Comparison of Paresthesia Mapping to Anatomical Placement in Burst Spinal Cord Stimulation: Initial Trial Results of the Prospective, Multicenter, Randomized, Double-Blinded, Crossover, CRISP Study

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Introduction: In this prospective, multicenter, double-blinded, randomized, crossover study, we compared the therapeutic efficacy of burst SCS delivered using a lead implanted with the paresthesia mapping approach to a lead implanted with an anatomical placement approach.

Materials and Methods: Subjects with chronic low back pain were implanted with two leads, one using paresthesia-mapping approach (PM) and the second using anatomical placement procedure (AP). Stimulation contacts were chosen using the standard intraoperative paresthesia-testing procedure for the paresthesia-mapped lead or an activated bipole overlapping the T9-T10 junction for the anatomical lead. Amplitude for either lead was selected such that no sensory percepts were generated. Subjects were assessed at baseline and after a trial period during which they tested each lead for two weeks in random order. Eligible subjects had the option to receive permanent implants using their preferred AP or PM approach at end-of-trial.

Results: Of the 53 subjects who completed both trial periods, 43 (81.1%) experienced at least 50% back pain relief with at least one lead. Nearly half of these (20; 46.5%) were profound responders who experienced at least 80% back pain relief with either leads. Primary and secondary outcomes, at the end of trial, showed significant improvements for both AP and PM leads from baseline yet were not significantly different from each other.

Discussion: The trial results of this study suggest that similar clinical outcomes can be achieved in burst SCS when performing lead placement either using paresthesia mapping or anatomical placement with imaging references.

Keywords: Burst, burst spinal cord stimulation, failed back surgery syndrome, implant techniques, neuropathic pain

Conflict of Interest: Dr. Adnan Al-Kaisy received travel sponsorship and speaker fees from Medtronic and Nevro Corp, is principal investigator in separate studies sponsored by Medtronic, Nevro, and Abbott, and has financial interest in Micron Devices. Dr. Stefano Palmisani received speaker fees and sponsorships to attend professional meetings from Medtronic and Nevro, and is principal investigator in a study sponsored by Saluda Medical. Dr. David Pang received sponsorship to attend professional meetings from Medtronic and Nevro. Dr. Ganesh Baranidharan serves as a paid consultant for Abbott, Nevro, Boston Scientific, and Nalu. Mr. Adil Raza and Dr. Filippo Agnesi are employees of Abbott. All remaining authors have no conflict of interest.

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INTRODUCTION

Spinal cord stimulation (SCS) is a well-established therapy for the treatment of chronic, intractable pain. A systematic meta-analysis of the literature reported that SCS reduces pain, improves quality of life, reduces medication use, allows some patients to return to work, and may also result in significant cost savings over time for the health-care system, while having minimally significant adverse events in patients with neuropathic back and/or leg pain (1). Conventional tonic SCS utilizes electrical pulses delivered regularly at, generally, 40–60 Hz. To be effective, this type of stimulation is delivered at intensities that produce a tingling sensation, known as paresthesia, which overlaps the painful area (2). The burst SCS stimulation design, on the other hand, consists of short, known as paresthesia, which overlaps the painful area (2). The burst SCS stimulation design, on the other hand, consists of short, high-frequency pulse trains that are presented at a consistent rate. BurstDR stimulation (Abbott, Plano, TX, USA) delivers bursts—five pulses at 500 Hz—at a frequency of 40 Hz; repolarization occurs in the inter-burst interval (2). Burst SCS is generally delivered at a pulse amplitude that is lower than the patient’s sensory threshold (and can be as little as 10% of those necessary for tonic SCS) and can therefore be paresthesia-free (2–4).

The usual strategy for percutaneous SCS implantation is to thread a lead into the epidural space using a Touhy needle. The lead is advanced to an approximate target vertebral level and then incrementally adjusted in both its physical location and active contact(s) based on awake intraoperative paresthesia mapping. For this, one or more contacts are activated, and the patient is queried regarding the site of the resultant perceived paresthesias and any stimulation-related discomfort. The leads may then be moved, and/or different contacts activated, along with ongoing patient feedback to refine the paresthesia distribution. The paresthesia-mapping lead placement method is well suited to tonic SCS treatment because it achieves paresthesia coverage of painful regions, which is necessary for pain relief (5). Intraoperative paresthesia mapping may not, however, be necessary nor desirable for burst SCS treatment. Because burst SCS is delivered as sub-sensory amplitudes, it does not create paresthesias and therefore there may be no need to achieve precise pain-paring overlap and the likelihood of uncomfortable stimulation is low. Furthermore, intraoperative testing with paresthesia-based tonic stimulation may not correlate with the location necessary to achieve analgesia with burst SCS.

