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Very Low Frequencies Maintain Pain Relief From Dorsal Root Ganglion Stimulation: An Evaluation of Dorsal Root Ganglion Neurostimulation Frequency Tapering

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ABSTRACT

Background: Dorsal root ganglion neurostimulation (DRG-S) is effective in treating various refractory chronic pain syndromes. In preclinical studies, DRG-S at very low frequencies (<5 Hz) reduces excitatory output in the superficial dorsal horn. Clinically, we have also observed the effectiveness of DRG-S at low frequencies. We conducted a case series to describe the effect of very low-frequency DRG-S stimulation on clinical outcomes.

Materials and Methods: DRG-S for refractory low back pain was initiated at parameters consistent with published values. Thereafter, the stimulation frequency of DRG-S was reduced in a stepwise fashion to the lowest frequency that maintained pain relief. Pain intensity, disability, and general health status data were collected at baseline, prior to initiation of tapering, and at four weeks after each patient's lowest effective stimulation frequency was reached.

Results: After device activation ($N = 20$), DRG-S frequency was tapered from 16 to 4 Hz over a 4- to 17-week period, reducing charge-per-second by nearly two-thirds. Even so, pain relief was maintained at more than 75%, with consistent findings in the other measures.

Conclusion: DRG-S may have utility in treating chronic pain at lower stimulation frequencies than previously recognized. We have previously theorized that the mechanism of action may involve preferential recruitment of low-threshold mechanoreceptor fibers via the endogenous opioid system. Of clinical relevance, lower frequency stimulation maintains DRG-S efficacy regarding improvements in pain, disability, and quality of life. It can extend battery life and may potentially lead to the development of smaller implantable pulse generators.

Keywords: Dorsal root ganglion stimulation, frequency, low-threshold mechanoreceptors

Conflict of Interest: The authors have declared that no competing interests exist.

INTRODUCTION

Spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRG-S) are common forms of neuromodulation that are effective in treating chronic neuropathic pain (1-4). It is suggested that SCS is dependent on mechanisms that are limited to Aβ fibers in the dorsal columns and the corresponding Aβ associated gating mechanisms (5). DRG-S is a newer treatment modality that differs from SCS in its site of action and thus likely depends on other mechanisms underlying pain relief (6,7). The DRG houses the cell bodies of all primary afferent neurons transmitting sensory information from the periphery to the spinal cord, allowing modulation of the fibers that travel through it (6,8). Stimulation at the DRG leads to increased filtering of nociceptive input at the T-junction within the DRG, in addition to reduction of ectopic firing (9,10).

Several case series have demonstrated DRG-S to be an effective treatment for chronic low back pain and post-surgical joint pain; pain conditions traditionally considered nociceptive, or mixed pain syndromes (11-14). Improvements in function, quality of life, and psychological benefits with DRG-S have been robust, especially for syndromes that are typically less responsive to SCS (15). A functional MRI study in rodents demonstrated that DRG-S

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attenuates the blood oxygen level dependent (BOLD) response to noxious stimulation in regions of the brain associated with the salience, motivational, and emotional aspects of pain that are outside of the sensory-discriminative pain pathway (16). This response may partly explain the greater improvements in mood and function seen with DRG-S vs. SCS in clinical studies.

Two effective targets for DRG-S in treating low back pain have been identified: T12 and L2 (11,14,17). In a previous review article, we described a comprehensive hypothesis for the mechanism of action of DRG-S in relieving low back pain. We presented evidence from the literature that the effects of DRG-S may extend beyond the individual level to which it is applied and may affect more than just Aδ and C nociceptive fibers. Key mechanisms include 1) convergence and 2) low-threshold mechanoreceptor (LTMR) mediated inhibition (18). In addition to fibers carrying nociception, there are non-nociceptive Aδ-, Aβ-, and C- LTMR fibers traveling through the DRG that transmit innocuous light touch and mechanosensation (19-21). These LTMR signals are modulated by enkephalins and dynorphin (22,23). In the physiologic state, LTMRs typically fire at frequencies of 0.5–5 Hz (24-26); *in vitro* studies showed that applying very low-frequency stimulation to primary afferent neurons at the DRG or the dorsal root reduces excitatory output in the superficial dorsal horn (25-27). These converging lines of published evidence suggest that a key mechanism of action for DRG-S is the preferential recruitment of LTMR fibers at very low frequencies to modulate pain transmission through endorphin-mediated inhibition (18,28).

