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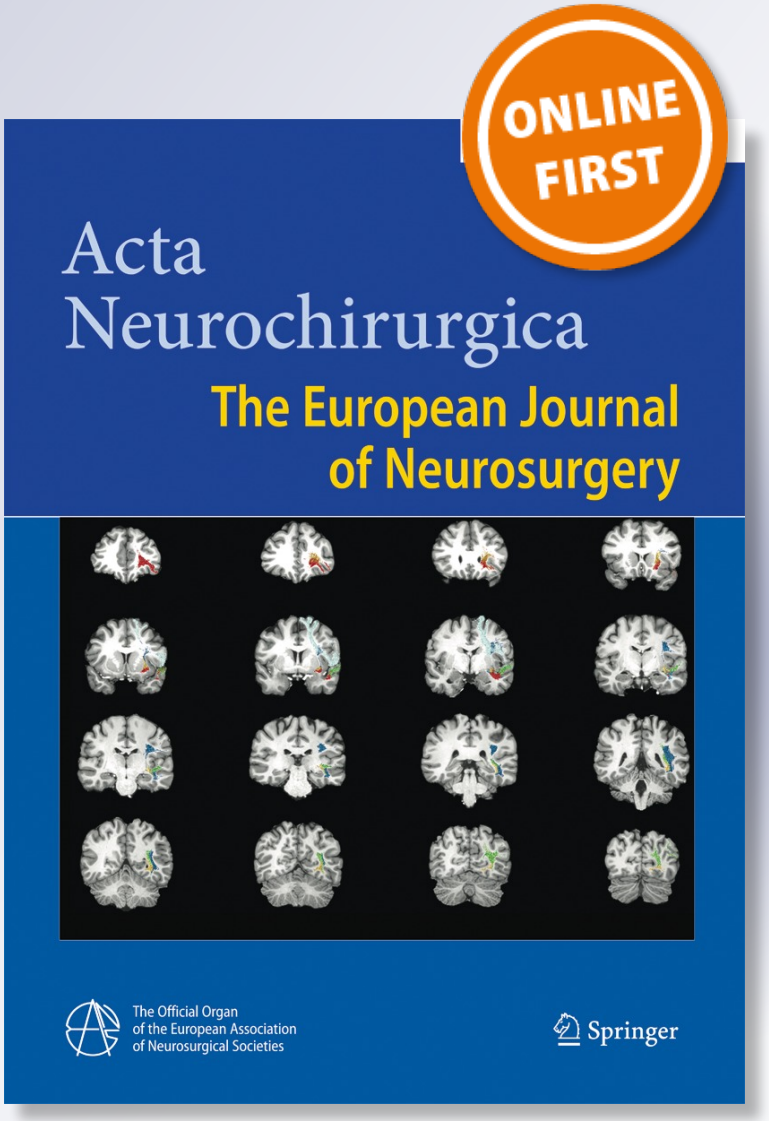

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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - PAIN

Prospective randomized feasibility study comparing manual vs. automatic position-adaptive spinal cord stimulation with surgical leads

Kara Beasley[1] · Christie Zakar[1] · Steven Hobbs[2] · Vinod Kantha[3] · Sigita Burneikiene[1,3]

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Abstract

Background The majority of patients experience uncomfortable stimulation associated with posture changes, especially when lying down. The spinal cord moves within the intrathecal space in response to positional changes affecting the size of the stimulated area accordingly and causing overstimulation or understimulation. To accommodate for positional changes, patients have to manually adjust the stimulation parameters; therefore, an automatic position-adaptive SCS was designed to address these issues. The primary objective of this study was to establish the extent of position-related variations in SCS stimulation parameters experienced by chronic pain patients implanted with surgical, laminectomy-type leads under both automatic and manual SCS conditions.

