ORIGINAL ARTICLE

Dorsal Root Ganglion Stimulation Normalizes Measures of Pain Processing in Patients with Chronic Low-Back Pain: A Prospective Pilot Study using Quantitative Sensory Testing

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■ **Abstract**

Background: Dorsal root ganglion stimulation (DRG-S) is used as a treatment for chronic low-back pain (CLBP), although its underlying mechanisms remain elusive. CLBP patients have been found to have reduced mechanoreceptive perception, reduced endogenous analgesia, as well as deep-tissue hyperalgesia when compared with healthy controls. Using quantitative sensory testing (QST), we studied if DRG-S in CLBP patients results in changes in pain processing.

Methods: Quantitative sensory testing was performed in patients before trial implantation of a DRG-S system for CLBP and just before the trial lead removal or at 1-month follow-up after the permanent implant. We determined the pressure pain threshold (PPT) and mechanical detection threshold (MDT) at the most painful lower-back location. PPT was also measured on the contralateral shoulder as a control. We obtained a measure of endogenous inhibitory pain modulation using conditioned pain modulation (CPM).

Results: We enrolled 11 patients (60 ± 16 years). Pain decreased from 8.5 ± 1.0 at baseline to 2.0 ± 1.5 on a 0-10 numerical rating scale with DRG-S ($P < 0.01$). From baseline to with DRG-S, PPT on the most painful location on the low back increased from 28.7 ± 13.6 to 43.4 ± 17.2 N/cm^2 ($P < 0.01$). MDT on the same location decreased from 8.1 ± 10.4 to 3.4 ± 4.7 mN ($P = 0.07$). PPT on the control location and CPM did not change significantly.

Conclusions: Our results suggest that DRG-S in CLBP patients reduces deep-tissue hyperalgesia in the low back, while improving mechanoreceptive perception. These changes in both neuropathic and nociceptive components of CLBP were accompanied by clinical improvements in pain and function. ■

Key Words: chronic low-back pain, conditioned pain modulation, dorsal root ganglion stimulation, pain processing, quantitative sensory testing

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INTRODUCTION

Chronic low-back pain (CLBP) is the most common musculoskeletal ailment globally.[1] CLBP is also the leading global cause of functional limitation and absenteeism from work resulting in substantial disease burden to patients and significant economic cost to societies.[2]

Changes in the neurophysiological processing of nociceptive information may play an important role in CLBP.[2] Both peripheral and central sensory processing changes associated with CLBP can be assessed using quantitative sensory testing (QST). QST consists of measuring detection and pain thresholds when applying standardized stimuli such as pin pricks or pressure.[3] Conditioned pain modulation (CPM) measurements are often incorporated in QST paradigms to quantify endogenous analgesia capacity through spinal descending inhibition.[4] Using QST, CLBP patients have been found to have reduced mechanoreceptive and proprioceptive perception,[5–8] reduced endogenous analgesia,[9] as well as deep-tissue hyperalgesia when compared with healthy controls.[3,10]

Neuromodulation is a treatment option for CLBP after conservative measures, interventional procedures, and potentially surgery have failed.[11,12] Spinal cord stimulation (SCS) is a neuromodulation treatment that delivers electrical impulses to myelinated, large-diameter sensory fibers in the dorsal columns to interrupt pain transmission. Although SCS is a suitable therapy for many CLBP patients,[13–15] there is a considerable proportion of patients who are not helped enough.[16–18] QST studies in CLBP patients implanted with SCS systems have reported no consistent significant effect of SCS on the sensory processing abnormalities observed in CLBP patients.[19]

Recently, electrical stimulation of the dorsal root ganglion (DRG-S) has emerged as a form of neuromodulation. DRG-S has demonstrated statistical superiority in a randomized controlled trial against SCS in the treatment of complex regional pain syndrome (CRPS)[20] and has shown promise in the treatment of low-back pain as well.[21–23] Because the DRG contains the cell bodies of all peripheral sensory neurons at each spinal level,[24] DRG-S delivers electrical impulses to more afferent fiber types when compared with SCS. DRG-S is believed to decrease pain through increased filtering of nociceptive signaling at the DRG and through the reduction of ectopic firing within the DRG.[25] DRG-S may have effects in the dorsal horn of the spinal cord as well.[21,26]

The effect of DRG-S on the neurophysiological processing of nociceptive information in CLBP patients is largely unknown. The aim of this pilot study was to utilize QST to analyze the effects of DRG-S on pain processing in order to provide insight into potential underlying mechanisms of action with DRG-S. We hypothesized that DRG-S in patients with CLBP would reduce deep-tissue hyperalgesia while increasing mechanoreceptive perception as well as endogenous pain modulation.

