Randomized Trial

Sensor-Driven Position-Adaptive Spinal Cord Stimulation for Chronic Pain

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Background: Variation in the intensity of neurostimulation due to body position is a practical problem for many patients implanted with spinal cord stimulation (SCS) systems because positional changes may result in overstimulation or understimulation that leads to frequent need for compensatory manual programming adjustments.

Objectives: The purpose of this study was to assess the safety and effectiveness of a novel type of SCS therapy designed to automatically adapt stimulation amplitude in response to changes in a patient's position or activity. The primary objective of the study was to demonstrate that automatic position-adaptive SCS benefited patients in terms of pain relief and/or convenience compared with neurostimulation adjusted with conventional manual programming. Secondary objectives included assessment of worsened pain relief with automatic adjustment; change in pain score; and the number of manual programming adjustments with position-adaptive neurostimulation compared with manual programming.

Study Design: Prospective, multicenter, open-label, randomized crossover study.

Setting: Ten interventional pain management centers in the US.

Methods: Patients were enrolled a minimum of one week after a successful SCS screening trial. They were then implanted with the RestoreSensor™ neurostimulation device (Medtronic, Inc., Minneapolis, MN) that could be programmed to either automatic position-adaptive stimulation (AdaptiveStim™) or manual adjustment of stimulation parameters. After implant, all devices were programmed to conventional manual adjustment for a 4-week postoperative period. The patients were then randomized to either conventional manual programming adjustment or position-adaptive stimulation with crossover to the opposite treatment arm occurring at 6 weeks after randomization. The patients were followed for another 6 weeks after crossover. This study was conducted under an FDA-approved Investigational Device Exemption (IDE) and approval of the responsible Institutional Review Boards (IRBs) of the study centers.

Results: Seventy-nine patients were enrolled in the study. In an intent-to-treat analysis, 86.5% of patients achieved the primary objective of improved pain relief with no loss of convenience or improved convenience with no loss of pain relief using automatic position-adaptive stimulation compared with using conventional manual programming adjustment alone. This was statistically significantly greater than the predefined minimum success rate of 25%, $P < 0.001$ (exact one-sided 97.5% lower confidence limit was 76.5%). Only 2.8% of patients reported worsened pain relief during position-adaptive stimulation compared with manual programming. There was a statistically significant reduction in the mean numeric pain rating scale score compared with baseline scores in both treatment arms. Additionally, position-adaptive stimulation demonstrated a statistically significant 41% reduction in the daily average number of programming button presses for amplitude adjustment compared with manual programming (18.2 per day versus 30.7 per day, $P = 0.002$). Functional improvements reported with position-adaptive stimulation included: improved comfort during position changes (80.3%); improved activity (69%); and improved sleep (47.9%). Adverse events associated with uncomfortable sensations from stimulation did not differ significantly between treatment arms. The incidence of device-related serious adverse events was 3.9%.

Limitations: Patients and physicians were not blinded to whether devices were programmed to automatic position-adaptive stimulation or manual adjustment. Responses to assessment questionnaires were based on patient recall.

Conclusions: The study demonstrated that automatic position-adaptive stimulation is safe and effective in providing benefits in terms of patient-reported improved pain relief and convenience compared with using manual programming adjustment alone.

Key words: spinal cord stimulation, neurostimulation, position sensing, physical activity accelerometer, neuromodulation, effectiveness, pain relief, position-adaptive stimulation, posture-adaptive stimulation, AdaptiveStim
Clinical Trial: NCT01106404

The gate control theory of pain, first proposed by Melzack and Wall in 1965 (1), set the stage for modern spinal cord stimulation (SCS). Shealy (2) used the gate control theory as the basis for successfully implanting the first SCS pain relief system in 1967 involving implantation of a monopolar electrode via thoracic laminectomy. Since then, SCS has evolved into a powerful nondrug therapy with proven effectiveness for the treatment of intractable neuropathic pain including chronic leg and back pain in well-selected patients (3-11). Technological improvements over the past 40 years have made SCS more useful for an increasing number of patients. SCS systems are now highly programmable, rechargeable, and capable of delivering stimulation to wide areas of the spinal cord with multiple leads using different electrode configurations. Variation in the intensity and quality of stimulation due to changes in body position has been a challenge that has vexed SCS since its early days. None of the system enhancements to date have addressed this issue. Patients undergoing SCS perceive paresthesias which are directed to cover the painful area through electrode positioning and programming. Changes in the intensity of this paresthesia resulting from positional changes may result in either understimulation, including complete loss of stimulation, or overstimulation. Overstimulation has been described by some patients as an uncomfortable jolting or surging sensation. It often requires manual adjustment of stimulation parameters, which can present a significant barrier to successful SCS therapy in some cases (12,13).