Anecdotally, in our clinic, we have observed excellent outcomes with DRG-S at much lower frequencies than have been previously reported in the literature (11,29). This is entirely consistent with the literature evidence as described in our previous review (18). The aim of this report was to summarize data from our patients treated with very low-frequency DRG-S.

MATERIALS AND METHODS

Subjects

This study was carried out with the oversight of the Northwell Institutional Review Board, which waived the requirement to obtain written consent. We collected clinical outcomes from a consecutive series of 20 patients who underwent DRG-S implantation as standard of care at a multidisciplinary pain management center for refractory low back pain with or without lower extremity involvement between August 2019 through January 2020. A total of 20 patients were included; 18 underwent a successful one-week DRG-S trial with >50% pain relief followed by permanent implantation with an implantable pulse generator (IPG) device using the Proclaim system (Abbott Laboratories, Abbott Park, IL, USA). An additional two patients had preexisting SCS systems that were explanted due to loss of efficacy and converted directly to DRG-S without a trial. For all patients, DRG-S leads were placed at T12 to cover their primary complaint of low back pain, together with additional leads at the L1 to S1 levels, based on their additional pain distribution (11). DRG-S was programmed at sub-perceptive levels at the time of permanent implantation with DRG-S settings at or above 16 Hz, and pulse widths of approximately 260 μsec based on average settings used in the ACCURATE trial (1). Patients were included only after reporting sustained pain relief for a minimum of one month after permanent implantation. Frequency tapering trials proceeded as described below.

Stimulation Settings and Clinical Tapering Strategy

Initial parameter settings including stimulation amplitude, pulse width, and frequency were recorded. Patients were assessed every two to four weeks and the stimulation frequencies were reduced by 25% or more at each visit while maintaining an amplitude that was adjusted to 0.025 mA below the paresthesia threshold. Pulse width was typically unchanged after initial dermatomal mapping. Based on the patient's response to treatment, it was at the physician's discretion to decrease the frequency to a greater or lesser degree at each visit. Tapering was performed as part of routine clinical care and repeated at each patient visit until the patient experienced a diminution of effect or reached the lowest frequency setting. The 4 Hz is the lowest device setting for the Abbot Proclaim IPG. Overall charge-per-second deliveries (C/s) reported in microcoulombs per second (μC/s) pretaper and posttaper were calculated as the product of the frequency (Hz), pulse width (μsec), and amplitude (mA) settings to assess changes in total charge delivered at different frequencies (30,31). The IPG was also interrogated to determine battery voltage consumption 1) during the tapering period and 2) from initial implant until the last clinical evaluation.

Clinical Outcomes

Clinical outcome domains were collected as per IMMPACT recommendations (32). Questionnaires were completed pre-implantation, prior to initiation of tapering, and one month after the frequency tapering endpoint was reached. The primary outcome measures were pain rating on a 100-mm visual analog scale (VAS), disability ratings as measured by the Oswestry Disability Index (ODI), and general health status ratings as measured by the Euro QOL 5-dimensions (EQ-5D) instrument. Secondary outcome measures included daily opioid morphine milligram equivalent (MME) usage prior to DRG-S, at initiation of frequency tapering, and at post-taper assessment; and the total number of additional pain interventions/procedures required during the taper period. Additionally, procedures performed for two years prior to DRG-S implantation were averaged per year and the total number of procedures performed post DRG-S implantation were recorded to allow for comparison. Opioid medication dosages were converted to MME using an opioid analgesic equivalent calculator based on the American Pain Society guidelines (33) and several reviews regarding equianalgesic dosing (34-36).

