

A 2-center Comparative Study on Tonic Versus Burst Spinal Cord Stimulation

Amount of Responders and Amount of Pain Suppression

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Introduction: Spinal cord stimulation is a safe and effective procedure applied for medically intractable neuropathic pain and failed back surgery syndrome. Recently, a novel stimulation paradigm was developed, called burst stimulation consisting of intermittent packets of closely spaced high-frequency stimuli. The design consists of 40 Hz burst mode with 5 spikes at 500 Hz per burst, with a pulse width of 1 ms and 1 ms interspike interval delivered in constant current mode.

Methods and Materials: A retrospective analysis is performed looking at 102 patients from 2 neuromodulation centers, 1 in Belgium and 1 in the Netherlands. This consisted of 2 groups, 1 group who had become failures to tonic (conventional) stimulation and 1 group who still responded to tonic stimulation. All patients were switched from tonic to burst stimulation and the amount of responders as well as the amount of pain suppression was assessed.

Results: Overall burst stimulation was significantly better than tonic stimulation and baseline. On average the pain on numeric rating scale (NRS) improved from 7.8 at baseline to 4.9 with tonic to 3.2 with burst stimulation. For the Belgian and Dutch centers combined, 62.5% of nonresponders to tonic stimulation did respond to burst stimulation, on average, with 43% pain suppression. Most responders to tonic further improved with burst stimulation; on average, pain suppression improved from 50.6% to 73.6.3%. The results (from both centers) did not differ for the amount of obtained pain suppression, only for the amount of responders, which could be related to the different profile of the 2 participating centers.

Conclusions: Burst seems to be significantly better than tonic stimulation. It can rescue an important amount of nonresponders to tonic stimulation and can further improve pain suppression in responders to tonic stimulation.

Key Words: burst, tonic, stimulation, neuromodulation, failed back surgery syndrome, pain, neuropathic

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Spinal cord stimulation (SCS) is a safe and effective procedure applied for medically intractable neuropathic pain and failed back surgery syndrome.¹ An extradural wire or paddle electrode is inserted using a posterior percutaneous or open surgical approach, positioning the electrode extradurally over the dorsal columns of the spinal cord. After a successful externalized trial period, the stimulation lead is connected to an internal pulse generator that delivers programmable electrical pulses to the spinal cord. This adaptation from pacemaker technology² has become a mainstream treatment for medically intractable neuropathic limb pain.

Whereas initially it was thought that the pain-suppressing effect of SCS was based on a local spinal cord mechanism, involving stimulation of large Aβ fibers and, thereby, suppressing pain-transmitting small fibers, it has become clear that the effect is related to a combination of a spinal and supraspinal mechanism.^{3,4} The spinal mechanism involves antidromic activation of ascending dorsal column fibers, but SCS might also interact by orthodromic ascending fibers with descending serotonergic pain modulatory systems.⁵ SCS is associated with enhanced GABA⁶ and acetylcholine⁷ and reduced glutamate release in the dorsal horn.⁶

Recently, a novel stimulation paradigm was developed called burst stimulation.⁸ Burst stimulation consists of intermittent packets of closely spaced high-frequency stimuli, 40 Hz burst mode with 5 spikes at 500 Hz per burst, with a pulse width of 1 ms and 1 ms interspike interval delivered in constant current mode. The cumulative charge of the five 1 ms spikes is balanced during 5 ms following the spikes.⁸ After an initial nonplacebo-controlled study,⁸ a placebo-controlled study was performed,⁹ confirming the results of the nonplacebo-controlled study. In comparison with placebo, burst stimulation was significantly better for pain suppression. In comparison with tonic (conventional) stimulation, burst stimulation was significantly better for general pain, as well as for attention to pain and to changes in pain.⁹

On the basis of the differences in PVAQ scores and on brain activity by tonic and burst stimulation, the authors proposed that the burst stimulation influences the medial pain system more than tonic stimulation. The electroencephalographic analysis demonstrated that burst stimulation activated the dorsal anterior cingulate and right dorsolateral prefrontal cortex more than tonic stimulation.

