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Spinal Cord Stimulation for the Treatment of Chronic Back Pain Patients: 500-Hz vs. 1000-Hz Burst Stimulation

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Objective: Spinal cord stimulation is a commonly used, safe, and effective procedure applied for medically intractable failed back surgery syndrome, as well as other neuropathic pain syndromes. Recently, a novel stimulation paradigm called burst stimulation has been developed that is paresthesia-free and has a more pronounced suppressive effect on neuropathic pain.

Materials and Methods: Fifteen patients who were being treated with burst spinal cord stimulation for failed back surgery syndrome participated in an open-label trial to verify whether their pain suppression could be further ameliorated by changing the burst pattern. Burst stimulation with packets of five electrical pulses delivered at 500 Hz with 1000-μsec pulse width 40 times per second was changed to burst mode delivering five spikes at 1000 Hz with 500-μsec pulse width 40 times a second. As the amplitudes did not differ between the two groups, the total delivery of current to the spinal cord was not different between the two modes of burst stimulation. Scores on visual analog scales for pain and paresthesia, the Pain Catastrophizing Scale, the Pain Vigilance and Awareness Questionnaire, and the Short Form 36 quality of life measurement were compared between the two modes of burst stimulation. [Correction added on 06 Feb 2015, after first online publication: this paragraph has been revised to signify the comparison of amplitudes between two groups]

Results: No statistically significant differences were found between the two modes of stimulation.

Conclusion: The results suggest that increasing the frequency from 500 to 1000 Hz while keeping the pulse width constant does not add any extra benefit in suppressing pain. Further studies should verify whether increasing the frequency above 1000 Hz has a similar lack of effect.

Keywords: 1000 Hz, 500 Hz, burst, failed back surgery syndrome, neuromodulation, pain, stimulation

Conflict of Interest: Dr. De Ridder holds intellectual property rights related to burst stimulation. This study was conducted with no financial support from St. Jude Medical (which commercializes burst stimulation in Europe). Mr. Vancamp is also an employee of St. Jude Medical. The other authors did not report any conflicts of interest.

INTRODUCTION

At the end of the 1960s, spinal cord stimulation was developed as a treatment modality for medically intractable neuropathic pain, predominantly targeting failed back surgery syndrome (1). The original concept was based on the pain gate mechanism, which postulated that stimulation of large Aβ fibers suppresses pain transmission via the small unmyelinated C fibers and small Aδ fibers. The treatment's exact working mechanism has remained elusive but most likely involves a combination of local spinal and supraspinal mechanisms (2,3). At the spinal level, the ascending dorsal column fibers, as well as the opioidergic (4) and serotoninergic (5) descending pain modulatory systems, might be implicated in the pain-suppressing effect.

Recently, a novel stimulation paradigm called burst stimulation has been developed (6), consisting of intermittent packets of five high-frequency stimuli delivered at 500 Hz (500-Hz spike mode) 40 times per second (40-Hz burst mode), with a long pulse width of 1000 μs and an interspike interval of 1000 μs delivered in constant-current mode. The monophasic pulses are charge-balanced at the end of the burst, differentiating it from clustered high-frequency tonic firing. In view of the paresthesia-free nature of burst stimulation, we took the opportunity to perform a placebo-controlled study (7), which confirmed the results of a non-placebo-controlled study (6): for all measures of pain, including limb, back, and global pain, burst was better than placebo, and in comparison with tonic stimulation it was significantly better for global pain perception, as well as for attention to pain and to changes in pain (7). This has

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recently been evaluated after a longer follow-up, and in this study, analyzing 102 patients with burst stimulation vs. tonic stimulation, it is shown that burst stimulation is capable of better suppressing both back pain and leg pain in comparison with conventional tonic stimulation (8).

In view of the promising results of burst stimulation and the likely different working mechanism, it is imperative to know whether the stimulation design can be further improved by changing the parameters in the burst pattern. The original stimulation design consisted of a 500-Hz spike mode, based on a maximal postsynaptic inhibition obtained by 500-Hz burst firing in basic neuroscientific studies (9). However, in this study, higher spike frequencies were not tested, and considering the clinically beneficial results obtained with high-frequency tonic spinal cord stimulation (10,11), it is possible that 1000-Hz spike mode could be better than 500-Hz spike mode. We therefore conducted a clinical study comparing 500-Hz burst stimulation versus 1000-Hz burst stimulation. In order to keep the current delivery similar, the pulse width was halved to 500 μsec when applying the 1000-Hz frequency, resulting in a comparison of the following stimulation designs: 500-Hz bursts (i.e., five stimuli at 500 Hz) presented 40 times per second with a pulse width of 1000 μsec vs. 1000-Hz bursts (i.e., five stimuli at 1000 Hz) presented 40 times per second with a pulse width of 500 μsec.