Methods A total of 18 patients completed a single-center, prospective, non-blinded, randomized (1:1), feasibility clinical study with a two-arm crossover design. All patients undergoing SCS treatment for chronic refractory back and or leg pain associated with failed back surgery, post-laminectomy, or radicular pain syndromes that were refractory to conservative and surgical interventions were eligible for enrollment. After the manual stimulation mode, the patients were randomized to one of two study arms: manual or automatic position-adaptive stimulation and then crossed over to a different arm. All patients were followed for a total of 5 months (± 2 weeks).

Results Analysis indicated statistically significant differences between therapeutic and threshold stimulation intensity for the supine position compared with all other body positions when using either automatic position-adaptive stimulation or manual stimulation, except for threshold amplitudes in the prone position for automatic stimulation.

Conclusion Similar variations were reported for manual and automatic stimulation intensity in response to positional changes.

Keywords Position adaptive SCS · Prospective study · Surgical leads

Abbreviations and acronyms

ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
DOS	Duration of symptoms.
EBL	Estimated blood loss.
F	Female
M	Male
N	Number
ODI	Oswestry Disability Index
OR	Operating room
PSQI	Pittsburgh Sleep Quality Index
RM	Repeat measure
SCS	Spinal cord stimulator
VAS	Visual analog scale

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Introduction

Spinal cord stimulation (SCS) is a well-recognized method of managing a variety of chronic neuropathic conditions that are refractory to conservative treatment including failed back surgery or postlaminectomy syndrome, arachnoiditis, and

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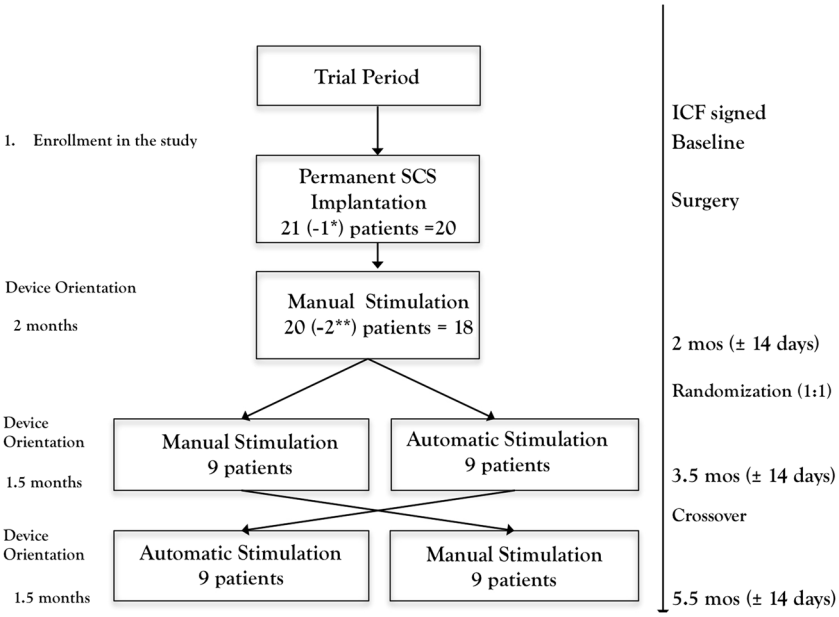

Fig. 1 Flow chart of the progress through the phases of a randomized clinical study with a two-arm crossover design. *Subject did not undergo surgery. **Lost to follow-up

complex regional pain syndrome. For patients with failed back surgery syndrome, SCS has been proven to be a more effective therapy compared with conventional medical management alone for pain relief, health-related quality of life, and functional capacity [8]. However, the majority of patients experience uncomfortable stimulation associated with posture changes, especially when lying down [3, 7]. The spinal cord moves within the intrathecal space in response to positional changes, becoming closer to the stimulation electrodes when lying supine and further away in the standing or prone positions [2, 12] affecting the size of the stimulated area accordingly [6] and causing overstimulation or understimulation. To accommodate for positional changes, patients have to manually adjust the stimulation parameters; therefore, an automatic position-adaptive SCS was designed to address these issues. The position-adaptive SCS system uses an accelerometer to detect changes in body position and adjusts stimulation according to patient-specific stimulation settings [15].

