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Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation

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Objective: Spinal cord stimulation (SCS) is used for treating intractable neuropathic pain. It has been suggested that burst SCS (five pulses at 500 Hz, delivered 40 times per second) suppresses neuropathic pain at least as well as conventional tonic SCS, but without evoking paraesthesia. The efficacy of paraesthesia-free high and low amplitude burst SCS for the treatment of neuropathic pain in patients who are already familiar with tonic SCS was evaluated.

Materials and Methods: Forty patients receiving conventional (30–120 Hz) tonic SCS for at least six months were included. All patients received high and low amplitude burst SCS, for a two-week period in a double blind randomized crossover design, with a two-week period of tonic stimulation in between. The average visual analogue scale (VAS) scores for pain during the last three days of each stimulation period were evaluated as well as quality of life (QoL) scores, and patient's preferences.

Results: Average VAS score for pain were lower during high (40, $p = 0.013$) and low amplitude burst stimulation (42, $p = 0.053$) compared with tonic stimulation (52). QoL scores did not differ significantly. At the individual level 58% of the patients experienced significant additional pain reduction (>30% decrease in VAS for pain) during high and/or low amplitude burst stimulation. Eleven patients preferred tonic stimulation, fifteen high, and fourteen low amplitude burst stimulation.

Conclusion: Burst stimulation is in general more effective than tonic stimulation. Individual patients can highly benefit from burst stimulation; however, the therapeutic range of burst stimulation amplitudes requires individual assessment.

Keywords: burst stimulation, crossover study, diabetic neuropathic pain, failed back surgery syndrome, neuropathic pain, peripheral neuropathy, spinal cord stimulation, stimulation amplitude, tonic stimulation

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

For the past four decades electrical stimulation of the dorsal spinal cord (SCS) has demonstrated to be a safe and effective therapeutic tool for relieving several neuropathic pain conditions, which is difficult to treat with medication. SCS is commonly administered by using implantable pulse generators to deliver tonic constant current or constant voltage pulses with adjustable frequency, pulse width, and amplitude to aim for optimal pain relief. This tonic mode of SCS is generally accompanied by paraesthesia in the area covered by the stimulation, which has been considered mandatory to obtain pain suppression for a very long time.

In the last few years, it has been shown (1–6) that bursts of electrical pulses (five spikes at 500 Hz, delivered 40 times per second) delivered at the dorsal columns not only suppress neuropathic pain of various etiologies at least as well as tonic stimulation, but also can do that without evoking paraesthesia.

Burst stimulation could therefore be an effective stimulation option for people who either perceive the paraesthesia as uncomfortable or patients who do not achieve sufficient effects of tonic stimulation. However, very little is known about the working mechanisms of burst and therefore the optimal burst stimulation settings. So far, burst SCS is generally programmed as it was introduced by De Ridder (1), as five 500 Hz spikes of 1 ms duration at an amplitude just below sensation threshold, but the therapeutic range of burst stimulation might include a larger variety of stimulation settings. The purpose of this study is to further elucidate the paraesthesia-free pain relieving effects of burst SCS by performing a randomized, controlled, double-blind clinical study, and examining the therapeutic effects of both high and low amplitude burst stimulation in patients with neuropathic pain who are already familiar with SCS.

MATERIALS AND METHODS

Patients

Patients were recruited at the department of neurosurgery of Medisch Spectrum Twente (Enschede, the Netherlands). Patients (>18 years) with neuropathic pain in the lower extremities, who

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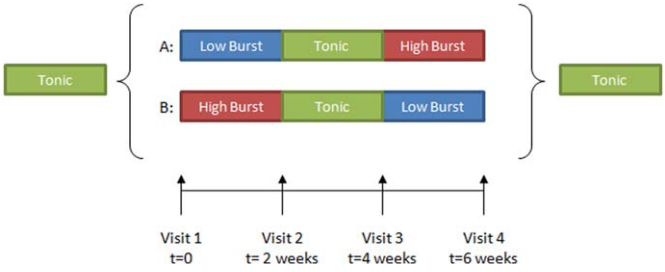

Figure 1. Study design. Patients received high and low amplitude burst SCS, each for a two-week period in a double blind randomized crossover design, with a two week wash-out period with their own tonic stimulation in between.

