Research Paper

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Spinal cord stimulation attenuates temporal summation in patients with neuropathic pain

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Abstract

Evidence has shown that electrical stimulation at the dorsal columns attenuated the "wind-up" phenomenon in dorsal horn neurons in nerve-injured rats. This study was aimed to test the effect of spinal cord stimulation (SCS) on temporal summation (TS), the clinical correlate of the wind-up phenomenon in patients with radicular leg pain. Eighteen patients with SCS implants were tested both 30 minutes after SCS activation ("ON") and 2 hours after turning it off ("OFF"), in a random order. Temporal summation was evaluated in the most painful site in the affected leg and in the corresponding area in the contralateral leg by applying a tonic painful heat stimulus (46.5°C; 120 seconds) and simultaneous recording of the perceived heat pain intensity. Patients were also requested to report their clinical pain intensity (0-100 numerical pain scale) during SCS "ON" and "OFF". The Wilcoxon signed rank test was used in the comparisons between SCS "ON" and "OFF". Spinal cord stimulation activation significantly attenuated clinical pain intensity (from 66 ± 18 to 27 ± 31, $P < 0.001$). In the nonpainful leg, SCS activation failed to produce an effect on TS (24 ± 20 vs 21 ± 24 in SCS "OFF" and "ON", respectively; $P = 0.277$). In contrast, a significant decrease in the magnitude of TS in the affected leg was observed in response to SCS activation (from 32 ± 33 to 19 ± 24; $P = 0.017$). These results suggest that attenuation of TS, which likely represents suppression of hyperexcitability in spinal cord neurons, is a possible mechanism underlying SCS analgesia in patients with neuropathic pain.

Keywords: Radicular pain, Dermatome, Wind-up, Quantitative sensory testing, Analgesia

1. Introduction

Spinal cord stimulation (SCS) is an effective neuromodulatory intervention for treating various forms of otherwise refractory chronic pain, particularly neuropathic pain.[5] Lumbar radicular pain, which is the most common form of neuropathic pain, has shown responsiveness to SCS in at least 2 randomized controlled trials.[7,10] Yet, the exact mechanisms underlying SCS-induced analgesia for neuropathic pain have not been fully explored.[19,20]

Electrophysiological studies in animal models of neuropathic pain provide critical information both on the neurobiology of neuropathic pain and the mechanisms by which various interventions provide analgesia. Thus, studies have shown that dorsal column stimulation blocked wind-up of wide dynamic range (WDR) neurons in the superficial dorsal in a rat model of spinal nerve injury.[4,18]

Temporal summation (TS) constitutes an increased pain response to repetitive (>3 Hz) or prolonged nociceptive stimulation at C-fiber-activating intensity. Temporal summation is regarded as the human experimental correlate of the electrophysiological "wind-up" phenomenon.[14,15] Hence, based on the results obtained from the animal studies, we hypothesized that SCS will attenuate TS in patients with neuropathic pain. This study aimed to verify this hypothesis.

2. Methods

2.1. Patients

The study was conducted at the Pain Research Unit, Institute of Pain Medicine, Rambam Health Care Campus, Haifa, Israel, after approval by the Institution Ethics Committee. Patients aged 18 to 80 years were considered eligible if: (1) they provided written informed consent before enrollment, (2) they had either temporary or permanent SCS implants for the treatment of otherwise intractable unilateral radicular leg pain, after at least 1 back surgery, and (3) the SCS could be programmed in such a way that the perceived sensation of paresthesia was restricted to the affected leg. Patients were excluded if: (1) they had a neurological condition causing symmetrical polyneuropathy (ie, diabetes mellitus), (2) they had received a new pain therapy within 2 weeks before enrollment, (3) they had any other pain elsewhere in the body, unrelated to their radicular pain, and (4) exhibited a higher heat pain threshold than 46.5°C at the most painful site in the affected limb.

2.2. Pain measures

2.2.1. Temporal summation

The Thermal Sensory Analyzer (TSA 2001-II device; Medoc, Ramat Yishai, Israel) with a 30 × 30-mm thermode was used to administer painful thermal stimuli in this study.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Tonic noxious heat stimulation was applied to the selected sites using a ramp and hold method. The baseline temperature was set at 32.0°C and was increased at a rate of 1°C/s up to a destination temperature of 46.5°C and then remained constant for 120 seconds.[16] Throughout the test (a total duration of 135 seconds), subjects continuously rated the magnitude of their perceived pain using a computerized visual analog scale (0-100), which automatically recorded every 0.1 seconds. The effect of SCS on TS was determined as the primary outcome measure of this study.