Table 1 Selected demographic, clinical, and surgical parameters. *BMI*, body mass index; *DOS*, duration of symptoms; *EBL*, estimated blood loss; *F*, female; *M*, male; *N*, number; *OR*, operating room. Values are presented as numbers, means, and ranges

N	18
F/M	8/10
Age (years)	56.7 (43–73)
BMI	30.9 (22.9–48.8)
DOS (months)	50.9 (8–24)
Neuropathy pain scale score	56.7 (16–85)
Surgical levels	T7–T10
EBL (mL)	19.7 (5–75)
OR time (min)	51.5 (22–120)

The primary objective of this study was to establish the extent of position-related variations in SCS stimulation parameters experienced by chronic pain patients implanted with surgical, laminectomy-type leads.

Methods

A single-center, prospective, randomized (1:1), non-blinded, feasibility clinical study with a two-arm crossover design was conducted (Fig. 1). The enrollment period lasted from September of 2013 to December of 2016. A total of 21 patients were enrolled; however, one patient did not undergo surgery and two patients were lost to follow-up, leaving a total of 18 patients. All patients undergoing SCS treatment for chronic refractory back and or leg pain associated with failed back surgery, post-laminectomy, or radicular pain syndromes that were refractory to conservative and surgical interventions were eligible for enrollment. The patients with previous SCS treatment and surgically remediable spinal conditions were excluded. There were additional permanent electrode implantation criteria used: the effectiveness of SCS and tolerance of paresthesias had to be satisfactory after a trial period according to the patients and treating physician's judgment. Laminectomies were performed and paddle electrodes implanted during trials in 15 (71%) patients. The rest of the patients had percutaneous electrodes, which were replaced with permanent paddle 5-6-5 leads after the trial. The lead placement and stimulus configuration were selected to maximize paresthesia coverage of the painful area during intraoperative testing.

A manual stimulation adjustment mode was used for all patients for the first 2 months (±2 weeks), after which the patients were randomized to one of two study arms: manual

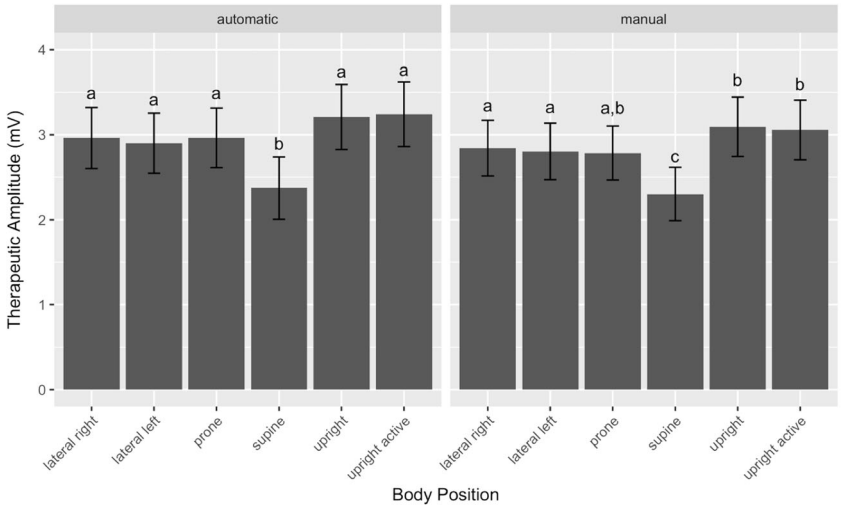

Fig. 2 Mean therapeutic amplitude (mV) for a given body position for automatic and manual randomization groups. Body positions that lack a common letter above a bar (e.g., a, b, or c) are significantly different. Error bars are ± 1 standard error

or automatic position-adaptive stimulation (period 1). Research coordinators randomly assigned subjects to the treatment groups using GraphPad Prism version 7.0 (La Jolla, CA). The random numbers were generated using a Gaussian distribution. After 1.5 months (± 2 weeks) of the initial treatment assignment, patients crossed over to a different arm for an additional period of 1.5 months (± 2 weeks, period 2). All patients were followed for a total of 5 months (± 2 weeks).

