Prospective Study

Targeted Nerve Root Stimulation Alleviates Intractable Chronic Limb Pain Associated with Complex Regional Pain Syndrome - A Prospective Multi-Center Feasibility Study

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Background: There are limited therapeutic options to treat complex regional pain syndrome (CRPS). Spinal cord stimulation and dorsal root ganglion stimulation are proven therapies for treating chronic low limb pain in CRPS patients. There is limited evidence that stimulation of dorsal nerve roots can also provide relief of lower limb pain in these patients.

Objectives: To demonstrate that electrical stimulation of dorsal nerve roots via epidural lead placement provides relief of chronic lower limb pain in patients suffering from CRPS.

Study Design: Prospective, open label, single arm, multi-center study.

Setting: The study was performed at the Center for Interventional Pain and Spine (Exton, PA), Millennium Pain Center (Bloomington, IL), and the Carolinas Pain Center (Huntersville, NC). It was approved by the Western Institutional Review Board-Copernicus Group Institutional Review Board and is registered at clinicaltrials.gov (NCT03954080).

Methods: Sixteen patients with intractable chronic severe lower limb pain associated with CRPS were enrolled in the study. A standard trial period to evaluate a patients' response to stimulation of the dorsal nerve roots was conducted over 3 to 10-days. Patients that obtained 50% or greater pain relief during the trial period underwent permanent implantation of a neurostimulation system. The primary outcome was the evaluated pain level after 3 months of device activation, based on NRS pain score relative to baseline. Patients were followed up for 6 months after activation of the permanently implanted system.

Results: At the primary endpoint, patients reported a significant (P = 0.0006) reduction in pain of 3.3 points, improvement in quality of life, improved neuropathic pain characteristics, improved satisfaction, and an overall perception of improvement with the therapy. Improvements were sustained throughout the duration of the study up to the final 6-month visit.

Limitations: Due to the COVID-19 pandemic occurring during patient enrollment, only 16 patients were enrolled and trialed, with 12 being permanently implanted. Nine were able to complete the end of study evaluation at 6 months.

Conclusions: The results of this short feasibility study confirm the functionality, effectiveness, and safety of intraspinal stimulation of dorsal nerve roots in patients with intractable chronic lower limb pain due to CRPS using commercially approved systems and conventional parameters.

Key words: Complex regional pain syndrome (CRPS), dorsal nerve root (DNR), neuromodulation, lower extremities chronic pain

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Complex regional pain syndrome (CRPS) is associated with difficult to treat chronic pain. Conservative estimates place its annual incidence between 5.5 and 26.2 per 100,000 people, meaning that more than 17,000 people develop CRPS every year (1-3). Current taxonomy classifies CRPS as CRPS-I, without known causation, or CRPS-II or causalgia, with known nerve trauma preceding onset. Classical symptoms associated with CRPS include pain disproportionate with the inciting event, hyperalgesia, hyperesthesia, allodynia, vasomotor changes with skin color and temperature asymmetry, autonomic and inflammatory response, sweating, trophic changes in hair, nails or skin, motor dysfunction, decreased range of motion, tremors, and dystonia (4). CRPS can initiate in a region, such as the lower leg, or can be localized to a small focal area, to later spread to adjacent regions or to the opposite extremity. During flare-ups, pain can also extend from the origin site to a larger region. However, there are limited therapeutic options to treat CRPS. A recent review concluded that the multidimensional nature of CRPS prevents a singular therapy from being generally effective (5). Current treatments include physical therapy, psychotherapy, pharmacotherapy, or a combination of them, reserving neuromodulation treatments such as spinal cord stimulation (SCS) or dorsal root ganglion stimulation (DRGS) as last resources.

SCS and DRGS utilize charge-balanced pulses with frequencies ranging between 40-250 Hz. The applied electric field induces paresthesia that can be steered to overlay with the pain location by appropriate positioning of the electrodes and modification of electrical parameters (frequency, pulse width, amplitude, etc.). This paresthesia-based treatment is hypothesized to act via the Gate Control Theory of pain, which suggests that electrically induced paresthesia masks nociceptive afferent signals travelling to the brain, thus reducing painful sensations (6). In addition to alleviating chronic pain, electrical neuromodulation improves blood flow to stimulated regions and downregulates neuroinflammatory molecular pathways (7-9). Clinical studies have demonstrated the effectiveness and safety of paresthesia-based SCS on CRPS in a couple of randomized controlled trials (RCT) (10-12). SCS utilizes electrodes positioned in the dorsal epidural space to activate nerves that generate paresthesia in the afflicted region. This covers pain dermatomes in a large anatomical range, beyond just the afflicted area, where patients may be experiencing focalized pain. In contrast, DRGS achieves targeted coverage of painful areas using a smaller charge dose and placing electrodes at the foramen adjacent to the dorsal root ganglion (DRG) where peripheral afferent nerves associated to specific dermatomes are located. DRGS has been proven clinically effective for treating CRPS in the lower limbs, although only one of these studies is a RCT (11,13-15). An issue with DRGS is the larger risk of adverse events related to implanting and anchoring the stimulating lead and the complex surgical intervention required for lead removal (16). A study of the effectiveness and safety of DRGS versus SCS as a treatment for lower limb chronic pain associated with CRPS reported that 81% of patients utilizing DRGS compared to roughly 50% of patients treated via SCS experienced ≥ 50% pain reduction (11). The study noted 38 more adverse events after treatment with DRGS than with SCS. The top 3 causes of adverse events were lead migration, inadequate pain relief, and weakness/pain/numbness in the limbs. These were all related to lead positioning which is challenging and requires appropriate training by specialized implanters.

