

Effectiveness of tonic and burst motor cortex stimulation in chronic neuropathic pain

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Paweł Sokal¹
Marek Harat²
Agnieszka Malukiewicz¹
Michał Kiec³
Milena Świtońska¹
Renata Jabłońska¹

¹Department of Neurosurgery and Neurology, Jan Bizioł University Hospital nr 2, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; ²Division of Preventive Medicine and Healthy Policy, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; ³Department of Neurosurgery, The 10th Military Clinical Hospital, Bydgoszcz, Poland

Background: Motor cortex stimulation (MCS) is an intracranial, invasive method for treatment of chronic pain. Main indications for MCS are central post stroke pain, neuropathic facial pain, phantom limb pain and brachial plexus or spinal cord injury pain. Spinal cord stimulation (SCS) with burst waveform has been proved to be more effective than tonic mode in chronic pain. Necessity to replace depleted batteries of motor cortex tonic stimulators gave us an opportunity of applying burst stimulation. The objective of the pilot study was to evaluate the effects of burst stimulation applied on motor cortex in patients with chronic pain syndromes as well as comparison to tonic mode.

Materials and methods: We have evaluated 6 patients (females N=3, males N=3) belonging to the group of 14 cases (females N=5, males N=9) who had undergone surgical procedure of MCS in years 2005–2017. Selected for the study were 6 patients with thalamic pain N=3, with facial pain N=3 (anaesthesia dolorosa and neuropathic trigeminal neuralgia). The patients were subjected to both modes of stimulation then they chose which one was better in relieving pain: tonic or burst. Pain intensity was assessed with the visual analogue scale (VAS) before the replacement of implanted pulse generator (IPG) and after the stimulation with tonic and burst modes.

Results: In the study, 5 out of 6 patients with MCS found burst mode more effective than tonic mode. Baseline VAS score in patients that had at least 3 months depleted battery of tonic IPG was 95 mm. After implantation of a new IPG mean VAS score on tonic stimulation was 72 mm, on burst 53 mm.

Conclusions: The most preferred option of MCS in selected group of patients was burst stimulation. This study has shown, that the burst stimulation of cerebral cortex is a promising modality when tonic stimulation is not sufficient in refractory, neuropathic pain.

Keywords: motor cortex stimulation, burst stimulation, neuropathic pain

Introduction

Motor cortex stimulation (MCS) and deep brain stimulation (DBS) are established intracranial methods for treatment of chronic, neuropathic pain. Main indications for MCS are central post stroke pain, neuropathic facial pain, phantom limb pain, brachial plexus injury pain or spinal cord injury pain.^{1–7} In our previous study good response on tonic MCS in chronic neuropathic pain has been observed in over 50% with postoperative follow-up of 1 year.⁸ These findings were consistent with the results of other reports.^{9–11} Cortical stimulation has also been used in such conditions as Parkinson's disease and tinnitus.^{12,13} Mechanisms underlying the analgesic effect of MCS has not yet been elucidated, but may be due to stimulation of cortico-subcortical fibers, which inhibits hyperactive sensory units in the thalamus. MCS

Correspondence: Paweł Sokal
Department of Neurosurgery and Neurology, Jan Bizioł University Hospital nr 2, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Ujejskiego 75, Bydgoszcz 85-168, Poland
Tel +4 852 365 5505
Email pawel.sokal@cm.umk.pl

