± 3.5	13.8 ± 5.6*

Data represent mean ± SEM.
*$p < 0.05$.
POMS, Profile of Mood States; SEM, standard error of the mean; VAS, visual analog scale.

the same paresthesia intensity when standing as compared with lying supine. This may be due in part to the location of the DRG inside the vertebral foramen (21,47); they are presumably relatively physically stable throughout a subject's changes in position, unlike the highly mobile spine. Although it is possible that the DRGs may shift inside their enclosures with the effects of gravity, any such movements are likely to be slight, given their size and conformation. Thus, assuming stable lead placement via anchors and strain relief loops, it is anticipated that a patient's body movement would result in very little movement of the DRG or lead relative to each other.

Other secondary endpoints, including quality of life, functional status, and mood, all improved during this study. Subjective ratings in these domains are often associated with clinically significant reduction in pain (48–50). Although the mediating effects of an individual's personal outlook (which may incorporate hope and resiliency (51)) and frequent contact with a pain specialist through study visits cannot be ruled out, these results suggest that improvement in pain through DRG stimulation establishes lifestyle improvements that would be appreciated holistically.

This study incorporated two reversal periods (also known as A-B-A) during which stimulation was temporarily stopped for a brief period of time. Pain ratings were captured during the stimulation-off periods, and again at resumption of the therapy. This internal-control methodology is more robust than a design implementing continuous therapy and may address the criticism inherent to pain research that an individual's historical (baseline) pain reporting may