have received conventional (30–120 Hz) tonic SCS for at least six months were informed about the study and asked to participate. To ensure that included patients are a cross section of the patient population with SCS in Medisch Spectrum Twente hospital, patients were contacted based on the pulse generator implantation date (either replacement or new implantation). No selection was made based on pain etiology, resulting in a heterogeneous group of patients with failed back surgery syndrome (FBSS), peripheral neuropathy (PN), diabetic neuropathic pain (DNP), multiple sclerosis (MS), and complex regional pain syndrome (CRPS). Exclusion criteria were hospitalization or another form of serious decline of general health, severe pain that is interfering with the pain the SCS is used for, incapable of filling out questionnaires or following instructions, and experience with burst SCS in the past. All included patients had an implanted Eon C pulse generator (St. Jude Medical, Plano). Patients that dropped out of the study prematurely were replaced. The study conformed to the Declaration of Helsinki and has been approved by the Twente ethics committee. Written informed consent was obtained from all patients.

Study Design

First, in all patients a baseline evaluation of their conventional tonic stimulation was performed. Thereafter, patients received high and low amplitude burst SCS, each for a two-week period in a double blind randomized crossover design, with a two week wash-out period with their own tonic stimulation in between to prevent carry over effects between the two burst stimulation periods (Fig. 1). The study was registered in a clinical trial register (Nederlands trial register, www.trialregister.nl, NTR 4479).

Stimulation Settings

At baseline and during the two-week period of tonic stimulation, patients received stimulation with their conventional tonic stimulation settings. During burst stimulation patients received 500 Hz bursts consisting of five pulses of 1 ms with 1-ms inter pulse interval, delivered 40 times per second. For the high amplitude burst condition, stimulation amplitude just below the individual sensation threshold was used, as recommended by De Ridder (1). For the low amplitude burst condition, standard stimulation with 0.1 mA bursts was used. This condition was expected to be subtherapeutic and initially intended as sham stimulation.

Study Parameters

The primary outcome measure is the visual analogue scale (VAS) score for pain. During all phases of the study, patients were requested to fill in a pain diary, including as VAS scores (on a scale of 0–100) for pain in their back, legs, and feet separately. The average VAS scores for pain during the last three days of each stimulation period (tonic at baseline, low amplitude burst, and high amplitude burst) were used to assess the pain score for that period, thereby the score of the most affected body part, defined as the body part with the highest VAS score at baseline during tonic stimulation, was used.

Secondary parameters are the scores on the McGill Pain Questionnaire (MPQ) and the VAS for quality of life (QoL). The patients filled in the MPQ and a VAS score for QoL before each visit. From the MPQ questionnaire the total number of words chosen (NWC), the pain rating index of these words (PRI), and the MPQ-QoI were extracted (7). The NWC and PRI are scores that evaluate pain, while the MPQ-QoL is a score for QoL, ranging from 0 to 27, which increases when daily activity or sleep are disturbed by pain.

Study parameters are collected in all patients for all three stimulation settings (conventional tonic, high, and low amplitude burst stimulation). In addition, at the end of the study, each patient was asked which stimulation setting he/she preferred.

Statistical Analysis

The results are checked for period effects as a period affect was found in a previous study evaluating high frequency stimulation (8). The period effect is evaluated by comparing the difference in VAS scores for pain during high and low amplitude burst stimulation (VAS high burst − VAS low burst) from patients who first receive low amplitude burst stimulation (group A) with the scores from patients from who first receive high amplitude burst stimulation (group B). This comparison is done by using a Mann–Whitney *U* test. The potential period effect on patient's preference was evaluated by using a Chi-squared test. If there is no statistically significant difference between both groups in the difference in VAS score and patient's preference, it is assumed that there is no period effect, and all patients are grouped for further analysis regardless of their study arm (A or B).

To evaluate the effect of different stimulation settings (tonic, high amplitude burst, and low amplitude burst) on the primary and secondary outcome parameters, group comparisons were performed using repeated measurement analysis.

In addition to group comparisons, we also evaluated which individual patient benefitted from burst stimulation, thereby clinically relevant pain reduction was defined as more than 30% extra pain reduction as compared with tonic stimulation.

