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Is Preoperative Pain Duration Important in Spinal Cord Stimulation? A Comparison Between Tonic and Burst Stimulation

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Objective: Conflicting data have been published as to whether the success rate of spinal cord stimulation (SCS) is inversely proportional to the time interval from the initial onset of symptoms to implantation. Recently, a new stimulation design called burst stimulation has been developed that seems to exert its effect by modulating both the medial and lateral pain pathways and has a better effect than tonic stimulation on global pain, back pain, and limb pain.

Materials and Methods: We analyzed the effect of preoperative pain duration on the degree of pain suppression by both tonic and burst stimulation in a group of patients ($n = 49$) who underwent both tonic and burst SCS.

Results: Using Pearson correlation analysis and controlling for age and duration of SCS, no correlation could be found between the preoperative pain duration and the success of SCS, either for tonic or for burst SCS, as defined by a numeric rating scale for pain. Using a different analysis method, dividing patients into groups according to preoperative pain duration, the same absence of influence was found. Pain was better suppressed by burst stimulation than tonic stimulation, irrespective of the preoperative pain duration.

Conclusions: These results suggest that the duration of pain is not an exclusion criterion for SCS and that similar success rates can be obtained for longstanding pain and pain of more recent onset.

Keywords: burst, dorsal column, duration, pain, spinal cord stimulation, tonic

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. He has received no financial or other support for this study. The other authors did not disclose any conflicts of interest.

INTRODUCTION

There are multiple modalities of pain management, and one technique that is commonly used for medically intractable pain is spinal cord stimulation (SCS) (1). It is known that in the absence of some large Aβ fibers the small unmyelinated C fibers start firing spontaneously (2–4). The pattern of this spontaneous firing is burst firing (3), that is, a series of high-frequency, closely spaced action potentials followed by a period of quiescence (5). This spontaneous firing is based on stochastic opening and closing of Na^+ channels. In axons <0.3 μm, input resistance is large enough that spontaneous opening of single Na^+ channels at the resting potential can produce "Na^+ sparks" that can trigger action potentials in the absence of any other inputs (6,7). In other words, when the "brake" of the large Aβ fibers is removed, the small pain-mediating C fibers start firing spontaneously, inducing a hyperalgesic state (3).

This is in agreement with the pain gate mechanism, postulated in the 1960s to explain neuropathic pain (8), which was used as the pathophysiological basis to develop spinal cord stimulation (9). The mechanistic view of the pain gate mechanism has evolved from a local effect at the level of the spinal cord, involving stimulation of large Aβ fibers and thereby suppressing pain-transmitting small unmyelinated C fibers and small Aδ fibers through a combination of local spinal and supraspinal mechanisms (10,11).

Recently, a new way of applying electrical stimuli to the nervous system has been developed; it was initially done at the level of the auditory cortex (12) but later translated to the spinal cord (13). This novel mode of stimulation is called burst stimulation (13). It was hypothesized that mimicking the firing pattern of the pain gate mechanism by neurostimulation could exert a more physiological and therefore better effect on pathological burst firing activity associated with neuropathic pain (14). Although different forms of burst

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firing exist, the initial studies mimicked thalamocortical bursts as seen in the bursting pattern noted in chronic pain (15). Following a successful initial open-label, non-placebo-controlled study (15) it was noted that pain suppression could be obtained without paresthesia (13), permitting a placebo-controlled study (14), which yielded basically the same result. Based on differences in Pain Vigilance and Awareness Questionnaire scores suggesting that burst stimulation modulates affective pain pathways, which was confirmed by source-analyzed resting state electroencephalogram during placebo, burst, and tonic stimulation, it has been determined that burst stimulation suppresses the salience attached to the pain (14). Whereas over a short period, that is, in a 1-week trial, burst stimulation was not better than tonic stimulation for leg and back pain, over a long period burst stimulation was better than tonic stimulation for both back and leg pain suppression (16), especially for purely neuropathic pain, but also for failed back surgery syndrome (17). Furthermore, it has been shown that burst stimulation can rescue about 60% of failures to respond to tonic stimulation (16). This raises the question of whether burst stimulation might be able to better improve longstanding pain, as it has been shown that over time, SCS becomes dramatically less efficient (18). Indeed, in one study, for patients with pain duration less than 2 years, the success rate was greater than 80%, but this decreased to less than 50% above 5 years and less than 10% for pain lasting longer than 10 years (18). Kumar et al. defined success rate as the number of patients who respond to SCS (19). Some other studies could not replicate this finding, but these analyzed the degree of pain suppression, rather than the number of responders (20–22). A recent systematic review and meta-analysis reported that pain duration was a predictor of efficacy in pain suppression for SCS in a univariate metaregression analysis but not in a multivariate analysis (23); thus, there is conflicting evidence with regard to pain duration as a predictor for SCS success.