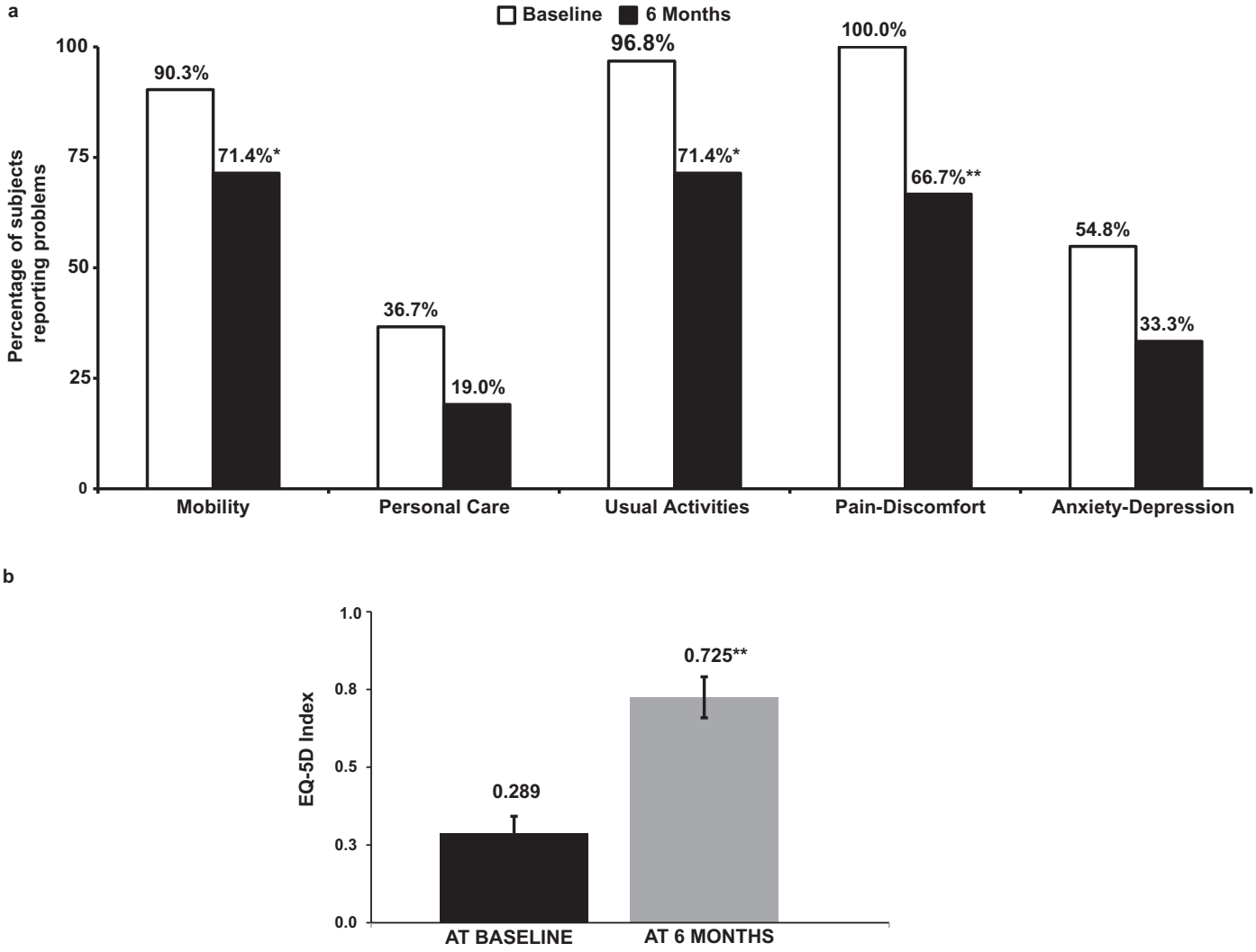

Figure 7. (a) EQ-5D-3L domains are listed with the percentage of subjects who reported any problem at baseline and 6 months follow-up. (b) EQ-5D index value was significantly higher at the 6 month follow-up (*$p < 0.05$, **$p < 0.001$).

Table 5. Pain Interference and Pain Severity Measured by Brief Pain Inventory Demonstrated Sustained Decrease From Baseline.

	Baseline ($N = 32$)	One week ($N = 32$)	Four weeks ($N = 29$)	Two months ($N = 22$)	Three months ($N = 29$)	Six months ($N = 24$)
Pain interference	6.6 ± 0.4	4.1 ± 0.5*	3.5 ± 0.5*	3.1 ± 0.5*	3.6 ± 0.6*	4.0 ± 0.6*
Pain severity	6.9 ± 0.2	4.3 ± 0.4*	4.0 ± 0.4*	4.0 ± 0.5*	3.9 ± 0.5*	3.9 ± 0.6*

*$p < 0.001$.

be influenced by faulty recall or psychological processes (52). This assumption is admittedly complicated by the fact that the subjects were unblinded. Pain ratings rebounded at both reversal time points, which may lend credibility to the effectiveness of this therapeutic intervention and its durability over time. However, at the second reversal point, the rebound pain was statistically lower than baseline reports; this may represent a reluctance on the part of the subjects to report the full magnitude of effect, a possible increase in the use of rescue pain medications during the stimulation-off period, or a simple artifact of sample size.

Interpretation of this study should be informed by a number of points. First, pain relief in this study was calculated as percentage reductions in the VAS, as opposed to the verbal rating scale ("on a scale of one to ten . . ."). Although the verbal scale is more convenient for many pain physicians to incorporate into clinical practice, the visual scale has been demonstrated to more closely represent the actual pain experience of the individual (53,54). The verbal scale should more properly be considered interval data than ratio, establishing dichotomous statistical assumptions (54). Several recent landmark SCS trials, including the PROCESS study that was discussed

previously in this section, have incorporated visual scales in their design (11,14). However, much of the published literature makes use of the verbal scale, presumably for ease of use. Comparability of the results of this study with others using different pain rating methods should thus be interpreted judiciously, given that numeric ratings are used in the calculation of the percentage of pain relief relative to baseline. Additionally, external experiences may influence pain ratings; subjects may have learned, over the difficult course of dealing with a chronic pain condition, communication methods involving VAS ratings as part of their self-management (55,56). Competing motivations in pain ratings contribute to the subjective nature of pain research. This issue is inherent, however, with all pain studies, and given that converging results were obtained across a number of different measures in this study, a high degree of confidence in the clinical outcomes of DRG neurostimulation can be assumed.

