Burst Spinal Cord Stimulation: Toward Paresthesia-Free Pain Suppression

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INTRODUCTION: Spinal cord stimulation is commonly used for neuropathic pain modulation. The major side effect is the onset of paresthesia. The authors describe a new stimulation design that suppresses pain as well as, or even better than, the currently used stimulation, but without creating paresthesia.

METHODS: A spinal cord electrode (Lamitrode) for neuropathic pain was implanted in 12 patients via laminectomy: 4 at the C2 level and 7 at the T8–T9 level for cervicobrachialgia and lumboischialgia, respectively (1 at T11 at another center). During external stimulation, the patients received the classic tonic stimulation (40 or 50 Hz) and the new burst stimulation (40-Hz burst with 5 spikes at 500 Hz per burst).

RESULTS: Pain scores were measured using a visual analog scale and the McGill Short Form preoperatively and during tonic and burst stimulation. Paresthesia was scored as present or not present. Burst stimulation was significantly better for pain suppression, by both the visual analog scale score and the McGill Short Form score. Paresthesia was present in 92% of patients during tonic stimulation, and in only 17% during burst stimulation. Average follow-up was 20.5 months.

CONCLUSION: The authors present a new method of spinal cord stimulation using bursts that suppress neuropathic pain without the mandatory paresthesia. Pain suppression seems as good as or potentially better than that achieved with the currently used stimulation. Average follow-up after nearly 2 years (20.5 months) suggests that this stimulation design is stable.

KEY WORDS: Burst, Pain, Paresthesia, Spinal cord stimulation, Tonic

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The management of chronic, intractable neuropathic pain by electrical spinal cord stimulation (SCS) is a well-established clinical method.[1] The method is based on the gate-control theory of Melzack and Wall,[2] who postulated that activity in large-diameter cutaneous fibers (Aβ fibers) inhibits the transmission of noxious information to the brain. Electrical stimulation of these large afferents by an electrode placed dorsomedially in the epidural space elicits a tingling sensation (paresthesia) in the corresponding dermatomes. To obtain successful treatment of chronic neuropathic pain by SCS, the stimulation-induced paresthesia must cover the pain area completely.[3,4]

In SCS, an electrode is positioned over the spinal cord and connected to an internal pulse generator. All pulse generators currently available deliver tonic pulses that can be modified by altering the pulse width, frequency, and amplitude to get maximal pain suppression. The internal pulse generators can use either constant voltage or constant current to modulate the underlying cells or networks.

ABBREVIATIONS: IPG, implantable pulse generator; **SCS**, spinal cord stimulation; **VAS**, visual analog scale

Some neurons in the central nervous system including the spinal cord fire in groups of action potentials followed by periods of quiescence (bursts), whereas others, in the same stage of sensory processing, fire in a tonic continuous manner. Information theory suggests that both bursting and tonically firing model neurons efficiently transmit information about the stimulus. Burst and tonic firing might be parallel firing modes in certain sensory systems.[5,6]

Based on animal studies, it is suggested that burst firing is more powerful than tonic firing in activating the cerebral cortex.[7-10] This may be

TABLE 1. Overview of Patients for Age, Sex, Indication, Surgeries, Electrode Used, and Electrode Position[a]

Patient/Age, y/ Sex	Indication	Surgeries	Electrode Used	Electrode Position
1/51/F	Bilateral CB + LI	2: CL C4–C7, ADF C5–C7	44C	C2
2/44/F	Left CB	1: ADF C5–C6	44C	C2
3/38/M	Bilateral CB	1: CL	44C	C2
4/58/M	Bilateral LI	2: LD L4–L5, fusion L4–L5	88	T8
5/66/M	Bilateral LI	2: LL L4–L5, L5–S1	88	T8
6/58/M	PNP	0	44C	C2
7/54/F	LI, left < right	2: ALIF L5–S1, fusion L5–S1	44C	T8
8/47/M	Bilateral I	2: LD L4–L5 ×2	Quad	T11
9/45/M	Right I	8: LD ×7, fusion L4–L5	44C	T8
10/53/M	Bilateral LI	5: LD ×4, LL L3–L4	44	T8
11/52/M	Bilateral LI	2: LD L4–L5	44C	T8
12/62/F	Bilateral LI	2: LD L4–L5, LL L3–S1	44C	T8