Variation in paresthesia intensity caused by changes in position or activity is an inherent aspect of SCS therapy, because the strength of the electrical impulse traveling from the epidural space where the electrodes are placed to the targeted spinal tissue depends on the distance between the electrode and the neural target. This distance varies at different spinal levels and changes dramatically with body position (14-18). Anatomically, the distance between an epidural electrode and the spinal cord is a function of the thickness of the tissues and spaces separating the two, which includes the epidural vasculature and adipose tissue, the dura mater, arachnoid membrane, cerebrospinal fluid (CSF), and pia mater. Of these, the thickness of the dorsal cerebrospinal fluid (DCSF) layer is the most variable and comprises nearly all of the distance between the target neural fibers and the SCS electrodes (14).

Measurements of the DCSF layer have shown variations in thickness among individuals and changes with alterations in body position and posture (13,14). In the supine position, the DCSF layer was 2.0 to 6.0 mm at T-11 and 1.5 to 4.5 mm at T-12 (13,14). In the prone position, the thickness of the DCSF layer increased by approximately 2.2 mm at T-11 and 3.4 mm at T-12 (13,14). Position-related changes in the DCSF layer will result in either a decrease or an increase in the distance between an epidural neurostimulation lead and the spinal cord, which may in turn result in over- or understimulation, respectively.

Consequently, the strength of stimulation needed to achieve optimal paresthesia intensity can be highly variable with position changes. Understimulation can result in less than adequate pain relief, while overstimulation can result in mild to intense discomfort. These differences have been noted and studied by physicians for many years. Olin et al (12) demonstrated that the perceptual threshold of stimulation paresthesia was directly related to body position. Specifically, thresholds for the sitting and standing positions were found to be significantly higher than for the supine position for the majority of patients. This work was confirmed by Abejon and Feler (13) who subsequently demonstrated significant differences in the energy required to achieve comfortable paresthesia for standing, sitting down, lying down, and walking. Thus, variability in stimulation delivered at the target neural fibers would be expected to impact the overall effectiveness of SCS therapy (12,13,21,22).

To maintain optimum paresthesia intensity and pain management, patients must manually adjust their stimulation parameters with their neurostimulator programmer in order to counter changes in stimulation associated with changes in body position (13). Alternatively, patients may change their body position rather than change stimulation parameters. Despite improvements in patient programmers that include enhancements to the display and interface, some patients may be reluctant to make frequent or repetitive programming changes during their daily activities. Patients may also forget to bring their programmers with them or may lose them. As a result, the ongoing need for and inconvenience of programming adjustments can compromise pain relief, cause patient frustration, and decrease overall patient satisfaction with SCS therapy.

The automatic position-adaptive stimulation feature was designed to detect changes in body position or activity in real time and to automatically adjust stimulation amplitude according to patient preferences. To assess the potential benefits and risks of this

position-adaptive stimulation feature, we conducted a prospective, multicenter, open-label, randomized crossover study comparing automated programming adjustment to conventional manual programming adjustment.

Methods

Patient Selection

This study was conducted under an FDA-approved Investigational Device Exemption (IDE) and approval of the responsible Institutional Review Boards (IRBs) of the study centers. To participate in the study, patients were at least 18 years of age and were indicated for implantation of an SCS system for the treatment of chronic trunk and/or limb pain. Patients were willing and able to attend visits and comply with the study protocol. Additionally, they were judged capable of using the patient programmer and recharging the implantable neurostimulator and were able to read and answer questionnaires in English without assistance.

Patients were excluded if they had a prior implantable SCS system; were currently enrolled or had plans to enroll in another device or drug trial during the study period; had unresolved legal issues related to their pain condition for which they would be receiving neurostimulation; were pregnant; or required cervical placement of leads.

Study Design

The schema for the study is shown in Fig. 1. Patients were enrolled only after a successful SCS screening trial and a minimum one-week post-screening waiting period without stimulation. The definition of a successful SCS screening trial was based on the physician's usual criteria for success and standard of care for pain management. Concomitant medical therapy was allowed, and no specific medications were contraindicated or required during the study. Since pain medication changes are rarely initiated solely to treat positional changes, which are transitory in nature, pain medication usage was not tracked during the study. Patients enrolled were not selected on the basis of any demonstrated need for stimulation adjustment during position changes.

After enrollment, patients completed a numerical pain rating scale (NPRS) diary for 7 days in order to assess baseline pain. Thus, a minimum of 2 weeks without stimulation was required between the end of a successful SCS trial and implantation of the neurostimulation device. Enrolled patients were implanted with the RestoreSensor rechargeable neurostimulator (Medtronic, Inc., Minneapolis, MN) which included the optional position-adaptive stimulation feature known as AdaptiveStim.

