ORIGINAL ARTICLE

Stimulation of Dorsal Root Ganglia for the Management of Complex Regional Pain Syndrome: A Prospective Case Series

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■ **Abstract**

Background: Complex regional pain syndrome (CRPS) is a chronic and progressive pain condition usually involving the extremities and characterized by sensorimotor, vascular, and trophic changes. Spinal cord stimulation (SCS) is an effective intervention for this condition, but is hampered by the technical challenges associated with precisely directing stimulation to distal extremities. Dorsal root ganglia (DRG) may be more effective as a physiological target for electrical modulation due to recruitment of the primary sensory neurons that innervate the painful distal anatomical regions.
Methods: Eleven subjects diagnosed with uni- or bilateral lower-extremity CRPS were recruited as part of a larger study involving chronic pain of heterogeneous etiologies. Quadripolar epidural leads of a newly developed neurostimulation system were placed near lumbar DRGs using conventional percutaneous techniques. The neurostimulators were trialed; 8 were successful and permanently implanted and programed to achieve optimal pain–paresthesia overlap.
Results: All 8 subjects experienced some degree of pain relief and subjective improvement in function, as measured by multiple metrics. One month after implantation of the neurostimulator, there was significant reduction in average self-reported pain to 62% relative to baseline values. Pain relief persisted through 12 months in most subjects. In some subjects, edema and trophic skin changes associated with CRPS were also mitigated and function improved. Neuromodulation of the DRG was able to provide excellent pain–paresthesia concordance in locations that are typically hard to target with traditional SCS, and the stimulation reduced the area of pain distributions.
Conclusions: Neuromodulation of the DRG appears to be a promising option for relieving chronic pain and other symptoms associated with CRPS. The capture of discrete painful areas such as the feet, combined with stable paresthesia intensities independent of body position, suggests this stimulation modality may allow more selective and consistent targeting of painful areas than traditional SCS. ■

Key Words: complex regional pain syndrome, dorsal root ganglion, spinal cord stimulation, neuromodulation, prospective case study

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a pain disorder involving the extremities and is usually initiated after an injury, surgery, or vascular accident, although spontaneous development is also described. In addition

to experiencing regional pain disproportionate to the inciting event,[1] patients with CRPS may experience sensory, vasomotor, sudomotor abnormalities, and motor/trophic changes.[2,3] Muscle wasting can occur in the affected limb over time.[4] Fracture is the most common injury leading to CRPS, with upper extremities being affected more than lower extremities.[5]

According to the International Association for the Study of Pain (IASP), CRPS can be recognized as 2 distinct conditions: CRPS type I (formerly called reflex sympathetic dystrophy [RSD]) and CRPS type II (causalgia).[6] More recently, the clinical diagnostic criteria for CRPS, also known as the "Budapest criteria," have been revised. These describe CRPS as "an array of painful conditions that are characterized by a continuing regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time."[7]

Epidemiological data are imprecise regarding CRPS due in part to historical changes in taxonomy (including RSD, causalgia, and algodystrophy[8]) and the misdiagnosis of early-stage CRPS as other disorders including normal post-traumatic processes,[9] but incidence rates may be approximately 5 to 25 cases per 100,000 person-years, with women at 4 times the risk of men.[2,5,10]

CRPS is thought to be initiated and maintained by a complex interaction of the sensorimotor, autonomic, and inflammatory systems. The pathophysiology involves peripheral, afferent, efferent, and central mechanisms. In the periphery, release of substance P and calcitonin gene-related peptide[11] and a number of cytokines such as interleukin-6 and tumor necrosis factor-alpha[12] contribute to neurogenic inflammation. Vasoconstriction appears to be under the influence of altered levels of endothelin-I and nitric oxide.[13] Skin biopsies from the affected limbs of patients diagnosed with CRPS-1 show degeneration of cutaneous nociceptors (reductions in C- and Aδ-nerve endings in the epidermis[14]). As with other neuropathic pain conditions, sensitization of primary afferent, spinal, and/or supraspinal neurons occurs in CRPS.[15] This may indicate that maladaptive feedback loops and neuroplasticity are established after the initiating insult. Additionally, although some patients may have experienced the stigma of perceived mental health issues, a recent review found no relationship between psychological factors and the emergence of CRPS type 1.[16] It should be noted that psychological comorbidities such as depression are common as a result of chronic pain in general.[17] This also applies to CRPS.