hypothetically modulates thalamic nuclei, cortical somatosensory areas, striatum, cerebellum and inhibits spinothalamic tracts.^{2,14–16} MCS can also control intracortical horizontal fibers instead of direct stimulation of the pyramidal tract.¹⁷ Tonic stimulation with low frequency in MCS has been applied for years.^{1,4,8–10,18} A new generation of stimulators with the burst waveform are available in spinal cord stimulation (SCS).^{19–21} Necessity of replacement of depleted batteries, which used to provide tonic mode only, gave us an opportunity to use these new generation of cortical stimulators applying other modes including burst stimulation. The burst firing is able to overdrive ongoing tonic firing.²² Burst auditory cortex stimulation has been applied in tinnitus patients with better effect on noise-like tinnitus than with tonic stimulation.²³ In the literature there is one case report on the effects of burst MCS in chronic pain.²⁴ SCS with burst waveform has been more effective than tonic in neuropathic pain.²⁵ The main feature of commonly used tonic stimulation was low frequency not exceeding 100 Hz.^{26,27} Frequency and pulse can influence the number of recruited neurons. The burst stimulation in contrast to tonic SCS correlates with the amount of neurons and different neurotransmitter mechanisms of action.²⁵ The pattern of SCS burst stimulation is such that 500 Hz stimulation is delivered in groups of five pulses with 1-ms pulse width and it is repeated 40 times per second in stimulators of spinal cord.²⁵ The objective of the pilot study was to evaluate the effects of burst stimulation applied on motor cortex in patients with central neurogenic pain as well as comparison to tonic stimulation.

Materials and methods

We evaluated 6 patients (females N=3, males N=3) belonging to the group of 14 cases (females N=5, males N=9) who had undergone surgical procedure of MCS in our institution in years 2005–2017 [Table 1](#).

Approval was obtained from the Ethics Committee at the Military Medical Chamber in Warsaw, Poland (138/16) in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient. Replacement of a new, implantable pulse generator (IPG) was performed under local anaesthesia with sedation, unlike surgeries of implantation of cranial electrodes and primary IPGs. They had been conducted under general anaesthesia without myorelaxation with the use of MRI based neuronavigation. Craniotomy over the dura covering the motor strip had been performed, motor evoked potentials had been used

to confirm proper localization and then four paddle type 4-contact electrodes were placed perpendicular to precentral gyrus [Figures 1 and 2](#) or one 16-contact electrode along this gyrus [Figure 3](#).⁸

Half of the selected subjects for the study were patients with thalamic pain N=3, and other half with atypical facial pain N=3 (anaesthesia dolorosa and neuropathic trigeminal neuralgia). Unfortunately all of them had to wait on replacement of IPG for at least 3 months on a waiting list and meanwhile they were complaining about pain exacerbation. These patients received stimulators capable of inducing both tonic or burst stimulation and were given an opportunity to choose the most efficient program of neuromodulation using their own patients' programmer. Patients could change program after 5–7 days of stimulation between tonic and burst. Outcome was based after at least 4 weeks during a control visit basing on personal choice of patients who were selecting the most frequently applied program causing the most efficient pain relief. Pain intensity was assessed with the visual analogue scale (VAS) after the stimulation with both tonic and burst mode. VAS is a continuous line scale, which begins with 0, no pain and ends with 100 mm describing as pain "as bad as it could be".²⁸ Baseline VAS score was defined as score attained before surgical replacement of IPG when there was no effective stimulation due to depleted battery of tonic stimulator.

Results

In the study 5 out of 6 patients found burst mode of motor cortex stimulation more effective than tonic. Baseline VAS score without stimulation due to depletion of battery in patients who had been treated previously with tonic MCS was 95 mm. Mean VAS score after tonic stimulation was 72 mm and improvement after burst stimulation was 53 mm on average [Figure 4](#). Intensity of pain after subsequent periods of tonic and burst stimulation is presented in [Table 2](#).

Discussion

MCS is supposed to be last resort of treatment for chronic, neuropathic pain of central and peripheral origin; pain that is refractory to pharmacological treatment and that cannot be treated with other stimulation techniques such as SCS and peripheral nerve stimulation. Frequently after long-term MCS the analgesic effects of neuromodulation are diminished due to habituation on stimulation.⁸ In our series we examined patients with central neurogenic, ie thalamic syndrome after stroke or traumatic brain injury, and

Table 1 Characteristics of patients.