During a 4-week postoperative period, only conventional manual adjustment of stimulation was enabled

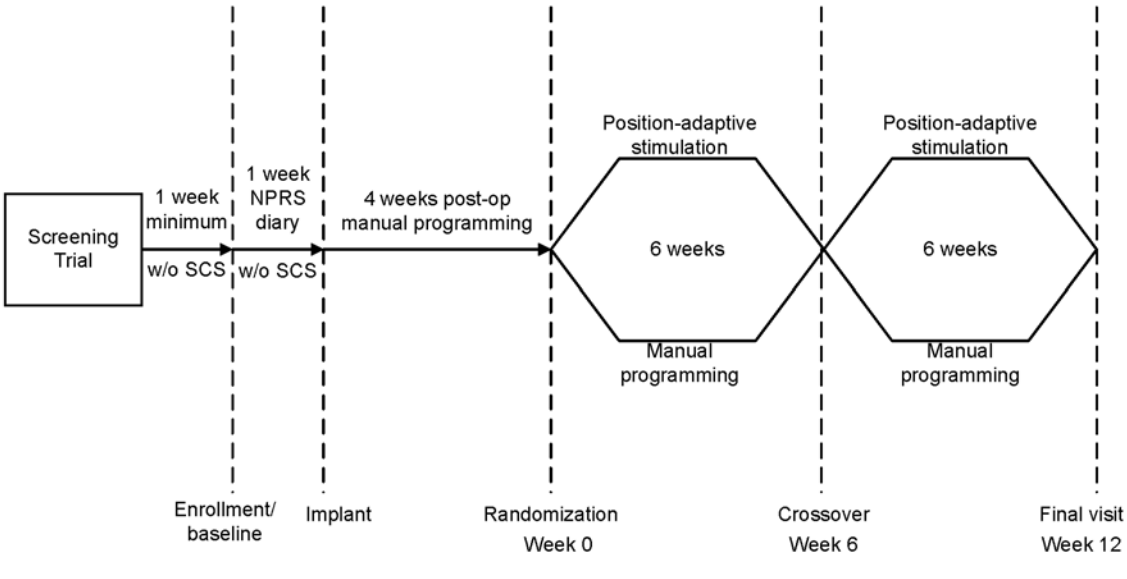

Fig. 1. *Study design for the prospective, open-label, randomized, crossover study from the screening trial through the final visit at week 12. SCS (spinal cord stimulation); NPRS (numerical pain rating scale).*

and patients were educated on the use of the patient programmer. Since use of the patient programmer was critical to the evaluation of pain relief and convenience, all patients were required to demonstrate the ability to use the programmer by the end of the 4-week postoperative period. Patients were then randomized to first receive either SCS with conventional manual adjustment of stimulation parameters or position-adaptive stimulation. Crossover to the opposite type of stimulation occurred at 6 weeks post-randomization followed by 6 additional weeks of that SCS therapy for a total of 12 weeks of follow-up.

Implantable Neurostimulation System

Physicians could place up to 3 percutaneous leads in the lumbar or thoracic epidural space. The RestoreSensor® study device could be programmed to deliver position-adaptive stimulation while allowing additional manual programming adjustment with a patient programmer, or to deliver conventional neurostimulation therapy alone. Position-adaptive stimulation must be enabled by the clinician. It can then be turned on and off by the patient or disabled by the clinician. When the position-adaptive stimulation feature was disabled, the RestoreSensor neurostimulator was functionally equivalent to the currently market-released RestoreUltra neurostimulator (Medtronic, Inc., Minneapolis, MN).

A patient programmer modified for the study automatically recorded the number of individual button presses and adjustments. The programmer served as an automated diary that reliably captured manual therapy adjustments. The patient programmer could be used to fine-tune adjustments regardless of whether the position-adaptive stimulation feature was activated or disabled.

Position-Adaptive Stimulation

The position-adaptive stimulation feature used a 3-axis accelerometer and associated software contained in the implantable neurostimulator. The accelerometer automatically sensed the patient's body position and activity, and the software automatically adjusted stimulation amplitude for that position to a level previously defined by the patient and clinician. The default parameters are designed to detect position change prior to the patient achieving a final position. The moment of detection in the arc of movement is programmable. The system provided automatic adjustment for 6 positions: sitting or standing upright; lying supine; lying prone; lying on the right side; lying on the left side; and upright and active. Device orientation was required prior to use of position-adaptive stimulation. During the orientation process, patients were positioned upright, lying back or lying front, lying left, and lying right. Data from the 3-axis accelerometer were linked to positions selected with the clinician programmer via the position-adaptive stimulation algorithm. The position-adaptive stimulation feature was customized for each patient, and the clinician defined the amplitudes for all or a subset of the positions to meet specific patient needs.

Follow-up

Patients were followed weekly during the 4-week postoperative period. After randomization, patient follow-up was: telephone contact at weeks 1, 3, and 5 and office visits at weeks 2 and 4. Crossover to the opposite type of stimulation occurred at week 6, and follow-up included: telephone contact at weeks 7, 9, and 11 and office visits at weeks 8 and 10. The final follow-up occurred at week 12.

At follow-up visits, programmed settings could be adjusted consistent with the assigned treatment arm, and the device could be reoriented. Patients were asked to complete a 7-day pain diary prior to crossover at week 6 and prior to the final office visit at week 12. At the final visit, patients were asked to complete a questionnaire comparing position-adaptive stimulation with manual programming adjustment.