Threshold and therapeutic stimulation parameters in response to postural changes for each patient were established and measured before entry into a 2-month conventional manual treatment period and before entry into each 1.5-month crossover treatment. We have excluded from statistical analysis the stimulation parameters measured at the 5-month time interval (after period 2) to represent a balanced crossover design (each patient is represented twice, once in each period

Table 2 Repeat measures ANOVA and Bonferroni-corrected paired *t* test results. Amplitudes for each body position: percent/95% confidence interval of the upright body position and mean ± standard deviation and significance as compared with the supine body position

Automatic					
Therapeutic amplitude ($p < .001$, ANOVA)					
	Lateral R	Lateral L	Prone	Upright	Upright active
Supine					
73.7% (64.7–82.7)	93.8% (86.8–100.9)	100% (92.1–107.8)	73.7% (64.7–82.7)	100%	101.4% (98.8–103.9)
2.37 ± 1.55	2.96 ± 1.53	2.90 ± 1.50	2.96 ± 1.36	3.21 ± 1.63	3.24 ± 1.62
	$p < .001$	$p < .001$	$p = .002$	$p = .001$	$p < .001$
Threshold amplitude ($p = .003$, ANOVA)					
Supine					
78.7% (64.9–92.5)	100.4% (88.2–112.6)	100.2% (87.6–112.7)	99.2% (83.2–115.2)	100%	101.1% (98.8–103.4)
2.14 ± 1.49	2.70 ± 1.55	2.69 ± 1.55	2.63 ± 1.21	2.86 ± 1.76	2.92 ± 1.91
	$p = .001$	$p = .003$	$p = 1.0$	$p = .02$	$p = .005$
Manual					
Therapeutic amplitude ($p < .001$, ANOVA)					
Supine					
73.6% (63.9–83.4)	91.2% (85.5–96.9)	89.9% (84.3–95.4)	96.7% (86.4–107.0)	100%	98.6% (96.4–100.8)
2.30 ± 1.33	2.84 ± 1.39	2.80 ± 1.42	2.78 ± 1.28	3.10 ± 1.49	3.06 ± 1.49
	$p = .002$	$p = .005$	$p = .002$	$p < .001$	$p = .002$
Threshold amplitude ($p < .001$, ANOVA)					
Supine					
70.5% (60.5–80.5)	90.1% (84.1–96.1)	93.0% (73.2–112.7)	93.7% (85.0–102.4)	100%	100% (100–100)
1.94 ± 1.22	2.48 ± 1.35	2.41 ± 1.34	2.36 ± 1.13	2.74 ± 1.40	2.74 ± 1.40
	$p = .001$	$p = .004$	$p = .002$	$p < .001$	$p < .001$

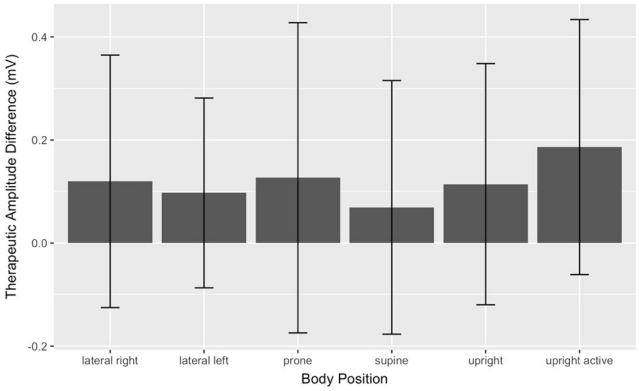

Fig. 3 Mean therapeutic amplitude differences (mV) between randomization groups (automatic − manual) at every body position, with 95% confidence interval error bars. All confidence intervals include 0, indicating no significant differences in therapeutic amplitudes between randomization groups at any body position

and once in each randomization group). The stimulation parameters included are as follows: amplitude, impedance, pulse width, and rate and were collected in different postures (lying right, left, prone, supine, upright, and upright active).