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Although long-term results are favorable to reoperation¹⁰ or conventional pain management,¹¹ not everyone responds to SCS and the results of SCS seem to decrease in time,^{12–14} resulting in a group of patients who are insufficiently helped by the SCS. After long-term stimulation (range, 2 to 9 y) about 50% of patients still experience about 50% pain reduction.^{12,13,15}

In view of the promising results of burst stimulation and the likely different working mechanism, the question arises whether patients who fail classical neurostimulation for whatever reason can still be rescued by changing the stimulation design to burst stimulation and also whether patients undergoing tonic stimulation can be further improved by switching to burst stimulation. As burst stimulation was shown to yield a stronger effect on the affective pain measures, but not the pain in the limbs, it is especially important to evaluate this pain component, which was not different between tonic and burst stimulation. As such, the real difference in the amount of responders can be evaluated for a pain measure that is not supposed to be different between stimulation designs. A study was therefore initiated to retrospectively evaluate whether burst stimulation in patients who do and do not respond to tonic stimulation improved their pain. To verify whether the data obtained in one center are reproducible, the same data were collected in a second independent center from another country. This is important as the study was retrospective and not based on placebo-controlled stimulation.

PARTICIPANTS

Patients with an Eon IPG (St. Jude Medical, Plano, TX) and using tonic SCS for at least 6 months were tested for burst stimulation for 2 weeks. Fifty-seven patients were treated at the Twente University Hospital. Their average age was 56 years (range, 29 to 80 y). Forty-five patients were treated at the University Hospital Antwerp. Their average age was 53 years (range, 32 to 78 y). See Table 1 and Figure 1 for overview of the baseline pain scores. All patients were intractable to conservative medical management, including NSAIDs, opioids, and antiepileptics, as this is a mandatory requirement for reimbursement for SCS. The average pain duration was 10.69 years (range, 3 to 50 y). All patients were diagnosed with neuropathic pain, mostly related to failed back surgery syndrome or diabetic neuropathy.

The study conformed to the Declaration of Helsinki and was approved by the Institutional Review Board of Twente and University Hospital Antwerp. Before implantation of the SCS system all patients underwent a psychological screening and filled out a numeric rating scale (NRS). These data were used to define the baseline situation of the patients. Most patients had received implantation for lumboschialgia related to FBSS or diabetic neuropathic pain. On average, patients had between 10 and 11 years (range, 1 to 50 y) of pain before they were implanted with a SCS system. Most patients underwent implantation of a lamitrode (SJMedicalneuro, Plano, TX) by laminectomy under general anesthesia. Most patients were implanted with an electrode at Th8-9.

TABLE 1. Overview of the Baseline Pain Scores

	Mean	SD	Minimum	Maximum
Belgium	7.68	1.48	4.00	10.00
The Netherlands	7.88	1.11	4.50	10.00
Total	7.80	1.28	4.00	10.00

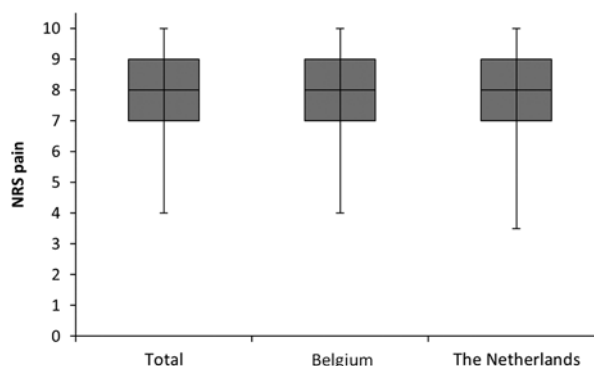


FIGURE 1. Overview of the baseline pain scores.

Measurements

Outcome measures were the NRS for pain for the baseline, during tonic and during burst stimulation. In addition, an NRS was used to measure the leg pain and back pain for both tonic and burst stimulation.

Tonic and Burst Stimulation

To acquire the data on tonic stimulation, patients visited the hospital and filled out questionnaires about their pain and experiences with tonic stimulation. Burst stimulation was programmed with settings similar to those used before (5 spikes at 500 Hz spike mode, 40 Hz burst mode, 1 ms pulse width) and amplitude was set at 90% of the paresthesia threshold, after which patients evaluated the burst stimulation for 2 weeks. During this evaluation period patients were at home. After 2 weeks patients visited the hospital again, filled out an NRS about their pain.

Statistical Analysis

A repeated measures analysis of variance was conducted with stimulation (tonic and burst stimulation) as within-subjects variable and centers (Belgium, The Netherlands) as a between-subjects variable. A 2-sample paired *t* test was conducted to compare leg and back pain between tonic and burst stimulation. We defined responders as a group that had at least a reduction of >10% on the NRS pain.