2.2.2. Clinical (radicular) pain

Patients were asked to verbally report the level of their clinical (radicular) pain intensity using a 0 to 100 numeric pain scale. The effect of SCS on clinical (radicular) pain was a secondary outcome measure of this study.

2.3. Procedure

After obtaining written informed consent, eligible patients underwent a training session aimed at familiarizing them with the TS procedure. The most painful site in the affected leg was then determined and marked, as well as the corresponding area in the contralateral leg. The affected dermatomes were tested for possible light touch deficit using gentle strokes with a paintbrush. Temporal summation was tested in an area within the affected dermatome where no light touch deficit could be detected. Patients were then randomized to undergo the tests according to 1 of the following 2 orders: either 30 minutes after SCS activation (SCS "ON") first and then 2 hours after turning it off (SCS "OFF") or in a reversed order (SCS "OFF" first, followed by SCS "ON"). The randomization sequence was computer-based (blocks of 4). Heat stimuli were applied first to the contralateral leg (in the area corresponding to the most painful site in the affected leg) and to the most painful site in the affected leg 10 minutes later. The perceived heat pain intensity was continuously recorded (computerized visual analog scale). The intensity of the clinical (radicular) pain was assessed immediately before the initiation of the TS test in the affected leg, with both SCS "ON" and "OFF." Patients were requested not to take any analgesic medication for at least 2 hours before testing initiation.

2.4. Statistical analysis

All analyses were conducted using the SPSS for Windows Version 19 statistical package (SPSS Inc, Chicago, IL). The response to the tonic heat stimulation typically consists of peak pain intensity, immediately after reaching the destination temperature, followed by a decrease in intensity to a nadir and then again increased intensity up to a second peak.[12,13,16] Data of pain ratings during the heat stimulation were obtained every 5 seconds leading to 28 readings for the entire test period (ie, time 0-135 seconds). Then, the lowest (nadir) and the highest heat pain intensities (second peak) for each patient were identified, and the calculated difference in pain intensities between these 2 points was regarded as the TS. The individual TSs were then averaged for the entire group for each condition (ie, SCS "ON"/"OFF").

Because the study population included 18 subjects, the Shapiro–Wilk test of normality was performed and showed that both TS values and clinical pain intensities did not distribute normally. Therefore, the Wilcoxon signed rank test was used in the comparisons of TS values and clinical pain intensities between the SCS "ON" and "OFF" conditions. Spearman's test was used to study coefficient correlations between the change in pain intensity and the change in the magnitude of TS in response to SCS activation and between the elapsed time since SCS implantation and the change in the 2 outcome measures (ie, pain intensity and in TS). $P < 0.05$ was considered significant.

3. Results

3.1. Patients

Eighteen patients, including 17 men and 1 woman, met the inclusion criteria and completed the study. Their mean ± SD age was 59 ± 7 (median, 60; range, 47-72) years. The mean ± SD pain duration was 11.3 ± 5.3 (median, 10; range, 2-21) years, and the mean ± SD time elapsed since SCS implantation was 5.6 ± 3.3 (median, 7; range, 0.7-11) years. Maximal pain intensity was consistent with dermatomes L5 (9 patients) and S1 (5 patients), followed by L4 (3 patients) and L3 (1 patient.). All patients were using concomitant analgesic medication. All patients underwent at least 1 back surgery in their past. All have tried multiple medications, epidural steroid injections, physical therapy, and various types of complementary medicine. A routine psychological evaluation was performed in all patients before the temporary SCS implantation. The individual demographic and clinical characteristics of the patients are summarized in **Table 1**.

3.2. Effects of spinal cord stimulation on temporal summation

Activation of the SCS failed to produce a significant effect on TS in the nonpainful leg (TS with SCS "OFF": mean ± SD, 24 ± 20; median, 21; range, 0-73 and SCS "ON": mean ± SD, 21 ± 24; median, 16; range, 0-97; $P = 0.277$). In contrast, a significant decrease in the magnitude of TS at the most painful site in the affected leg was observed in response to SCS activation (SCS "OFF": mean ± SD, 32 ± 33; median, 28; range, 0-95 and SCS "ON": mean ± SD, 19 ± 24; median, 9; range, 0-84; $P = 0.017$) (**Fig. 1**). Noticeably, baseline TS (SCS "OFF") in the affected leg was higher than the TS in the nonaffected leg (32 ± 33 vs 24 ± 20, respectively) but not at a statistically significant level. The individual TS and clinical pain readings are presented in **Table 2**.