[a] CB, cervicobrachialgia; LI, lumboischialgia; CL, cervical laminectomy; ADF, anterior (cervical) discectomy and fusion; LD, lumbar discectomy; LL, lumbar laminectomy; PNP, polyneuropathy; ALIF, anterior lumbar interbody fusion.

related to the fact that burst activation requires less temporal integration to reach the threshold of a neuron, and bursts may therefore activate neurons that are not activated by tonic stimulations (unmasking dormant synapses).[11]

This basic neuroscience knowledge has never been translated to clinical research. The authors present the first results of a new stimulation design (burst) that seems capable of suppressing neuropathic pain better than tonic stimulation without the mandatory paresthesia induction.

PATIENTS AND METHODS

The study and treatment were approved by the ethical committee of the University Hospital Antwerp, Belgium.

Patient Data

Twelve patients, 8 men and 4 women, were included in this study. All patients were analyzed prospectively according to the Belgian requirements for reimbursement for SCS. All patients were selected by the first author, and after multidisciplinary discussion with a pain physician, a psychological and psychiatric evaluation was performed to rule out psychogenic pain and psychiatric morbidity, contraindicating an implant. After authorization by the psychologist and psychiatrist, an implant was offered.

Patient age ranged from 38 to 66 years, with a mean of 52.3 years. The mean pain score on a visual analog scale (VAS) preoperatively for axial pain was 6.25 out of 10 (range, 5-10) and 7.54 out of 10 for limb pain. The mean McGill Short Form preoperative sensory dimension of pain score was 18.18, with an affective dimension of pain experience score of 7. All patients except 1 (with polyneuropathy) had lumboischialgia (n = 8) or cervicobrachialgia (n = 3) recurring after back or neck surgery (Tables 1 and 2).

Trial Stimulation Via Externalized Extension Wires

All patients underwent implantation of a Lamitrode (SJMedical Neurodivision, Plano, Texas) via laminectomy while under general anesthesia. It was implanted in 4 patients at the C2 level and in 7 patients at the T8–T9 level for cervicobrachialgia and lumboischialgia, respectively. One patient (patient 8) had received an implant at the T11 level at another center, but, because pain suppression failed, it was externalized and offered stimulation in tonic mode and burst mode as well. During the mandatory period of external stimulation, which is minimally 1 month according to Belgian health care requirements for reimbursement, each patient underwent a trial, applying the classic tonic stimulation (40 or 50 Hz) and the new burst stimulation with the same electrode configuration on separate days to prevent a carryover effect. To be able to compare tonic and burst stimulation, only patients who responded to tonic constant-current stimulation were further evaluated. After an initial tonic programming session to define pole activation by paresthesia coverage, at least 2 trial sessions of 1 hour in the tonic mode and 2 equally long trial sessions in the burst mode were offered, in random order, to which the patient was blinded. After these 4 trial sessions, all patients were offered continuous SCS using an external Eon implantable pulse generator (IPG) (SJMedical Neurodivision) in their preferred mode for the rest of the mandatory period of externalized stimulation (1 month); all patients preferred the burst mode.

The burst stimulation consisted of a 40-Hz burst mode with 5 spikes at 500 Hz per burst. The pulse width was fixed at 1 ms with 1-ms interspike interval delivered in constant current mode. The cumulative charge of the five 1-ms spikes was balanced during 5 ms after the spikes (Figure 1). The burst mode was programmed in a standard Eon IPG using custom-made software and a programming device. The clinical effects, both pain suppression and the presence of paresthesia, of the 2 stimulation designs were compared. Pain scores were measured using a VAS score from 0 to 10 and a McGill Short Form (15 items, each scored from 0 to 3; sensory and affective dimension) during preoperative evaluation and while undergoing tonic and burst stimulation. The McGill preoperative data for the sensory dimension for 2 patients were lost, and therefore analysis was performed on 10 patients. For the affective dimension of the McGill Short Form, preoperative data for only 1 patient were lost, and therefore analysis was performed on 11 patients. Paresthesia caused by the stimulation was scored as present (= 1) or not present (= 0)