We therefore investigated a group of 49 patients who underwent SCS by tonic stimulation and switched them to burst mode, comparing the responses by both the number of responders and the degree of pain suppression, as these were used as outcome measures in previous studies, and correlating the degree of pain suppression with the preimplantation pain duration.

MATERIALS AND METHODS

The study was designed conform to the Declaration of Helsinki and was approved by the Institutional Review Board of Twente Hospital, Enschede, The Netherlands.

Patients with an Eon implantable pulse generator (St. Jude Medical, Plano, TX, USA) who had been using tonic spinal cord stimulation for at least 6 months tested burst stimulation for 2 weeks. Forty-nine patients treated at the Medisch Spectrum Twente Hospital in the Netherlands were tested. The study was a reanalysis of a patient group that was examined in a previous study; demographic and clinical details on this group were given in the report of that study (17). All patients for whom data were available with regard to the preimplantation duration of pain were included in the reanalysis. Their average age was 56.2 years (range: 32–70 years). All patients were resistant to the most intensive conservative management, including opioid pain medication and antiepileptics. The average duration of pain prior to implantation was 9.6 years (range 3–24). Twelve patients were diagnosed with diabetic neuropathic pain, 23 had failed back surgery syndrome, and 14 had unclassified/miscellaneous pain. Patients had been undergoing stimulation for 2 years on average and for 6 months at minimum (mean = 2.07 years, SD = 1.08, range: 6 months to 5 years). Prior to implantation of the SCS system, all patients underwent a psychological screening and filled out a visual analog scale on pain intensity. These data were used to define the baseline situation of the patients.

Outcome Measures

The outcome measure was patient score on a numeric rating scale (NRS; 0 representing no pain, 100 worst pain imaginable) for global pain for baseline and after tonic and burst stimulation.

Tonic and Burst Stimulation

Patients visited the hospital and scored their pain under tonic stimulation on the NRS. Burst stimulation was programmed with settings similar to those used previously (five spikes at 500-Hz spike mode, 40-Hz burst mode, 1 msec pulse width), and amplitude was set at 90% of the paresthesia threshold, after which patients evaluated the burst stimulation at home for 2 weeks. After 2 weeks, patients visited the hospital again and scored their pain under burst stimulation on the NRS.

Statistical Analysis

We used SPSS 22.0 to analyze the data. We applied Pearson correlations to understand the associations of pain duration, age, and SCS duration with the effects of tonic stimulation and burst stimulation. We calculated the effects of tonic stimulation and burst stimulation by subtracting the baseline pain NRS score from the pain NRS scores for tonic and burst stimulation, respectively. Partial correlations were computed to find the effects on pain reduction of tonic and burst stimulation controlled for age and SCS duration, as well as their potential combined influence. In addition, we applied the method used by Kumar and Wilson (18), dividing patients into groups according to pain duration (i.e., 2 to 5 years, 5 to 8 years, 8 to 11 years, 11 to 15 years, and more than 15 years) to compare the number of patients who responded and failed to respond to SCS with 10- and 20-point reductions on the NRS for pain (i.e., baseline pain NRS score − tonic stimulation pain NRS score, or baseline pain NRS score − burst stimulation pain NRS score). Likelihood ratios were calculated to verify if pain duration group had an effect on response rate. To compare the absolute effects of tonic and burst stimulation, we applied paired *t*-tests for the entire group, for patients who had had pain for ≤10 years, and for the group with more than 10 years of pain.

RESULTS

The average baseline pain score for patients was 78 (SD = 11.43), while the average pain score was 48 (SD = 27) for tonic stimulation and 36 (SD = 27) for burst stimulation.

Pain duration, age, and SCS duration were not significantly correlated with the effects of either tonic stimulation or burst stimulation. After controlling for age and SCS duration, both separately and combined, no significance was found for the partial correlations of pain duration with tonic stimulation and burst stimulation. See Table 1 and Figure 1 for an overview of the results obtained.