Data and Statistical Analysis

Descriptive statistics for nominal (*N*, %) and continuous data (mean, standard deviation) were calculated for reporting. Normality of the data was assessed using the Shapiro–Wilk test. Aggregated data are presented as mean ± standard deviation for normally distributed data whereas non-normally distributed data are presented as mean with range. The clinical outcomes were compared using paired *t*-tests and repeated measures ANOVA for normally distributed values and the Wilcoxon signed rank test or ANOVA on ranks for non-normally distributed data and *p* values are reported for all testing. If a significant effect for "Time" in repeated measures analysis was found, post-hoc testing with Bonferroni correction was performed to assess pairwise comparisons. A type I error rate (alpha) of 0.05 was used for statistical significance.

RESULTS

Twenty DRG-S patients with predominant low back pain with or without associated lower extremity pain were included in the study. Data from three patients have previously been reported from the period prior to the tapering of DRG-S frequency (11). Patient demographics and characteristics are summarized in Tables 1 and 2. Most patients had extensive back pain management histories, including instrumentation (n = 8) and previous laminectomy or discectomy without fusion (n = 2). All patients had bilateral T12 leads to cover lower back pain and a combination of unilateral or bilateral S1 or other lumbar leads to cover lower extremity pain.

Pretaper device programming settings were a mean frequency of 16 Hz, pulse width of 251 μsec, and amplitude of 0.467 mA (Table 3). Mean stimulation parameters on completion of the frequency taper trials were a frequency of 4 Hz, pulse width of 257 μsec, and amplitude of 0.642 mA. Of note, 95% of patients who completed the frequency taper trial reached the device's lowest frequency setting of 4 Hz. The one patient who did not reach 4 Hz for treatment did nonetheless continue to have good outcomes with a lower frequency (8 Hz), but further frequency tapering was interrupted by the development of high-impedance secondary to lead fracture that is currently awaiting revision.

Frequency was significantly lower at the post-taper assessment than at the pretaper assessment ($p < 0.0001$), whereas amplitude was higher by a small but statistically significant amount (0.14 mA; $p < 0.0001$). Overall charge was significantly reduced from a mean of 1.875 μC/s to 0.660 μC/s ($p < 0.0001$). The length of time to taper the stimulation frequencies ranged from four 4 to 17 weeks (80 days on average).

The battery voltage remained unchanged over the tapering period. Overall battery usage decreased from an initial 3.00 V at implant to an average of 2.99 V (range 2.96–3.00 V) at a mean (range) of 366 days (79–439 days) of device usage at last generator evaluation. Based on the manufacturer's published battery longevity charts (37), we estimate that this reduction in charge usage, relative to the pretaper settings, would result in the trajectory of battery life being extended by approximately 25%.

Table 1. Demographic and Clinical Characteristics.

Male/female sex, *n*	8/12
Age in years, mean (range)	56 (36–71)
Low back pain, *n*	20
Prior lumbar fusion, *n*	8
Prior laminectomy/discectomy without fusion, *n*	2
Prior failed SCS trial, *n*	2
Prior implanted SCS with loss of efficacy, *n*	3
Additional pain diagnoses/body areas with pain diagnosis	
Hip, *n*	3
Knee, *n*	1
SI joint, *n*	7
Ankle, *n*	1
Diabetic peripheral neuropathy, *n*	1
Chemotherapy-induced peripheral neuropathy, *n*	1
DRG-S lead location	
T12, n of leads	38
L1, n of leads	4
L3, n of leads	1
L4, n of leads	1
S1, n of leads	33

Primary Clinical Outcomes

Pain scores as measured by VAS improved by over 75% from a pretrial baseline of 88 ± 8 mm to 20 ± 13 mm post implantation ($p < 0.0001$, Fig. 1a). There was no statistically significant difference in mean VAS score from the initial DRG-S frequency setting post implantation to the final frequency setting after tapering (20 ± 13 mm vs. 22 ± 13 mm respectively, $p = 0.6437$). DRG-S also significantly reduced disability in the patient cohort over time. The ODI scores improved from a mean of 67 ± 13% pre-implantation to 19 ± 13% at the initial post implantation follow up visit ($p < 0.0001$, Fig. 1b). Mean ODI score remained statistically unchanged after tapering the stimulation frequency (19 ± 13% vs. 19 ± 11%, $p = 1.0000$). General health ratings significantly improved from pretrial baseline compared to post-implantation

Table 2. Secondary Clinical Outcomes.