Objectives

Effectiveness

The primary effectiveness objective was to demonstrate that use of position-adaptive stimulation provided benefits to patients in terms of pain relief and/or convenience compared with not using the feature. Secondary effectiveness objectives were to summarize the percent of patients who had worsened pain relief during the position-adaptive stimulation arm relative to the conventional manual programming arm; to compare the number of manual patient programmer adjustments during both arms of the study; and to compare the changes in NPRS score from baseline to follow-up visits. Additional effectiveness objectives were to collect and summarize patients' experiences regarding the use and benefit of position-adaptive stimulation as well as physician impressions of the clinical benefit of the feature.

Safety

The safety objectives were to compare the number of patients who experienced adverse events as-

sociated with uncomfortable sensations from stimulation occurring during the 2 arms of the study. Additionally, all adverse events reported from implant to completion of study visits or discontinuations were summarized.

Assessment Methods

The primary effectiveness objective (% success) was assessed by determining the percent of patients who had improved pain relief with no loss of convenience or improved convenience with no loss of pain relief when using position-adaptive stimulation compared with manual programming. Pain relief and convenience were assessed with separate 5-point Likert scales at the 12-week follow-up visit. There was no validated tool to assess the benefits of position-adaptive stimulation. The commonly used Likert scale was chosen to assess experience with pain relief and convenience because it could be easily understood by patients and responses could be readily interpreted.

For the secondary objective assessing worsened pain relief with position-adaptive stimulation relative to manual programming adjustment, the Likert scale scores for pain relief were used. All manual button presses for stimulation adjustment were logged by the patient programmer. For the secondary objective summarizing the change in pain scores from baseline to follow-ups, patients were asked to complete pain diaries for 7 consecutive days at baseline and before the 6- and 12-week follow-up visits. Pain was assessed on the 11-point NPRS with 0 meaning "no pain" and 10 meaning "pain as bad as you can imagine." The average scores of the last 3 of 7 diary collection days were used for the pain scores for that visit. Patients and physicians independently completed questionnaires at the 12-week follow-up visit comparing the benefits of position-adaptive stimulation to manual programming adjustment. Patients entered their answers directly onto the case report forms without physician assistance or oversight. Device programming parameters were collected on the device printout during patients' clinic visits. To evaluate stimulation amplitudes by patient position, all programs for the upright and supine positions in use at the last study visit during the position-adaptive stimulation phase were analyzed. Note that a program is a specific preset combination of the pulse width, rate, and amplitude settings acting on a specific electrode combination. Most patients had more than one program available to them.

Sample Size

For the primary objective, assessing the benefits of position-adaptive stimulation, the percent of patients who reported improved pain relief with no loss of convenience or improved convenience with no loss of pain relief during position-adaptive stimulation arm relative to conventional manual programming was required to be statistically > 25%. Assuming the true percent success was 50%, a sample size of 60 patients provided 97% power to demonstrate the hypothesis using an exact binomial one-sided test. To account for possible attrition, up to 80 patients could be enrolled.

Randomization

Patients were assigned in a 1:1 ratio to receive first either position-adaptive stimulation or conventional manual adjustment of stimulation parameters, followed after 6 weeks by assignment to the alternative adjustment method for an additional 6 weeks. Each site received a box of envelopes containing the randomization sequence, and the envelopes were opened in the provided order. Randomization was stratified by study center. All physicians and patients were aware of the assigned therapy sequence.

Statistical Analysis

Analysis of the primary objectives was based on intent-to-treat with the exception of patients who discontinued from the study due to lead migration or infection prior to the 12-week post-randomization follow-up. A priori, these events were not considered relevant to the evaluation of position-adaptive stimulation. For patients who dropped out for other reasons, the missing data at 12 weeks was imputed as not successful for position-adaptive stimulation representing a conservative handling of the missing data. A one-sided P value of < 0.025 was considered statistically significant for the primary objective.

Analysis of the secondary objectives and additional study measures included all implanted patients who provided a response. The number of manual programming adjustments and the change in NPRS scores from baseline to various follow-up points were assessed using the Wilcoxon signed rank test. The number of patients with adverse events associated with uncomfortable stimulation was compared in the 2 arms of the study using McNemar's test.