Another lead positioning method exists, in which leads are simply placed based on anatomical landmarks without intraoperative paresthesia testing or patient feedback. This method does not require the patient to participate in an iterative feedback process during the implantation procedure, a valid consideration when patient reporting may be compromised by anesthesia or medications, anxiety, acute discomfort, and/or surgical positioning. Another benefit of this method may be shorter procedural times due to anatomical or landmark-based (vs. patient feedback-based) lead placement process, as confirmed in a feasibility study that compared lead placement via paresthesia mapping with lead placement methods that do not rely on patient feedback (6). Anatomical lead placement generally results in broad paresthesias; for leads at T8-T11, coverage may include much of the back and legs. This method is commonly used for high-frequency stimulation lead placement which also uses a paresthesia-free SCS stimulation design (7). Because the stimulation is not perceptible, it is speculated, there is no need to verify paresthesia overlap of the painful area. Indeed, the use of high-frequency stimulation with leads placed via anatomical positioning has demonstrated sustained back and leg pain relief over a period of 24 months in 65 patients (7) and outcomes that were statistically superior to those with conventional SCS using leads placed via paresthesia mapping through 12 months in 171 patients (5).

Paresthesia mapping is the default method for lead placement in tonic SCS and burst SCS implantation methods have generally also incorporated paresthesia mapping often to maintain the option of reverting to a paresthesia-based, tonic stimulation design should it be clinically necessary. However, there is no data to support whether or not this is ideal. The simpler method of placing the leads using anatomical positioning may hold utility in burst SCS, given that it may be an efficient use of the procedure room while achieving effective outcomes in a paresthesia-free SCS waveform option. This study was designed to compare the therapeutic efficacy of paresthesia mapping-based SCS lead implantation strategy with the anatomical positioning approach during treatment with burst SCS. In this report, we discuss the results of the SCS trial phase. A planned publication will detail long-term treatment outcomes up to 12 months.

METHODS

This was a prospective, randomized, double-blinded, crossover study conducted at two centers in the EU between 2017 and 2019. The study was publicly registered on ClinicalTrials.gov as NCT02986074, was approved by York NRES ethics committee (EC), and all subjects gave informed consent.

Subjects

Subjects were recruited from the investigators’ clinical practices. Adults of both genders were included based on their diagnosis of failed back surgery syndrome (FBSS) and intractable predominant low back pain with intensity of at least 60 on a 100-mm visual analog scale (VAS), provided that medical examination indicated that they were good candidates for a neurostimulation system. Exclusions for participation included current or planned pregnancy, contraindications to SCS treatment, and medical, psychiatric or social conditions that could compromise safety or study data interpretation. Subjects agreed to hold their customary dosage of pain medications stable throughout the four-week trial period.

Treatment

Subjects underwent an SCS trial (Invisible Trial system; Abbott, Plano, TX, USA) during which two octopolar cylindrical leads were implanted percutaneously. To allow for within subject comparison, different methods for placement of each lead were employed. One lead was placed using paresthesia mapping to maximize the overlap between painful regions and evoked paresthesia, based on active stimulation and patient feedback during the lead placement procedure. The other lead was implanted according to an anatomical approach extending over the T9-T10 junction, without paresthesia mapping (see Fig. 1). For both leads, three different programs were applied. For the anatomical lead, program 1 corresponded to a bipolar directly over the T9-T10 disc, program 2 was above the T9-T10 disc, and program 3 was below the T9-T10 disk. These programs were utilized to optimize therapy efficacy. Three programs were also provided for the paresthesia mapping lead. Once an adequate paresthesia mapping program was identified, it was effectively duplicated in the two additional programs using the same set of contacts and parameters to preserve patient blinding (Fig. 1).
Standard practice for the sites involved in the study, is to evaluate subjects during the trial phase for two weeks. Since two implant approaches were evaluated, each arm was tested for two weeks in a randomized fashion. Moreover, typical of practices performed outside of the United States, one site used permanent 615