	Pre-DRG implantation	Prefrequency tapering	Postfrequency tapering	*p*-value
Daily dose of opioid medication prescribed in MME, mean (range)	87 (7.5–600)	43 (0–150)	43 (0–150)	0.19
Interventional procedures/month, mean (range)	0.5 (0–1.7)	0.04 (0–0.18)	0.04 (0–0.18)	<0.01

Table 3. Comparison of Stimulation Parameters Achieved After Tapering With Typical Settings for Tonic SCS and HF SCS in Terms of Overall Charge.

	Frequency (Hz)	Pulse width (μsec)*	Amplitude (mA)	Charge/sec (μC/sec)
DRG-S pretaper	16	251	0.47	1.88
DRG-S posttaper	4	257	0.64	0.66
Tonic SCS†	50	400	3.5	70
HF10†	10,000	30	2.5	750

*Pulse width requires conversion from μsec (10^{-6}) to ms (10^{-3}) for calculation.
†Broadly representative parameters based on the published literature, provided for comparison/context (see text).

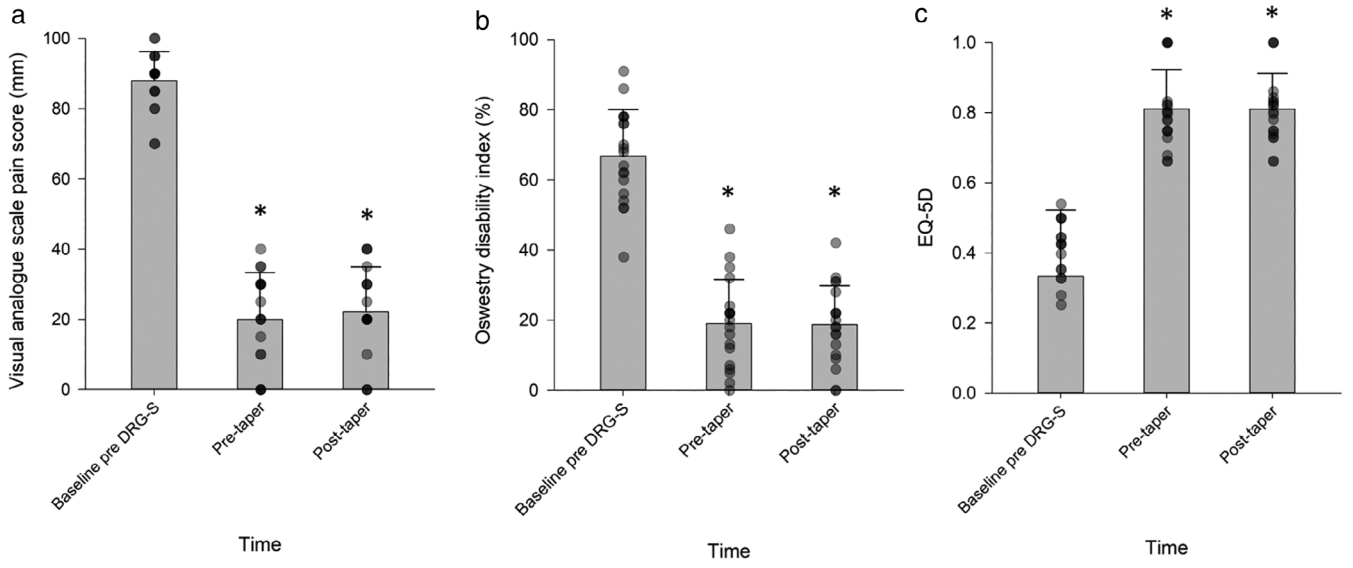

Figure 1. Mean and standard deviation of primary clinical outcomes visual analog scale pain score (a), Oswestry disability index (b), and EuroQOL 5D quality of life score (c) at pre DRG-S baseline, after DRG-S pre tapering of frequency, and post frequency tapering. Individual patient data points are visualized as dots. * $p < 0.01$ vs. preimplantation.