An alternative is needed to stimulate afferent nerve fibers prior to synapsing at the dorsal horn, which can provide targeting of focalized and distal pain dermatomes without a large risk of adverse events. A systematic review suggested that epidurally implanted leads targeting alternative intraspinal structures may be a valuable option in the treatment of challenging painful conditions (17). Stimulation of sensory afferents can be achieved by using the lead and the introduction technique used in SCS and directing the lead to the lateral portion of the dorsal epidural space. Alo et al. first demonstrated that electrical stimulation of the lumbar and sacral nerve roots could be utilized for the treatment of chronic pain as an alternative to SCS (18). Stimulation of dorsal nerve roots (DNR) may provide specific and targeted analgesia in the structures affected by CRPS that may not be covered satisfactorily by SCS and which may be difficult to achieve with DRGS. A single-center, prospective, non-randomized study compared the effects of paresthesia-based SCS with stimulation of the DNR (19). The results indicate that both therapies provide similarly significant long-term pain relief relative to baseline pain while having similar safety profiles. A limited subset of patients (n = 9) in that study were diagnosed with CRPS, but specific outcomes from them were not reported.

This study reports results of a prospective, multicenter, single-arm clinical trial that assesses the pares-

thesia-based stimulation of the DNRs associated with specific painful dermatomes in patients with lower limb chronic pain associated with CRPS by using a neurostimulation system and electrical parameters approved for market use for SCS by the FDA.

Methods

This is a multi-center, prospective, open-label, single-arm, feasibility study that evaluated the effectiveness of electrical stimulation of the lumbar DNRs in patients with lower limb chronic pain associated with CRPS during a 6-month period. The study was conducted in compliance with the US Code of Federal Regulations, Good Clinical Practice Guidelines, and the 18th World Medical Assembly of Helsinki. The protocol and informed consent form were approved by the Western Institutional Review Board-Connexus (WCG IRB). The study was prospectively registered with clinicaltrials.gov (NCT03954080). Sixteen patients were enrolled in 3 investigational sites across the United States. Table 1 shows the key inclusion/exclusion criteria. Informed and consented patients that complied with all the eligibility criteria were enrolled. Patients were scheduled for a trial period which consisted of the implantation of a temporary percutaneous lead and programming of electrical parameters commonly used for conventional SCS, although at reduced amplitudes due to the characteristics of the DNRs.

Lead Placement and Programming

Depending on the painful area, one octapolar lead (Vectris 1x8 Compact, Medtronic Inc.) was placed in the epidural lumbo-sacral region, spanning L2 down to S1 to target DNRs, allowing for more focal paresthesia coverage. As deemed appropriate by the implanting investigator, the lead was introduced using an anterograde or a retrograde approach and was guided to the targeted location using fluoroscopic x-ray imaging. The final position was confirmed with lateral and anterior-posterior images. During the trial the lead was connected to a wireless external neurostimulator (Intellis 92725, Medtronic Inc.) that delivered electrical pulses within the conventional FDA approved parameters. The amplitude and pulse width of the stimulating pulses were adjusted perioperatively to map paresthesia in the appropriate pain dermatomes as reported by patients. Further programming to adjust comfortable paresthesias over the painful area was done postoperatively. Programming of the therapy was performed by a clinical field technician under the guidance of the study investigator. At the end of the 3-10 days trial, the patient completed assessments and the temporary lead was removed. Patients who experienced ≥ 50% reduction in CRPS pain were considered successful and eligible for a permanent implant. A lead (Vectric Surescan 1x8 Compact, Medtronic Inc.) was placed according to the trial procedure and connected to a neurostimulation system (Intellis 97715, Medtronic Inc.) implanted in a subcutaneous pocket. Therapy was programmed after patients had recovered from the surgical procedure and were trained on the operation and recharging of the device.

Physicians followed standard practice procedures for prophylactic antibiotics and post-surgery analgesics. Patients were followed up with for postoperative care and programming adjustments to optimize the therapy. Patients visited the clinic for study visits at one, 3, and 6 months post device activation. A general flow of the study process is depicted in Fig. 1.