Spontaneous remission can occur in early stages,[10] and best evidence suggests that early treatment may result in better outcomes,[18] as the percentage of subjects recovering from chronic or severe CRPS is low.[19] Treatment for CRPS typically involves an interdisciplinary approach.[20] The treatment for both types of CRPS is primarily aimed at alleviating pain and restoration of function with secondary goals of improving other signs and symptoms. Based on the predominant symptom, therapies could be focused on addressing the inflammation (free radical scavengers, bisphosphonates,[21,22] and steroids), vasomotor disturbances (vasodilator therapies, including limited areas for sympathetic blocks[23,24]), motor (baclofen[25]), and sensory (antineuropathic pain medication) abnormalities.[26,27] Medical management typically includes pharmacological options in accordance with international guidelines for neuropathic pain [28] and physical therapy.[29] Good outcomes in CRPS include the reduction in pain, return of normal function to the affected limb, minimization of edema, and increased strength and range of motion at each of the affected joints.[30]

Spinal cord stimulation (SCS) is the recommended next-line intervention for patients with CRPS that is refractory to conventional approaches,[2,4,31,32] based on the available evidence.[33] SCS has been successfully applied since 1967 as a treatment modality for the management of chronic, intractable pain in the trunk, and/or limbs.[34] Mechanisms of SCS are based upon the gate control theory in which the non-noxious SCS paresthesias, carried via large, rapidly conducting nerve fibers, inhibit the input from small-diameter pain fibers.[35] Specific to CRPS, SCS may relieve its non-nociceptive pain by increasing GABAergic activity in the dorsal columns, thereby reducing sensory excitation from the periphery and by increasing peripheral vasodilation.[36]

Spinal cord stimulation has been demonstrated to improve CRPS pain and quality of life outcomes in a randomized controlled trial, and to be cost effective in the first 2 years after implantation.[37–39] However, comparing its benefit against conventional therapy could not demonstrate a statistically significant difference at 5 years.[40] Others report that 56% of CRPS patients have 50% pain relief at an average of 4.4 years

postimplant[41] and that approximately 40% of patients have better than 30% pain relief through 11 years.[42] Limitations experienced are lead breakage and migration, loss of coverage (stimulation-induced paresthesias), or partial coverage of the pain area.[43,44] Pathophysiological changes in the DRG may be a contributory factor to the development of CRPS, and therefore, stimulation of this target may have beneficial effects on the painful symptoms associated with CRPS.

Prospectively identifying which CRPS patients will respond successfully to SCS remains difficult. One obstacle to optimum results with SCS is to achieve optimal pain–paresthesia overlap in distal extremities while simultaneously limiting the side effect of extraneous stimulation.[45,46] SCS is acknowledged to provide incomplete or inconsistent coverage of some areas, including the low back, buttocks, feet, groin, pelvis, and neck.[47] Furthermore, SCS systems are susceptible to postural effects due to the potential for lead movement in the epidural space.[48,49] Variations in the intensity of neurostimulation due to body position are a problem because positional changes may result in over- or understimulation, which can lead to frequent compensatory manual programming adjustments. Therefore, alternative neuromodulatory approaches may be needed. Dorsal root ganglion (DRG) stimulation, in which the electrodes are placed adjacent relatively immobile spinal structures and activate highly specific sensory neurons, has shown promise for precisely steering pain-mitigating paresthesias into hard-to-reach locations.[50–53] This report describes the effects of DRG stimulation on CRPS symptoms in a small prospective cohort. It was hypothesized that this stimulation modality would achieve good pain–paresthesia overlap and that meaningful pain relief would be realized.