follow-up. EQ-5D index scores improved from a mean of 0.33 ± 0.19 at baseline to a mean of 0.81 ± 0.11 at initial post-implantation follow-up visit ($p < 0.0001$, Fig. 1c) and remained statistically unchanged after frequency tapering was complete (mean of 0.81 ± 0.11 vs. 0.81 ± 0.10, $p = 1.0000$). This represents a greater than 150% improvement in general health rating with DRG-S therapy that was maintained after tapering down the frequency.

Secondary Clinical Outcomes

Five out of the 20 patients were opioid naïve prior to DRG-S and maintained that status after implantation. The mean dose of opioid medication in the remaining 15 patients who were prescribed opioid medication was 87 MME (range 7.5–600 MME) prior to DRG-S implantation, Table 2. The average post-implantation dose was 43 MME (range 0–150 MME) prior to tapering of frequency, a dose that was maintained during tapering. Overall, 9 out of the 15 patients who were receiving opioid medication achieved a lower daily MME dose with DRG-S. The mean number of interventional procedures per month was 0.5 before DRG-S therapy and this rate was reduced to a mean of 0.04 per month at the completion of the follow-up period ($p = 0003$).

DISCUSSION

Principal Findings

The aim of this study was to determine whether lowering the stimulation frequency in patients who were successfully treated with DRG-S for axial low back pain with or without associated lower extremity pain would affect the therapeutic response in terms of pain, disability, and general health ratings. The results show that DRG-S is equally effective in preserving pain relief, disability, and general health status at 4 Hz (the lowest programmable device setting) as it is at the initial program frequency average of nearly 16 Hz. Furthermore, the average daily MME dose per patient was unchanged and patients did not require additional interventional procedures during this period.

Comparison to Prior Studies

The improvements seen with DRG-S therapy in this cohort are comparable to those published in other studies on DRG-S for axial low back pain (11,14,17). However, published data on the pain-relieving effects of varying stimulation frequencies in DRG-S is limited. The Neuromodulation Appropriateness Consensus Committee noted that best practice for programming are general principles, since individual patients may require different patterns, amplitudes, and spatial arrays of stimulation (29). Pulse frequency on current FDA approved devices have a programmable range of 4–80 Hz with a default value of 20 Hz based on the median frequency that was found to be effective in patients diagnosed with complex regional pain syndrome or causalgia in the lower extremities from the ACCURATE trial (1). There have been no dedicated clinical investigations thus far to explore optimal frequency settings with DRG-S in chronic pain conditions.

Our findings are consistent with the PROCO study, a randomized controlled trial that investigated the effects of different frequencies on analgesia in kHz frequency SCS, where SCS at a given frequency requires titration of pulse width and amplitude to balance total charge delivered for efficacy (38). To balance total charge in this study, amplitude was adjusted as pulse width was maintained to capture dermatomal coverage. However, charge deliveries in conventional SCS (39) and HF-SCS (40) are approximately 100 times and 1000 times greater, respectively, than DRG-S (Table 3), based on values from large clinical trials. Therefore, the adjustments needed for DRG-S parameter settings were not as significant in comparison. The mean amplitude was increased slightly while tapering the frequency, but not of the same order of magnitude as the frequency reduction, so the total charge delivered per second was still reduced by ~60%, reducing the DRG-S charge delivered to an even smaller proportion than that of conventional or HF SCS.