RESULTS

General Pain

A repeated measure revealed a significant effect for stimulation at both centers (see Table 2 for overview). A pairwise comparison revealed that burst stimulation had a better pain suppression effect than both tonic stimulation and baseline (Fig. 2). The suppression for burst stimulation was 34.58% compared with tonic stimulation and 59.08% compared with baseline. In addition, an effect was obtained between the baseline and tonic stimulation, indicating that tonic stimulation had a suppression effect of 37.46% in comparison with the baseline. A similar effect was obtained for the 2 centers separately, namely Belgium and The Netherlands (see Table 2 for overview). For the Belgian center a suppression effect was obtained of 53.85% for burst stimulation compared with tonic stimulation and 72.98% compared with the baseline. A suppression effect of 41.47% was also obtained for tonic stimulation in comparison with the baseline. For the center in the Netherlands a more pronounced suppression effect was revealed for burst, 21.36% better in comparison

TABLE 2. A Comparison Between Baseline, Tonic, and Burst Stimulation

	Baseline	Stimulation		<i>F</i>	Effect Size (η^2)
		Tonic	Burst		
Belgium	7.68 ^a	4.50 ^b	2.08 ^b	96.58***	0.82
The Netherlands	7.88 ^a	5.18 ^b	4.07 ^c	57.87***	0.68
Total	7.80 ^a	4.88 ^b	3.19 ^c	137.50***	0.73

A different superscript letter indicates a significant difference ($P < 0.001$).

*** $P < 0.001$.

with tonic stimulation and 48.39% in comparison with baseline. A pain suppressive effect of 34.37% was obtained for tonic stimulation in comparison with the baseline.

Leg and Back Pain

A *t* test on the whole group revealed that burst stimulation yielded a significantly better pain reduction than tonic stimulation, both for limb ($t = 4.66$, $P < 0.001$) and back ($t = 3.94$, $P < 0.001$) pain. On average, back pain was improved by 29.82% and limb pain by 31.84% compared with tonic stimulation. This was noted for both the Belgian site (limbs: $t = 3.01$, $P < 0.01$; back: $t = 3.00$, $P < 0.01$), as well as for the Dutch site (limbs: $t = 3.53$, $P = 0.001$; back: $t = 2.64$, $P = 0.01$). For Belgium, average back pain reduction with burst stimulation was 41.42% better than tonic stimulation. For limb pain 34.98% improvement was seen in comparison with tonic stimulation. For the Netherlands, on average, back pain was suppressed 20.62% more by burst stimulation than tonic stimulation and limbs by 29.70%. See Figure 3 for an overview.

Responders and Pain Reduction

When we look at the responders versus the non-responders, overall 76.47% respond to tonic stimulation with a pain reduction of 50.56%, whereas 23.53% of the patients have a response that is lower than 10%. When we look at the Belgian center we see that the response rate to tonic stimulation was 86.67% with a reduction of 47.80%, whereas the center in the Netherlands had a response rate of 68.42% with a reduction of 50.56%. Overall, for the patients who did not respond to the tonic stimulation, 62.50% responded to burst stimulation (Belgium: 83.33% and the Netherlands: 55.56%) with a reduction rate of 43.04% (Belgium: 45.77% and the Netherlands: 41.68%). Overall, 37.50% did not respond to tonic stimulation and did not respond to burst stimulation. Interestingly, for

those patients who respond to tonic stimulation, 94.87% had even a better effect on burst stimulation with a reduction of 73.59%. In the Belgium center 97.44% had a better improvement on burst stimulation, although they responded to tonic stimulation as well. For the Netherlands this was 92.23%. For these 2 groups a reduction of 91.30% for Belgium and 65.44% for The Netherlands was obtained for burst stimulation. An overview can be seen in Figures 4 and 5.

DISCUSSION

Burst stimulation has been recently developed to improve neuromodulation for different disorders such as tinnitus^{16,17} and pain.^{8,9} Burst stimulation has been used to modulate activity in the brain,⁹ spinal cord,⁹ and peripheral nerve^{9,18} without obvious side effects related to the burst paradigm.

The results of this study confirm previous data of burst stimulation applied to the spinal cord^{8,19} and extend them by showing that burst can improve pain reduction in an important amount of patients (62.5%) who have become nonresponders to tonic stimulation. Furthermore, patients who were successfully treated with tonic stimulation seemed to get a further improvement with burst stimulation, on average from 50.6% pain reduction to 73.6% pain suppression. Thus, where tonic stimulation can improve baseline pain from 7.8 to 4.9, burst can further improve this to 3.2 on an NRS. This holds both for limb pain and back pain.