Figure 1. Examples of lead placements. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 2. Study flowchart. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 3. Tornado diagram showing back pain relief relative to baseline for each of the leads, at the end of their respective trial periods. Data are plotted individually for each of the 43 subjects, with orange bars indicating pain relief with the lead placed via paresthesia mapping (PM) and blue bars indicating pain relief with the lead placed using anatomical positioning (AP). Subjects above the solid line were profound responders (pain relief greater or equal to 80%). [Color figure can be viewed at wileyonlinelibrary.com]

Standard practice for the sites involved in the study, is to evaluate subjects during the trial phase for two weeks. Since two implant approaches were evaluated, each arm was tested for two weeks in a randomized fashion. Moreover, typical of practices performed outside of the United States, one site used permanent
leads during the trial procedure requiring additional steps such as anchoring the leads.

During the trial phase burst stimulation was used (five-pulse bursts [1-ms pulses; 500 Hz] in both leads at an overall rate of 40 Hz (2,8)) with stimulation amplitude at 60% of sensory threshold (subsensory, paresthesia-free).

Study Design
At a baseline pre-treatment visit, subjects completed assessments of their pain (VAS [back-specific, and leg-specific]), quality of life (EuroQol assessment [EQ-5D] (9)), and disability (Oswestry Disability Index [ODI] (10)).

Subjects completed two weeks of trial stimulation with one lead and then crossed over to two weeks of trial stimulation with the other lead (see Fig. 2). The order of presentation was randomized and subjects, investigators, and study personnel responsible for collecting outcomes were blind to the sequence. Because the burst SCS stimulation design does not create a sensory percept, it was anticipated that stimulation with the two leads would not be distinguishable on the basis of treatment effects. After each two-week trial period, subjects repeated the outcome assessments. Subjects who completed both two-week trial periods and had at least 50% reduction of their baseline pain (calculated as the mean of back VAS scores across three-day pain diaries) during at least one of them, stated a preference for either the first or second two-week period, thus selecting their preferred lead. If the subject had no preference, the lead placed using the anatomic positioning technique was arbitrarily activated.

Data Analysis
All tests were conducted using SAS 9.4. Changes relative to baseline were calculated for each subject. Order effects due to the crossover study design and group differences between the two implantation strategies were determined. Unless otherwise stated, data are presented as means, standard deviations (SD), or proportions. A repeated measures ANOVA (RMANOVA) was performed to determine any differences between the two groups from baseline. Tukey’s post hoc comparisons were also performed to determine specific pairwise differences.

RESULTS
The study enrolled 60 subjects: the cohort was comprised of 43.3% men and 56.7% women with a mean age of 51.4 years (±12.1). All subjects had chronic FBSS pain of the back and legs (see Table 1). Six subjects were withdrawn from the study prior to the trial periods. Specifically, three subjects were excluded due to protocol violations (low back pain of <60 mm) and three subjects decided not to pursue SCS treatment for personal reasons. One subject was explanted during the trial period due to an adverse event (see below).

Table 1. Subject Demographics and Baseline Characteristics.

| All enrolled subjects |
|-----------------------|
| **N**                | 60 |
| **Gender**           | 26 (43.3%) men; 34 (56.7%) women |
| **Age**              | 51.6 (±12.1) years |

Of the 53 subjects who completed both trial periods, 43 (81.1%) experienced at least 50% back pain relief with either the anatomical positioned lead and/or the paresthesia mapped lead. Nearly half of these (20; 46.5%) were profound responders who experienced at least 80% back pain relief with either leads (see Fig. 3). When asked which lead was preferred during the trial period, 21 subjects (48.8%) selected the one placed via paresthesia mapping (PM) and 21 (48.8%) subjects selected the one placed with anatomical positioning. One (2.4%) subject had no preference, so the anatomically placed lead was activated for this subject. There were no obvious differences in subject group demographics based on lead preferences. In addition, no order effects were observed between the two groups (p < 0.36).

For back pain, the VAS at baseline was 78.9 (±12.5) mm which improved to 24.6 (±21.3) mm when the anatomically placed lead was activated (p < 0.001) and 22.5 (±19.2) mm when the
The paresthesia mapping lead was activated ($p < 0.001$) (see Fig. 4). There were no statistically significant differences in back pain scores between the paresthesia mapped lead vs. the anatomically placed lead ($p < 0.8501$).