Outcome Measurements

Patients self-assessed pain intensity using a standard 11-point Numeric Rating Scale (NRS). This is among the most reliable scale of patient reported

Table 1. *Key inclusion and exclusion criteria.*

Inclusion Criteria	1. Adult patient (≥ 18 years old) 2. Predominant pain in one or both of the lower limbs attributed to CRPS or causalgia refractory to conservative therapy for at least 3 months. 3. Average pain intensity ≥ 6 on the numeric rating scale (NRS). 4. Appropriate candidate for spinal cord stimulation 5. On a stable dose of pain medication regimen for at least 1 month.
Exclusion Criteria	1. Systemic infection. 2. Any other active implanted device. 3. Evidence of serious neurological, psychological, or psychiatric disorders. 4. Previous posterior decompressive laminectomy that precludes appropriate posterior epidural placement of stimulation lead(s). 5. Medical conditions or pain in other areas that could interfere with study procedures, and/or confound evaluation of study end points.

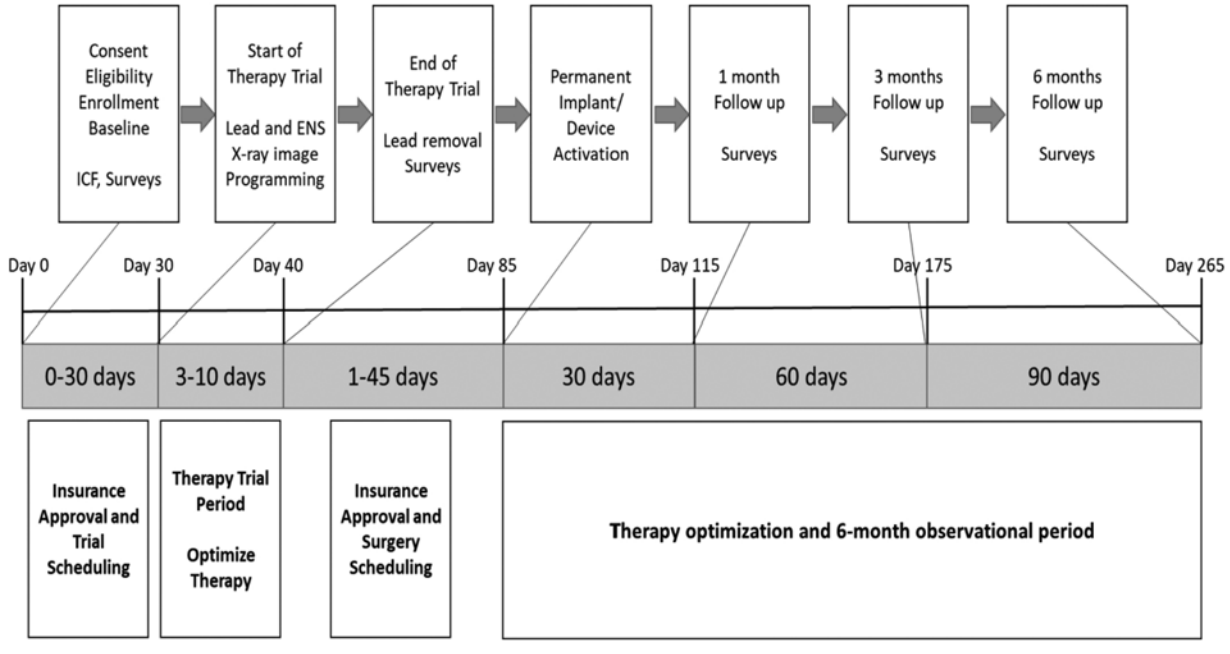

Fig. 1. *Flow diagram of the study process.*

outcomes for measuring pain intensity (20). The primary endpoint was the mean reduction in pain intensity at the 3-month follow up, calculated as the average of the difference between NRS score at 3 months post device activation and baseline for each patient. Reduction in pain intensity from baseline was also assessed at the one, and 6-month follow up visits. Other secondary endpoints included responder rate (percent of patients experiencing ≥ 50% pain reduction), quality of life evaluated by the Short-Form-20 (SF-20), neuropathic pain characteristics (recorded using the DN4 questionnaire), patient satisfaction survey, and the level of improvement reported using a Patient Global Impression of Change (PGIC) questionnaire. Assessments were done at different timepoints throughout the study. A sample size calculation indicated that up to 20 patients should provide appropriate power (> 80%) and significance ($P < 0.05$ double sided) for a pain reduction of at least 2 points relative to the baseline NRS with a SD of 3 points. Results are reported as the mean ± SD unless otherwise indicated. A statistical analysis based on the analysis of variance, or the t-test was conducted for continuous outcomes. A *P* value below 0.05 indicates statistical significance of changes in measurements relative to the baseline.