N	Initials	Sex	Diagnosis	Location	Pain period in years	Tonic MCS period in years	Pharmacotherapy reduction
1	Patient 1	M/62	Thalamic syndrome	LUE left	13	7	Tramadol
2	Patient 2	F/48	Anesthesia dolorosa	V2 V3 left	7	2	Tramadol, gabapentin
3	Patient 3	F/70	Atypical facial pain	V1 V2 V3 right	16	10	Tramadol
4	Patient 4	M/57	Thalamic syndrome	LUE right	16	5	Tramadol
5	Patient 5	M/64	Thalamic syndrome	LUE left	13	8	Tramadol
6	Patient 6	F/62	Neuropathic neuralgia after schwannoma surgery	V2 V3 left	11	3	None
Mean values					12.7	5.8	

Abbreviations: Distribution of pain: LUE, lower and upper extremity; MCS, motor cortex stimulation; V1, first branch of trigeminal nerve; V2, second branch of trigeminal nerve; V3, third branch of trigeminal nerve.



Figure 1 Four-paddle type electrodes placed on motor cortex in a patient 1 with thalamic pain predominantly in left upper extremity. 62 years old male with thalamic pain and MCS for 4 years had VAS=90 mm on tonic and VAS=70 mm on burst mode. **Abbreviations:** MCS, motor cortex stimulation; VAS, visual analogue scale.

neuropathic facial pain. Out of 14 patients who received MCS, 6 were subjected to burst stimulation of the cerebral cortex. Patients with refractory pain lasting for a long period approximately 16 years (mean value) treated with tonic MCS for approximately 6 years (mean value) posed a challenge for achieving a satisfactory pain reduction.



Figure 2 Electrodes placed on motor cortex in a patient 3. 60 years old female with atypical facial pain and with tonic MCS for 10 years had VAS=70mm on five tonic programs and VAS=40mm on burst mode. **Abbreviations:** MCS, motor cortex stimulation; VAS, visual analogue scale.

Primary waveform of MCS was tonic stimulation with frequency of 10–50 Hz with amplitudes from 1–10 mA. Although tonic MCS in the majority of patients with all types of central pain after long-term of stimulation had provided moderate effects, patients demanded reimplantation of IPG, when the battery had been depleted. After the implantation of the new IPG, patients were able to choose between tonic and burst stimulations. The most preferred option was burst stimulation. Due to exacerbation of pain in the period before replacement, patients were receiving



Figure 3 Electrode 2×8 contact placed on dura along motor strip in patient 2, 48 year old female with anaesthesia dolorosa on face with MCS for 2 years; VAS=70mm on tonic and 50 on burst mode.

Abbreviations: MCS, motor cortex stimulation; VAS, visual analogue scale.

analgesics such as tramadol. After surgery they were asked to reduce doses or withdraw it. The majority of them were taking 1 or 2 tramadol daily but no one noticed significant improvement after it. Gabapentin was the medicine administered permanently in unchanged doses to patient 2 before and during both tonic and burst stimulation.

The efficacy of MCS is dependent on proper selection of patients, accurate localization of electrodes and optimal adjusting of parameters.^{1,3,4,7} Suitable location of electrodes nearby central sulcus provide more expressed analgesia than over precentral gyrus.²⁹ In tonic MCS—efficacy of pain treatment can be attained by titration of amplitude of current intensity, diversification of contacts or cyclization.³⁰ Cycling stimulation was initially recommended by Nguyien, recent Vancouver group presented programming algorithm in which cyclization 15 minutes on and 15 minutes off was the most preferred setting.^{4,31,32} According to Fontaine et al chronic stimulation with parameters 40 Hz, PW 210 can, not only reduce the pain, but also improve sensory discrimination.³³ Thermal sensory restoration induced by MCS have been noticed also after repetitive transcranial magnetic stimulation (rTMS). Thus sensory changes are the result of reorganization