In a second analysis, we applied the method used by Kumar and Wilson (18), dividing patients into groups according to pain duration and comparing the number of patients who responded and failed to respond to SCS with 10- and 20-point reductions on the

Table 1. Correlations and Partial Correlations of Age, Pain Duration, and Spinal Cord Stimulation With the Effects of Tonic and Burst Stimulation.

		r	Partial correlation controlling for …			
			Age	Pain duration	SCS duration	The other two variables
Pain duration	Tonic stimulation	0.23	0.23	—	0.22	0.22
	Burst stimulation	0.16	0.16	—	0.11	0.11
Age	Tonic stimulation	0.04	—	0.03	0.02	0.04
	Burst stimulation	0.05	—	0.05	0.01	0.01
SCS duration	Tonic stimulation	0.07	0.06	–0.01	—	–0.02
	Burst stimulation	0.17	0.17	0.13	—	0.12

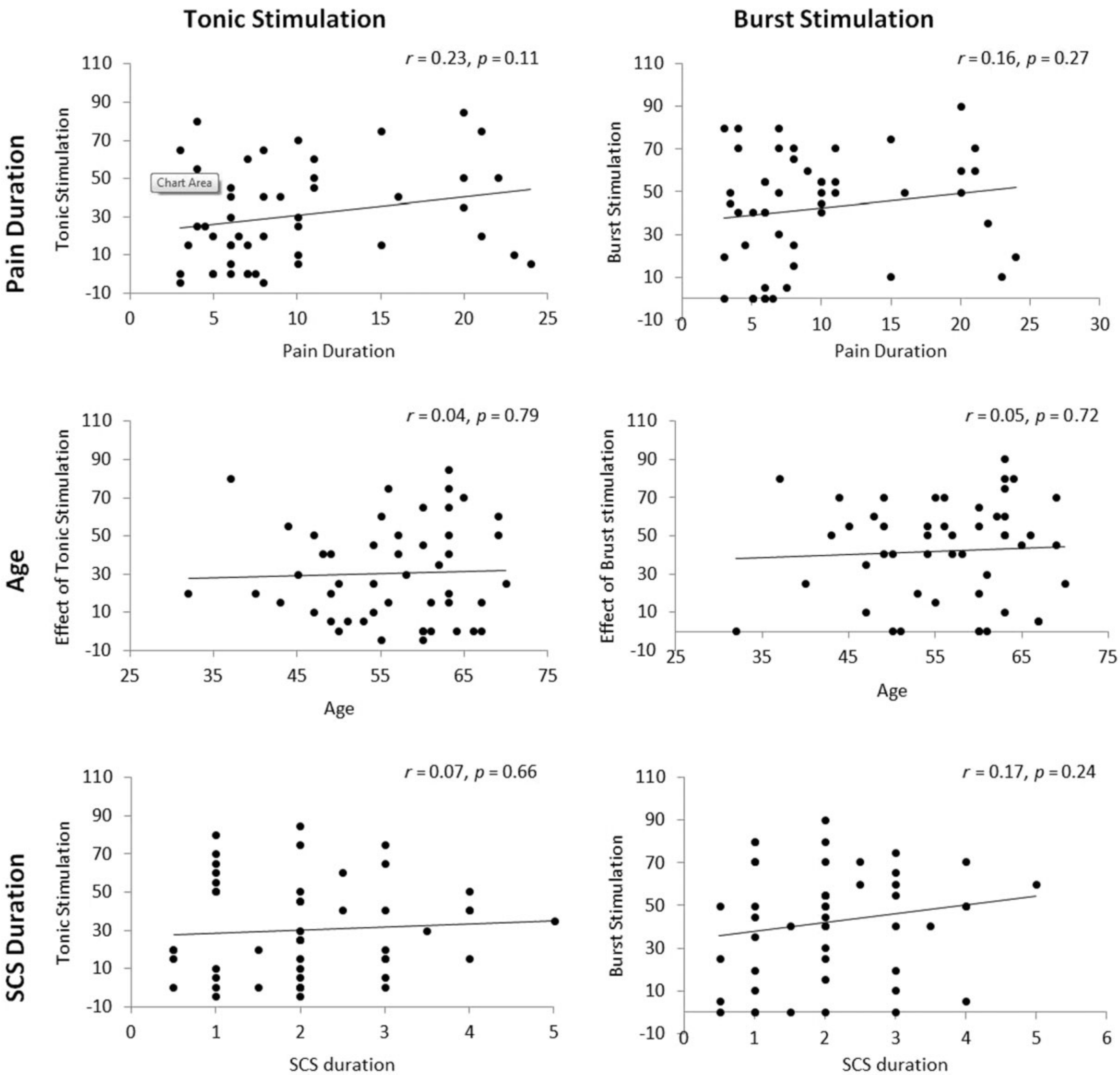

Figure 1. Analysis of correlations of the degree of pain improvement with tonic and burst stimulation with pain duration, age, and spinal cord stimulation duration, respectively. The degree of pain suppression is not related to the pain duration before SCS initiation for either tonic or burst stimulation.