Leg pain, likewise, improved during the trial. When the anatomically placed lead was activated, leg pain was reduced from 60.4 ($\pm$26.9) mm at baseline to 17.7 ($\pm$17.5) mm ($p < 0.001$). Similarly, when the paresthesia mapped lead was activated, leg pain was reduced to 15.7 ($\pm$19.5) mm ($p < 0.001$). There were no statistically significant differences in leg pain scores between the paresthesia mapped lead vs. the anatomically placed lead ($p < 0.9081$).

Similarly, both quality of life and disability measures were significantly improved from baseline, for both lead placement approaches. The average EQ5D score was 0.37 ($\pm$0.14) at baseline, which improved to 0.71 ($\pm$0.15) when the anatomically placed lead was activated ($p < 0.001$) and 0.67 ($\pm$0.15) when the paresthesia mapped lead was activated ($p < 0.001$). The improvements in both groups did not statistically differ from each other ($p = 0.4427$). The average ODI score was 59.0 ($\pm$12.3) at baseline, with 91% of subjects rating their disability as “severe” or worse (score of 40 or higher (11)). When the anatomically-placed lead was activated, the average ODI score decreased to 38.4 ($\pm$17.5). At this point, 43% of subjects continued to rate their disability as “severe” or worse. When the paresthesia mapped lead was activated, the average ODI score was 39.6 ($\pm$16.1) after the trial, where 53% of subjects continued to rate their disability as “severe” or worse. The improvements in both groups were statistically significant relative to baseline ($p < 0.001$) but did not statistically differ from each other ($p = 0.9357$); see Figs. 5 and 6.

Overall, there were 21 reported adverse events by 12 subjects before the end of the trial phase. Of these, 10 adverse events by 7 subjects were classified as either related to the procedure or

![Figure 6](image-url)

**Figure 6.** The proportion of subjects with severe pain-related disability, as rated by the ODI, decreased during the trial for subjects in both groups, but did not statistically differ between groups. [Color figure can be viewed at wileyonlinelibrary.com]
device. Specifically, these adverse events were numbness in pain areas ($n = 2$), increase in pain ($n = 3$), unpairing with the IPG ($n = 2$), headache ($n = 1$), dural puncture ($n = 1$), and nonremoval of suture ($n = 1$). The subject who reported the postural headache due to the dural puncture was explanted. One subject who reported an increase in pain had the device switched off and started experiencing pain relief once the device was switched back on. All other adverse events were resolved by reprogramming and subject education.

**DISCUSSION**

In this randomized, double-blind cross-over study of 43 subjects, burst proved to be an effective intervention for chronic lower back pain. Enrolled subjects reported significant reduction from baseline levels in VAS scores and disability levels, and significant increases in quality of life during the trial. In fact, 81% of subjects reported 50% or more pain relief, and 46.5% achieved 80% pain relief.

The study’s key aim was to establish whether lead implantation method was an important factor affecting the efficacy of burst SCS. Subjects were randomized to a trial period with stimulation from a lead placed by one method—paresthesia mapping or anatomical placement—and then crossed over to stimulation with a lead placed by the other method. Subjects’ preference during the trial was evenly divided; 21 subjects selected the paresthesia-mapped lead while 21 selected the lead implanted using anatomical positioning. No statistical or clinically significant differences in ratings of pain, disability, or quality of life were observed between subjects in the two groups. An even distribution in preferences was expected given that the two implantation techniques were equivalent in providing pain relief and reduction of associated disabilities.

Thus, this study suggests that equivalent clinical outcomes can be obtained with burst treatment regardless of choice of lead placement methods. Since, on average, both implant methods appear to be equally effective, implanters have the option to employ the method that is most appropriate to the circumstances or patient characteristics. Paresthesia mapping may be employed to ensure full recruitment of the dorsal column afferents corresponding to the painful area; a benefit of the paresthesia-free burst waveform is that any extraneous paresthesia coverage during intraoperative testing can be largely disregarded, as it will not be perceived during sub-sensory stimulation. Leads may also be implanted using only anatomical imaging references, which may establish a more streamlined and time-efficient treatment continuum and reduce hospital costs through shorter operating room times (6). Furthermore, as anatomical lead implantation does not require patient input, there is no need to reduce sedation and/or analgesia during the procedure in order to gain the patient’s cooperation for accurate reporting. This may improve surgical outcomes by reducing patient discomfort and stress.