Results

Patient Demographics

Table 2 shows a summary of patient demographics and patient disposition is shown in Fig. 2. Sixteen patients with chronic pain in lower limbs associated with CRPS were enrolled into 3 sites from August 2019 to November 2021. The cohort of patients consisted of 5 men (31%) and 11 women (69%) with a mean age of 56.0 ± 9.5 years and who have had chronic pain associated with CRPS for an average of 8.5 ± 7.8 years. The baseline NRS pain score was 7.1 ± 1.0. All patients reported in this study demonstrated unilateral CRPS lower limb pain in either the leg, knee, foot, or a combination thereof.

One patient was withdrawn at the start of trial due to a narrow epidural space that prevented placement of the lead. Another patient withdrew during the trial period due to personal reasons. By the end of the trial, one patient did not like having paresthesias and another was withdrawn by the investigator. Thus, 12 patients continued to get the permanent neurostimulation system and remained in the study for at least 1 month. After one month, one patient left the study voluntarily. One patient missed the 3-month primary endpoint visit due to a mandatory lockdown due to the COVID-19 pandemic. Two patients did not complete the 6-month

visit. One experienced lead migration that required a surgical revision, which could not be scheduled timely due to COVID-19 restrictions. While the other did not complete the study as the assessment window was not open at the time of study closure.

Stimulation Parameters

Figure 3 shows typical fluoroscopic anterior-posterior images of a lead placed for DNR stimulation using either an anterograde or retrograde approach. Since all patients had unilateral lower limb pain, only one lead was placed ipsilateral and in such a way that the paresthesia was made to overlap with the painful dermatome via adjustment of the lead position as well as the intensity and width of the stimulating pulses. The mean ± SD values for the optimal programs were a frequency of 52 ± 20 Hz, a pulse width of 291 ± 134 μs and an intensity of 1.5 ± 1.0 mA. When accounting for all leads placed at the start of trial and the permanent implants (n = 23), 74% of leads were placed in a retrograde fashion as this provided an easier access to the posterior/lateral aspect of the lower lumbar epidural levels.

Change in Pain Intensity at 3 months (Primary Endpoint) Relative to Baseline

Results for the primary endpoint are summarized in Table 3. When comparing the baseline and 3-month pain scores of only the 10 patients that completed the assessment, the mean reduction is 3.3 ± 2.0 points. The reduction in the pain intensity obtained from mean NRS scores at 3 months (n = 10) and baseline (n = 16) is similar (3.4 points). Reduction in pain intensity between the 3-month point and baseline was significant ($P = 0.0006$) and equivalent to a mean pain relief of 47.3 ± 28.9%.

Mean Pain Reduction Relative to Baseline Pain at the End of Trial, One Month, and 6 Months

The mean pain intensity scores are seen in Fig. 4. The mean percent reduction in pain intensity relative to the baseline are summarized in Table 4. The mean pain intensity reduction at the end of trial (EOT) of patients that completed the assessment (n = 14) is 4.4 ± 1.3 points on the NRS. The reduction in mean values between EOT and baseline NRS scores was significant ($P < 0.0001$) and corresponds to a mean pain reduction of 62.8 ± 15.2%. One month post operation the reduction in pain inten-

Table 2. *Demographics of patients and location of pain associated with CRPS (n = 16).*

Gender		
Man	n (%)	5 (31.2%)
Woman	n (%)	11 (68.8%)
Age (years)	Mean ± SD	56.0 ± 9.5
	Minimum	43
	Maximum	85
Baseline Pain (NRS)	Mean ± SD	7.1 ± 1.0
	Minimum	6
	Maximum	9
Duration CRPS Pain (Years)	Mean ± SD	8.5 ± 7.8
	Minimum	0.75
	Maximum	23
Location of Pain	Foot Only	6 (37.5%)
	Leg Only	4 (25%)
	Knee Only	3 (18.75%)
	Multiple Limb Locations*	3 (18.75%)

* Two with foot and back of knee, one with ankle and foot.