In a *post-hoc* analysis, the effect of the different stimulation settings on the VAS score for the back pain component was analyzed in the subgroup of patients with FBSS. Burst stimulation is suggested to modulate both the medial and lateral pain system instead of only the lateral pain system that is modulated by tonic stimulation (2). Therefore, the low back pain component in FBSS, which is often difficult to treat with tonic stimulation, might be covered better with burst stimulation.

All statistical analyses were performed in SPSS (version 22.0).

RESULTS

Patients

Fifty-two patients were informed about the study protocol and asked to participate. Ten patients declined study participation, because they thought the study visits to the hospital too time-consuming or for other practical reasons ($n = 5$), because they just started another pain treatment program ($n = 2$) or because they were satisfied with their current stimulation settings and preferred nothing to be altered ($n = 3$). One patient did not show-up during

Table 1. Patient Characteristics.

Sex	24 male, 16 female
Age	Average 58 years, range: 41–73
Pain etiology	32 failed back surgery syndrome (FBSS) 3 peripheral neuropathy (PN) 3 diabetic neuropathic pain (DNP) 1 multiple sclerosis (MS) 1 complex regional pain syndrome (CRPS)
Pain duration before implantation	Average 10 years, range 1–35
Postimplantation time	Average 28 months, range 6–124

the first study visit. The other 41 patients were included in the study, one of them dropped out prematurely, because of problems with the electrode lead (three invalid electrode contacts). The remaining 40 patients completed the study and their data has been analyzed (Table 1).

Stimulation Settings

The patients who participated in the study used a broad range of conventional, tonic stimulation settings. The amplitude of tonic stimulation varied between 0.4 and 19 mA, with pulse widths between 100 and 500 μs, and frequencies between 30 and 120 Hz. Thirteen patients had multiple programs they could switch between during tonic stimulation. For burst stimulation only one electrode contact configuration could be programmed, which was the configuration the patient used most often during tonic stimulation.

The individually adjusted amplitude of high amplitude burst stimulation varied between 0.1 and 6.4 mA. The standard amplitude for low burst stimulation was 0.1 mA. Since low amplitude stimulation was intended to be subtherapeutic, an exception was made for one patient who received high amplitude burst at 0.1 mA, this patient received low amplitude burst at 0.05 mA.

Period Effect

The order of the stimulation was of no influence on the difference in VAS scores (VAS high burst–VAS low burst) ($p = 0.51$). Also no significant period effect was found in patient's preference ($p = 0.97$).

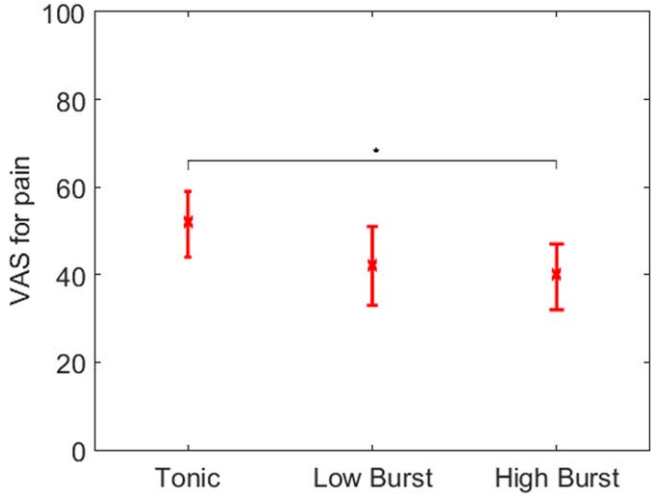

Figure 2. Mean VAS scores of the most affected body part for pain during tonic stimulation (baseline), low amplitude burst stimulation and high amplitude stimulation. Error bars represent 95% CI, * $p < 0.05$.

Table 2. Mean Values and 95% CI During Tonic Stimulation (Baseline), Low Amplitude Burst Stimulation and High Amplitude Stimulation and the Results of Repeated Measurement Analysis of the Different Outcome Parameters.