METHODS

This prospective experimental study was conducted at a large private interventional pain management institute with four locations across the New York City metropolitan area. Eligible participants were adults who were successfully treated with DRG-S as part of their standard of care for a primary diagnosis of CLBP between December 2019 and February 2020 (success criteria for DRG-S trial are defined below in the section "Dorsal Root Ganglion Stimulation"). CLBP was defined as low-back pain existing at least 6 months. We excluded patients with diabetes mellitus, peripheral neuropathy, shoulder pain, or those taking medications that could interfere with results from QST.[27] We did not exclude patients with a history of failed back surgery, as we wanted to study a sample of patients generally representative of the population receiving DRG-S for CLBP in our practice. This study was approved by the Western Institutional Review Board (WIRB) and was conducted in accordance with the Declaration of Helsinki.[28] All patients provided written informed consent. We did not prospectively register our study because it did not meet federal definitions of a clinical trial required to be submitted.[29,30]

Dorsal Root Ganglion Stimulation

Dorsal root ganglion stimulation leads (Proclaim™; Abbott, Plano, TX, U.S.A.) were implanted according to standard methods.[31] As per our usual practice, trials were performed unilaterally with trial leads placed on the more painful side of the low back. Based on our prior work on DRG-S for CLBP, leads were placed at the T12 DRG to address CLBP.[21] Additional leads were placed on other levels when coverage of additional areas was required. Paresthesia-based programming was performed, with settings subsequently being lowered to subthreshold levels for treatment. Trials lasted up to 5 to

7 days. After a successful trial, defined as pain improvement of more than 50% on a standard 0 to 10 numerical rating scale (NRS), patients were offered an internalized system. The internalized system had leads placed according to pain distribution, unilaterally or bilaterally. Typically, patients were programmed with standard bipolar contact configurations spanning the DRG. The average parameters were: pulse width of 260 ms, frequency of 14 Hz, and amplitude of 0.35 mA. Patients were instructed to decrease their amplitude in the event that paresthesias were perceived.

Quantitative Sensory Testing

Quantitative sensory testing has been used for decades in experimental and clinical research to measure somatosensory function,[32] and there is robust precedent for the use of QST to measure within-subject changes due to treatment.[33–37]

Quantitative sensory testing was performed by one investigator to ensure consistency and reproducibility of the results. All testing was performed in the same clinical out-patient treatment room with the same equipment. Patients were asked to abstain from using caffeine- or nicotine-containing products on the days of testing. Baseline testing was performed prior to the DRG-S trial or implant and again at either the end of the trial before the trial leads were removed or after 1 month of treatment with the permanent implant. Consistent with previously demonstrated neurophysiological pain-processing changes in CLBP,[3,5–10] the QST protocol tested three modalities: pressure pain thresholds (PPTs), mechanical detection thresholds (MDTs), and CPM. Patients were asked not to talk unless instructed to and not to perform attention-distracting activities during all tests.

A pressure algometer (Wagner Instruments, Greenwich, CT, U.S.A.) with a 1-cm^2 probe was used to assess PPTs. PPTs were averaged over three assessments for the two tested sites, with an interval ~15 seconds between each assessment to prevent wind-up effects. The algometer was placed perpendicular to the skin. Pressure was increased gradually by approximately 5 N/s and patients were asked to say "yes" as soon as the feeling became painful, throbbing, or burning. The algometer was then removed. First, PPTs were measured at a neutral reference point at the deltoid muscle contralateral to the most painful side of the back (a nonpainful site for all patients). This point was included to assess if DRG-S leads to any changes in central processing of pain. We chose the deltoid muscle as control area to avoid any potential influence from back pain pathology on lower-extremity dermatomes. The deltoid muscle is a testing site that is used in recognized QST paradigms for PPT testing.[38] PPTs were then measured at the most painful site on the low back, which was between the T12 and L5 vertebrae in this patient population. This site was also utilized for the MDT and CPM testing.