Clinical outcomes were evaluated by using visual analog pain scale (VAS) to measure pain intensity, Oswestry Disability Index (ODI) [5]—to quantify disability, and Pittsburgh Sleep Quality Index (PSQI)—to evaluate sleep quality [4]. Likert Scale [9] was used to assess convenience and satisfaction.

Statistical analysis

Stimulus amplitude and impedance across body positions at 2.5 and 3.5 months for both threshold and therapeutic stimulations in both automatic and manual randomization groups were compared by repeat measure (RM) ANOVAs followed by Bonferroni-corrected paired *t* tests. When sphericity assumptions for the repeat measures ANOVA test were violated, we used a conservative Greenhouse-Geisser *p* value correction to reduce the degrees of freedom for the *F* test statistic in proportion to the degree of assumption violation.

Difference in stimulus amplitude and impedance between automatic and manual randomization groups across the 2- and 3.5-month follow-up time points at each body position were evaluated by paired *t* tests and 95% confidence intervals (CI). The point estimates used in these CIs were calculated by subtracting the measured variable under the manual stimulus condition from the measured variable under the automatic stimulation condition ($A - M$). A positive range of values indicates higher values for the automatic condition, while a negative range indicates lower values and a range including zero indicates no significant difference.

Clinical outcomes for pain medication score, PSQI, ODI, and leg and back pain at 2-, 3.5-, and 5-month follow-ups were compared with the baseline scores using paired *t* tests.

For clinical outcome Likert scale questions, a binomial test was used to evaluate the null hypothesis that improvement and impairment responses account for equivalent amounts of non-neutral responses.

Results

A total of 8 female and 10 male patients with an average age of 56.7 years (range, 43–73) completed the study. Selected demographic, clinical, and surgical criteria are presented in Table 1.

Therapeutic stimulation

Mean therapeutic amplitudes at each body position, combined over 2- and 3.5- month follow-ups are displayed for each randomization group in Fig. 2. Significant differences were

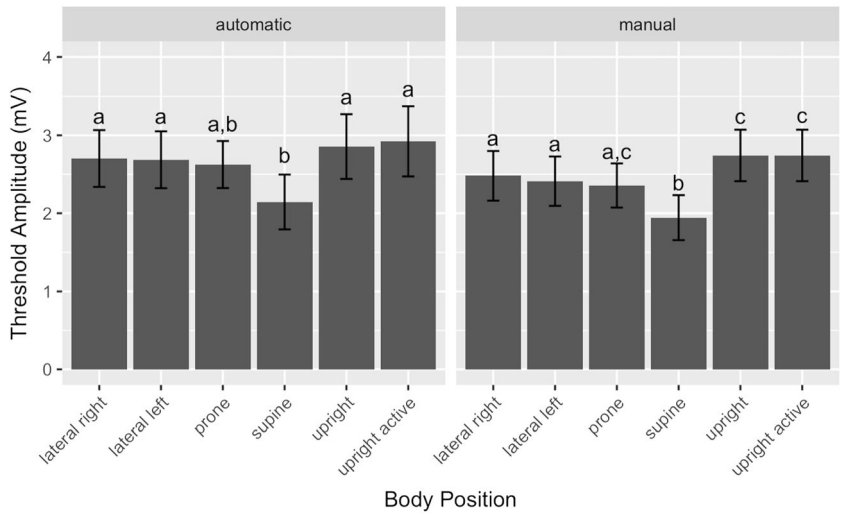

Fig. 4 Mean threshold amplitude (mV) by body position for the automatic and manual randomization groups. Body positions that lack a common letter above a bar (e.g., a, b, or c) are significantly different. Error bars are ± 1 standard error