3.3. Effects of spinal cord stimulation on clinical (radicular) pain

Mean pain intensity 2 hours after turning the SCS "OFF" was 66 ± 18 (median, 67; range, 30-95). With SCS "ON" for 30 minutes, the recorded mean pain intensity decreased to 31 ± 27 (median, 22; range, 0-85). The Wilcoxon signed rank test showed that SCS had a significant effect on the clinical (radicular) pain ($P < 0.001$) (**Fig. 2**).

3.4. Correlations between temporal summation, analgesia, and time elapsed since surgery

Spearman's test failed to show significant coefficient correlation between the changes in pain intensity and the change in the magnitude of TS in response to SCS activation ($r = -0.19$; $P = 0.45$). Significant correlations have also not been found between the time elapsed since SCS implantation and the reported change in pain intensity ($r = 0.08$; $P = 0.75$) or in TS in the affected limb ($r = -0.26$; $P = 0.30$).

4. Discussion

The main findings of this study were the following: (1) SCS significantly reduced TS in the affected limb of patients with

Table 1

The individual demographic and clinical characteristics of the patients.

Patient number	Gender	Age, y	Pain duration, y	Tested dermatome	Time since SCS implantation, y	Co-treatments				
						Opioids	Antidepressants	Anticonvulsants	NSAIDs/simple analgesics	Other
1	M	60	12	L5	6	+	+			
2	M	72	10	L5	7	+	+	+		
3	M	61	14	S1	8	+	+	+	+	
4	M	60	4	L5	3		+			
5	M	58	10	L5	4			+	+	
6	F	57	6	L4	4		+	+		
7	M	47	10	S1	9	+			+	
8	M	56	13	L4	8				+	
9	M	67	10	L5	7	+		+		
10	M	60	18	L5	11	+				
11	M	67	20	L5	8	+	+	+		
12	M	65	12	L4	10	+		+		
13	M	60	16	S1	7	+			+	+*
14	M	49	4	L5	0.7			+		
15	M	46	2	S1	0.8	+				
16	M	54	21	L3	0.7	+		+		
17	M	64	10	L5	0.7	+		+		+†
18	M	41	7	S1	0.5	+				+†

* Baclofen tablets.
† Medical marijuana.
NSAIDS, nonsteroidal anti-inflammatory drug; SCS, spinal cord stimulation; y, years.

radicular pain, but not in the contralateral unaffected side, and (2) SCS significantly reduced clinical (radicular) pain.

4.1. Effects of spinal cord stimulation on temporal summation

Several previous attempts to test the effects of SCS on various forms of evoked pain have shown that SCS elevates thresholds to mechanical and electrical stimuli.[2,3,6,8,9] However, because their primary focus has been the quantitative testing of various pain thresholds, these earlier studies provided only limited information related to potential mechanisms of SCS analgesia in humans. To the best of our knowledge, TS has not been studied so far in the context of SCS, although it can potentially point toward mechanisms by which SCS induces analgesia. Temporal summation has been suggested to be the clinical correlate of the electrophysiological wind-up phenomenon, which has been attenuated in response to dorsal column stimulation in at least 2 studies on animal models of neuropathic pain.[4,18] Thus, the results of this study may suggest that in humans, SCS induces analgesia, at least in part, by reducing hyperexcitability in spinal cord neurons. At the same time, we wish to emphasize that additional potential mechanisms such as attenuating spinal pain transmission by activation of afferent Aβ fibers (the "gate control" theory) can also explain SCS-induced analgesia. This mechanism has gained emphasis because of the fact that paresthesia "covering" the painful area is generally required for effective SCS-induced analgesia.[10] Notably, this notion has recently been challenged by studies suggesting that very high–frequency (10 kHz) SCS can result in analgesia without accompanying paresthesia.[1,11,17]

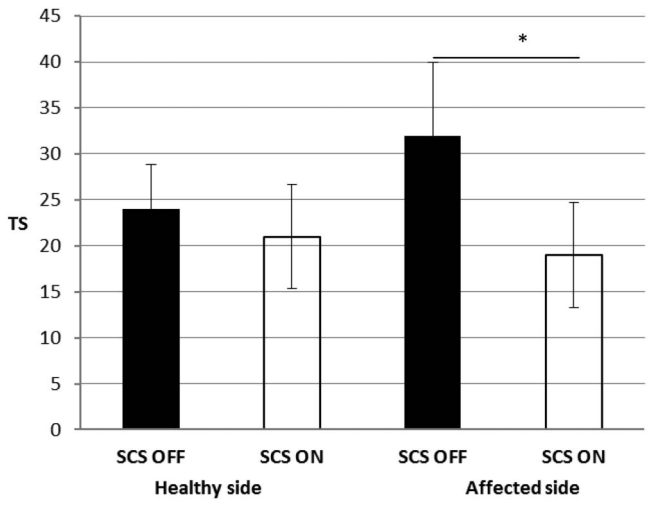

Figure 1. Effects of SCS on TS in the affected and nonaffected legs. Bars represent mean ± SEM. *$P < 0.05$. SCS, spinal cord stimulation; TS, temporal summation.