Mechanical detection thresholds were determined using a standardized set of von Frey filaments, applied in the following order of force: ascending, descending, and ascending/descending.[39] Patients were asked to say "yes" when they first felt a stimulus. The MDT was averaged over the three series.

Conditioned pain modulation was assessed using a cold pressor test as the conditioning stimulus and PPT at the back location as test stimulus.[40] Patients were asked to submerge the hand contralateral to the most painful side of the back in ice-cold water and maintain the hand submerged up to the wrist until the pain became unbearable (NRS of 10, or a maximum of 2 minutes). PPTs were measured before and directly after the cold pressor test. The CPM effect was determined as the relative change (%) in pain threshold.[41]

Clinical Data Collection

We collected demographics and information on diagnosis and clinical treatment. Additionally, we measured back pain, back pain related disability, and general health at baseline and with DRG-S, using the NRS, Oswestry Disability Index (ODI), 36-Item Short Form Survey (SF36), and Euroqol 5-D (EQ-5D), respectively.

Data and Statistical Analysis

Data are presented as *N* (%) and mean with standard error. Individual patient data points are presented as dots in each figure, in addition to the group average. Clinical outcome and QST measurement data at baseline and with DRG-S were compared using paired *t*-tests or the Wilcoxon signed-rank test, based on the distribution of the data. Normality of data was assessed using the Shapiro-Wilk test. Significance was set at $\alpha < 0.05$ for all testing. *T* and *Z* test statistics are provided. Sigmaplot 14 (Systat, Chicago, IL, U.S.A.) was used for analysis and visualization of data. No formal power analysis was performed for this pilot study.

Table 1. Patient Characteristics

Male/female sex, *n* (%)	5/6
Age in years, mean (SD)	60 (16)
Low-back pain, *n* (%)	11 (100)
Primary low-back pain diagnosis, *n* (%)	
Failed back surgery	6 (55)
Facet arthropathy	3 (27)
Facet arthropathy and discogenic pain	2 (18)
Additional pain diagnoses/body areas with pain diagnosis	
Leg, *n* (%)	8 (73)
Ankle/foot, *n* (%)	2 (18)
DRG-S lead location	
T12, *n* of leads	20
L4, *n* of leads	2
L5, *n* of leads	1
S1, *n* of leads	19

RESULTS

Eleven patients with an average age of 60 ± 16 years were enrolled. Complete data sets were obtained for all patients. Demographic and clinical information is presented in Table 1. In the 2 years preceding the study, a combined total of 13 epidural steroid injections, 13 lumbar medial branch blocks, 11 medial branch radiofrequency ablations, and two sacroiliac joint injections were performed in the 11 patients. All patients received bilateral or unilateral leads at T12 and S1; two patients required additional unilateral leads at L4, and one patient required a unilateral lead at L5. The leads at other levels, in addition to the T12 level targeted for CLBP,[21] were placed to cover a sacroiliac or radicular component of pain in addition to the CLBP. Four participants had their follow-up evaluation at the end of their DRG-S trial, and seven had their evaluation approximately 1 month after permanent implantation.

Dorsal root ganglion stimulation treatment reduced the mean back pain NRS from 8.5 ± 0.3 at baseline to 2.0 ± 0.5 with DRG-S ($t = 13.95$, $P < 0.01$, Figure 1A). Concomitant improvements in back pain-related disability (55 ± 3 to 21 ± 6, $t = 5.30$, $P < 0.01$, Figure 1B), general health (0.41 ± 0.04 to 0.74 ± 0.02, $Z = 2.37$, $P = 0.02$, Figure 1C), physical functioning (23 ± 2 to 47 ± 4, $t = 3.91$, $P = 0.02$, Figure 1D), and mental functioning (42 ± 7 to 52 ± 6, $t = 4.81$, $P < 0.01$, Figure 1E) were observed.