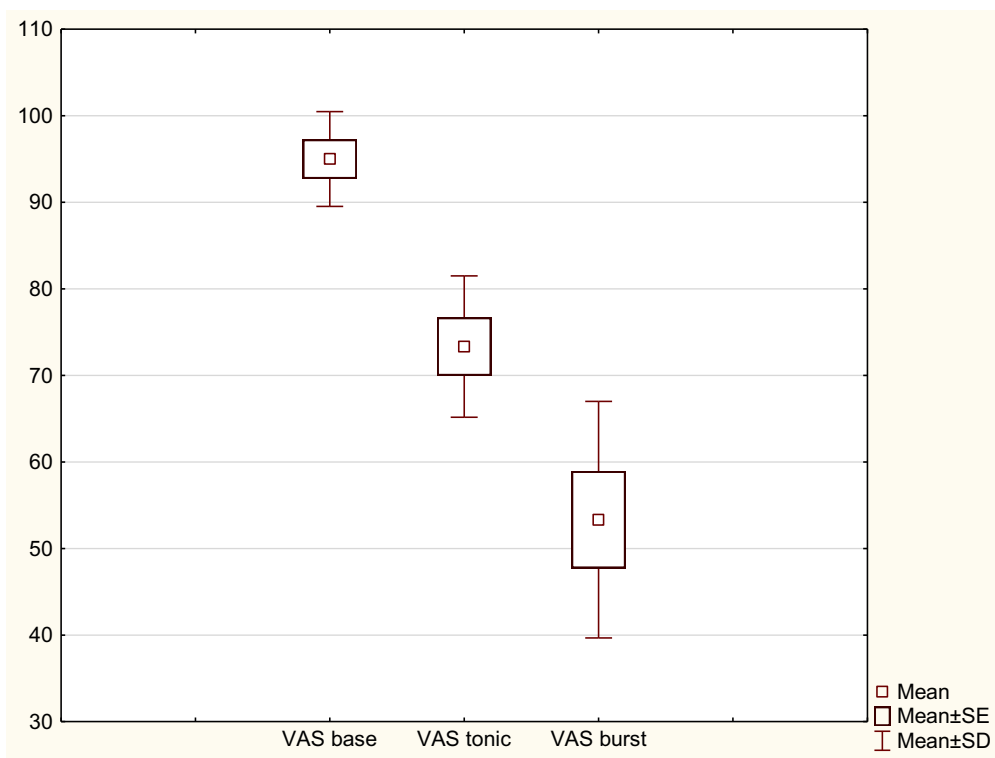


Figure 4 Results of tonic and burst cortical stimulation in VAS score in mm.

Notes: Statistical analysis was performed with software package Statistica Version 10.0. Data were expressed as means \pm SD. Comparisons between groups were performed with analysis of nonparametric repeated measures test ANOVA chi square. (N=6, df=2)=1156522 P=0.00308. A value of $P < 0.05$ was considered statistically significant. Coefficient of concordance =09638, average rank $r=095653$.

Table 2 Level of pain assessed with VAS in mm before application of MCS, on tonic MCS and on burst MCS, with parameters of burst MCS.

N	Initials	VAS base	VAS tonic	VAS burst	Parameters of burst MCS
1	Patient 1	100	90	70	20 Hz/500 Hz/1000 μ s/2.2 mA
2	Patient 2	90	70	50	40 Hz/1000 μ s/6.0 mA
3	Patient 3	90	70	40	40 Hz/500 Hz/1000 μ s/0.8 mA
4	Patient 4	100	70	50	40 Hz/500 Hz/1000 μ s/1.0 mA
5	Patient 5	90	70	40	40 Hz/500 Hz/1000 μ s/0.7 mA
6	Patient 6	100	70	70	40 Hz/500 Hz/1000 μ s/3.0 mA

Notes: Patient 2 received IPG Precision Novi (Boston Scientific, Marlborough, USA) and patients 1, 3, 4, 5, and 6 received Proclaim IPG (Abbot, Chicago, USA). Patients 3, 4, 5, and 6 had standard burst stimulation with different amplitudes. Patient 1 had 20 Hz frequency in burst stimulation. Patient 2 was under burst stimulation modified by Boston Scientific.