METHODS

This study was conducted at 4 pain management clinics or hospitals in Europe and Australia under local ethical committee approval and with full informed consent of the subjects. Standard clinical diagnostic criteria for CRPS were employed (Budapest criteria for clinical use[7,18,30]): chronic pain that is disproportionate to the original injury and cannot be explained by another diagnosis, with the presence of at least 3 symptoms and at least 2 signs among sensory, vasomotor, sudomotor/edema, and motor/trophic categories.[7,18] Subjects were part of a larger prospective, open-label, single-arm clinical trial involving DRG stimulation for the treatment of chronic pain; this study has been described previously.[52,53] Briefly, after baseline assessments, subjects were implanted with the Axium™ Neurostimulator System (Spinal Modulation, Inc., Menlo Park, CA, U.S.A.) with quadripolar percutaneous leads placed near the DRG relevant to their pain distribution (Figure 1). If the trial period was successful, as defined by relief of 50% or more of overall pain, subjects received a fully implantable stimulator after approximately 1 week without stimulation. Clinical follow-ups occurred at 1 week, 1 month, 5 weeks, 2, 3, 6, and 12 months postimplant and collected outcome measures across domains recommended by the IMMPACT group for multidimensional evaluations in pain clinical studies.[54] At all time points, overall pain and pain specific to leg and foot distributions were assessed via a 100-mm visual

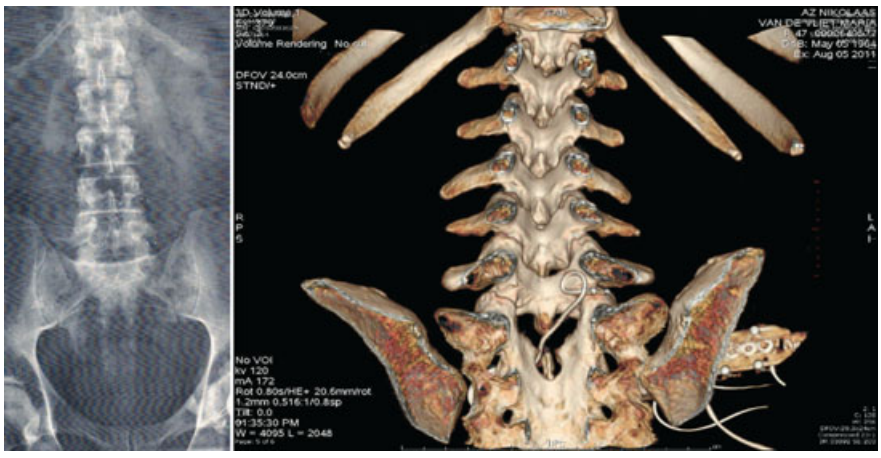

Figure 1. Anterior–Posterior (AP) view of leads implanted at right L4 and L5 dorsal root ganglia (DRGs) (left). 3-D reconstruction of a lead at L5 DRG using a computed tomography (CT) scan (right).

analog scale (VAS) in which 0 mm indicated no pain and 100 mm indicated the worst imaginable pain. The Brief Pain Inventory (Short Form, BPISF)[55] was used to further assess the impact of pain, mood was assessed with the Profile of Mood States (Short Form, POMS),[56] and quality of life was assessed with the EuroQOL five dimensions questionnaire (EQ-5D-3L).[57] Safety outcomes (frequency of adverse events [AEs]) were tracked throughout the study. Trends are expressed in this report as means ± SEM or as percentages of baseline values, and hypothesis testing used 2-tailed *t*-tests with significance levels set at 0.05. Qualitative outcomes are also reported to provide context and clinical relevance.

RESULTS

Eleven subjects with CRPS were recruited and trialed with the DRG neuromodulation system. Two subjects reported < 50% improvement in their pain relief, whereas 1 subject had 100% pain relief in 1 foot and no pain relief in the other.

The average age of the 8 subjects (6 women and 2 men) with successful trial stimulation was 43.9 years (± 5.6; range: 18 to 65). At baseline, their overall pain was 77.9 (± 4.2) mm. During the trial period, these subjects reported a minimum of 50% pain relief; the average pain with trial stimulation was 14.0 (± 4.2) mm, an 81.9% reduction relative to baseline. Stimulation was discontinued at the end of the trial phase for about a week. During this period, the average pain rating rebounded to 73.8 (± 4.9) mm, which was statistically indistinguishable from baseline ($P > 0.05$).