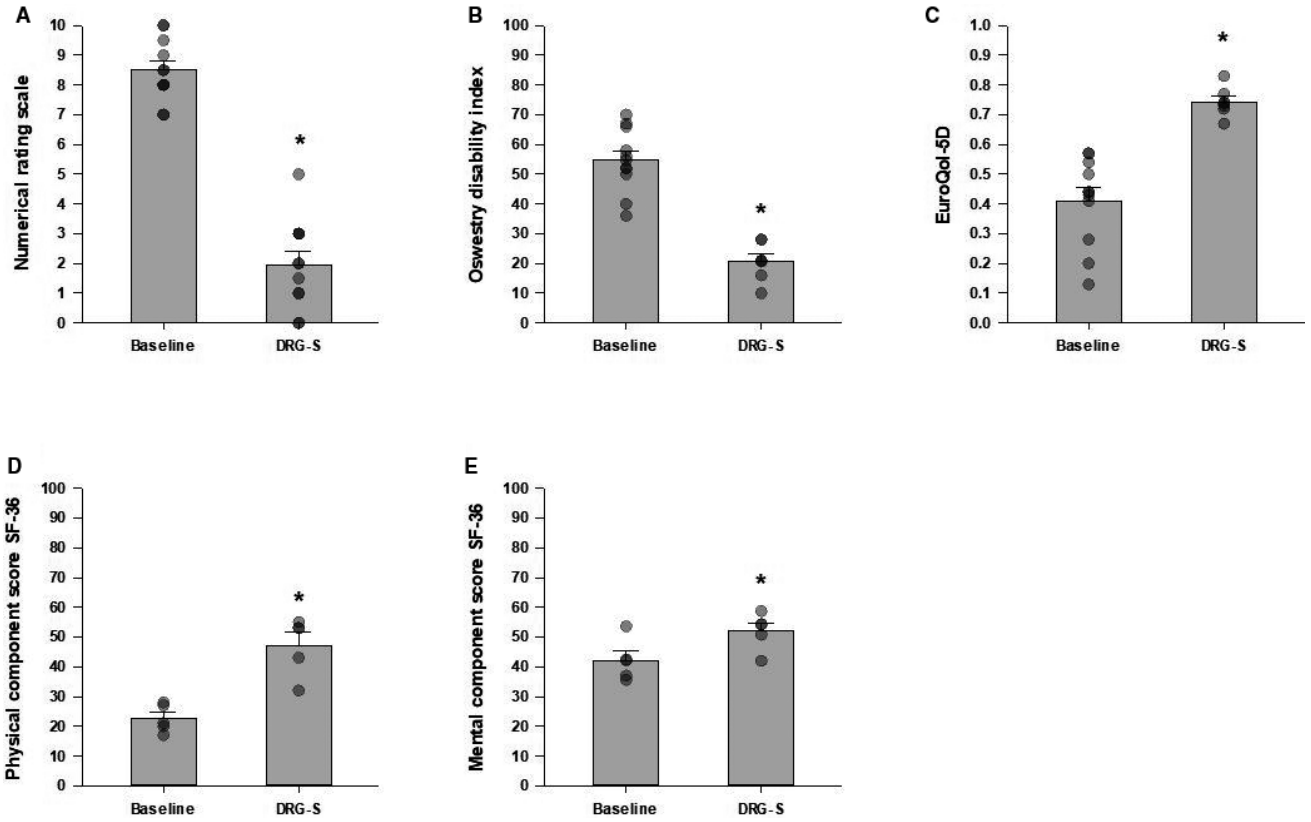

Figure 1. Clinical measurements at baseline and with dorsal root ganglion stimulation (DRG-S). Pain, back pain-related disability, general health, physical functioning, and mental functioning are presented in panels A to E, respectively. Individual patient data points are presented as dots. *$P < 0.05$.