A limitation of this study is the small size of each group; it is possible that the study lacked statistical power to detect a difference in pain ratings between groups. However, the even split of blinded subjects’ preference for each of the lead implant methods supports the notion that they do indeed deliver equivalent outcomes. Furthermore, another limitation of the study is that paresthesia mapping to perform the pain paresthesia overlap was performed using one lead while practitioners typically use two leads to improve the pain-paresthesia overlap. While this may result in sub-optimal paresthesia coverage, our trial results demonstrate clinical and statistical improvements from baseline. Moreover, since BurstDR is programmed below paresthesia thresholds (sub-perception), optimal pain-paresthesia overlap may not be necessary to produce effective pain relief with this waveform.

Overall, this study has shown that, in addition to burst being a new effective SCS waveform for treatment of chronic pain, it offers physicians options in implantation methodology by delivering good outcomes for leads placed either with paresthesia mapping and based on anatomical locations. Efficacy data for burst treatment throughout the 12 months of the study follow-up after the permanent SCS implant are planned for a forthcoming report.

**Authorship Statement**

Dr. Al-Kaisy, Dr. Baranidharan, Dr. Palmisani, Dr. Pang, Dr. Agnesi, and Mr. Raza designed the study. Dr. Al-Kaisy, Dr. Baranidharan, Dr. Palmisani, Dr. Pang, Ms. Will, Mr. Wesley, Ms. Crowther, Mr. Ward, and Mr. Castino conducted the study including patient recruitment and data collection. Mr. Raza provided statistical support in analyzing the data with input from Dr. Al-Kaisy, Dr. Baranidharan, Dr. Palmisani, and Dr. Agnesi. Dr. Al-Kaisy, Dr. Baranidharan, Dr. Palmisani, Dr. Agnesi, and Mr. Raza prepared the manuscript draft with important intellectual input from Dr. Pang, Ms. Wil, Mr. Wesley, Ms. Crowther, Mr. Ward, and Mr. Castino. All authors approved the final manuscript.

All authors made a substantial contribution to the study’s concept and design and all authors approved the final version of the manuscript. The authors thank Allison Foster, PhD, an independent medical writer, for her intellectual contribution to the drafting of the manuscript.

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COMMENTS

This is a very interesting study that demonstrates burst spinal cord stimulation achieves similar outcomes at a group level irrespective of whether one uses paresthesia mapping based or anatomical placement of the electrode. This could change the way in which electrodes are currently being placed with this technology. It seems obvious implanters will start positioning the electrode based on anatomical references, as this can be done under general anesthesia, and is more time-efficient. However, it is important to realize that if the pain suppression is insufficient, meaning that the patient scores his/her pain >3/10, it may still be worthwhile to reposition the electrode using paresthesia mapping, as some individual patients are clearly better suited using this approach. Thus, apart from reducing the amplitude or charge delivered to the spine, it gives an extra tool to optimize patient outcomes.

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The authors take advantage of dual percutaneous trial leads to test alternative methods of placing BURST-DR electrodes. Fundamentally, they are attempting to address the question of whether paresthesia mapping adds value in the placement of electrodes for a paresthesia-free therapy. The results are helpful in clinical practice. As a group, within the limits of a small sample size the two techniques appear to be similar in efficacy. While this is helpful to know, the study also demonstrates that some patients respond dramatically more to electrode placement with one method than the other. This draws attention to the larger challenge facing the neuromodulation community when it comes to the treatment of pain. When I have insurance approval to trial stimulation for my patient, the question on my mind is not “will BURST-DR work for this patient,” but “what will help this patient the most?” This work reassures us that each practitioner can place the trial leads with the technique they are most comfortable, and the results are comparable. At the same time, it confirms that whichever technique is chosen, a percentage of the patients will fail the trial who would have shown improvement had the other technique been selected. Would the best response across all patients would be found by routinely placing the electrodes as they did in this study, end-to-end for a greater longitudinal coverage and testing along this axis to find the point of maximum pain relief for that individual patient? This study provides a helpful step toward answering these important questions and provides formative information for our next set of questions.

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Anatomic placement had been previously utilized successfully during (paresthesia-free) Senza trial. This is a major first step to establish anatomic placement for Burst DR with short term success.

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