The similarities in outcome between the 2 independent centers suggest the data are reliable, although they are not placebo controlled. Intriguing is the fact that burst stimulation applied to the brain for a different disorder (tinnitus) demonstrates similar results. In a study of 43 patients

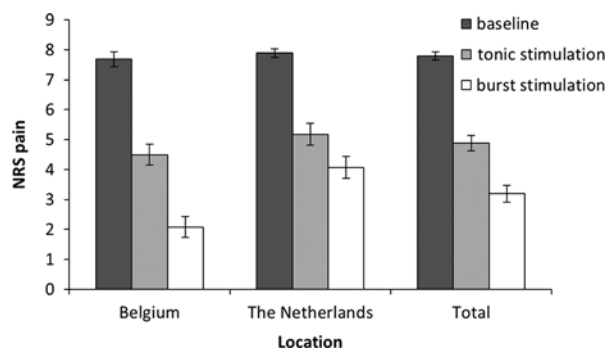


FIGURE 2. Results of burst and tonic spinal cord stimulation versus baseline. Burst stimulation is significantly better than baseline and tonic stimulation.

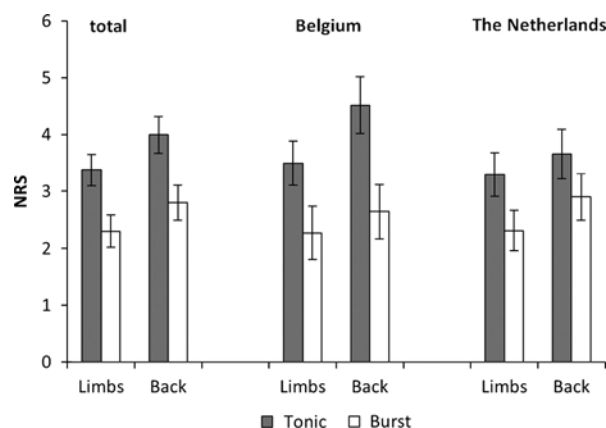


FIGURE 3. Results of burst and tonic spinal cord stimulation for limb and back pain. Burst stimulation is significantly better than tonic stimulation, both for limb and back pain.