A preclinical study by Koetsier et al. compared low- (1 Hz), mid- (20 Hz), and high-(1000 Hz) frequency DRG-S in an animal model of painful diabetic polyneuropathy and found no significant differences in maximal pain-relieving effects across the different frequencies. Low-frequency DRG-S did, however, result in a delayed

wash-out effect that was not observed at the higher frequencies. This led the authors to conclude that low frequency 1 Hz DRG-S may represent a more optimal stimulation frequency compared to the higher settings studied (41).

A thorough understanding of how DRG-S inhibits pain is limited. In addition to local effects at the DRG which include enhanced T-junction filtering of action potentials (42), there is evidence that there are upstream effects occurring in superficial dorsal horn circuits. Multiple studies show that dorsal root fibers inhibit pain transmission in the superficial dorsal horn through low frequency action potential signaling. An *in vitro* study on rat neurons showed that low-frequency stimulation of 0.2–1.0 Hz of afferent A fibers reduced nociceptive transmission in the superficial dorsal horn (25). Low dose naloxone, an opioid receptor antagonist, blocked the effects, pointing to endogenous opioid system involvement (25,27). Another study demonstrated that 1.0 Hz stimulation of Aδ dorsal root fibers resulted in long-term depression of superficial dorsal horn output (26). Arcourt et al. showed that LTMR stimulation has a strong analgesic effect at low firing frequencies of less than 5 Hz. Additionally, they demonstrated that stimulation pulses generated action potentials 1:1 in LTMR fibers at frequencies up to 20 Hz, referred to as phase-locking or entrainment (24,31), while above 20 Hz, the LTMR fibers generated exponentially lower action potentials as the pulse frequency increased (24). Upstream effects occurring in superficial dorsal horn circuits are further theoretically supported by computational studies (43). Taken together, these findings indicate that very low frequency stimulation of LTMR fibers at the DRG induces pain relief through upstream modulation of dorsal horn pain processing circuits. The sustained therapeutic efficacy at lower stimulation frequencies seen in our patient cohort further supports that DRG-S analgesia is at least partially mediated through low frequency LTMR stimulation at the DRG reducing nociceptive transmission within the dorsal horn.

Implications

We observed that there was very little draw on the device's battery voltage during the frequency-tapering period (mean of 80 days) which may translate to a substantial increase in battery life because of the lower energy output compared to the pretaper parameter settings. This could have further implications of utilizing lower stimulation frequencies for DRG-S for clinical practice, such as the development of a smaller IPG. Figure 2 depicts typically used settings for different neuromodulation strategies and illustrates the marked reduction in total charge with a low-frequency DRG-S paradigm vs. conventional SCS or HF-SCS.

Limitations

Limitations of this study include the small sample size and relatively short follow-up period in some patients. Previous studies have demonstrated long-term efficacy with DRG-S (15,44), but whether the clinical outcome measures seen at lower stimulation frequencies in our patient cohort are sustained long-term needs to be further explored. A better strategy might be to compare the responses of matching patients with low and high frequency DRG-S over a much longer period. Moreover, in all but one patient, the frequency taper trial was limited to the lowest device setting of 4 Hz. This suggests that, although the device's floor is 4 Hz, the DRG's physiological floor may be lower still. This aligns with preclinical studies that demonstrated that stimulation of dorsal root fibers as low as 0.2–1.0 Hz frequency inhibits superficial dorsal horn output (25,26). Furthermore, informing patients that stimulation would be reduced before decreasing frequency settings could have resulted in a negative expectation that pain would return or increase, but as the results bear, that did not occur in our cohort. Nevertheless, future prospective trials should be double-blinded to avoid potential bias.