A P value of < 0.05 was considered statistically significant for secondary objectives. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Study Population

Seventy-nine patients from 10 interventional pain management centers in the United States were enrolled in the RestoreSensor Study between April 20, 2010 and September 3, 2010. An IRB associated with each participating center approved the study protocol, and all patients provided written informed consent. Of the 79 patients enrolled in the study, 32 (40.5%) were male, and 47 (59.5%) were female. The mean age was 52.6 years (range 27-85 years). The most frequently reported pain etiologies included radicular pain syndrome or radiculopathies, degenerative disk disease or herniated disk pain, postlaminectomy pain, and failed back syndrome. Patients usually had more than one pain etiology. Seventy-six patients were implanted with a RestoreSensor neurostimulation device and randomized. Thirty-six patients were assigned to receive automatic adjustment of therapy with position-adaptive stimulation first followed by manual programming adjustment second. Forty patients were assigned to receive neurostimulation with manual programming adjustment first and position-adaptive stimulation second. The baseline characteristics in both sequences were similar (Table 1). All enrolled patients were naïve to a permanently implanted SCS device, and no minimum NPRS score was required for enrollment. In this regard, the study population was representative of the real-world pain patient population. Seventy-one of the 79 enrolled patients completed both treatment arms. Three patients were discontinued prior to implant, and 5 were discontinued after implant for the reasons shown in Fig. 2. Patients were followed for at least 16 weeks post-implant. Of the 76 patients randomized, 74 were included in the intent-to-treat analysis for the primary effectiveness objective. Two patients with infections leading to explant were excluded from the intent-to-treat analysis as predefined in the protocol.

Primary Effectiveness Objective

In the intent-to-treat analysis, 86.5% (64 of 74) patients reported improved pain relief with no loss of convenience or improved convenience with no loss of pain relief while using position-adaptive stimulation compared with using manual programming only (Table 2). Three of the 74 patients who did not complete the study were imputed as treatment failures for the purposes of the analysis. The exact one-sided 97.5% lower confidence limit was 76.5%, which was statistically significantly greater than the predefined minimum success rate of 25%, ($P < 0.001$). The percent success did not differ according to randomization sequence ($P = 0.33$).

Secondary Objectives

Worsened Pain Relief

Of the 71 patients with complete data, only 2 (2.8%) reported worsened pain relief during the position-adaptive stimulation arm relative to the manual program-

Table 1. *Baseline characteristics.*

Variable	Position-adaptive stimulation – Manual programming adjustment study arm	Manual programming adjustment– Position-adaptive stimulation study arm	*P* value
Age in years			
Mean (SD), N	52.5 (13.0), 36	53.1 (14.1), 40	0.846[a]
Gender			
Female	18	27	0.121[b]
Male	18	13	
Baseline NPRS scores			
Average pain in past 24 hours Mean (SD), N	6.26 (1.48), 36	5.88 (2.15), 39[c]	0.380[a]
Worst pain in past 24 hours Mean (SD), N	7.60 (1.15), 36	7.60 (1.63), 39[c]	0.991[a]

[a] t-test
[b] Chi-square test
[c] One patient had a missing pain diary at baseline
NPRS= numerical pain rating scale