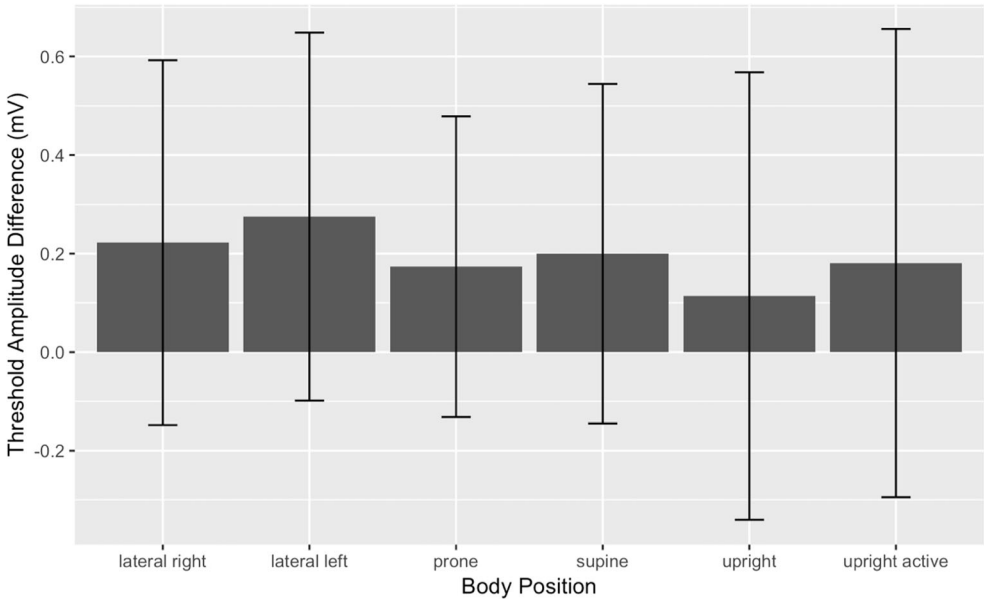

Fig. 5 Mean threshold amplitude differences (mV) between randomization groups (automatic − manual) at every body position with 95% confidence interval error bars. All confidence intervals include 0, indicating no significant differences in threshold amplitudes between randomization groups at any body position

found between therapeutic amplitudes at various body positions for both automatic ($p < .001$) and manual ($p < .001$) randomization groups (RM ANOVA). In particular, therapeutic amplitudes were significantly lower for the supine body position compared with all other body positions in both automatic ($p \leq .002$) and manual ($p \leq .005$) groups (Table 2). This table also contains stimulus amplitudes at each body position as a percentage and 95% confidence intervals of the upright position. Additionally, in the manual group, therapeutic amplitudes were significantly higher in the upright body position compared with lateral left ($p = .017$) and lateral right ($p = .043$) positions (Bonferroni tests).

Therapeutic amplitudes were not significantly different between randomization groups at any body position (paired *t* tests). Mean therapeutic amplitude differences between randomization groups ($A - M$) with 95% confidence intervals are shown in Fig. 3.

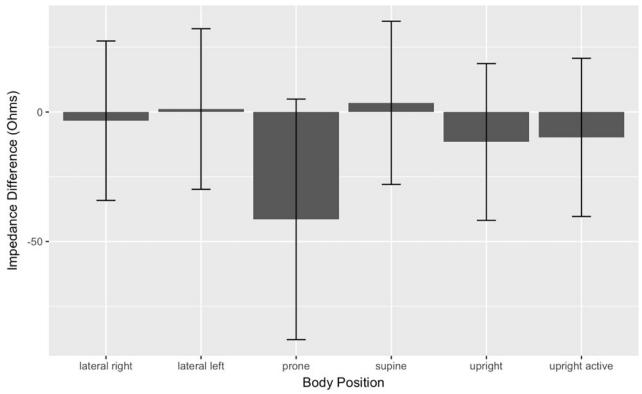

Fig. 6 The mean impedance differences (Ohms) between randomization groups (automatic − manual) at every body position with 95% confidence interval error bars. All confidence intervals include 0, indicating no significant differences in impedance between randomization groups at any body position

Threshold stimulation

Mean threshold amplitudes at each body position combined over 2- and 3.5-month follow-ups are displayed for each randomization group in Fig. 4. Threshold amplitudes at each body position, combined across 2- and 3.5-month follow-ups were statistically significant for both automatic ($p < .005$) and manual ($p < .001$) randomization groups (RM ANOVA). Threshold amplitudes were significantly lower for the supine body position compared with all other body positions in both automatic ($p \leq .02$) and manual ($p \leq .004$) groups except for the prone position in the automatic group (Table 2, Bonferroni tests). This table also contains stimulus amplitudes at each body position as a percentage and 95% confidence intervals of the upright position. Additionally, in the manual group, the threshold amplitude in the lateral left body position was significantly lower than the upright ($p = .004$) and upright active ($p = .004$) positions (Bonferroni tests).