	Tonic		Low burst		High burst		
	Mean	95% CI	Mean	95% CI	Mean	95% CI	*p*-value
VAS pain	52	44–59	42	33–51	40	32–47	0.012*
NWC	11.1	9.5–12.7	10.7	9.2–12.2	10.0	8.5–11.5	0.32
PRI	20.4	17.2–23.6	19.7	16.3–23.1	18.0	14.7–21.2	0.34
VAS QoL	57	50–64	55	47–63	54	47–62	0.86
MPQ QoL	10.8	9.2–12.5	10.7	9.1–12.3	10.5	8.9–12.0	0.58

*Pairwise comparison after repeated measurement analysis showed a significant difference between the VAS pain score during high burst stimulation and tonic stimulation at baseline.
VAS pain, VAS score of most affected bodypart; NWC, number of words chosen; PRI, pain rating index; VAS QoL, VAS score for QoL; MPQ QoL, score for QoL based on McGill Pain questionnaire. A high level of pain is associated with a high VAS score for pain, a low NWC and a low PRI. A high QoL is associated with a high VAS QoL and a low MPQ QoL.

Since there was no period effect, patients of both arms were grouped for further analysis.

Pain

Average VAS scores for pain in the most affected body part were lower during high (40, $p = 0.013$) and low amplitude burst SCS (42, $p = 0.053$) compared with tonic SCS at baseline (52) (Fig. 2). No significant differences were found in NWC or PRI, although these scores were slightly lower, indicating less severe pain, in high amplitude burst (Table 2).

In total 23 patients (58%) had additional clinically relevant pain reduction with (low and/or high amplitude) burst stimulation as compared with tonic stimulation at baseline. Nine (23%) had only clinically relevant pain reduction during high amplitude burst stimulation, five (13%) only during low amplitude burst stimulation and nine (23%) during both low and high burst stimulation.

A subanalysis in the 32 FBSS patients showed no statistically significant differences in average VAS for back pain during tonic (40), high amplitude burst (37), and low amplitude burst (39) stimulation (Fig. 3). In this subgroup of 32 FBSS patients, thirteen patients had additional clinically relevant reduction of their back pain component with (low and/or high amplitude) burst stimulation. Six of them had only clinically relevant reduction of their back pain during high amplitude burst stimulation, two only during low amplitude burst stimulation and five during both low and high amplitude burst stimulation.

Quality of Life

The VAS scores for QoL reported by the patients did not differ significantly between burst SCS and tonic stimulation. Also no differences in MPQ-QoL were found (Table 2).

Patient's Preference

Eleven patients preferred tonic stimulation (1 DNP, 10 FBSS patients), fifteen preferred high amplitude burst (1 DNP, 1 PN, 1CRPS, 12 FBSS patients) and fourteen (1 DNP, 2 PN, 1 MS, 10 FBSS patients) preferred low amplitude burst SCS. Patients who preferred the low burst stimulation, had on average a much lower stimulation

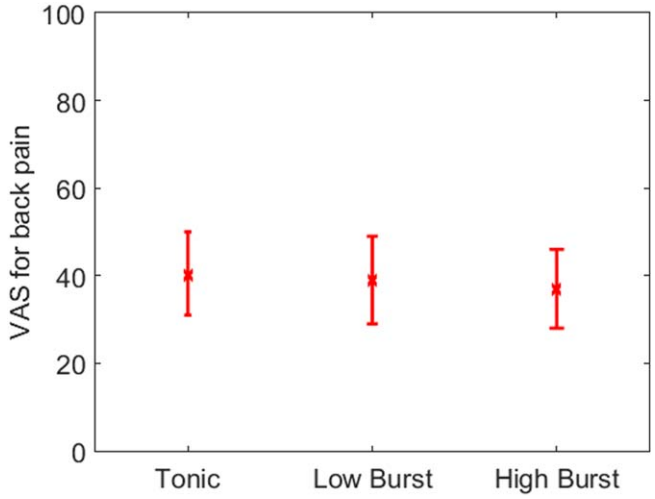

Figure 3. VAS scores for the back pain component in the subgroup of patient with FBSS ($n = 32$) during tonic stimulation (baseline), low amplitude burst stimulation and high amplitude stimulation. Error bars represent 95% CI. Differences were not statistically significant.

amplitude for the high amplitude burst stimulation (0.8 mA) than patients who preferred tonic (1.9 mA) or high burst (2.1 mA).