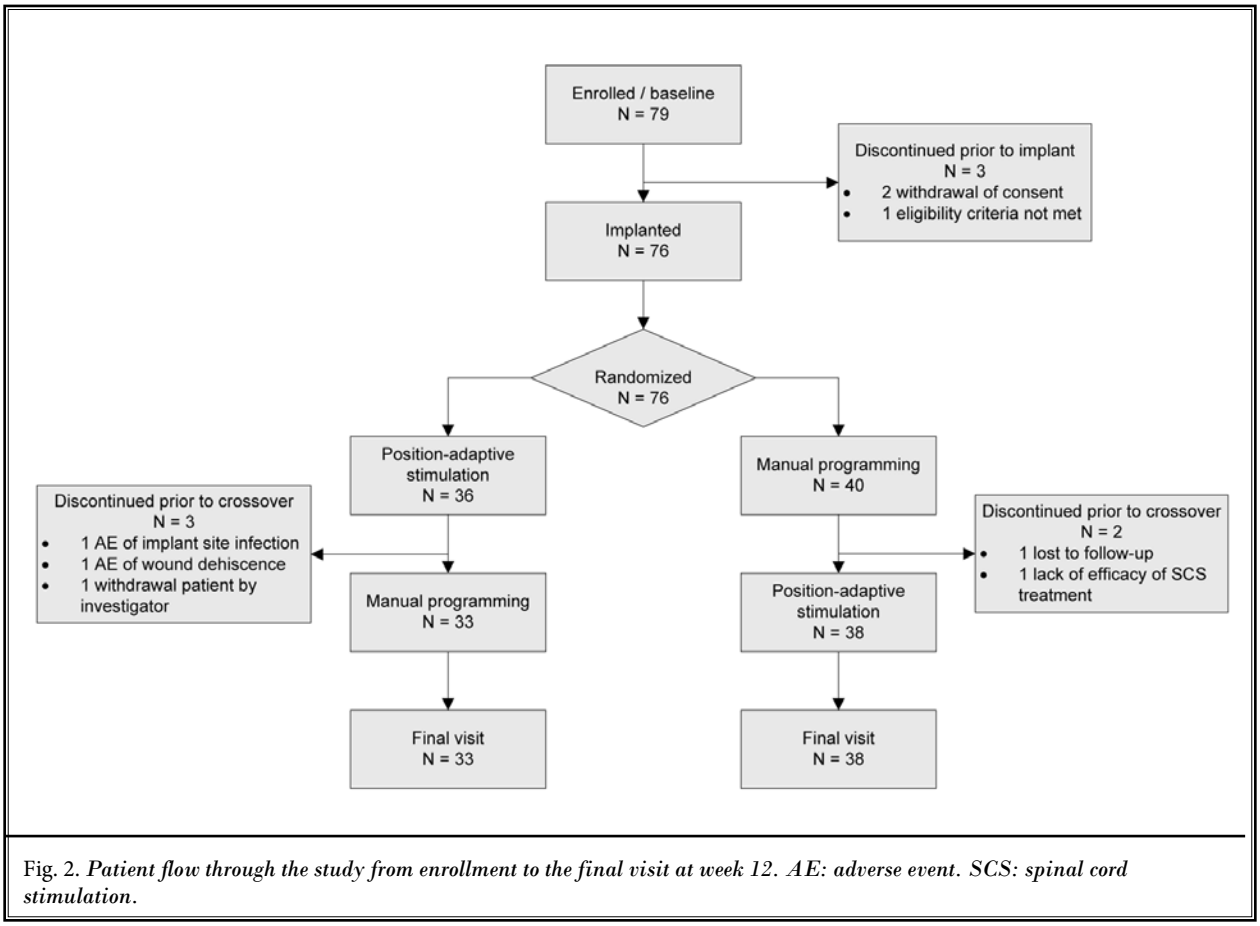

Fig. 2. *Patient flow through the study from enrollment to the final visit at week 12. AE: adverse event. SCS: spinal cord stimulation.*

Table 2. *Primary Effectiveness Objective: Pain Relief and Convenience*

With position-adaptive stimulation ON compared with OFF	Much worse pain relief	Somewhat worse pain relief	No difference in pain relief	Somewhat better pain relief	Much better pain relief	Discontinued patients included in ITT analysis	Total
Much less convenient	1		1		1		3
Somewhat less convenient			2				2
No difference in convenience		1	1				2
Somewhat more convenient			1	7	5		13
Much more convenient			1	16	34		51
Discontinued patients included in ITT analysis						3	3
Total	1	1	6	23	40	3	74

ITT = intent-to-treat. The shaded area represents the combination of relative pain relief and convenience that was defined as success for the primary effectiveness objective.

ming arm. One of these patients chose to leave position-adaptive stimulation on at the end of the study.

Programming Adjustments

Regardless of whether the patient was in the position-adaptive stimulation or manual programming adjustment arm of the study, the patient programmer could be used to adjust stimulation parameters. The daily average number of button presses for amplitude adjustment in the position-adaptive stimulation arm was 18.2 per day (standard deviation [SD] 38.9), which was significantly lower than the 30.7 per day (SD 63.5) in the manual adjustment arm (N = 69, $P = 0.002$). The 41% reduction in the average number of daily button presses for amplitude adjustment is considered a clinically significant decrease in the programming burden for the patients to manage their pain. Additionally, patients in the position-adaptive stimulation arm had an average of 15.9 days (SD 12.3 days) out of 42 days without any manual adjustment compared with 12.5 days (SD 12.2 days) out of 42 days during the manual programming arm, a statistically significant reduction, $P = 0.018$.

Change in Pain Score

Overall pain scores decreased significantly for patients in both study arms over the short course of follow-up, $P < 0.001$. Patients in the position-adaptive stimulation arm demonstrated greater improvement in the NPRS score compared with those in the manual programming adjustment arm, though the difference fell short of statistical significance. The mean reduction in the NPRS score for average pain from baseline to the end of the position-adaptive stimulation arm was 1.78, representing a significant decrease from 5.92 to 4.14, $P < 0.001$. The mean reduction in the NPRS score for average pain from baseline to the end of the manual programming arm was 1.48 representing a significant decrease from 5.97 to 4.49, $P < 0.001$.

Patient and Physician Assessments

At the final week 12 visit, patients provided responses to questions about their experience with position-adaptive stimulation relative to manual programming adjustment. All patients who provided responses to specific questions were included in the analyses. Of the 71 patients who recorded preferences on the case report forms, 90.1% intended to leave position-adaptive stimulation on all or most of the time or turn it off as needed. Additionally, many patients reported improvements in functional areas when using position-adaptive stimulation. Specifically, 80.3% reported improvement in comfort during position changes, 69% reported improved activity, and 47.9% reported improvement in sleep (Table 3). Physicians reported that position-adaptive stimulation provided added clinical benefit for 88.7% of patients.

Stimulation Amplitude by Positions

Stimulation amplitude data for each program in use at the last follow-up visit during the position-adaptive stimulation arm (n = 200) were available for 72 of the 76 randomized patients. A bar chart of the relative percentage of stimulation amplitudes for 2 of the 6 positions (supine versus upright) is shown in Fig. 3. Most programs had lower amplitudes for the supine position than for the upright position. On average, stimulation amplitude for the supine position was 84% of the upright position, with a range of 5-174%.