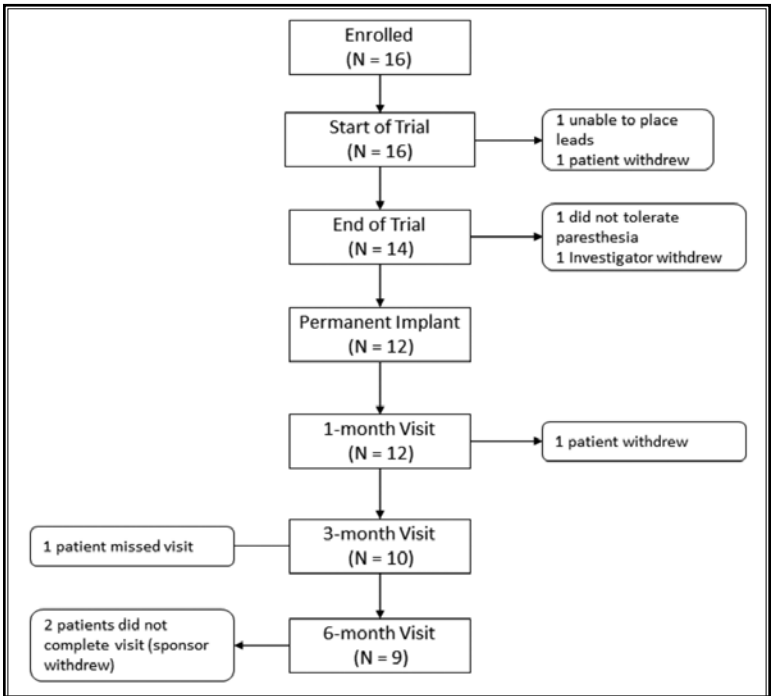

Fig. 2. *Flow of patient disposition throughout the duration of the study.*

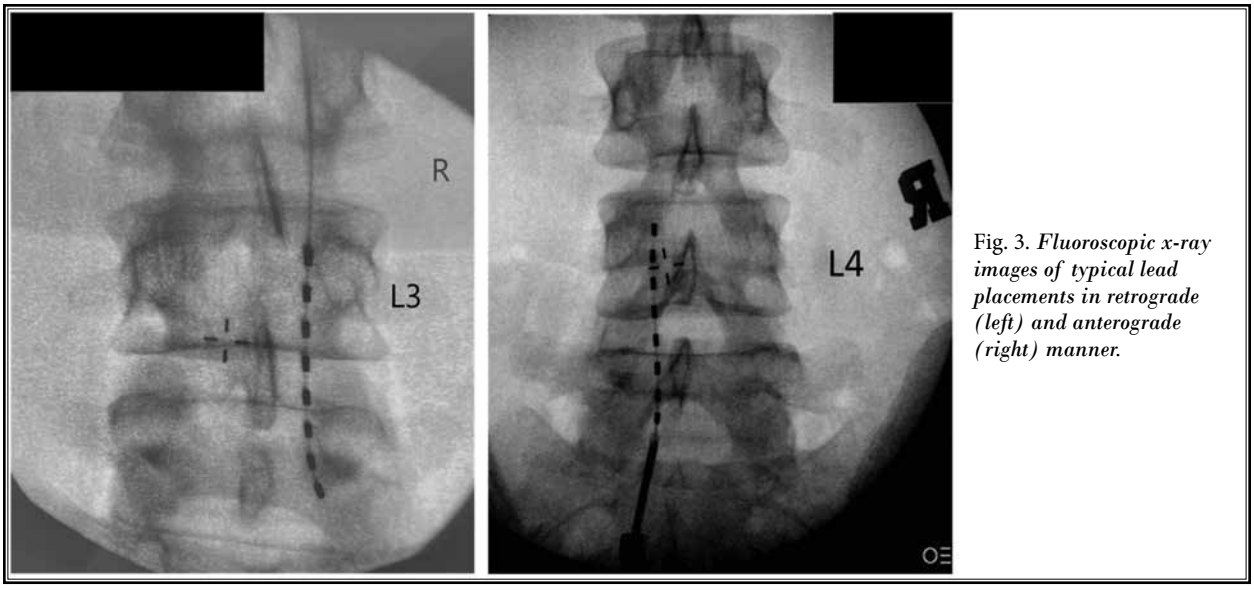

Fig. 3. *Fluoroscopic x-ray images of typical lead placements in retrograde (left) and anterograde (right) manner.*

Table 3. *NRS Pain Scores after DNR stimulation in study patients that completed assessment at 3-months.*

	Baseline Pain Score (NRS)	3-month Pain Score (NRS)	Pain Reduction
n	10	10	10
Mean	7.0	3.7	-3.3
SD	1.1	2.0	2.0
Min	6	0	-6
Max	9	8	1
P-value vs baseline		0.0006	

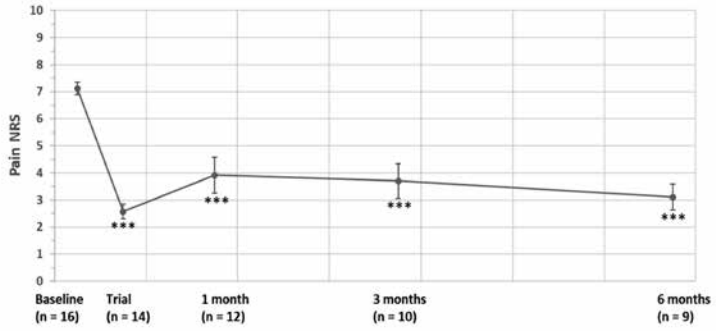

Fig. 4. *Mean NRS rating from patients at specified timepoints throughout the study. All NRS scores after treatment are significantly reduced relative to baseline ($P < 0.0001$). ***-denotes significance.*

sity of 3.2 ± 1.7 was also significant ($P < 0.0001$) and corresponds to a mean pain relief of 46.4 ± 27.1%. Mean pain reduction at the final 6-month assessment in the study was 4.0 ± 1.2 points on the NRS. Significant reduction relative to baseline ($P < 0.0001$) was sustained throughout the duration of the study and corresponds to 57.0 ± 19.6%.