Subanalysis showed that people who prefer a certain stimulation setting indeed perceived on average the most pain reduction with that setting (Table 3). Patients with a preference for high amplitude burst stimulation perceived on average 21% pain reduction with low amplitude burst stimulation, and 48% pain reduction with high amplitude burst stimulation compared with their tonic stimulation. Patients with a preference for low amplitude burst stimulation had on average 11% pain reduction with high burst stimulation and 34% reduction with low amplitude burst stimulation.

Pain reduction was not the only factor that influenced the preference. Five patients reported that they liked the absence of paraesthesia during burst stimulation, and that they felt freer without having to use the patient programmer to adjust the stimulation amplitude during different postures or circumstances, while another five patients with fluctuating pain intensities reported that they missed the sensation and would like to be able to increase stimulation intensity. Patients who are used to use multiple programs are more used to adapt their stimulation settings depending on their level of pain and activities, however from the 13 patients who used multiple tonic programs only two preferred tonic stimulation.

Side Effects

Four patients (10%) experienced side effects of the high amplitude burst stimulation. Three patients reported a heavy feeling or pressure in their legs or feet, while one reported increased sensation of local stimulation around his IPG. Although burst stimulation was intended to be paraesthesia free, three patients did receive soft paraesthesia at least once during the two weeks high amplitude burst stimulation period.

DISCUSSION

In this study double-blind randomized controlled study, we evaluated the efficacy of high and low amplitude burst SCS in 40 neuropathic pain patients who were familiar with tonic SCS.

Pain Scores

On average, both high and low amplitude burst stimulation resulted in lower VAS scores for pain than tonic stimulation. Although, burst stimulation might not be the solution for everyone, burst stimulation can be very beneficial for many patients. More than half of the patients (58%) had clinically relevant additional pain reduction during low and/or high amplitude burst stimulation, defined as a decrease in VAS score for pain of at least 30% compared with their own tonic stimulation. A previous, non-randomized study at our centre showed a similar percentage of patients with pain reduction during burst stimulation, however during this study only high amplitude burst stimulation was evaluated (4).

A study from de Ridder et al. in 15 patients naïve to SCS showed a reduction of 55% of baseline pain during high burst stimulation, while tonic stimulation resulted in 31% pain reduction (2). In this study, on average 35% additional pain reduction was obtained using burst stimulation in comparison to tonic stimulation, which is higher than the 23% additional pain reduction in our study. In addition, all patients in the study of De Ridder preferred burst stimulation, while we showed that indeed the majority of the patients preferred burst stimulation, but that tonic stimulation might be beneficial for some others. These differences can be explained by the difference in patient population: De Ridder et al. included SCS naïve patients, while we included patients familiar with SCS, which means that the settings for tonic stimulation have been optimized during several visits.

Currently, a prospective, randomized multicenter study designed to support U.S. approval of St. Jude Medical's Burst stimulation is performed. Analyses of the first 85 included patients showed that 69% of the patients preferred burst stimulation over tonic stimulation (9).

Recently, Schu et al. performed a study in 20 FBSS patients familiar with SCS as well (5). In their study, patients evaluated burst stimulation (comparable to our high amplitude burst stimulation), 500 Hz tonic stimulation, and placebo stimulation during a one-week period. Their study showed an improvement in VAS scores during burst stimulation (47) compared with conventional tonic stimulation (56), which is comparable to our results. In their study, a much larger percentage of the patients (80%) preferred burst stimulation, and only 10% preferred conventional tonic stimulation. This difference can be explained by the fact that their group is more homogeneous, including only FBSS patients 1–1.5 years post-implantation, while we included a cross-section of our complete SCS population, including patients who have been using tonic stimulation for up to 10 years.

A recent retrospective analysis, including a large cohort of 102 patient from two centers (Sint Augustinus Hospital, Belgium and our

Table 3. Subanalysis of the Differences in VAS Scores for Pain for the Groups of Patients That Preferred Tonic, Low Amplitude Burst or High Amplitude Burst Stimulation.