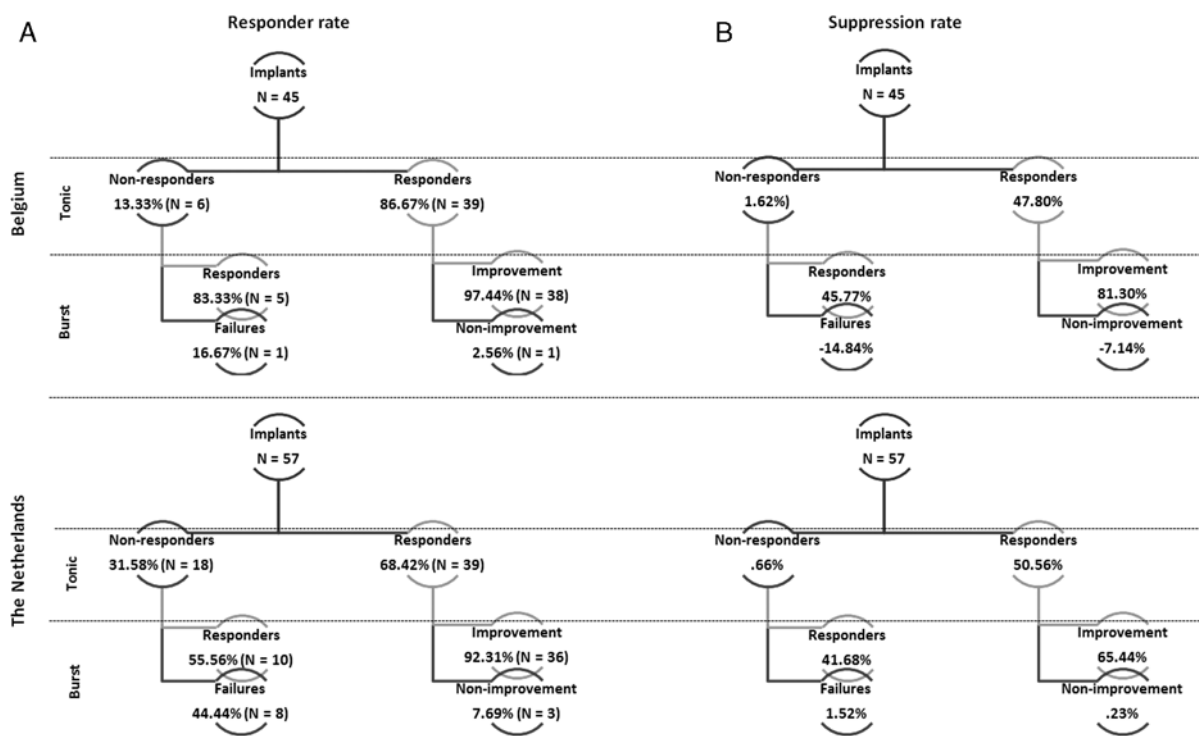


FIGURE 4. A, Indicate how many patients who were implanted with a spinal cord stimulator had a response on tonic and burst stimulation. For the Belgium center, 1 subject who was a nonresponder to tonic stimulation did respond to burst stimulation. For the Netherlands center, 10 nonresponders to tonic stimulation did respond to burst stimulation, and 8 nonresponders to tonic stimulation had no response to burst stimulation. B, The amount of pain reduction in the responders and nonresponders for tonic and burst stimulation. For Belgium, responders on tonic stimulation had, on average, pain reduction of 45.8%, and the nonresponders worsened with 14.8% more pain. Most responders to tonic further improved with burst stimulation; on average pain reduction went from 47.8% to 81.3%, with some patients worsening their pain by 7.1%. For the Netherlands, most responders to tonic further improved with burst stimulation; on average pain reduction went from 50.6% to 65.4%, with no worsening of their pain.

with tinnitus who underwent implant of an electrode overlying the posterior part of the superior temporal gyrus, that is, the secondary auditory cortex switching from tonic stimulation to burst stimulation, could also rescue an important amount of stimulation failures (48%) and could improve successful stimulations in 50% of the patients adding

an extra 50% of tinnitus suppression.¹⁶ This is very similar to the results obtained for SCS for neuropathic pain.

The results from the Belgium center are similar but not exactly the same. The Belgian center has a higher responder rate to tonic stimulation (86.7% vs. 65.4%), a higher responder rate to burst stimulation for nonresponders to tonic

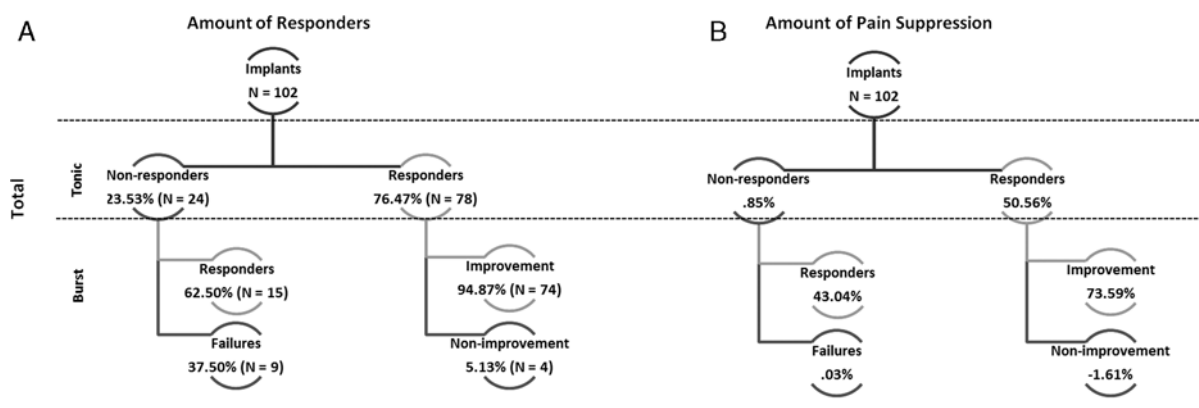


FIGURE 5. A, Indicate how many patients who were implanted with a spinal cord stimulator had a response to tonic and burst stimulation. Of those patients who had no response (N=24) on tonic stimulation, some patients responded (N=9) to burst stimulation and some fail for both stimulation designs (N=9). Of the responders on tonic stimulation, about 74 had an improvement during burst stimulation and 4 did not have an improvement. B, The amount of pain reduction in responders and nonresponders for tonic and burst stimulation. Most responders to tonic further improved with burst stimulation; on average, pain suppression went from 50.6% to 73.63%, with nonresponders worsening their pain by 1.6%.

stimulation (81.3% vs. 65.4%), and a greater amount of improvement for responders to tonic stimulation when they are switched to tonic stimulation (81.3% vs. 65.4%). The other results were very similar, that is, the amount of responders to tonic stimulation who gain benefit from burst stimulation (97.4% vs. 92.3%), the amount of pain reduction obtained by failures to tonic stimulation when stimulated with burst (45.8% vs. 41.7%), and the amount of pain reduction obtained by tonic stimulation (47.8% vs. 50.6%). Thus, the greatest differences were obtained in the amount of responders not the amount of pain suppression. The fact that the amount of pain reduction obtained both by tonic and burst stimulation is similar between the 2 independent centers suggests that the results represent the real potential of this novel stimulation design. Further, larger placebo-controlled trials seem warranted to evaluate the value of burst stimulation in the setting of SCS.

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