Effectiveness of the device, and the validity of stimulation-related pain reductions, is further supported by the rebound to baseline levels during reversal periods. It should be noted, though, that subjects were certainly aware of the stimulation on/off status of their device based on the presence or absence of paresthesias. Thus, the placebo effect cannot be ruled out. Placebo has been estimated to account for approximately one quarter to one third of the observed effect in pain studies (57,58). Placebo-controlled studies are difficult or nearly impossible in neurostimulation, although some work has demonstrated that SCS outperforms placebo in experimental measures of pain (59). Further work, including stimulation at levels that are subthreshold for inducing paresthesias but may be effective for pain mediation, will be needed to investigate the role of the intervention versus placebo. Continued surveillance is also necessary to confirm durable effectiveness, as these six-month results are preliminary. With any novel device there may be scope for further optimization of the therapy over time and experience and there may be potential for improved programming and lead placement algorithms.

CONCLUSION

Neuromodulation of the DRG was effective for relieving chronic pain and was able to consistently provide discretely defined paresthesia coverage in challenging anatomical regions such as the back and foot. Consistent intensities of paresthesias were reported throughout tests involving different body positions, demonstrating a clinically important lack of positional effects. Device performance demonstrated good safety profile and subjects in this trial experienced improvements in health-related quality of life, mood, and pain symptoms. These results suggest that SCS of the DRG is a robust new tool for the pain physician's armamentarium.

Authorship Statement

Drs. Levy, Deer, and Kramer designed the study and interpreted the data. Dr. Kramer also analyzed the data and drafted the manuscript. All the other authors conducted the study, including patient recruitment and data collection. All authors approved the final manuscript. This manuscript was drafted with intellectual input from Allison Foster, PhD, an independent medical writer. The authors thank Jeyakumar Subbaroyan, PhD, an employee of Spinal Modulation, Inc., for his help with manuscript preparation. The study was sponsored by Spinal Modulation, Inc.

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REFERENCES

1. Gildenberg P. History of electrical neuromodulation for chronic pain. *Pain Med* 2006;7:S7–S13.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971–979.
3. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth Analg* 1967;46:489–491.
4. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *JAMA* 1998;280:147–151.
5. Blyth FM, March LM, Brnabic AJ, Cousins MJ. Chronic pain and frequent use of health care. *Pain* 2004;111:51–58.
6. Praeger J. Estimates of annual spinal cord stimulator implant rises in the United States. *Neuromodulation* 2010;13:68–69.
7. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg* 2004;100:254–267.
8. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. *Spine* 2005;30:152–160.
9. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *Eur J Pain* 2006;10:91–101.
10. Kumar K, Taylor RS, Jacques L et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;132:179–188.
11. Kumar K, Taylor RS, Jacques L et al. The effects of spinal cord stimulation in chronic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectivness of spinal cord stimulation. *Neurosurgery* 2008;63:762–770.
12. Kemler MA, Barendse GAM, Van Kleef M et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;343:618–624.
13. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2004;55:13–18.
14. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg* 2008;108:292–298.
15. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery* 2006;58:481–496.
16. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lunbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery* 2005;56:98–106.
17. North RB. Neural interface devices: spinal cord stimulation technology. *Proc IEEE* 2008;96:1108–1119.
18. He J, Barolat G, Holsheimer J, Struijk JJ. Perception threshold and electrode position for spinal cord stimulation. *Pain* 1994;59:55–63.
19. Holsheimer J, Khan YN, Raza SS, Khan E. Effects of electrode positioning on perception threshold and paresthesia coverage in spinal cord stimulation. *Neuromodulation* 2007;10:34–41.
20. Mathew L, Winfree C, Miller-Saultz D, Sonty N. Transcutaneous electrical nerve stimulator trial may be used as a screening tool prior to spinal cord stimulator implantation. *Pain* 2010;150:327–331.
21. Hogan QH. Labat lecture: the primary sensory neuron: where it is, what it does and why it matters. *Reg Anesth Pain Med* 2010;35:306–311.
22. Sapunar D, Kostic S, Banozic A, Puljak L. Dorsal root ganglion - a potential new therapeutic target for neuropathic pain. *J Pain Res* 2012;5:31–38.
23. Van Zundert J, Patijn J, Kessels A, Lame I, van Suijlekom H, van Kleef M. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. *Pain* 2007;127:173–182.
24. McCallum JB, Kwok WM, Sapunar D, Fuchs A, Hogan QH. Painful peripheral nerve injury decreases calcium current in axotomized sensory neurons. *Anesthesiology* 2006;105:160–168.
25. Rush AM, Dib-Hajj SD, Liu S, Cummins TR, Black JA, Waxman SG. A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proc Natl Acad Sci U S A* 2006;103:8245–8250.
26. Fields RD. New culprits in chronic pain. *Sci Am* 2009;301:50–57.