One point deserves consideration. Based on findings from animal studies that have showed enhanced wind-up of WDR neuronal response in nerve-injured rats,[4] we expected to find higher baseline (SCS "OFF") values of TS in the affected leg compared with the nonaffected leg. Nonetheless, although a considerable difference in TS (8 visual analog scale points) between the 2 legs was found, it has not reached statistical significance. This finding can be explained by the limited number of patients who participated in this study. Another possible explanation for the discrepancy between the animal wind-up findings and our human TS results is the difference between the stimulation modes; in the animal studies, repeated electrical or mechanical stimuli were used,[4,18] whereas in our experiment, constant heat pain stimuli were administered. The continuous heat paradigm was chosen based on 2 observations; first, it reliably produces TS in patients,[12,13,16] and second, in our laboratory, it produces a large average magnitude of TS (typically over 20 visual analog scale points) in contrast to negligible magnitude (around 5 points) in response to application of repeated mechanical stimuli. Lastly, all patients were taking

Table 2

Individual clinical pain and TS readings (see text for details).

Subject	TS												Clinical pain intensity (VAS)	
	Affected side						Nonaffected side						Affected	
	ON			OFF			ON			OFF			ON	OFF
	Nadir	Second peak	TS	Nadir	Second peak	TS	Nadir	Second peak	TS	Nadir	Second peak	TS		
1	7	41	34	60	94	34	37	53	16	41	62	21	25	55
2	6	6	0	7	7	0	2	39	37	5	15	10	30	50
3	78	88	10	88	99	11	96	99	3	78	99	21	30	70
4	15	99	84	5	99	94	2	99	97	10	37	27	50	80
5	4	66	62	19	61	42	7	32	25	3	33	30	20	60
6	1	23	22	10	83	73	1	1	0	2	16	14	20	30
7	3	3	0	43	45	2	22	41	19	12	29	17	60	80
8	26	50	24	2	97	95	2	47	45	50	97	47	0	50
9	16	42	26	1	34	33	27	55	28	24	27	3	60	80
10	13	15	2	23	46	23	15	31	16	25	77	52	20	40
11	99	99	0	99	99	0	99	99	0	99	99	0	60	80
12	0	0	0	63	63	0	0	0	0	49	65	16	0	80
13	13	21	8	9	16	7	46	58	12	49	99	50	70	90
14	19	20	1	0	61	61	17	23	6	49	78	29	20	75
15	37	65	28	47	83	36	56	77	21	50	80	30	10	75
16	7	7	0	22	22	0	14	14	0	15	15	0	0	50
17	62	100	38	26	88	62	52	100	48	27	100	73	0	65
18	100	100	0	100	100	0	94	100	6	100	100	0	85	95

TS, temporal summation; VAS, visual analog scale.

medications, including opioids, antidepressants, and anticonvulsants, which might have reduced the baseline TS in the affected side.

4.2. Effects of spinal cord stimulation on clinical (radicular) pain

The long-term efficacy of SCS for chronic radicular pain has already been shown in a multi-center, randomized controlled trial.[7] Although the primary outcome of this study was not measuring the effect of SCS on clinical pain, and certainly not in the long term, it is noticeable that the magnitude of the effect of SCS on radicular pain (approximately 50% pain reduction) in our study falls within the previously reported range. The fact that no significant coefficient correlation was also found between the time elapsed (since SCS implantation to testing) and the reported change in pain intensity suggests that SCS produces persistent analgesia in these patients.

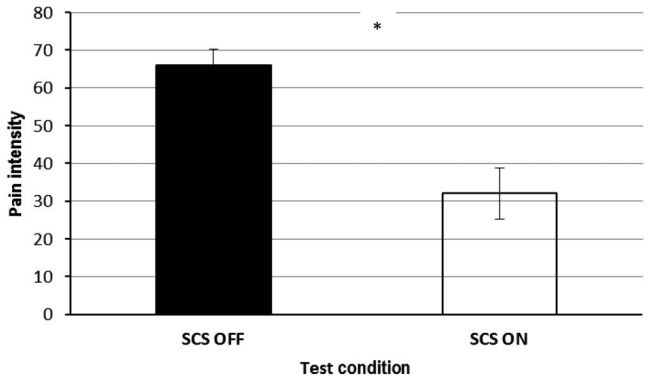

Figure 2. Effect of SCS on clinical (radicular) pain. Bars represent mean ± SEM. *$P < 0.001$. SCS, spinal cord stimulation.