All 8 subjects received a permanently implanted neurostimulator (INS). One week after subjects received the INS (week 1), subjects reported that their average overall pain was reduced to 27.1 (± 7.6) mm, which represented an average 65.2% (± 10.3%) decrease from baseline ($P < 0.001$). At 1 month, the average pain was 30.0 (± 10.0) mm, a decrease of 62.1% relative to baseline ($P < 0.005$). Stimulation was temporarily suspended after the 1-month assessment to verify intrasubject effectiveness. After a week without stimulation (week 5), subjects reported that their overall pain returned to 55.6 (± 12.7) mm, which was not statistically significantly different from baseline ($P > 0.05$). At this point, 1 subject's INS was explanted due to unsatisfactory pain relief. At 3 months postimplant ($n = 7$), the average overall pain rating was 26.1 (± 11.6) mm ($P < 0.001$), a 68.4% (± 13.0%) decrease from baseline. At 6 months postimplant, average pain was 29.4 (± 11.3) mm, a 63.1% (± 13.2%) reduction from baseline ($P < 0.005$). At 12 months, subjects reported an overall pain of 30.3 (± 12.7) mm, a 61.7% (± 16.4%) decrease from baseline ($P < 0.05$), and 5 of the 7 subjects (71.4%) had greater than or equal to 50% pain relief. Similar patterns of responsiveness were observed for the foot- ($n = 8$) and leg-specific ($n = 7$) pain scores. These data are depicted in Figure 2.

Both foot pain and leg pain were significantly lower with active stimulation at all follow-up time points compared with the baseline (ps < 0.05). At 12 months, 6 of the 7 subjects with foot pain (85.7%) and 4 of the 5 subjects with leg pain (80.0%) had greater than or equal to 50% pain relief in those regions.

With respect to secondary end points, the BPISF revealed statistically significant reductions relative to baseline at the 12-month follow-up time points in the pain severity and pain interference domains. Quality of life improved, as reflected in EQ-5D-3L VAS and utility index scores at 12 months, and this instrument's pain–discomfort dimension also indicated a reduction in pain at 12 months. Mood disturbance was decreased over the course of the study, and significant improvements were identified across tension, depression, and anger domains. These secondary endpoint data are presented in Table 1.

As illustrated by the exemplar subject in Figure 3, the distribution of painful areas generally shrank after the initiation of stimulation and remained stable over time and across body positions. Exact pain–paresthesia concordance was often achieved, even to the degree of recruiting a single toe.

Some subjects showed obvious neurovascular changes and improvement in mobility. For example, a subject with severe erysipelas in his left leg and foot at baseline (Figure 4A) reported reduced swelling and improved coloration in the affected foot after 1 month (Figure 4B). By 6 months postimplant, the swelling had entirely resolved (Figure 4C). The subject reported that his function was "100% improved" and rated his quality of life after the initiation of INS as "100 out of 100." Another subject reported that, in addition to pain relief, her foot also regained normal flexion parameters and she regained better mobility, especially in climbing stairs. A third subject evidenced better mobility by being able to walk around the house with only 1 crutch. Interestingly, 2 subjects reported bilateral CRPS in both their lower limbs. One of those subjects reported nearly complete pain reduction in both feet; the other subject had excellent improvement in 1 limb, but poor outcome in the second limb.