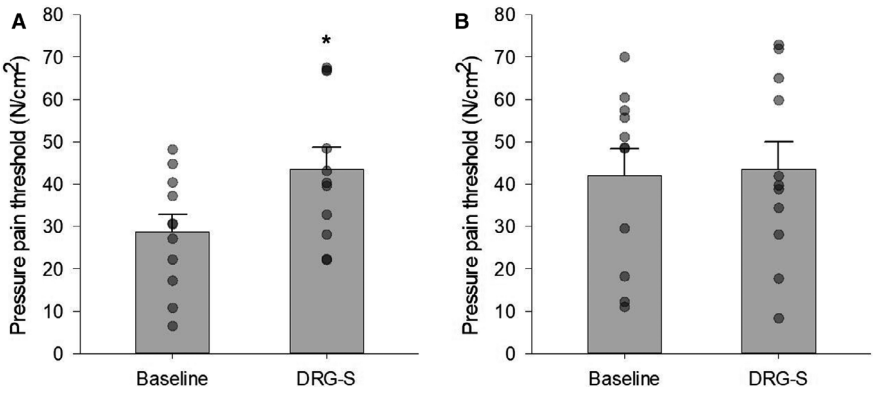

Figure 2. Pressure pain threshold (PPT) testing results at baseline and with dorsal root ganglions stimulation (DRG-S). Mean PPT at the most painful side of the low back is presented in panel A. Mean PPT at the control side on the deltoid muscle at baseline and follow-up is presented in panel B. Individual patient data points are presented as dots. $*P < 0.05$.

Quantitative Sensory Testing

Pressure pain threshold at the most painful side of the back increased from 28.7 ± 4.1 N/cm^2 at baseline to 43.4 ± 5.2 N/cm^2 with DRG-S ($t = 3.63$, $P < 0.01$)—Figure 2. PPT at the deltoid muscle did not change significantly from baseline to with DRG-S ($t = 0.38$, $P = 0.71$). MDT on the most painful side of the back showed a decreasing trend from an average of 8.1 ± 3.1 mN at baseline to 3.4 ± 1.4 mN with DRG-S ($Z = 1.84$, $P = 0.07$)—Figure 3. CPM did not change significantly with DRG-S compared with baseline ($t = 0.80$, $P = 0.44$)—Figure 4.

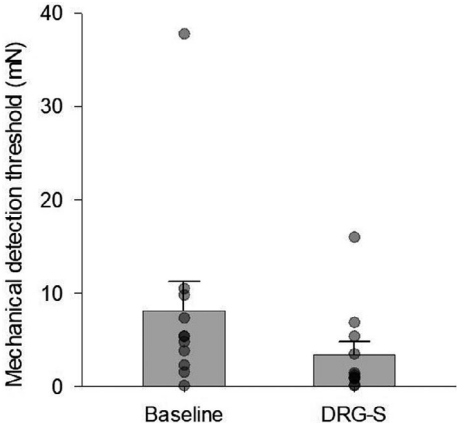

Figure 3. Mechanical detection threshold on the most painful side of the lower back at baseline and with dorsal root ganglions stimulation (DRG-S). Individual patient data points are presented as dots.

DISCUSSION

Principal Findings

The aim of this study was to utilize QST to analyze the effects of DRG-S on pain processing in order to provide insight into potential mechanisms underlying the efficacy of DRG-S in treatment of CLBP. Consistent with our hypothesis, we found that DRG-S therapy caused PPT to increase significantly at the most painful location of the low back, while MDT on the same location decreased. PPT at the pain-free deltoid control location and CPM did not change significantly. Pain, functioning, and quality of life scores improved substantially with DRG-S.

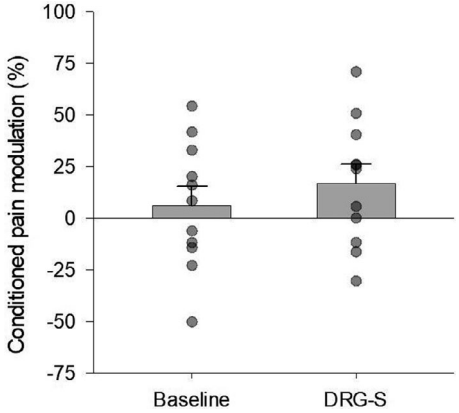

Figure 4. Conditioned pain modulation effect at baseline and with dorsal root ganglion stimulation (DRG-S). Individual patient data points are presented as dots.

Pressure Pain Thresholds

In previous studies, CLBP patients have been found to have deep-tissue hyperalgesia when compared with healthy controls.[3,10] This pressure hyperalgesia has been

described both at the low back[42] and at sites of the body distant from the low back.[10] We found that DRG-S therapy caused PPT to increase significantly on the most painful spot of the low back in CLBP patients implanted with DRG-S at T12. DRG-S thus decreased hypersensitivity to deep tissue pressure in the area specifically affected by CLBP. The observed increase in PPT is in line with a study by Mehta et al.[37] that measured low-back PPT in patients with CLBP at baseline and after DRG block or pulsed radiofrequency treatment. Similar to our study, they found increased PPTs after the DRG treatments, indicating a normalization of pain processing.[37] Kinfe et al.[36] performed QST in patients with CRPS of the knee by comparing thresholds to the contralateral knee before and with DRG-S. Consistent with our results, they found a trend ($P < 0.10$) toward increased PPTs with DRG-S, and the mean PPT value became closer to reference data in healthy individuals, indicating a normalization of sensitivity.