MATERIALS AND METHODS

Fifteen patients who had not been involved in any burst study before and were being treated by burst SCS for FBSS at Sint Augustinus Hospital in Antwerp, Belgium, participated in an open-label trial to verify whether their pain suppression could be further ameliorated by changing the burst pattern from 500-Hz burst mode to 1000-Hz burst mode. Both patients and evaluator were blinded to the stimulation design applied. Patients were randomized to either 500-Hz burst mode or 1000-Hz burst mode. The 1000-Hz burst mode used consisted of delivering five spikes at 1000 Hz 40 times a second with 500 μs pulse width, as opposed to standard burst settings of delivering five spikes at 500 Hz 40 times per second with 1000 μs pulse width. The comparison between the amplitudes used at 500 Hz (M = 3.67, SD = 0.82) and 1000 Hz (M = 3.07, SD = 1.22) stimulation did not yield a significant effect (t = 1.96, p = 0.07). Furthermore, no significant correlation was demonstrated between the amplitudes used at 500 Hz and 1000 Hz (r = .38, p = 0.16), indicating that the amplitudes at 500 Hz were not systematically higher or lower than the ones used at 1000 Hz. As the amplitudes were not different between the 2 groups the total delivery of current to the spinal cord between the 2 burst stimulation designs can be considered similar. The patients were stimulated for 2 weeks with either 500 Hz burst or 1000 Hz burst mode, after which they were re-evaluated and switched to the other burst stimulation mode. [Correction added on 06 February 2015, after first online publication: this paragraph has been revised to show the comparison and significant correlation, if any, between the amplitudes used at 500 and 1000 Hz burst mode]

The study population consisted of 8 men and 7 women. Patients' ages ranged between 34 and 71 years, with a mean of 52 years. The pain suppression obtained by burst stimulation was not as good as expected on the basis of previous studies using the same stimulation design (6,7,12).

The study was designed to conform to the Declaration of Helsinki and was approved by the Institutional Review Board of Sint Augustinus Hospital in Antwerp, Belgium.

Outcome Parameters

Primary Outcome Measures

Visual Analog Scale Pain scores for limb, back, and general pain were measured on a visual analog scale (VAS) consisting of a 100-mm line ranging from 0 ("no pain") to 10 ("maximal pain"). Patients were asked to score their average level of limb, back, and general pain. General pain was defined as global pain experienced during the past week.

Paresthesia caused by stimulation at amplitudes needed to suppress pain were scored on a VAS consisting of a 100-mm line.

Secondary Outcome Measures

Pain Catastrophizing Scale The Pain Catastrophizing Scale (PCS) indicates the catastrophizing impact of pain experienced by the patient. Catastrophizing is defined as experiencing pain as awful, horrible, and unbearable. The scale consists of 13 statements concerning pain experiences (e.g., "I feel I can't stand it anymore"), with possible responses ranging between 0 ("not at all") and 4 ("always") (13).

Pain Vigilance and Awareness Questionnaire The Pain Vigilance and Awareness Questionnaire (PVAQ) measures preoccupation with or attention to pain and is associated with pain-related fear and perceived pain severity (14). It consists of two separable factors that measure 1) attention to pain and 2) attention to changes in pain (14). It consists of 16 items (e.g., "I am very sensitive to pain") rated from 0 ("never") up to 5 ("always") (15).

Short Form 36 The Short Form 36 (SF-36) is an instrument designed to measure the overall health-related quality of life experienced by the patient. It is a self-administered questionnaire that assesses physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, and pain (16).

Statistical Analysis

The data were analyzed using SPSS 22.0. To compare the outcome measures between 500-Hz and 1000-Hz stimulation, we applied a paired sample t-test. To correct for multiple comparisons, we used a Bonferroni adjustment, dividing the p-value by the total number of comparisons.

RESULTS

A comparison of the primary outcome measures between 500-Hz and 1000-Hz stimulation revealed no significant difference for back pain (t = 0.13, p = 0.90), limb pain (t = –0.32, p = 0.76), or general pain (t = 0.62, p = 0.55) (Fig. 1). For paresthesia due to the stimulation, no significant difference was obtained between 500 Hz and 1000 Hz (t = 1.09, p = 0.30).