27. Struijk JJ, Holsheimer J, Boom HBK. Excitation of dorsal root fibers in spinal cord stimulation: a theoretical study. *IEEE Trans Biomed Eng* 1993;40:632–639.
28. Struijk JJ, Holsheimer J, van Veen BK, Boom HBK. Epidural spinal cord stimulation: calculation of field potentials with special reference to dorsal column nerve fibers. *IEEE Trans Biomed Eng* 1991;38:104–110.
29. The EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
30. Szende A, Oppe M, Devlin N. *EQ-5D value sets: inventory, comparative review and user guide (EuroQol Group Monographs).* 2010.
31. EQ-5D index calculator. www.economicsnetwork.ac.uk/health/EQ_5D_index_calculator.xls
32. Essink-Bot ML, Stouthard M, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol questionnaire. *Health Econ* 1993;2:237–246.
33. Cleemput I, Kind P, Kesteloot K. Re-scaling social preference data: implications for modelling. *Eur J Jealth Econ* 2004;5(4):290–298.
34. Kim D, Vakharyia R, Kroll HR, Shuster A. Rates of lead migration and stimulation loss in spinal cord stimulation: a retrospective comparison of laminotomy versus percutaneous implantation. *Pain Physician* 2011;14:513–524.
35. Kinfe TM, Schu S, Quack FJ, Wille C, Vesper J. Percutaneous implanted padded lead for spinal cord stimulation: technical considerations and long-term follow-up. *Neuromodulation* 2012;15:402–407.
36. Epstein LJ, Palmieri M. Managing chronic pain with spinal cord stimulation. *Mt Sinai J Med* 2012;79:123–132.
37. Hagg O, Fritzell P, Nordwall A, Group SLSS. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J* 2003;12:12–20.
38. Parker SL, Adogwa O, Paul AR et al. Utility of minimum clinically important difference in assessing pain, disability, and health state after transforaminal lumbar interbody fusion for degenerative lumbar spondylolisthesis. *J Neurosurg Spine* 2011;14:598–604.
39. Atkinson TM, Mendoza TR, Sit L et al. The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial considerations. *Pain Med* 2010;11:337–346.
40. Van Buyten J-P, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. *Neuromodulation* 2012; e-pub ahead of print. DOI: 10.1111/ner.12006
41. Moriyama K, Murakawa K, Uno T et al. A prospective, open-label, multicenter study to assess the efficacy of spinal cord stimulation and identify patients who would benefit. *Neuromodulation* 2012;15:7–12.
42. Oakley JC, Krames ES, Prager JP et al. A new spinal cord stimulation system effectively relieves chronic, intractable pain: a multicenter prospective clinical study. *Neuromodulation* 2007;10:262–278.
43. Pluijms WA, Slangen R, Bakkers M et al. Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: a pilot study. *Br J Anaesth* 2012;109:623–629.
44. de Leon-Casasola OA. Spinal cord and peripheral nerve stimulation techniques for neuropathic pain. *J Pain Symptom Manage* 2009;38 (2 Suppl.):S28–S38.
45. Saranita J, Childs D, Saranita AD. Spinal cord stimulation in the treatment of complex regional pain syndrome (CRPS) of the lower extremity: a case report. *J Foot Ankle Surg* 2009;48:52–55.
46. Olsson GL, Meyerson BA, Linderoth B. Spinal cord stimulation in adolescents with complex regional pain syndrome type I (CRPS-I). *Eur J Pain* 2008;12:53–59.
47. Haque R, Winfree CJ. Transforaminal nerve root stimulation: a technical report. *Neuromodulation* 2009;12:254–257.
48. Skevington SM. Investigating the relationship between pain and discomfort and quality of life, using the WHOQOL. *Pain* 1998;76:395–406.
49. Turk DC, Okifuji A. Assessment of patients' reporting of pain: an integrated perspective. *Lancet* 1999;353:1784–1788.
50. Deyo RA. Measuring the functional status of patients with low back pain. *Arch Phys Med* 1988;69:1044–1053.
51. Pincus T, Williams ACdC, Vogel S, Field A. The development and testing of the depression, anxiety, and positive outlook scale (DAPOS). *Pain* 2004;109:181–188.
52. Haas M, Nyiendo J, Aickin M. One-year trend in pain and disability relief recall in acute and chronic ambulatory low back pain patients. *Pain* 2002;95:83–91.
53. Dworkin RH, Turk DC, Farrar JT et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113:9–19.
54. Ohnhaus EE, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain* 1975;1:379–384.
55. Jensen MP, Nielson WR, Kerns RD. Toward the development of a motivational model of pain self-management. *J Pain* 2003;4:477–492.
56. Turner JA, Calsyn DA, Fordyce WE, Ready LB. Drug utilization patterns in chronic pain patients. *Pain* 1982;12:357–363.
57. Carrette S, Marcoux S, Truchon R et al. A controlled trial of corticosteroid injections into facet joints for chronic low back pain. *N Engl J Med* 1991;325:1002–1007.
58. Mendelson G, Selwood TS, Kranz H, Loh TS, Kidson MA, Scott DS. Acupuncture treatment of chronic back pain: a double-blind placebo-controlled trial. *Pain* 1983;74:49–55.
59. Marchand S, Bushnell MC, Molina-Negro P, Martinez SN, Duncan GH. The effects of dorsal column stimulation on measures of clinical and experimental pain in man. *Pain* 1991;45:249–257.