TABLE 2. Overview For Tonic and Burst Stimulation Per Patient

Patient	Tonic					Burst				
	Frequency	Amplitude	Pulse Width	Energy/s	Charge Per Pulse	Frequency	Amplitude	Pulse Width	Energy, s	Charge Per Pulse
1	40	5	400	80 000	2000	40	0.7	1000	140 000	700
2	40	0.5	300	6000	150	40	0.05	1000	10 000	50
3	50	7	500	175 000	3500	40	0.7	1000	140 000	700
4	50	1.7	300	25 500	510	40	1.6	1000	320 000	1600
5	50	3.9	90	17 550	351	40	0.7	1000	140 000	700
6	50	1	90	4500	90	40	0.9	1000	180 000	900
7	50	2.4	400	48 000	960	40	0.4	1000	80 000	400
8	40	8	300	96 000	2400	40	0.2	1000	40 000	200
9	50	0.8	300	12 000	240	40	0.5	1000	100 000	500
10	50	1.8	300	27 000	540	40	1.4	1000	280 000	1400
11	50	1.8	300	27 000	540	40	0.3	1000	60 000	300
12	50	3.6	300	54 000	1080	40	0.4	1000	80 000	400

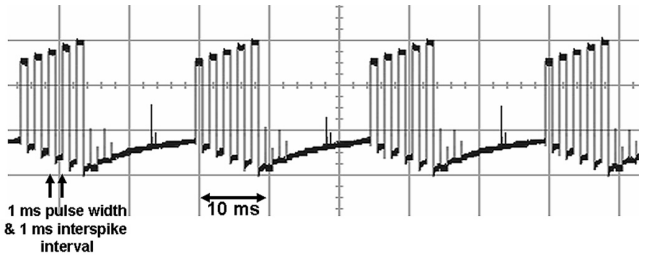

FIGURE 1. *Constant current burst mode (mA): 1-ms spikes with a 1-ms spike interval (500-Hz spike mode) and 5-ms charge balance firing at 40 Hz (40-Hz burst mode). Stimulation delivered by the Eon Implantable Pulse Generator (Advanced Neuromodulation Systems, Inc., Plano, Texas) via a custom-made program.*

at the stimulation amplitudes that are needed to suppress pain. The minimal amplitude at which maximal pain suppression was obtained was selected for permanent stimulation and for energy consumption/delivery calculations.

Permanent Stimulation Via an Implanted IPG

After the month of trial stimulation, the patients were reevaluated by the psychologist. If more than 50% pain suppression was obtained by tonic or burst stimulation during the externalized stimulation trial period, an IPG was implanted with the patient under general anesthesia, and burst mode was continued via the implanted IPG.

Electrical Charge Delivery

The amount of electrical charge delivered to the spinal cord is calculated by multiplying the current amplitude by the pulse width. Multiplying this electrical charge by the stimulation frequency yields the total amount of electrical current delivered per second to the spinal cord, ie, the electrically delivered dose. The difference in electrical current delivery was compared between tonic and burst stimulation, as were the current amplitudes used.

The charge per pulse was also calculated by multiplying the pulse width by the current amplitude.

Statistics

All analyses were performed with SPSS statistical software (version 15.0, SPSS, Inc., Chicago, Illinois). We performed paired samples *t* tests to verify whether there are differences between preoperative and postoperative VAS scores for axial, left, and right pain. A similar analysis was conducted for the McGill data. In addition, a paired-samples *t* test was performed of the overall results of tonic and burst stimulation. With regard to the paresthesia scores, a McNemar test was performed for tonic and burst stimulation vs preoperative scores because these scores were measured at a nominal level (yes vs no).

RESULTS

The shortest follow-up was 462 days (15.4 months), and the longest was 780 days (26 months), with an average of 613.8 days (20.5 months).

Trial Period: Externalized Stimulation in Tonic and Burst Modes

The maximum pain suppression scores obtained during either of the 2 stimulation sessions in tonic mode and the 2 stimulation sessions in burst mode were selected for further analysis.

The mean pain score on the VAS for axial pain was 4.42 with tonic stimulation and 1 with burst stimulation, resulting in an improvement in axial pain of 1.83 for tonic stimulation, whereas burst stimulation resulted in an improvement of 5.25 points on the VAS for axial pain, which is a clinically relevant and statistically significant improvement ($P = .05$ for tonic and $P < .001$ for burst; Figure 2).