For the secondary outcome measures, the comparison between 500 Hz and 1000 Hz yielded a significant difference in PCS score (t = 0.2.27, p = 0.04), with the score for 1000-Hz stimulation (mean = 0.23, SD = 0.32) lower in comparison with 500-Hz stimulation (mean = 0.50, SD = 0.56) stimulation. However, after correction for multiple comparisons using a Bonferroni adjustment, the difference in PCS score did not remain. A similar analysis for both subscales of the PVAQ showed no significant difference in attention to pain (t = –1.17, p = 0.26) or attention

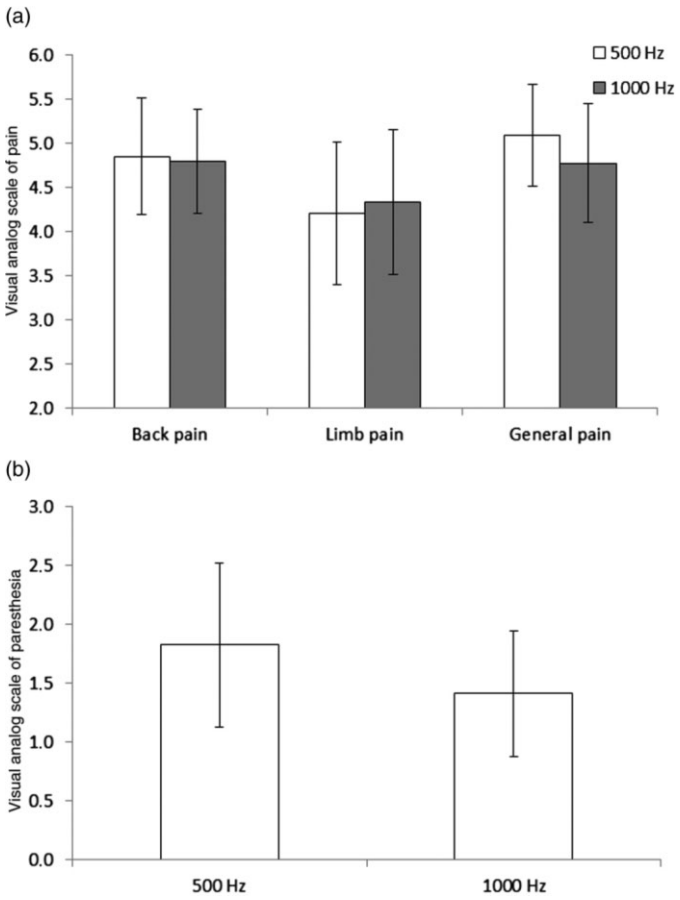

Figure 1. a. A comparison between 500-Hz and 1000-Hz burst stimulation revealed no significant difference between the two burst protocols with regard to effect on back pain, limb pain, or general pain. b. A comparison between 500-Hz and 1000-Hz burst stimulation revealed no significant difference between the two burst protocols with regard to paresthesia created by the stimulation.

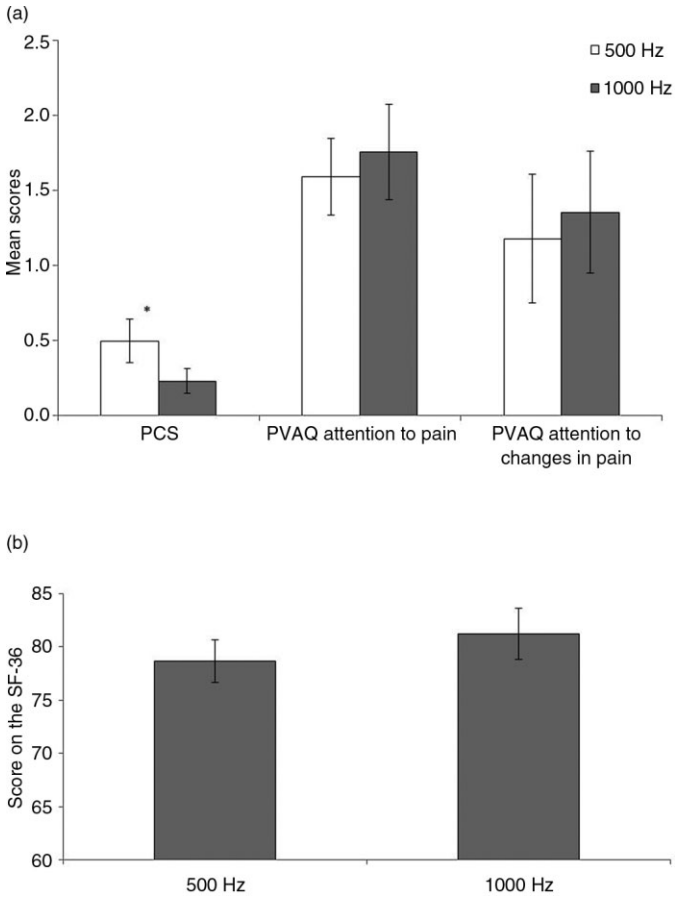

Figure 2. a. A comparison between 500-Hz and 1000-Hz burst stimulation revealed a significant difference in score for the for Pain Catastrophizing Scale (PCS), but not for the Pain Vigilance and Awareness Questionnaire (PVAQ) subscales of attention to pain and attention to changes in pain. The significance disappeared after Bonferroni correction for multiple comparisons. b. A comparison between 500-Hz and 1000-Hz burst stimulation revealed no significant difference in Short Form 36 (SF-36) score.

to changes in pain ($t = -.31$, $p = 0.76$). In addition, comparison of SF-36 scores indicated no difference between 500-Hz and 1000-Hz stimulation ($t = -1.45$, $p = 0.17$). See Figure 2 for an overview.