COMMENTS

This is an interesting time for the field of spinal cord stimulation. New wave forms and now new targets within the intraspinal space are being proposed. Although many have been using conventional SCS equipment in an off label fashion to stimulate nerve roots within the epidural space, it is only now that we have specifically designed equipment to stimulate the nerve roots and dorsal root ganglia. This is a report of consecutive cases from a group of centres. As ever there is a learning curve both with skill at the technique and with selection of cases. The net is thrown wide so that a number of indications have been described. This is helpful and hopefully will inform future more controlled studies. I remain concerned that failed trials of DRG stimulation are excluded from the overall treatment outcomes in this group as a whole when pivotal research, such as the PROCESS study, report their results on an Intention to Treat basis. This has the tendency to exaggerate the outcome of DRG stimulation compared to conventional SCS.

However DRG stimulation may well be superior to conventional SCS in certain situations. This now needs to be proven and not left to assumption.

DRG stimulation technique does require extra skill and time for lead placement and the implanter should be aware that the technique is more uncomfortable for the awake or sedated patient than conventional SCS.

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Congratulations to the authors on an overall impressive work and a very well written discussion with a reasonable amount of balance in the analysis of the results. Some areas can be improved such as the transparency of reporting SAEs and AEs in percentage in the results section, not simply in the discussion where it suits the purpose of the publication. An attempt should be made to standardize the nomenclature of the AEs with other neuromodulation studies for ease of comparison. As the approach to the epidural space is novel, I would have expected an incidence of accidental dural puncture. This is not reported as a complication; only one case of recurrent hygroma is reported: is this realistic?

Also the reader should be clearly cautioned, amongst all the good news reported that these are only 6-month results and that other neurostimulation studies have shown a decrement of effect over time. Finally it would have been useful to the reader as with every novel approach to collect operative times and report how long it takes on average to position a lead for DRG stimulation.

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As is often the case, advances in medicine are made in response to a problem. This study of a new device hopes to solve a historical problem of stimulation overflow outside the intended painful area by targeting discrete regions of the DRG. This is well designed and executed and opens the door to a new era of discrete intraspinal neurostimulation.

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