Responder Rates

Figure 5 shows the responder rate (% patients with ≥ 50% pain relief compared to baseline) based on patients assessed at each timepoint. This ranged from 67% at one month (n = 14) to 89% at 6 months (n = 9) post operation, being 70% at the primary endpoint (n = 10). Responder rates were 53.8% (n = 13) at the 3-month point and 66.7% (n = 12) at the 6-month point after accounting for patients who withdrew before assessment due to lack of adequate pain relief (including failed trials).

Effect of Treatment on Quality of Life (SF-20 forms)

The SF-20 assessed the effect of treatment on the quality of life at the EOT, and at 3 and 6 months after device activation. The SF-20 consists of 20 items arranged into 6 categories in which patients assess their functioning and perceptions. Table 5 summarizes scaled scores (0-100) for each of the assessment categories. The higher the score, the better the patient feels about their quality of life. Figure 6 shows the effect of

Table 4. *Mean percentage reduction in pain intensity relative to baseline*.*

	EOT (n = 14)	1-month (n = 12)	3-month (n = 10)	6-month (n = 9)
Mean	62.8%	46.4%	47.3%	57.0%
SD	15.2%	27.1%	28.9%	19.6%
Minimum	42.9%	0%	-14.3%	28.6%
Maximum	85.7%	100%	100%	100%

* Values are reported as positive since these reflect reduction from baseline.

treatment relative to baseline assessment. Each axis in the radar plot represents the scale score (0-100) in each of the different categories of the assessment.

Neuropathic Pain Characteristics

The DN4 questionnaire tracked the effect of the therapy on certain characteristics of neuropathic pain at the EOT, and after 3 and 6 months of treatment. Table 6 summarizes the mean scores based on the patients assessed at each time point. The baseline score was 7.3 ± 1.7 indicating that the patients were experiencing a large amount of neuropathic pain, which was significantly reduced by treatment at the EOT by 47%. Similarly, long-term treatment provided significant reductions ($P < 0.05$) at the 3-month (40%) and 6-month (27%) point.

Level of Satisfaction

The patients were also asked about how satisfied they felt with treatment using a 7-category Likert scale at the EOT, 3 months, and 6 months post treatment. Table 7 summarizes the percentage of patients' responses in each category. Overall, patients were positively satisfied with the therapy, with more than 89% of them ranking at least slightly satisfied throughout the evaluation period.

Level of Improvement (PGIC questionnaire)

Patients were asked about their perception of change with the treatment using a 7-category Likert scale of improvement at the EOT, 3-month and 6-month post treatment timepoint. Table 8 summarizes the percentage of patients' responses in each category. Overall, all the patients felt that they positively improved with treatment.

Frequency of Study-Related Adverse Events

There were 7 adverse events (AEs) affecting 6 of the patients during the course of the study, with 4 of these AEs being unrelated to the treatment. One of these unrelated AEs was acute bronchitis, although this was a serious AE no deaths were reported. Only 3 study-related AEs were reported (Table 9), all of them being anticipated. Two were of moderate severity and one of mild severity. Lead movement reduced therapeutic effect in the patient that was deemed to require a revision, which could not occur before study closure due to hospital restrictions caused the COVID-19 pandemic. Nerve irritation was resolved pharmacologically, while the replacement of an external component of the recharging hardware resolved the only device-related AE.

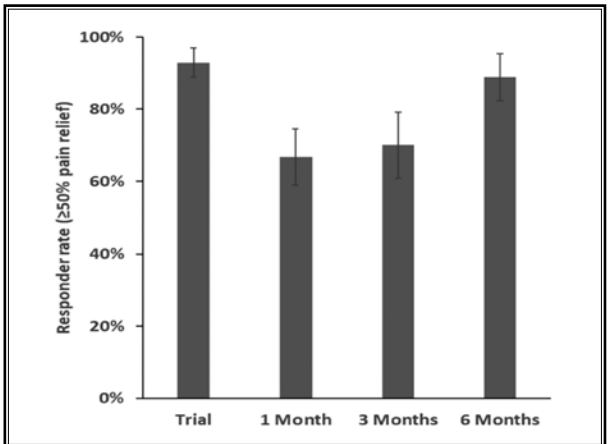

Fig. 5. *Responder rates throughout the study, based on patients that completed the assessment and reported ≥ 50% pain relief relative to basement.*

Table 5. *Scaled scores for SF-20 categories of quality of life.*

Category	Baseline	EOT	3-month	6-month
Pain Relief	21.3	32.3	40.0	44.4
Physical Functioning	31.8	35.1	40.8	43.5
Social Functioning	36.3	42.9	58.0	77.8
Mental Health	63.5	65.7	64.4	68.4
Role Functioning	14.1	19.6	17.5	30.6
Health Perceptions	53.1	61.8	59.5	66.1