DISCUSSION

This study demonstrates that there is no difference between 500-Hz burst mode and 1000-Hz burst mode when equal amounts of current are delivered to the spinal cord in each mode. As both burst stimulation modes produce almost no paresthesia (Fig. 1b), the patients could not distinguish which mode they were getting. Whereas the absence of a difference between 1000 Hz and 500 Hz might appear to call the value of this study into question, it is of major importance; although negative results are statistically less revealing than positive results, sometimes negative results are the only way to progress, analogous to Sherlock Holmes solving a murder because the dog did not bark (17).

The importance of this small study lies in the fact that it suggests that when the current delivery is kept constant, 500-Hz burst stimulation exerts a clinical effect similar to that of 1000-Hz burst stimulation; if this is confirmed for higher stimulation frequencies (e.g. 10,000-Hz stimulation at pulse width of 50 μsec), it is not the frequency that drives the clinical effect. This suggests that there are two factors that may potentially produce a difference between burst stimulation and tonic stimulation: 1) the way the stimuli are delivered and 2) the pulse width being of more importance than the frequency. Whether the way the stimuli are delivered—packets (i.e., burst) or constant current (i.e., tonic)—is important can be tested. One way of looking at this would be to compare 500-Hz tonic stimulation, in which every spike is charge-balanced, with 500-Hz burst stimulation, in which the charge balance occurs after five monophasic spikes. If burst stimulation really exerts its effect on pain by a different mechanism than tonic stimulation, as suggested by electroencephalogram data that suggest burst stimulation exerts its effect by modulating the medial pain pathway (7), 500-Hz burst stimulation should have a different clinical effect on neuropathic pain than 500-Hz tonic stimulation—and indeed, 500-Hz burst stimulation has been clearly shown to be superior to 500-Hz tonic stimulation in a prospective, randomized, double-blind, placebo-controlled study (18). Whether the pulse width is important can easily be tested as well; it has been shown that whereas pulse widths routinely used in current clinical neurostimulation practice (between 30 and 300 μsec) exert their effect on axons, larger pulse widths of ≥1000 μsec are essential for modulating dendrites or cell bodies (19) for a more physiological mode of stimulation. That

pulse widths are important for burst stimulation has been shown in an animal study demonstrating better suppression of firing rates with increasing pulse width up to 1000 μsec (20).

Our simple study raises more questions than it answers. On the other hand, it generates strong but testable predictions and serves as a first attempt to unravel whether more physiological modes of stimulation are of clinical benefit in treating intractable neuropathic pain.

A weakness of this study is that the investigated group might not be representative, as they were poor responders (pain was reduced to only 5/10 on the VAS in comparison with the normal 3/10). Another study with good responders needs to be performed to verify whether these results will be maintained in a possibly more representative study group (6,7,12).

In conclusion, burst stimulation yields the same degree of pain suppression at 500 Hz and 1000 Hz, suggesting that frequency in itself might not drive the clinical effect. Further studies are essential to better understand the mechanism and to optimize burst stimulation in clinical practice.

Authorship Statements

Dr. Van Havenbergh was responsible for designing the study and recruiting the patients. Mr. Vancamp and Mr. Van Looy were responsible for collecting the data. Mr. Van Looy was also responsible for programming. Dr. Vanneste analyzed the data and assisted Dr. De Ridder in writing the manuscript.

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COMMENTS

This article raises a lot of questions that hopefully will be answered in the future. Is the amount of energy delivery important? What is the optimal frequency? We have tried 600 and 1200Hz in some patients without a different outcome. Will other patterns of stimulation be better? Hopefully this paper will inspire others to further investigate and develop neuromodulation.

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Burst stimulation combining features of high-frequency stimulation with tonic stimulation was recently introduced, with some evidence of superiority in pain relief compared to conventional spinal cord stimulation. The exact characteristics of this new stimulation paradigm are still not clearly defined and this study provides new and interesting information about burst parameters that seems to be determinant.

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Even though a negative study this is a very important step towards understanding the mechanism of action of spinal cord stimulation. Comparison of tonic stimulation versus burst stimulation at various frequencies would be an important future research topic.

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