Safety Objectives

In the analysis of adverse events associated with uncomfortable stimulation, 7 patients experienced the events only during the position-adaptive stimula-

Table 3. *Functional improvement when using Position-Adaptive Stimulation Feature.*

Areas that have improved using Position-Adaptive Stimulation	N[a]	Percentage (N=71)
Comfort during position changes	57	80.3%
Activity	49	69.0%
Control of therapy	41	57.8%
Sleep	34	47.9%
Other improvements	13	18.3%
No improvements	6	8.5%

[a]A patient could report improvement in more than one functional area.

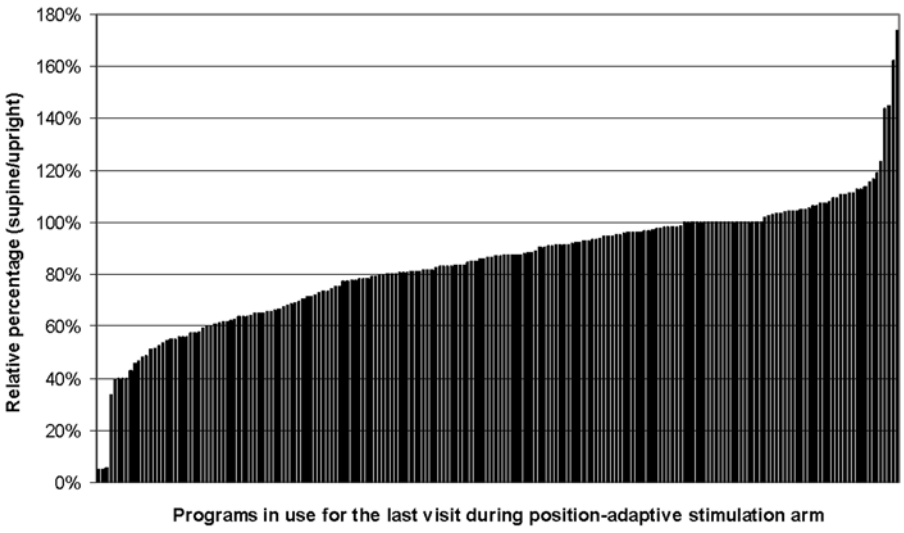

Fig. 3. *The relative percentage was calculated as the stimulation amplitude used for the supine position divided by that for the upright position and is shown for each program in use at the end of the position-adaptive stimulation arm. A relative percentage less than 100% indicates that lower stimulation amplitude was used for the supine position than for the standing position.*

tion arm; 9 patients experienced events only during the manual programming arm; and 4 patients experienced events during both arms. There was no statistical difference in the number of patients who reported uncomfortable sensations from stimulation during the position-adaptive stimulation and manual programming adjustment arms (McNemar's test, $P = 0.804$).

The adverse event profiles reported with and without the use of position-adaptive stimulation were similar, and no unanticipated adverse device effects were reported. There were no patient deaths during the study. Of the 76 patients who were implanted with a neurostimulator and included in the adverse events analysis, 66 reported 239 adverse events after implant (74 events were device related and 165 were not device related). The most frequently reported device-related adverse events (≥ 5%) for all patients in all phases of the study were undesirable change in stimulation (27.6%); pruritus at the neurostimulator pocket and/or lumbar site (6.6%); change in sensation of stimulation (5.3%); implant site irritation (5.3%); paresthesia (5.3%); and wound dehiscence (5.3%). Of the 25 events (in 21 patients) related to undesirable changes in stimulation, most were resolved by reprogramming within 2-3 weeks of event onset. Only 9 of these events had onset during the position-adaptive stimulation arm of the study. Three patients reported 3 serious device-related adverse events (3.9%). Two of the events (wound dehiscence; implant site infection) led to explant and patient withdrawal from the study. One patient who had a seroma completed the study. Seven device-related adverse events which occurred in 6 patients were due to lead migration/dislodgment, of which one led to lead revision prior to randomization.

Discussion

This prospective, randomized crossover study demonstrates that a position-adaptive stimulation feature incorporated into an implantable neurostimulation system can automatically adjust the amplitude of neurostimulation to accommodate for changes in body position and activity in a real-world clinical setting. Most patients reported improved pain relief and improved convenience when using this feature compared with neurostimulation requiring conventional manual programming adjustment. The study used a novel dual-effectiveness primary objective requiring that the use of automatic position-adaptive stimulation demonstrate improvement in either pain relief or convenience, without worsening of either, compared with conventional manual programming. The crossover design allowed patients to experience both alternatives and to directly compare their preference. The therapy alternatives

were presented in a randomized order, although the order did not influence preference.

To demonstrate the clinical benefits of position-adaptive stimulation, the study targeted the patient population currently indicated for SCS for the treatment of trunk and/or limb pain. There was no selection for history of pain during position changes. The study met the primary effectiveness objective with 86.5% of patients reporting improved pain relief with no loss of convenience or improved convenience with no loss of pain relief when using position-adaptive stimulation. Furthermore, nearly half of the patients reported both much better pain relief and much more convenience when using position-adaptive stimulation. The results of the study confirm previous research noting position-mediated variability in patients' perception of SCS and suggest that automatic position-adaptive stimulation could be of utility for many SCS patients.