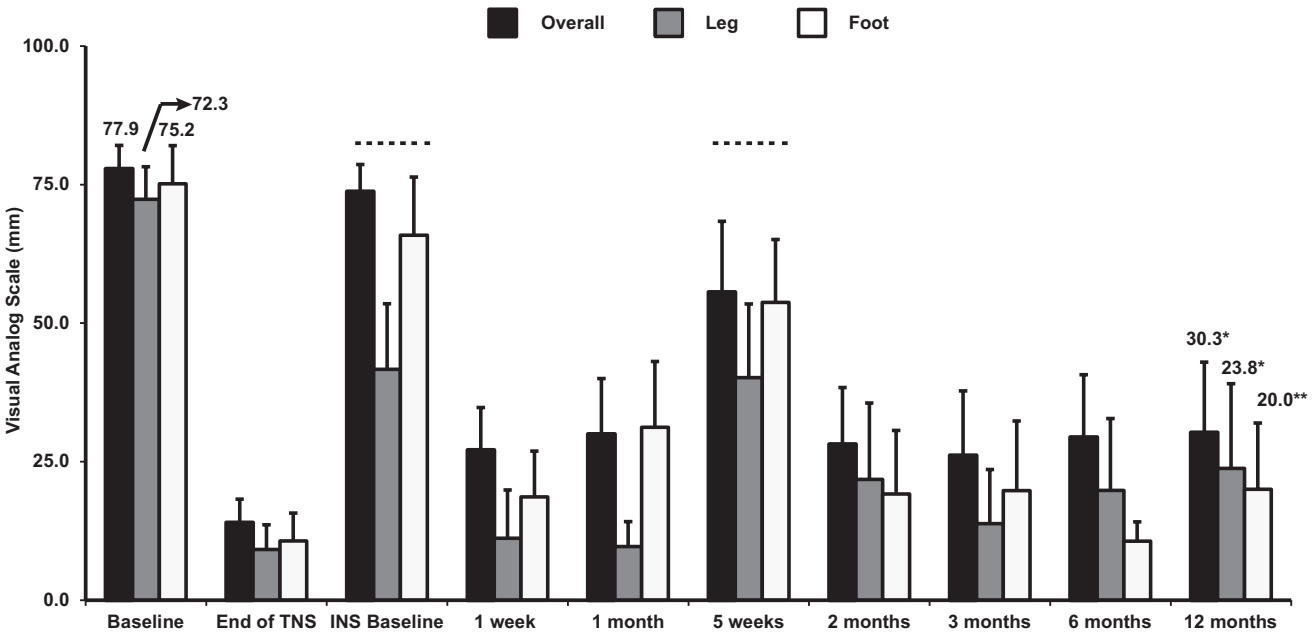

Figure 2. Average overall, leg, and foot pain rating during the trial and implantation phases of treatment with the dorsal root ganglia (DRG) stimulation unit. Error bars indicated standard error of the mean. The dotted bar represents time points when stimulation was turned off (1 week after the end of the trial period and at week 5) to evaluate pain in the absence of stimulation. *$P < 0.05$ and **$P < 0.005$.

Table 1. Statistically Significant Improvements from Baseline were Observed at the 12-Month Follow-Up in All Secondary Endpoint Comparisons

	Baseline (n = 8)	12 months (n = 7)
BPISF		
Pain severity	6.9 ± 0.4	3.2 ± 1.2*
Pain interference	7.3 ± 0.6	3.4 ± 1.3*
EQ-5D-3L		
VAS	39.9 ± 9.5	69.3 ± 11.6*
Utility index	0.25 ± 0.08 (n = 6)	0.70 ± 0.10* (n = 6)
POMS†		
Tension	8.3 ± 1.3	3.9 ± 1.2*
Depression	8.4 ± 1.7	2.6 ± 1.6*
Anger	7.6 ± 1.6	2.0 ± 1.1*
Total mood disturbance score	37.3 ± 5.4	10.4 ± 7.3*

*$P < 0.05$ relative to the baseline score of that dimension.
†Three other subscales, vigor, fatigue, and confusion improved from the baseline but did not reach significance.

Eleven AEs were reported in 4 subjects (not related to the device – 8, possibly related – 2, definitely related – 1); 3 were classified as mild, 5 as moderate, and 3 as severe. One of the AEs, discomfort associated with stimulation, was resolved by reprograming. No lead revisions were required. A complete list of AEs can be found in Table 2. Two serious AEs (prolonged hospital stay and lack of paresthesia coverage), both unrelated to the device, were reported in 2 different subjects. The former SAE was due to moderate pain experienced by the subject resulting in hospitalization (lack of caregivers at home) whereas the latter SAE was resolved through lead revision.