We also measured PPT in a pain-free control dermatome at the deltoid muscle. DRG-S did not induce changes in PPT at that location. The encountered increase in PPT at the affected low-back site, without a change in PPT at a nonaffected substantially distant dermatome, suggests that DRG-S for CLBP works either at the level of the DRG[26] or within the dorsal horn at areas where low-back afferent fibers converge.[26] It has previously been shown that DRG-S has cortical effects, in terms of relieving the interruptive effect of pain on cognition as measured through cortical gamma activity,[43] but the present study does not suggest that reversal of pain sensitization mediated in the brain is an important underlying mechanism of DRG-S for CLBP.

Mechanical Detection Threshold

Compared with healthy controls, CLBP patients have been found to have reduced mechanoreceptive and proprioceptive perception in the low-back area.[5–8] We found a trend toward a decreased MDT with DRG-S vs. baseline in our study, which suggests an improvement in mechanoreceptive perception.[5–8] The aforementioned study by Kinfe et al. also measured MDTs on the CRPS-affected knee with and without DRG-S, but did not find a change in mean MDT with DRG-S. However, they did find a significant decrease in the mechanical pain threshold with DRG-S. They concluded that in their CRPS population DRG-S led to normalization of pain sensitivity with limited effects on normalization of non-nociceptive perceptive thresholds, even though there was a decrease toward normalization in warmth detection thresholds.[36] Morgalla et al.[44] studied laser-evoked potentials before and with DRG-S in patients with neuropathic pain. Neuropathic pain is associated with disappearance of laser-evoked potentials. With DRG-S, Morgalla et al. found that evoked potentials reappeared, indicating a restoration of functional signal transfer from the periphery to supraspinal levels. They attributed this observation to effects on T-junction filtering in the DRG as well as to changes in cortical pain processing.[44]

Conditioned Pain Modulation

Chronic low-back pain patients have previously been found to have reduced endogenous analgesia,[9] as measured by CPM testing. We did not find a significant change in the CPM effect in CLBP patients with DRG-S. The aforementioned study by Mehta et al.[37] reported increases in CPM after DRG block or pulsed radiofrequency. Of note, the improvement in CPM in their study was not assessed with statistical testing, and a corresponding P value and the mean CPM values at baseline and after DRG treatments were associated with substantial variability. We similarly found an improvement in the mean CPM effect from a mean of ~ 6% at baseline to ~ 16% after DRG-S with substantial variability in both the baseline and DRG-S measurements. Along these lines, both our study and the study by Mehta et al. may serve as pilot studies that provide data for larger studies to assess with appropriate power whether DRG treatments improve descending inhibition as measured by CPM.

Quantitative Sensory Testing Studies in SCS Patients

A recent systematic review investigated QST changes with SCS and concluded that conventional tonic SCS does not seem to have an influence on most QST parameters.[45] The inconsistent QST results that Bordeleau et al. found were suggested to potentially be related to a broad range of pain disorders included, heterogeneity in the QST methods used, and heterogeneity in the study designs. Several studies have investigated QST measures in patients implanted with SCS specifically for CLBP.[46–48] Rasche et al.[46] performed QST in seven failed back surgery patients during periods when their SCS was on or turned off. At baseline they noted that, when compared with a nonpainful area, the painful areas exhibited reduced perception of cold, warmth, and mechanical stimuli (high thresholds). Similar to our

results, they found that stimulation resulted in improved MDT (lower thresholds), as well as improved detection of cold and warmth. Manresa et al.[47] studied 17 patients with radicular low-back pain with their SCS turned off and on. QST measures performed on the foot included electrical pain threshold and the intensity of electrical stimulation required to evoke a nociceptive withdrawal reflex. Additionally, they collected psychological surveys to assess if psychological factors were associated with the electrical pain threshold or nociceptive withdrawal reflex threshold. When SCS was turned on, they found no difference in the electrical pain threshold, but they found an increase in the current needed to evoke the nociceptive withdrawal reflex. Psychological factors were associated with the electrical pain threshold, but not with the nociceptive withdrawal reflex threshold. They concluded that pain relief from SCS is partially mediated by a decrease in the excitability of dorsal horn neurons in the spinal cord. Marchand et al. performed QST in eight failed back surgery patients by determining heat pain thresholds with SCS turned off and on.[48] They found that active stimulation increased heat pain thresholds.