		Preference for		
		Tonic ($n = 11$)	Low burst ($n = 14$)	High burst ($n = 15$)
VAS pain for:	Tonic	38	53	63
	Low burst	40	35	50
	High burst	41	47	33

People who prefer a certain stimulation setting, indeed perceived on average the most pain reduction with that setting.

hospital) also confirmed that burst stimulation was overall significantly better than tonic stimulation, however, with large variations in effect between individual patients (3). This study showed that burst stimulation could lead to further pain reduction in both responders and non-responders to tonic stimulation. The results of this study are, however, difficult to compare with our current study, due to the differences in the study protocol.

On average we found relatively high VAS scores for pain (52) at baseline during tonic stimulation. This might indicate that there is a selection bias of patients with a moderate response to SCS. A cross-section of patients were contacted for this study, however patients with a high level of pain are more likely to participate in this study when asked. Another explanation might be the high number of patients with FBSS in our study. These patients generally have a slowly diminishing response to SCS over time and the patients who participated in our study had already tonic stimulation for more than two years on average. In addition, patients who know that they will participate in an evaluation of new stimulation paradigms might exaggerate their current pain scores, hoping or expecting that the new paradigms will be more beneficial. In addition, some patients have developed pain of different etiology that influence their pain scores, even though they were asked to focus on the pain the SCS is aimed for.

We included a cross-section of our patient population, resulting in a heterogeneous group of patients and a large variation in pain scores. The large variation can also be partially explained by the fact that self-reported pain scores and questionnaires are subjective and susceptible to various interpretations by the patients. Yet, the advantage of including a cross-section of the complete SCS population is that this represents the clinical practice and it demonstrates that additional pain reduction can be achieved by further personalizing stimulation settings.

Subanalysis in FBSS patients showed on average no improvement of the back pain component, which might be explained by the fact that patients who have received SCS in our centre for FBSS have more severe leg pain than back pain. This results in already a relatively low VAS scores for back pain during tonic stimulation (40) and leaves little room for improvement. Out of the 32 FBSS patients, thirteen patients had clinically relevant additional pain reduction of their back pain when applying burst. At baseline (tonic stimulation), these thirteen patients had on average higher VAS scores for back pain (51 vs. 33) and for leg pain (51 vs. 39) in comparison with patients with no clinical additional relevant pain reduction during burst stimulation. Although, on average no improvement was found in the back pain component in FBSS patients, burst stimulation could be beneficial for individual FBSS patients with a severe back pain component.

Quality of Life

No effect was seen in scores for QoL, a two-week period is probably too short to cause substantial changes in QoL. Furthermore, QoL can be influenced not only by pain but also by other factors for which we cannot correct.

Patient's Preference

Eleven patients preferred tonic stimulation, fifteen preferred high amplitude burst and fourteen preferred low amplitude burst SCS. Patient's preference was not only influenced by pain, but also by other factors, like the feeling to be in control by the ability to use the patient programmer during tonic stimulation and the presence of paraesthesias. Although paraesthesias are experienced as unpleasant or annoying by some patients, others report positive aspects of paraesthesia and note that the feeling of paraesthesia is associated with pain reduction or provides distraction from the pain. Side effects of burst stimulation were only reported in a minority of patients (10%), and only during high amplitude burst stimulation, indicating that these patients might have been overstimulated in this condition.

Stimulation Settings

The low amplitude stimulation was intended to be subtherapeutic, and was originally included in the protocol as sham stimulation. However, the difference in amplitude between low (0.1 mA for every patient) and high amplitude (individually adjusted) burst stimulation was less than expected and only minimal in some patients. For this reason low amplitude burst was most likely not subtherapeutic in all patients and it is more appropriate to call this form of stimulation low amplitude burst stimulation instead of sham.

Our study showed that the therapeutic range of the burst stimulation highly varies between individual patients, and that the threshold for a therapeutic effect might be much lower than the sensation threshold. Patients who preferred the supposedly subtherapeutic low amplitude burst stimulation, had on average a much lower stimulation amplitude during high amplitude burst stimulation. This indicates that low stimulation might indeed not have been at a subtherapeutic level in those patients who preferred low amplitude burst stimulation. They even might have been overstimulated during high amplitude burst. For example, three out of the four patients with side effects during high burst stimulation preferred low burst stimulation and had relatively low stimulation amplitude during high amplitude burst stimulation (0.1–0.65). Therefore, the relatively good results with low burst stimulation in several patients are probably not purely a placebo effect, although the placebo effect still can play an important role. To control for placebo effects, the various burst stimulation intensities should be compared with stimulation off, which has been done in the study by Schu et al. (5). Their study showed significantly increased pain scores with placebo stimulation compared with conventional tonic stimulation or burst stimulation. This suggests that the positive results we found using low amplitude burst stimulation cannot be due to only a placebo effect, although we did not include a stimulation off period in our study protocol to confirm this. Further studies should be performed to get more insight in the optimal amplitude for burst stimulation, and how this can be determined for an individual patient.