NRS for pain. When we defined failure as <10-point reduction on the NRS for pain, on average 75% of the patients responded to tonic stimulation and 81% to burst stimulation. With failure defined as <20-point reduction on the NRS for pain, on average 65% of the patients responded to tonic stimulation, while 75% responded to burst stimulation. For both tonic stimulation and burst stimulation, likelihood ratios showed that pain duration group had no effect on rates of response with 10- or 20-point reductions on the VAS for pain (Fig. 2).

In addition, we compared the absolute degree of pain reduction between tonic and burst stimulation for the entire group (independent of the preimplantation pain duration) as well as for patients

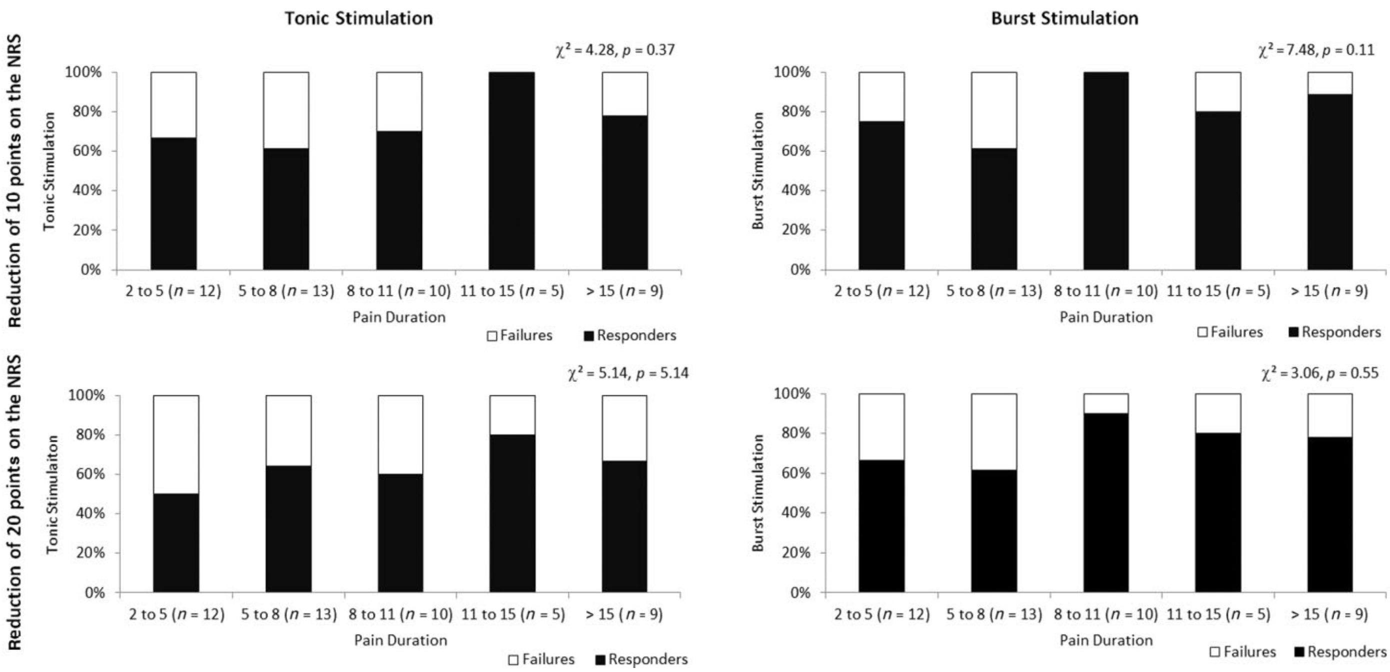

Figure 2. Response rates for tonic and burst spinal cord stimulation in relation to preoperative pain duration group.

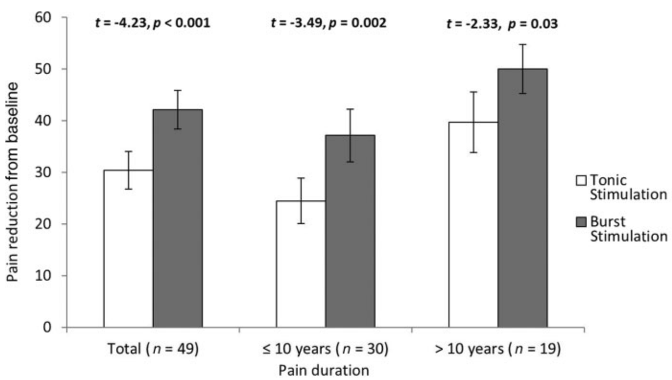

Figure 3. Comparison between degrees of pain suppression for tonic and burst stimulation in the entire group, in patients with pain for less than 10 years, and in patients with pain for more than 10 years. Burst stimulation induces significantly greater pain suppression than tonic stimulation.