DISCUSSION

All 8 subjects implanted with a DRG neurostimulator for CRPS reported some pain relief. Good results (greater than or equal to 50% pain relief in the foot) were reported after 12 months of treatment for 6 of the 8 subjects. This responder rate is similar to or better than reported outcomes with SCS for CRPS[37,38,40–42] and confirms DRG stimulation as a viable and effective intervention for this difficult pain condition. Mechanisms of action for DRG-mediated pain relief involve modulation of primary sensory neurons.[58] Pathophysiologic alterations of the primary sensory neurons are generally thought to contribute to the development and maintenance of chronic or intractable pain[59]; examples of such alterations may include abnormal expression and regulation of ion channels. Previous reports have implicated the DRG in the development and maintenance of chronic pain,[60,61] and electrical field stimulation has been demonstrated to alter the excitability of DRG neurons.[62]

Improvements in perfusion and trophic changes in the affected limbs were observed in some subjects, as has

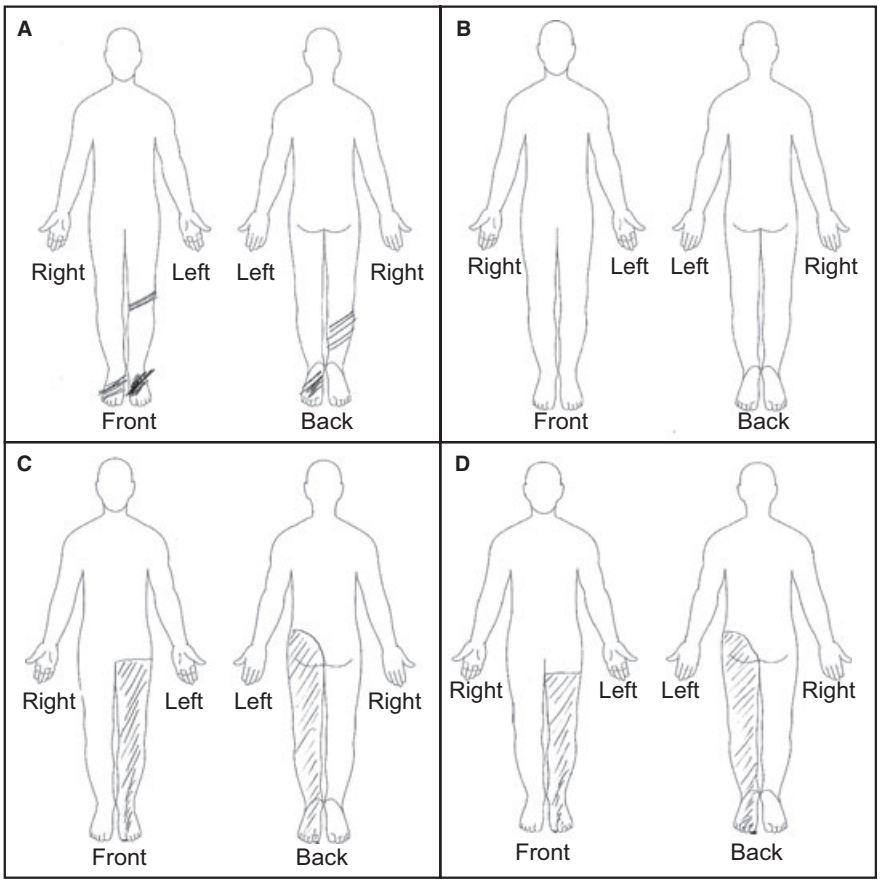

Figure 3. Pain distribution at (A) baseline and (B) week 1 of a representative subject with good treatment response. At 12 months, self-reported paresthesia distributions were identical whether the subject was (C) upright or (D) supine.

been reported in SCS.[4] With SCS, it is theorized that vascular changes occur due to the antidromic activation of sensory afferents, which in turn releases vasodilatory peptides[36]; it is likely that this mechanism is also applicable to DRG stimulation, in which primary sensory neurons are activated. With further research, it could be demonstrated that DRG stimulation may activate a reflex arc involving GABAergic interneurons that project to the sympathetic premotor neurons in the intermediolateral cell column, as has been theorized to underlie good CRPS outcomes with SCS.[36]

This study may be underpowered for some measures, and as with any small sample, it may not be possible to generalize the results of this cohort to the larger CRPS population. However, it should be noted that trends toward improvements were noted in other measures (back- and leg-specific pain, pain intensity, quality of life, and mood). Because converging results across multiple outcome measures (according to pain study design recommendations[54]) were obtained, the conclusions may be more robust.