The positive effect of low amplitude burst stimulation in several patients indicates that a higher amplitude during burst stimulation does not always lead to better pain control, even when it is still below the patient's sensation threshold. Amplitude setting of burst stimulation, therefore, should be optimized in each individual patient. In addition, also other parameters of burst stimulation including frequency, number of pulses per train and pulse duration can be adapted for further optimization. Recently, it was shown that increasing the frequency of the burst pulses from 500 to 1000 Hz does on average not lead to further pain reduction (10), however further optimization of burst stimulation parameters for the individual patient might still be very well possible.

CONCLUSION

In our randomized double-blind study we have demonstrated that burst stimulation is overall more effective than tonic stimulation, that 58% of the patients experienced additional clinically relevant pain reduction, and 73% of the patients preferred burst stimulation. However, burst stimulation is no panacea and its

therapeutic range in individual patients still needs to be determined. Offering patients the option of burst stimulation is an important step toward further personalized SCS therapy.

Acknowledgements

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Authorship Statements

Dr. Tjepkema-Cloostermans, Dr. de Vos, Miss Wolters, Mrs. Dijkstra-Scholten and Mr. Lenders designed and conducted the study, including patient recruitment, data collection, and data analysis. Dr. Tjepkema-Cloostermans and Dr. de Vos prepared the manuscript draft, and all authors approved the final manuscript.

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COMMENTS

This work highlights the appreciation that new waveform modalities are a giant step forward in the treatment of chronic pain and providing individualized programming with flexible settings seems to be important.

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This is an interesting study with intriguing results. Certainly, the study design would have been more robust by having a larger more homogenous patient population, including a placebo arm and perhaps a low amplitude (0.1 mA) tonic stimulation arm. However, the apparent efficacy of low-amplitude burst stimulation is eye-opening and, if confirmed by future studies, it may open the door to future research addressing many questions such as what neurons are activated by higher frequency subthreshold stimulation? While paresthesia-based stimulation is believed to trigger action potentials in dorsal column A-beta fibers, the effects of paresthesia-free high frequency stimulation are less clear. Indeed, while anatomic target specificity suggests a localized effect, a number of parameters remain ill-defined including which higher frequency is affecting what neuronal cell type and at which amplitude. The heterogeneous response of patients is equally interesting and warrants further study.

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In this issue of Neuromodulation, Tjepkema-Cloostermans et al. demonstrate that burst stimulation is more effective than tonic stimulation in patients experiencing neuropathic pain in the lower extremities (1). We observed an important discrepancy between the protocol as published in the Dutch national trial registry (www.trialregister.nl, registration number NTR4479) and the manuscript that was sent to Neuromodulation for review.

In the manuscript, the authors compare three types of stimulation: tonic, low amplitude burst, and high amplitude burst. However, their summary in the trial registry clearly indicates they planned to compare burst stimulation to a sham control. In addition, they propose to include the Patients' Global Impression of Change (PGIC) scale, and the estimated walking distance as secondary outcomes. These discrepancies were not addressed in the manuscript submitted for the first time, which gave reason to cautiously interpret their results. It led us to assume that the authors found no significant difference between burst stimulation and sham stimulation, which is clearly an undesirable conclusion.

Had the authors followed their original protocol this paper might have had other conclusions with different implications altogether. They could have concluded that burst and sham yield similar pain reduction and might therefore be attributed to a placebo effect, or that sham stimulation is not "sham" after all, and that it yields as much effect as "high burst" stimulation.

REFERENCE

1. Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MWPM. Effect of burst stimulation evaluated in patients familiar with spinal cord stimulation. Neuromodulation.

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Comments not included in the Early View version of this paper.