Abbreviations: VAS, visual analogue scale; MCS, motor cortex stimulation; IPG, implantable pulse generator

of the sensory cortex. Both MCS and rTMS can have influence on neural plasticity of somatosensory cortex.³⁴ rTMS have a positive predictive value on the effects of MCS.³⁵ Transcranial magnetic stimulation with paradigm of theta burst stimulation can modulate cognitive and neurologic function in chronic neurologic, psychiatric disorders and pain syndromes.^{36,37} TMS with burst mode has been successfully applied in tinnitus.²³ Initially burst stimulation has been applied on auditory cortex to suppress tinnitus more effectively than tonic stimulation.^{22,38} De Ridder was the first who reported improvement in trigeminal anesthesia dolorosa after somatosensory cortex stimulation with burst mode, but also to the anterior cingulate cortex and dorsolateral, prefrontal cortex.²⁴ Finally, burst stimulation has been developed for spinal cord stimulation.³⁹ Burst spinal cord stimulation is hypothesized to react, not only on lateral spinoreticular and spinothalamic ascending pathways and descending inhibitory pathway, but also on medial ascending pathway, which is responsible for affective component of pain. Burst stimulation with 500 Hz spike mode 40 times per second has been designed in a way that mimics burst firing in the thalamus engaged in generation of tinnitus and pain.^{40,41} This phenomenon can explain better improvement after burst stimulation in MCS in our series (mean VAS=72 after tonic and mean VAS=48 after burst). While the burst stimulation and high frequency stimulation in SCS are supposed to be paraesthesia-free methods, MCS both with tonic and burst generally do not induce paraesthesias. This phenomenon may confuse patients in assessment of effects of MCS. The confusion might be associated with the lack of perception of active brain stimulation, which is in general devoid of paraesthesia in both waveforms. In patients' opinion one of the greatest advantages of burst mode was the lack of paraesthesia and reduction of pain.

Contemporary neurostimulation systems allow patients to participate actively in the therapeutic process. Based on

reports of patients engaged in the study they acknowledged the possibility to change programs by themselves. This kind of a patient—controlled, neuromodulatory analgesia helps them become more independent. The limitation of the study is a small sample of participants, lack of randomization and lack of double-blind control, which can affect the reliability of this report. Nevertheless, this study has shown that some patients may benefit from the burst stimulation, which mimics the function of the central nervous system.

Conclusions

Reduction of pain after burst MCS has been clinically meaningful in comparison to tonic stimulation in chronic, neuropathic pain. According to results of this study—burst cortex stimulation is a promising modality in refractory pain in patients habituated to tonic stimulation. New generation stimulators enable improved efficiency of MCS. Further studies with larger cohorts are needed to confirm these preliminary results.

Author contributions

The study was designed by Pawel Sokal and Marek Harat. Pawel Sokal, Marek Harat recruited patients for the study. Pawel Sokal and Michał Kiec conducted the study including surgeries. Data collection was performed by Pawel Sokal, Agnieszka Malukiewicz and Renata Jablonska. Data analysis was performed by Milena Switonska and Renata Jablonska. Manuscript was prepared by Pawel Sokal with substantial intellectual input of Agnieszka Malukiewicz and Milena Switonska. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

Paweł Sokal reports financial and nonfinancial support from Medtronic, Abbot and Boston Scientific. Marek Harat reports nonfinancial support from Abbot and Boston Scientific. Agnieszka Malukiewicz reports nonfinancial support from Boston Scientific. Michał Kiec reports nonfinancial support from Abbot and Medtronic. The authors report no other conflicts of interest in this work.

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