No lead migration was reported through the 12-month follow-up in the 7 subjects, in contrast to the 11 lead repositionings that were required in 24 CRPS patients with SCS over the course of 5 years[40] or the annual mean intervention rate of 7% to 13% due to lead migration in another long-term study of CRPS patients with SCS.[42] Another striking outcome of this study was the demonstration of the specificity of pain–paresthesia overlap in distal extremities, to the extent of being able to achieve coverage of individual toes. Additionally, stimulation remained stable both over time and across different body positions. The precision and stability of the paresthesias produced with DRG stimulation has also been reported in a larger sample.[53] With traditional SCS, leads in the epidural space may change position in response to body movements or altered posture; as the leads move subtly closer to or farther from the dorsal columns, the perceived stimulation may become more or less intense.[45,63] In DRG neurostimulation, electrodes are closer to the target, allowing more focused neurostimulation, and are far

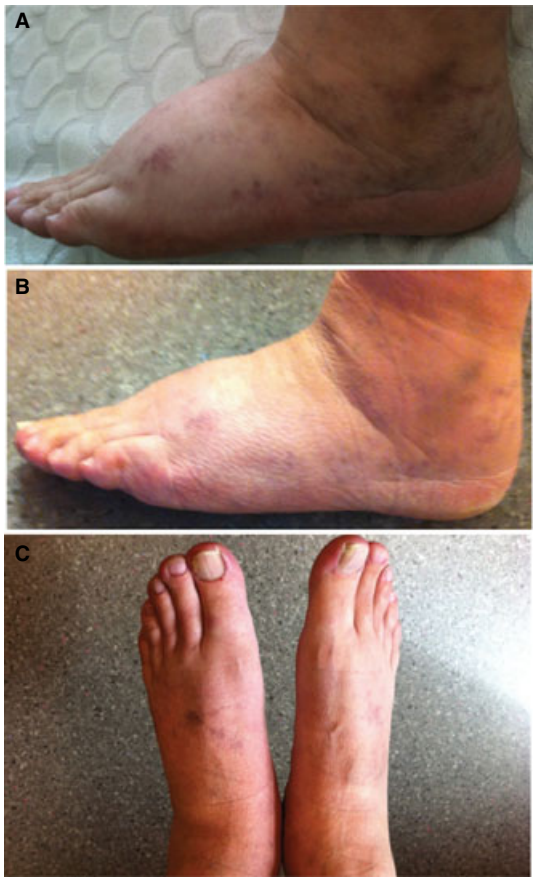

Figure 4. The neurovascular symptoms in the affected limb of 1 subject with good pain relief were greatly reduced from baseline (A) to 1 month (B) and 6 months (C). At 6 months, the subject reported that function was "100% improved."

Table 2. List of Adverse Events, their Severity, and Relationship to the Device

No.	Description	Severity	Relationship to Device
1	Prolonged hospital stay	Mild	Not related
2	Pain in right hip	Moderate	Not related
3	Cellulitis in lower legs	Moderate	Not related
4	Ulcer in right foot	Moderate	Not related
5	Knee replacement	Moderate	Not related
6	Pain in left buttock over IPG implant	Severe	Possibly related
7	Intermittent cramping in right calf	Severe	Possibly related
8	Nausea	Mild	Not related
9	Pain in hand and forearm	Mild	Not related
10	Discomfort from stimulation	Moderate	Definitely related
11	Increased foot pain	Severe	Not related

less likely to shift due to movement or postures. Given the localized nature of CRPS symptoms, DRG stimulation may thus be a more attractive intervention than SCS.

CONCLUSIONS

Although results were mixed, all subjects had some pain relief and 3-quarters of the subjects in this prospective cohort of DRG stimulation experienced better than 50% pain relief in addition to improvements in mood and quality of life. Some subjects reported improved mobility and showed remission in some sympathetically maintained symptoms such as swelling and discoloration. Qualitatively, subjects were enthusiastic. This establishes DRG stimulation as a promising emerging therapy in the application of CRPS for otherwise intractable cases.

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