4.3. Study limitations

A possible limitation of this study is the small number of participating patients. This limitation is reflected by the relatively large SDs, which represent large variability in the outcome measures. The large variability in the outcome measures may explain the fact that no correlation was found between SCS effect on TS and its clinical efficacy. At the same time, we cannot rule out the possibility that relationships between the present results and the clinical efficacy of SCS simply do not exist.

To avoid a type I error that may result from the abnormal distribution of the data, we used conservative statistics (ie, the Wilcoxon signed rank test) in the comparisons between the 2 different conditions ("ON" vs "OFF").

Another limitation is inherent in the nature of all traditional stimulation trials, in which blinding is not possible because of the accompanying paresthesia. Yet, the effect of SCS activation on TS in only the affected leg, but not on the healthy side, and the fact that the patients were unaware of how TS was calculated, reduce the likelihood for such bias to compromise the results of the study, although such bias cannot be completely excluded in our study. The new high-frequency stimulation that does not produce paresthesia seems to overcome this bias and has already been used in a recent double-blind study on SCS.[11] Unfortunately, conventional implanted devices cannot produce such high-frequency stimulation.

5. Conclusions

In line with data from animal studies, the results of this study suggest that attenuation of TS, which likely represents suppression of hyperexcitability in spinal cord neurons, is a possible

mechanism underlying SCS-induced analgesia in patients with neuropathic pain. Replication of these results in future, larger, preferably multi-center studies, also aimed at looking for relationships between the effects of SCS on TS and on clinical neuropathic pain in humans, is clearly required.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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References

[1] Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain Med 2014;15:347–54.
[2] Alo KM, Chado HN. Effect of spinal cord stimulation on sensory nerve conduction threshold functional measures. Neuromodulation 2000;3: 145–54.
[3] Eisenberg E, Backonja M, Fillingim RB, Pud D, Hord DE, King GW, Stojanovic MP. Quantitative sensory testing for spinal cord stimulation in patients with chronic neuropathic pain. Pain Pract 2006;6:161–5.
[4] Guan Y, Wacnik PW, Yang F, Carteret AF, Chung CY, Meyer RA, Raja SN. Spinal cord stimulation-induced analgesia: electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. Anesthesiology 2010;113:1392–405.
[5] Kapural L. Spinal cord stimulation for intractable chronic pain. Curr Pain Headache Rep 2014;18:406.
[6] Kemler MA, Reulen JP, Barendse GA, van Kleef M, de Vet HC, van den Wildenberg FA. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: a randomized trial. Anesthesiology 2001;95:72–80.
[7] Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 2008;63:762–70.
[8] Lindblom U, Meyerson BA. Influence on touch, vibration and cutaneous pain of dorsal column stimulation in man. PAIN 1975;1:257–70.
[9] Mironer YE, Somerville JJ. Pain tolerance threshold: a pilot study of an objective measurement of spinal cord stimulator trial results. Pain Med 2000;1:110–5.
[10] North RB, Ewend MG, Lawton MT, Kidd DH, Piantadosi S. Failed back surgery syndrome: 5-year follow-up after spinal cord stimulator implantation. Neurosurgery 1991;28:692–9.
[11] Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, Rosato M, Bovet N, West S, Bovy M, Rutschmann B, Gulve A, Garner F, Buchser E. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. Neuromodulation 2013;16:363–9.
[12] Potvin S, Stip E, Tempier A, Pampoulova T, Bentaleb LA, Lalonde P, Lipp O, Goffaux P, Marchand S. Pain perception in schizophrenia: no changes in diffuse noxious inhibitory controls (DNIC) but a lack of pain sensitization. J Psychiatr Res 2008;42:1010–6.
[13] Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat 2012;2012:938595.
[14] Price DD, Von der Gruen A, Miller J, Rafii A, Price C. Psychophysical analysis of morphine analgesia. PAIN 1985;22:261–9.
[15] Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. PAIN 1994;59:165–74.
[16] Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res 2008;1230:73–9.
[17] Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation 2013; 16:59–66.
[18] Yakhnitsa V, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. PAIN 1999;79:223–33.
[19] Yang F, Carteret AF, Wacnik PW, Chung CY, Xing L, Dong X, Meyer RA, Raja SN, Guan Y. Bipolar spinal cord stimulation attenuates mechanical hypersensitivity at an intensity that activates a small portion of A-fiber afferents in spinal nerve-injured rats. Neuroscience 2011;199:470–80.
[20] Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. Brain Res 2014;1569:19–31.