Discussion

This feasibility study demonstrates that DNR stimulation with electrical parameters available for conventional SCS could be effective and safe for the treatment of chronic lower limb pain associated with CRPS. DNR stimulation offered significant and sustained pain relief

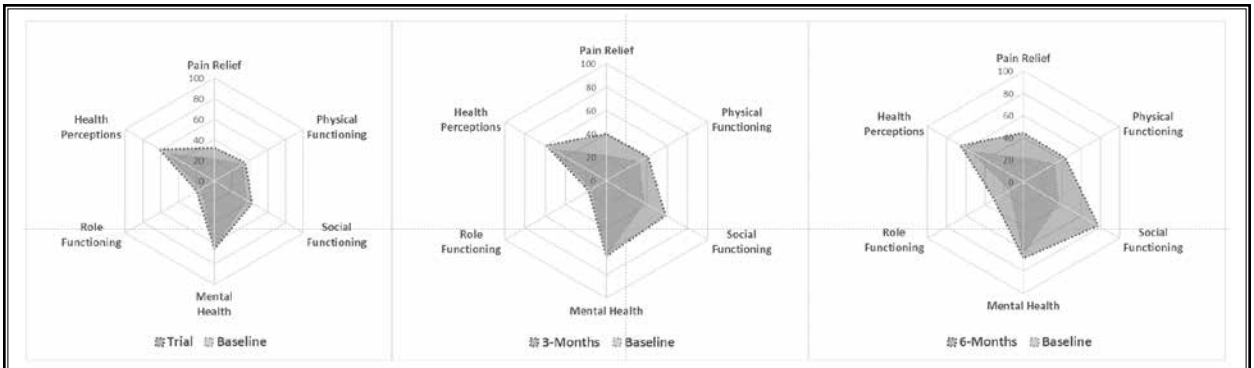

Fig. 6. *Radar plots showing scaled scores for each category of the SF-20 assessment of quality of life at each of the assessement visits (blue area) relative to baseline (orange area). Left: EOT, Center: 3-month, Right: 6-month. The higher the score and total area covered, the better the effect of the treatment.*

Table 6. *Mean DN4 scores (0-10 scale).*

	Baseline	EOT	3-month	6-month
n	16	12	10	9
Mean	7.3	3.9	4.4	5.3
SD	1.7	3.1	2.1	2.1
Minimum	5	0	0	0
Maximum	10	10	7	7
P-value vs baseline		0.003	0.002	0.030

Table 7. *Percentage of patients in each of the satisfaction categories.*

	EOT	3-month	6-month
n	14	9	9
Extremely Satisfied	57.1%	44.4%	33.3%
Moderately Satisfied	35.7%	33.3%	55.6%
Slightly Satisfied	7.1%	11.1%	11.1%
Not Sure	0%	0%	0%
Slightly Dissatisfied	0%	11.1%	0%
Moderately Dissatisfied	0%	0%	0%
Extremely Dissatisfied	0%	0%	0%

Table 8. *Percentage of patients in each of the PGIC categories.*

	EOT	3-month	6-month
n	14	9	9
Very much Improved	50.0%	33.3%	33.3%
Much Improved	42.9%	44.4%	55.6%
Minimally Improved	7.1%	22.2%	11.1%
Not Changed	0%	0%	0%
Minimally Worsened	0%	0%	0%
Much Worsened	0%	0%	0%
Very much Worsened	0%	0%	0%

with a low incidence of AEs related to the procedure or device. Patients with CRPS usually present with focalized pain which may be challenging to target and treat with the conventional paresthesia-based SCS. Some of these patients may also find it uncomfortable to feel paresthesia in areas where there is no pain. DRGS is an effective alternative option that provides better paresthesia targeting of painful areas while requiring less charge dosing. Unfortunately, DRGS is plagued with many AEs, particularly a high proportion of lead migrations that require difficult revisions. DRGS demands extensive training in order to master the implantation of leads near the targeted DRG. Our study shows that paresthesia-based intraspinal stimulation of the DNRs using commercially available neuromodulation systems with FDA-approved electrical parameters is a simple and promising alternative. The placement of one single lead ipsilateral in the affected limb, extending along the posterior aspect of the cauda equina, allows for precise stimulation of one or multiple dorsal roots and the generation of paresthesia in specific dermatomes, producing targeted pain relief.