The observed changes in stimulation amplitude associated with position changes demonstrate the need for programming adjustments and the benefits of automatic position-adaptive stimulation to enhance therapy effectiveness. The range of amplitude differences seen between the upright and supine positions also illustrates the need for individualization of automatic adjustments. In terms of convenience, the 41% fewer button presses during the position-adaptive stimulation arm validates the reported improvements in patient convenience, and is particularly noteworthy when considering that improvements in pain relief were also achieved along with reduced patient programming burden.

Physicians involved in the study reported that 88.7% of patients received clinical benefits from position-adaptive stimulation. From the clinicians' and patients' perspectives, orienting the position-adaptive stimulation feature of the device to the various body positions at the beginning of the study was reasonably simple and not burdensome. The favorable response to position-adaptive stimulation was quite pronounced with 90.1% of patients intending to either leave position-adaptive stimulation programmed on all or most of the time or turning it on or off as needed. This intention to continue use of the feature corroborates the benefits observed in the study. In terms of functional benefits, most patients reported improvement in comfort during position changes and activity. Nearly half the patients reported improvement in sleep.

Analysis of the secondary objective of worsened pain relief demonstrated that of the 71 patients who completed the study, only 2 reported worsened pain relief during the position-adaptive stimulation arm. Of note, the study also confirms the effectiveness of SCS therapy for chronic trunk and/or limb pain. The reduction in pain scores was statistically significant for patients in both programming arms. Reduction in pain with SCS devices has been demonstrated in previously published randomized, controlled trials of SCS effectiveness (3-5).

The study also demonstrated the safety of position-adaptive stimulation. There were no differences in the frequency of uncomfortable stimulation or other adverse events between the position-adaptive stimulation and manual programming arms. During the 4-month study period, only 3 patients (3.9%) experienced a serious device-related adverse event. Two of these patients were explanted, one because of wound dehiscence and the other because of wound infection. The third was a seroma that resolved after aspiration, allowing the patient to continue through the end of the study.

In view of the anatomic and physical basis for position-related variation in the intensity of neurostimulation, automatic position-adaptive stimulation capability for the device is a viable solution for this significant problem. With current technology, it is not possible to maintain a constant distance between the fixed lead and the spinal cord with changes in body position. Patients with implanted neurostimulators are bound to move and change positions in their activities of daily living, which for many patients is a goal of receiving SCS therapy. Experience with position-adaptive stimulation in this study demonstrates that neurostimulation systems with automatic position-adaptive programming adjustment can counteract variations in stimulation intensity associated with changes in position and activity. It is, therefore, anticipated that with automatic position-adaptive stimulation capabilities, SCS will become a more effective and more satisfying therapy for future patients with neuropathic pain.

Limitations

Due to the open label study design, physicians and patients were aware of the therapy assignment, though the randomized crossover study design was intended to mitigate the risk of physician or patient bias. The validity of the primary outcome measure is supported by the observation that 90% of patients chose to continue using position-adaptive stimulation after the study. Responses on questionnaires were subject to patient recall. At the time of assessment of the position-adaptive

stimulation feature relative to manual programming, approximately half of the patients had just completed 6 weeks of treatment with position-adaptive stimulation while the other half had just completed 6 weeks with manual programming. Statistical tests did not reveal an effect with regard to which treatment was experienced most recently. Investigator influence on patient assessment was mitigated by having patients independently enter responses to assessment questions directly on the case report forms.

Conclusions

This study demonstrates that automatic position-adaptive stimulation is safe and effective in providing benefits in terms of improvements in patient-reported pain relief and convenience compared with using manual programming adjustment alone in patients indicated for SCS for the treatment of chronic trunk and/or limb pain. Patients also reported improved comfort during position changes and activity as well as improvements in sleep with this new technology. Position-adaptive stimulation represents an important innovation in SCS therapy. When selecting a SCS system for the treatment of chronic trunk and/or limb pain, the benefits of position-adaptive stimulation merit consideration by clinicians and patients.

Affiliations

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Disclosures

Protocol

Author Contributions: Protocol was prepared by the Medtronic Neuromodulation RestoreSensor study team with input from investigators. The authors were elected based on their contributions to the study. All investigators were involved in the data collection and execution of the study. Dr. Schultz conducted a literature search and wrote the first draft of the manuscript. All authors provided review of the manuscript for intellectual content and subsequent incorporation of suggested revisions and final approval of the manuscript. Ms. Tan analyzed the data and Dr. Sun managed the study for the sponsor. The sponsor of the study had full control of the data and performed analysis. Based on the disclosures, the study was sponsored by Medtronic. All study authors and all study sites received fair market value payments for actual research work done as per the study agreement and no author, center or facility received any other incentive or payment.

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