Potential Clinical Implications

Although traditional SCS has shown to be associated with improvements in pain and quality of life in several studies,[13–15,49] 40–50% of CLBP patients treated with traditional SCS do not experience substantial pain relief.[16,17] Generally, pain relief also decreases over time.[18] The overall lower efficacy of traditional SCS in CLBP patients may be due to the fact that SCS tends to provide greater analgesic benefit in neuropathic pain conditions compared with nociceptive or mixed pain syndromes.[50–52] As the DRG houses all primary sensory neurons transmitting afferent nociception, it may be a better target for treating more nociceptive or mixed nociceptive/neuropathic pain syndromes, such as CLBP.[25] We,[21] and others,[22,23,53,54] have reported preliminary studies with DRG-S in patients with CLBP yielding promising results.

The QST findings in the present study are in line with the previously described effectiveness of DRG-S in CLBP.[21–23,53,54] CLBP has been described as a mixed nociceptive/neuropathic pain syndrome.[55] The nociceptive component of CLBP is understood to be pain arising from the vertebral column or its adnexa, evoked by noxious stimulation of structures in the lumbar spine, or from the deep soft tissues of the back (muscles and thoracolumbar fascia). PPT testing evokes pain from deep soft tissues and thus represents a test method pertaining to the mechanical Aδ- and C-fiber-mediated[56] component of CLBP. We found that DRG-S raises PPT in the painful area of the low back in CLBP patients, consistent with the presumed inhibition of nociceptive input with DRG-S.[26,57] The neuropathic component of CLBP may present as areas of numbness with decreased mechanoreceptive and proprioceptive perception.[5–8] The decreased MDT that we encountered with DRG-S in the present study represents an improvement of Aβ-mediated[39] mechanoreceptive perception related to neuropathic pain.

Limitations

Some limitations pertain to the present study. First, the sample size of this pilot study is relatively small. Second, five of the 11 included patients were over the age of 70, which may have influenced QST results. Pain thresholds increase with age[58] while analgesic effects due to CPM are reduced in older patients.[59] It is possible that more robust changes in QST would have been detected in a younger CLBP population. Additionally, we did not include a control cohort, which could have provided additional insight into the relationship of absolute QST values in CLBP patients vs. healthy individuals. However, such efforts have been well-described in previous publications,[3,5–10] and the present study was focused on DRG-S-induced within-group changes in sensory processing in patients with CLBP. Furthermore, for four patients, the trial period was used for data collection, while for seven patients 1 month of stimulation was used. This difference in stimulation period may have influenced the results in the two groups. The present subject group presents a convenience sample in which we obtained measurements during the two conditions of primary interest to the study: with vs. without DRG-S. In light of the very limited QST data in patients implanted with DRG-S systems (two studies[36,44] to our knowledge), we feel the presented work holds promise despite certain compromises that were made to be able to conduct the work in a clinical environment. Further, the use of patients who experienced a successful trial in addition to patients implanted after a successful trial is in line with the purpose of a trial in clinical practice, i.e., we investigated pain mechanisms in patients in whom DRG-S was demonstrated to work as a pain treatment. Finally, our QST protocol included CPM measurements to assess endogenous analgesia.

Another presumed measurement of central pain processing is the temporal summation of pain ('wind-up' phenomenon[60]), which is measured by determining the perception of pain to a brief series of repetitive stimuli.[61] It would be interesting to assess temporal summation of pain measurements in future studies on the neurophysiological effects of DRG-S.

CONCLUSIONS

Dorsal root ganglion stimulation appears to normalize measures of pain processing that are typically affected in CLBP patients. DRG-S decreased deep tissue hyperalgesia at the low back, while improving mechanoreceptive perception at the low back, indicating that DRG-S addresses both nociceptive and neuropathic components of CLBP.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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