who had had pain ≤10 years and patients who had had pain for more than 10 years. This analysis revealed that overall, burst stimulation (mean = 30, SD = 25) was more effective than tonic stimulation (mean = 42, SD = 26) ($t = -4.23$, $p < 0.001$). For the group who had had pain for ≤10 years, burst stimulation (mean = 24, SD = 24) had a larger pain-suppressing effect than tonic stimulation (mean = 40, SD = 26) ($t = -3.49$, $p = 0.002$). A similar effect was obtained for the group with pain for more than 10 years, with burst stimulation (mean = 37, SD = 28) having a larger effect than tonic stimulation (mean = 50, SD = 21) ($t = -2.33$, $p = 0.03$). See Figure 3 for an overview.

DISCUSSION

One finding of this study was that we could not replicate Kumar and Wilson's finding that the success rate of SCS was inversely proportional to the time interval from the initial onset of symptoms to implantation (18). This is in agreement with other previous studies (20–22) and with a recent systematic review and meta-analysis of predictors for success in spinal cord stimulation (23). In a multivariate regression meta-analysis, location of pain, history of back surgery, initial level of pain, litigation/worker's compensation, age, gender, duration of pain, duration of follow-up, publication year, continent of data collection, study design, quality score, method of SCS lead implant, and type of SCS lead all failed to predict the efficacy of SCS (23), although, in the same study, the regression did show that pain duration was correlated with obtainable degree of pain suppression (23).

Absolutely no correlation was found between preoperative pain duration and the success rate of SCS, either for tonic or for burst stimulation (Fig. 1a,b). This held when pain duration was controlled for age and duration of SCS (Table 1).

When analyzing the data in a somewhat different way, comparing responders to nonresponders, we could not find any correlation either. This was irrespective of whether we chose 10% or 20% pain reduction as the responder cutoff (Fig. 2a,b).

These results suggest that there is no reason to exclude patients with long-term pain from a trial of SCS. Indeed, some patients who had suffered pain for over 20 years prior to implantation still had very good pain suppression with both tonic and burst stimulation.

Further analysis demonstrated that burst stimulation was superior to tonic stimulation irrespective of how long the patients had had pain prior to implantation (Fig. 3). This suggests that modulating the affective/attentional component of pain via the medial pain pathway by burst stimulation (14) has a benefit even in longstanding pain. Even though patients were only stimulated for 2 weeks, this duration should have been enough to permit evaluation of whether how long patients had experienced pain before implantation was correlated to response rate with regard to both number of patients and degree of pain suppression. In general, an external trial period undertaken to help decide whether to continue with a permanent implant only lasts 1 week to a maximum of 4 weeks, and it has been shown that a difference between burst stimulation and tonic stimulation is noticeable within 1 week (13,14), becoming even greater over longer periods of time (16).

A weakness of the study is that these data were obtained in a nonblinded fashion, which could have biased the results. Subthreshold stimulation might also have induced a nocebo effect, as reduced pain became associated with the presence of paresthesia, creating additional potential for bias.

In conclusion, the current study could not replicate a previous study that found that the success rate of SCS was inversely proportional to the time interval from the initial onset of symptoms to the time of implantation (18), agreeing instead with a recent systematic review and meta-analysis on this topic (23) but extending its findings to burst stimulation. In patients with both short and long pain duration prior to SCS, burst stimulation is statistically superior to tonic stimulation. These results suggest that there is no reason to exclude patients with longstanding neuropathic pain or longstanding failed back surgery syndrome from a trial with SCS and that burst stimulation remains superior for global pain, even in patients with longstanding pain.

Authorship Statements

Dr. Lenders, Dr. De Vos, and Mr. Vancamp participated in the collection of the data. Drs. Lenders and De Vos also participated in screening the patients in the study. Drs. De Ridder and Vanneste wrote the manuscript, and Dr. Vanneste performed the data analysis.

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COMMENTS

This manuscript told readers two findings. First, the effect of SCS was not related to the duration of the pain. Second, burst stimulation is better than tonic stimulation. Burst stimulation is a new method in SCS treatment, which can suppress neuropathic pain without the mandatory paresthesia. (1)

Although this paper have some bias in clinical study design but the results showed us a trend towards better pain control and less side effect. Further rigorous study should be designed to answer those questions.

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This is already a selected group since they all are previously implanted. I would like to see studies where naive patients are tried with both tonic and burst. Anyway this support my opinion that there is no proof for excluding an individual based pain duration.

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Uppsala, Sweden

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