Paired *t* tests found no significant differences in threshold amplitude between randomization groups at any body position. The mean threshold amplitude differences between randomization groups ($A - M$) with 95% confidence intervals are shown in Fig. 5.

The recorded therapeutic and threshold impedances were identical within randomization groups and within body positions. No significant differences in impedance existed between body positions for both the automatic ($p = .30$) and manual ($p = .23$) groups (RM ANOVA). Impedance was not different between randomization at any body positions (Fig. 6).

Table 3 Responses to Likert scale questions about convenience and satisfaction with automatic stimulation turned on. The percent, number of patients responding, and 95% confidence intervals are provided for each response category. A binomial test was used to evaluate the null hypothesis that improvement and impairment responses account for equivalent amount of non-neutral responses. *p* values are presented for binomial tests that improvement and impairment responses account for equivalent amounts of non-neutral responses

Likert question	Modal response	Improvement responses	Neutral responses	Impairment responses
How convenient was having the adaptive stimulation turned on vs. off?	1 = Much more convenient with adaptive stimulation	1 = Much more convenient with adaptive stimulation 2 = Somewhat more convenient with adaptive stimulation	3 = No difference in convenience	4 = Somewhat less convenient with adaptive stimulation 5 = Much less convenient with adaptive stimulation
	56% ($n = 10$) (31%, 78%)	72% ($n = 13$), $p = .049$ (47%, 90%)	6% ($n = 1$) (0%, 27%)	22% ($n = 4$), $p = .049$ (10%, 53%)
How satisfied were you when the adaptive stimulation was turned on vs. off?	1 = Much more satisfied with adaptive stimulation	1 = Much more satisfied with adaptive stimulation 2 = Somewhat more satisfied with adaptive stimulation	3 = No difference in satisfaction	4 = Somewhat less satisfied with adaptive stimulation 5 = Much less satisfied with adaptive stimulation
	61% ($n = 11$) (36%, 83%)	89% ($n = 16$), $p = .001$ (65%, 99%)	0% ($n = 0$) (0%, 0%)	11% ($n = 2$), $p = .001$ (1%, 35%)

Pulse width threshold and therapeutic stimulation parameters for all positions were 526 ± 289 μs and 515 ± 290 μs for automatic and manual stimulation, respectively. Pulse rate threshold and therapeutic stimulation parameters for all positions were 98 ± 181 Hz and 100 ± 182 Hz for automatic and manual stimulation, respectively.

Clinical outcomes

Responses to Likert scale questions reporting convenience and satisfaction with adaptive stimulation on vs. off are summarized in Table 3. The most common responses were "much more convenient" (56%, 10 subjects) and "much more satisfied" (61%, 11 subjects) with adaptive stimulation on. Improvement responses were significantly more common than no improvement responses for satisfaction (89%, 16 subjects) and convenience (72%, 13 subjects). The means and standard deviations for all clinical outcomes at all time points are presented in Table 4. Clinical outcomes improved significantly from baseline at all time points for PSQI ($p \leq .028$), ODI ($p \leq .0006$), VAS leg ($p \leq .001$), and VAS back pain scores ($p \leq .014$). Pain medication scores were not significantly different at any time point ($p \geq .33$).