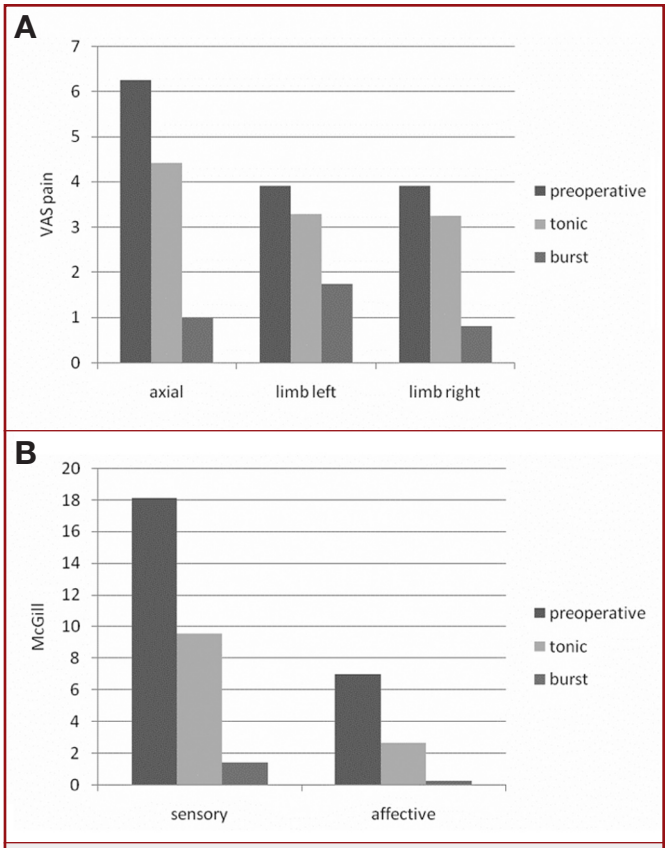

FIGURE 2. *Visual analog scale (VAS) and McGill Short Form.* **A**, *the VAS score preoperatively and with burst and tonic stimulation. A significantly greater decrease in the VAS score is noted during burst stimulation.* **B**, *McGill Short Form scores preoperatively and with burst and tonic stimulation. Significantly more improvement is noted with burst stimulation.*

The mean pain score on the VAS for limb pain was 3.13 with tonic stimulation and 0.25 with burst stimulation, resulting in an improvement in limb pain of 4.41 for tonic stimulation ($P < .001$), whereas burst stimulation resulted in an improvement of 7.29 points for limb pain ($P < .001$), which is a clinically relevant and statistically significant improvement (Figure 2)

The sensory dimension of pain experience on the McGill Short Form postoperatively for tonic stimulation was 9.60, an improvement of 8.58 points. For burst stimulation, the sensory dimension of pain experience postoperatively was 1.45, an improvement of 16.73 points, which is also a clinically relevant and statistically significant improvement ($P = .004$ for tonic and $P < .001$ for burst; Figure 2).

The affective dimension of pain experience on the McGill Short Form postoperatively for tonic stimulation was 2.70, an improvement of 4.30 points. For burst stimulation, the affective dimension of pain experience postoperatively was 0.27, an improvement of 6.73 points, which is also a clinically relevant and statistically significant improvement ($P = .001$ for tonic and $P < .001$ for burst; Figure 2).

Paresthesia was required in 11 patients (91.67%) to obtain pain suppression during tonic stimulation ($P < .01$ compared with preoperative scores), whereas during burst stimulation, only 2 patients (17%) felt paresthesia at amplitudes used to obtain pain suppression.

Long-term Results of Burst Stimulation With the Eon IPG

After a minimum of 1 year of follow-up, the results for paresthesia are not significantly different, suggesting that the burst stimulation design is stable and does not lead to habituation after 1 to 2 years. (Two participants were not included because they could not be a contacted.)

After more than 1 year of surgery, there was still a significant reduction in the VAS score for axial pain of 3.7 points ($P = .01$) and for limb pain of 5.15 points ($P = .01$).