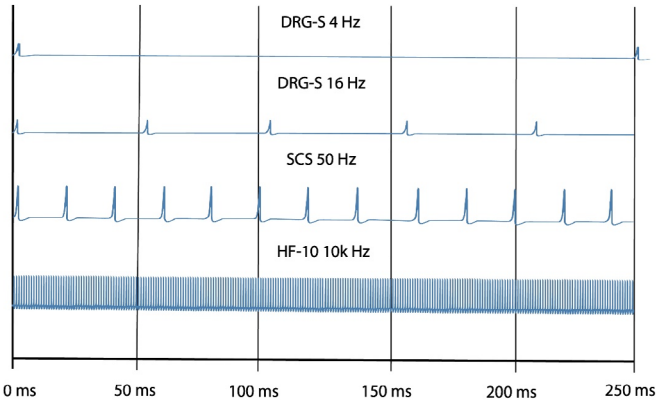

Figure 2. From top to bottom, pulse frequencies for very low-frequency DRG-S, DRG-S, conventional SCS, and HF10k waveforms are displayed over 250 milliseconds. [Color figure can be viewed at wileyonlinelibrary.com]

CONCLUSIONS

Tapering the stimulation frequency of DRG-S for treatment of chronic low back pain to low frequency (4 Hz) resulted in the maintenance of pain relief and functional improvement from DRG-S. By reducing energy requirements, this can prolong battery life and limit the exposure of patients to unnecessary electrical charge with maintained clinical efficacy. This study supports the concept that LTMR-mediated inhibition contributes to the relief of pain from DRG-S in addition to other spinal and supraspinal mechanisms. Larger, prospective studies are needed to corroborate this treatment approach.

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Authorship Statements

Kenneth B. Chapman, Tariq A. Yousef, and Noud van Helmond designed the study. Kenneth B. Chapman and Tariq A. Yousef acquired data. Kenneth B. Chapman, Tariq A. Yousef, Kris C. Vissers, Noud van Helmond, and Michael D. Stanton-Hicks analyzed and interpreted data. Kenneth B. Chapman prepared the manuscript draft with important intellectual input from Tariq A. Yousef, Kris C. Vissers, Noud van Helmond, and Michael D. Stanton-Hicks. Kenneth B. Chapman, Tariq A. Yousef, Noud van Helmond, Kris C. Vissers, and Michael D. Stanton-Hicks edited the manuscript. All authors approved the final manuscript.

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COMMENTS

This study is hampered by the small size of the trial reported. Nevertheless, the potential for serious application of this technique for pain states beyond those conventionally considered for implantable neuromodulation therapy is considerable.

Further clinical research efforts looking into optimizing this approach for durable, long term depression of A-delta fibers at the level of the DRG are needed to justify a broad application. Of note, wash-in and wash-out times for various disease states, particularly in CRPS and Postherpetic Neuralgia, are needed to better understand the optimization of the programming paradigms.

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Dorsal root ga Stimulation is inherently energy efficient due to the simple fact that it has very limited quantities of CSF to contend with. Combining that with the concept that the therapy can be just as effective while using extremely low frequencies that require even less energy is encouraging and exciting.

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This study makes a very important contribution to the quest for ever lower power consumption from implanted stimulator systems. It has obvious advantages to battery life, and theoretical advantages to therapy loss, if tolerance is a contributor to that. The authors are careful to state that a prospective trial is desirable, something which is possible to do on a blinded basis in the era of paresthesia free stimulation. It is also important to note the indications treated here do not include neuropathic pain syndromes such as CRPS, which may respond differently to frequency reduction. However I suspect the study will be influential in programming practice fairly immediately.

The study is not long enough to see the actual impact on battery longevity that the change results in, but information from the manufacturer's literature is presented that is very interesting: the reduction of 60% in power delivery to tissue is predicted to result in a prolongation of battery longevity of just 25%. This suggests that even at standard settings, the IPG itself is consuming more than half of the battery power. Assuming that internal power consumption is roughly constant, at the reduced settings achieved in this study, the internal circuitry of the IPG will account for more than three quarters of battery depletion. Power consumption in tissue can be reduced further. The authors have hit the 4 Hz floor of the device without being limited by therapy loss in a single case, so the frequency could almost certainly be lowered even more, device permitting. In addition, we have previously shown that careful anatomical positioning of DRGS leads within the exit foramen can substantially reduce power requirements (1). However, chipping away further at tissue power delivery will produce diminishing returns while the device itself is consuming most of the power. To fully realize the benefits of studies like this, we need devices that use less power internally. Over to you, manufacturers.

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