Discussion

This study compared position-related variations in SCS therapy that chronic pain patients implanted with surgical, laminectomy-type leads experience with manual and automatic stimulation. For both automatic position-adaptive or manual stimulation, therapeutic and threshold stimulation intensities were significantly reduced for the supine position relative to all other body positions with one exception. Within the automatic stimulation group, threshold amplitudes in the prone and supine positions were not significantly different, which seems counterintuitive, considering other highly significant positional variations. This most likely occurred due to a few missing values from patients who were uncomfortable lying in the prone position after surgery and to a small sample size. In addition, the patients regarded position-adaptive stimulation to be more convenient and associated with higher satisfaction rates.

We have not found any statistical differences in stimulation between randomization groups at any body position, but a general tendency should be noted that the mean stimulation amplitudes were slightly lower for manual as compared with automatic stimulation.

Similar results were reported by a prospective, multicenter study, which examined the effectiveness of position-adaptive

Table 4 Clinical outcomes, means ± standard deviation, paired *t* test. *ODI*, Oswestry Disability Index; *VAS*, visual analog scale

	Preoperative	2 months	*p* value	3.5 months	*p* value	5 months	*p* value
Pain medication score	7.2 ± 3.3	6.9 ± 3.3	.79	6.4 ± 3.4	.33	6.9 ± 3.5	.77
Pittsburg Sleep Quality Index	12.4 ± 4.5	9.1 ± 4.2	.028	8.7 ± 3.3	.006	8.8 ± 3.8	.002
ODI	45.9 ± 15.4	31.1 ± 18.8	.0002	33.7 ± 18.8	.0006	31.3 ± 18.6	.0001
VAS/back	6.1 ± 2.8	3.4 ± 2.8	.004	3.8 ± 3.0	.009	3.9 ± 2.4	.014
VAS/leg	6.4 ± 3.3	3.0 ± 2.3	.001	3.3 ± 2.2	.0003	3.1 ± 2.4	.001

SCS in 79 patients implanted with percutaneous leads and randomized to either manual or automatic position-adaptive stimulation [14]. The authors noted an improvement of pain relief without loss of convenience or improved convenience without loss of pain relief in 86.5% of patients while using automatic position-adaptive stimulation. On average, an 84% (range, 5–174%) decrease of the stimulation amplitude in the supine position compared with the upright position was reported. We also observed the greatest stimulation amplitude reductions when going from an upright to a supine position for both manual and automatic stimulation, but the differences were not as high as reported by Schultz et al. [14] This was most likely related to greater inherent stability of the implanted paddle electrodes used in our study and more accurately focusing stimulation on the target [10]. Consistent with the previous studies, the supine position required the lowest stimulus amplitudes due to the shortened distance between the spinal cord and electrodes and the relationship between CSF and the width of the spinal space rather than technological parameters [2].

A smaller prospective study (15 patients) using percutaneous leads for stimulation also reported higher patient satisfaction ratings for automatic compared with manual stimulation [13]. However, the paddle-type leads implanted via laminectomy used in our study are known to be associated with lower migration rates, more efficient pain and paresthesia coverage areas, and better clinical outcomes [11]. Previous to our study, these leads had not been directly evaluated for automatic position-adaptive stimulation.

Variations in impedance values were not significant for either manual or automatic stimulation with respect to positional changes. Abejon et al. also studied changes in impedance produced by position-related variations and found no correlations [1]. However, they reported significant differences in the impedance values for the supine position in the patients with a shorter time since implantation. The authors concluded that these differences were caused by the ability of percutaneous electrodes to move over time. By using paddle-type leads implanted via laminectomy in our study, we were able to avoid this type of variation in measurements.

Limitations

This study was designed to assess the feasibility and utilized a small sample of 18 subjects. Although statistically significant, results were reported; there may be a bias derived from a small sample size and the possibility that our findings do not reflect a true effect.

Conclusions

Similar variations were reported for manual and automatic stimulation intensity in response to positional changes.

Authorship statement Protocol development, data collection, data analysis, and manuscript preparation were performed by the authors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by IRB and registered: https://clinicaltrials.gov/ct2/show/NCT01874899?term=justin+parker+neurological&rank=1

Informed consent Informed consent was obtained from all individual participants included in the study.

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