For the sensory and affective dimensions of pain experience on the McGill Short Form, a significant improvement was still obtained after more than 1 year of surgery: 14 points for the sensory dimension ($P < .001$) and 3.4 points for the affective dimension ($P = .022$).

Energy Delivery/Consumption of Burst Mode

The average amplitude for tonic stimulation is 3.1 mA (range, 0.5-3.9 mA) vs 0.6 mA (range, 0.05-1.6 mA) for burst stimulation, a significantly lower amplitude for burst stimulation ($t_{11} = 3.32$; $P = .007$).

The average electrical charge per pulse for tonic stimulation was 1.03 μC and 0.654 μC for burst stimulation, a nonsignificant difference.

The average electrical current delivery per second for tonic stimulation was 47.7 mA vs 130.8 mA, a significant difference by a factor of 2.7 ($P = .024$).

DISCUSSION

Although incidental, the most important finding of this study was that the new burst stimulation design seems to suppress pain without the induction of paresthesia. Apart from its evident clinical advantage that paresthesia-free stimulation might be more pleasing and agreeable, the subthreshold (for paresthesia) burst stimulation will also allow double-blind, placebo-controlled studies of SCS, a feature that has never been possible until now because of the paresthesia.

Burst stimulation seems to suppress neuropathic pain better than tonic SCS. This has to be evaluated with care because we did not conduct a randomized, placebo-controlled study. It can therefore be predicted that results of future studies might not yield equally impressive results because of the fact that patients knew they were undergoing a new stimulation design. Thus, a placebo effect might be important in these patients, and it is not certain whether this stimulation results in better pain suppression. The fact that pain suppression persists for almost 2 years suggests, however, that it is not only a placebo effect. A new study, with a double-blind, placebo-controlled crossover design, has been initiated by the authors to verify whether the pain sup-

pression with burst stimulation is really better than tonic stimulation, as found in this study.

This improved pain suppression could be based on the fact that burst stimulation delivered significantly more charge per second than tonic stimulation. Another possible explanation is that burst activation requires less temporal integration to reach the threshold of a neuron and bursts may therefore activate neurons that are not activated by tonic stimulation (unmasking dormant synapses).[11] It has been shown that 5-Hz electrical sinusoidal stimulation activates C fibers and some Aδ fibers, but no Aβ fibers; 250 Hz activates Aβ and some Aδ fibers, but no C fibers; and 2000-Hz stimulation activates only Aβ fibers, without activation of C or Aδ fibers.[12-14] Whether the square waves of the presented burst stimulation have an effect similar to that of sinusoidal stimulation[12-14] is yet to be demonstrated. Burst firing, consisting of bursts of high-frequency spikes (500 Hz) could in a way, similar to high-frequency firing at 2000 Hz, selectively activate Aβ fibers without activating Aδ or C fibers, thereby suppressing pain according to the gate-control theory.[12,13] The absence of paresthesia could be the result of the lower amplitudes delivered with burst stimulation, resulting in subthreshold stimulation of these Aβ fibers. The charge per pulse does not differ significantly between burst and tonic stimulation, even though the amplitude is significantly lower. This is most likely because of the larger pulse width of the burst design. Burst stimulation could therefore already suppress pain via the electrophysiological gate-control mechanism before the clinical paresthesia threshold is reached.

It has also been demonstrated that opioid release from dorsal horn neurons is frequency dependent, with a maximal release at 500 Hz.[15] Although it is unclear whether opioid release is involved in SCS, this hypothetical mechanism can be explored in the future.

A limitation of the study is that only patients were included who already demonstrated a response to tonic stimulation because all patients underwent preliminary tonic stimulation programming to decide which poles to activate based on paresthesia coverage. Whether burst stimulation will be able to benefit patients who do not respond to tonic stimulation remains to be seen.

CONCLUSION

A new clinical electrical neurostimulation design is presented that consists of bursts of high-frequency stimuli. This stimulation design seems to suppress pain without the mandatory induction of paresthesia. Whether this novel burst stimulation design is really better than tonic stimulation at suppressing neuropathic pain, as these preliminary data suggest, must be clarified by future double-blind, placebo-controlled studies. This first clinical report warrants further research to explore the full capacity of burst SCS.

Disclosure

Dirk De Ridder, MD, PhD, has submitted a patent application for burst stimulation. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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