The mean age of the patients enrolled in the study was 56.0 years with an average duration of their chronic pain associated with CRPS being 8.5 years. About 80% of patients presented with focalized unilateral pain in their feet, legs, or knees, with the other 20% experiencing mixed pain on 2 or more lower limb areas. Patients in the study reported a mean pain NRS score of 3.7 after receiving DNR stimulation at the primary endpoint which was the 3-month follow-up. This significant (P = 0.0006) reduction of 3.4 points relative to the baseline pain corresponds to a 48% reduction in pain intensity. The effect of the treatment was sustained up to the

Table 9. *Summary of study-related AEs.*

Event description	Number of AEs	Patients with AE	Percentage of patients with AE (out of n = 16)	Severity
Lead movement	1	1	6.3%	Moderate
Nerve root irritation	1	1	6.3%	Moderate
Difficult connecting to implanted device to recharge	1	1	6.3%	Mild

6-month follow-up visit, in which patients reported a significant decrease in mean pain intensity by 4.0 points, representing a 57% pain reduction. The percentage of patients who experienced ≥ 50% relief was 54% at 3 months and 67% at 6 months after accounting for trial failures (one patient) or patients that withdrew due to unsatisfactory pain relief before these follow-up visits (2 patients). When only patients that were assessed are accounted for, responder rates are 70% and 89% at the 3-month and 6-month visits, respectively.

In addition to indicating significant pain relief, patients reported an improvement in their quality of life after treatment. These improvements were seen to increase gradually with time. At the 3-month primary endpoint there were improvements in pain relief (88% relative to baseline) and social functioning (60% relative to baseline). By 6 months, there were further increases in pain relief (109% from baseline), social functioning (115% from baseline), and role functioning (117% from baseline). There were also reasonable improvements in physical functioning (37% from baseline) and health perceptions (25% from baseline). In all categories but mental health, treatment provided improvements above 10 points at the 6-month visit. This might be because patients already had a high baseline mental health score of 63.5. Furthermore, at 6 months post-treatment, patients self-reported a more than 10-point increase in social functioning (+ 42 points), role functioning (+ 17 points), health perceptions (+ 13 points) and physical functioning (+ 12 points) relative to baseline. Significant improvements were also reported in the neuropathic pain characteristics experienced by the patients. Patients were positively satisfied with the therapy, with more than 89% of them reporting some level of satisfaction throughout the evaluation period. There was only one patient who was slightly dissatisfied at the 3-month self-assessment. Overall, 78% and 89% of patients reported being 'Extremely Satisfied' or 'Moderately Satisfied' at the 3-month and 6-month visits, respectively. All patients perceived that they were globally improved by the treatment. Relatedly, 78% and 89% of patients felt 'Very Much Improved' or 'Much Improved' at the 3-month and 6-month visits, respectively. Even the patient who was not satisfied at the 3-month evaluation reported feeling globally improved.

The efficacy of DNR stimulation observed in this study is in line with existing literature. In 2017, Levine et al (19) published a study using DNR stimulation on patients experiencing 5 different pain diagnoses, of which one was CRPS. At the 3-month follow-up patients (n = 26) reported a mean 3.2 cm VAS score corresponding to a 58.4% pain reduction from baseline (19). This study, however, did not follow the CRPS patients (9 of the original 41 trialed were identified as CRPS) and therefore it is not possible to tell the effect that DNR stimulation had on CRPS patients. In this study, 12-15% of patients experienced AEs, this frequency is slightly larger than what we observed, but is similar to the rates for patients that were treated with conventional SCS.

The safety results were in line with what is expected when using paresthesia-based SCS with the commercially approved neuromodulation system utilized in the study. Out of the 7 AEs reported in the study, 3 were related to the study procedures or devices, with none of these being unanticipated. This is also in line with the safety profile reported by Levine et al. in their study (19). It is important to note that DNR stimulation as implemented here implies a lower risk for incidence of AEs compared to DRGS. The other 4 AEs were unrelated to the study and only one of these was a severe AE.

A major advantage of the using DNR stimulation is that a single octapolar lead with an electrode span of about 5 cm placed laterally can provide focalized paresthesia to multiple painful areas which negates the need to target multiple DRGs in patients with more diffused lower limb pain.

DNR stimulation provided significant reduction in lower limb pain due to CRPS in the cohort of patients in this study. The extent of pain reduction ranging between 45-60% obtained using stimulation of the DNRs is congruent with the one provided by conventional SCS, although DNR stimulation allows for more precise targeting of the painful area. Similarly, responder rates obtained in this study (50-70% range) are congruent with those reported for SCS in larger studies. The ef-

fect of the DNR stimulation was sustained up to the 6-month duration of the study.

Limitations

The main limitation of this study is its small sample size. Although it was intended to enroll around 20 patients in a relatively short period, enrollment and logistics were highly affected because the study was executed during the COVID-19 pandemic. Another limitation is that the study was not designed to be compared to other treatments such as conventional SCS or even sham treatment. This last option would not have been possible due to the inherent presence of paresthesia during active treatment. An additional limitation is the relatively short duration (6 months) of the study, although it could be considered long enough for a feasibility study.

Conclusion

The results of this short feasibility study confirm the functionality, efficacy, and safety of intraspinal stimulation of the DNRs in patients with intractable chronic lower limb pain due to CRPS using commercially approved systems and conventional parameters. These results merit consideration for designing a larger and longer study and expanding its application to treat upper limb pain as well.

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