ORIGINAL PAPERS

Adv Clin Exp Med 2015, **24**, 2, 289–296
DOI: 10.17219/acem/40452

ISSN 1899–5276

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Motor Cortex Stimulation in Patients with Chronic Central Pain

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Motor cortex stimulation is one of the neuromodulation methods of treating refractory central neurogenic pain.
Objectives. The aim of this study was to retrospectively evaluate the effects of motor cortex stimulation.
Material and Methods. The study group consisted of 14 consecutive patients with thalamic pain, atypical facial pain, post-brachial plexus avulsion injury pain, phantom pain and pain in syringomyelia who were treated with motor cortex stimulation at the Department of Neurosurgery of the Military Research Hospital in Bydgoszcz, Poland, from 2005 to 2013. The procedures were conducted with the use of neurosurgical navigation and intraoperative neurophysiological monitoring. The outcomes were assessed in terms of visual analog scale scores. The long-term follow-up ranged from one to six years.
Results. A statistically significant reduction in the intensity of pain was noted in patients treated with motor cortex stimulation (pre-surgery median visual analog scale = 9, short-term result median visual analog scale = 3, $p = 0.0009$; long-term result median visual analog scale = 5, $p = 0.0036$). Over the long term, with follow-ups ranging from one to six years, the results were excellent (over 80% reduction in pain) in 31% of the patients and satisfactory (50–80% reduction in pain) in 23% of the patients. Unsatisfactory pain control (less than 50%) was noted in 31% of the patients and no improvement was noted in 15%. Significantly better relief of pain was observed in the early postoperative period. In this series of patients, the highest efficacy of motor cortex stimulation was observed in post-stroke or post-hemorrhagic thalamic pain (5/7 patients – 71%). Long-term outcomes were not related to the age or sex of the patient, the preoperative duration of the pain, or to the position or number of implanted electrodes.
Conclusions. MCS significantly reduces the intensity of neurogenic pain. The best long-term results in the present study were achieved in patients with thalamic syndrome. No significant predictors were found for a successful final outcome. The authors consider appropriate selection of patients, accurate placement of the electrodes and frequent adjusting of the stimulation parameters to be important factors increasing the efficacy of MCS (**Adv Clin Exp Med 2015, 24, 2, 289–296**).

Key words: motor cortex stimulation, chronic pain, neurogenic pain.

Motor cortex stimulation (MCS) is one of two main intracranial neuromodulative methods for treating chronic pain. Since Tsubokawa introduced MCS to treat central neurogenic pain, plenty of studies have proved the relative efficacy of this method [1–9]. Central pain is defined as the pain associated with a primary lesion of the central nervous system. Causes of central pain are mainly vascular lesions in the brain and spinal cord, such as infarctions, hemorrhages, multiple sclerosis, vascular malformations, traumatic brain and spinal cord injuries, syringomyelia and others [10]. The main indications for MCS are central post-stroke pain including thalamic syndrome, neuropathic facial pain, phantom limb pain or pain caused by brachial plexus or spinal cord injury [1–9, 11, 12]. In chronic neurogenic pain, a good response to MCS is observed in 55% of patients postoperatively, and in 45% after one year [12]. In neuropathic facial pain satisfactory improvement is observed in 84.7% of the patients [5]. Post-stroke thalamic pain is also a good indication, with a chance for pain alleviation in the majority of patients. In central pain 54% of the patients achieve good pain relief [8, 12]. Nguyen et al. reported satisfactory pain relief in

patients with post-stroke pain in over 70% of the patients in whom hemiparesis was absent or mild [8].

The mechanisms underlying the analgesic effect of MCS are not completely understood. Stimulation of the primary motor cortex must inhibit the primary somatosensory cortex, thalamus and spinothalamic tract *via* reciprocal pathways between the motor cortex and sensory cortex. Stimulation of cortico-subcortical fibers inhibits hyperactive sensory units in the thalamus [1]. Axonal depolarization of the pyramidal cells, involvement of the NMDA receptors and endogenous opioid receptors may play a role in the analgesic activity of MCS [13, 14]. In positron emission tomography (PET) studies Garcia-Larrea et al. observed an increase in blood flow in the medial thalamus, anterior cingulate/orbitofrontal cortex, anterior insula and upper brainstem during stimulation of the motor cortex, while no significant cerebral blood flow (CBF) changes appeared in the motor cortex areas [15]. MCS is more effective in patients with sustained superficial sensation than in patients with a loss of sensation in the area where the pain is located [6, 7].

Material and Methods

The study involved a retrospective review of a series of 14 cases of patients (females n = 5, males n = 9), ranging in age from 42 to 64 years (median 58) who underwent surgical motor cortex stimulation procedures in the Department of Neurosurgery of the Military Clinical Hospital in Bydgoszcz, Poland, in the years 2005–2013. The patients had central neurogenic pain associated with thalamic stroke or hemorrhage in the course of multiple sclerosis (n = 7), central pain due to syringomyelia (n = 1), atypical facial pain (n = 2; anesthesia dolorosa and neuropathic trigeminal neuralgia), pain caused by brachial plexus injuries (n = 3) and phantom pain (n = 1). The preoperative duration of pain ranged from 6 to 25 years (median 7.5 years). The pain intensity was assessed using a VAS preoperatively, post-operatively and at the follow-up times indicated in Table 1, ranging from 3 months to 6 years. The outcomes were reported as excellent (> 80% pain reduction), satisfactory – good (> 50% pain reduction), unsatisfactory – poor (30–50% pain reduction), no improvement (< 30% pain reduction). Factors influencing the final outcome were also evaluated, mainly taking into account the type of chronic pain, the duration of chronic pain, and the position and number of electrodes. Table 1 briefly summarizes the characteristics of the patients.

Statistical Analysis

To assess the correlations among the examined variables, non-parametric tests were used:

Table 1. Characteristics of patients

	Initials	Sex	Age	Dgn and previous treatment	Duration of pain and preoperative intensity	Date (month, year) of surgery and sort of electrode	Early post--operative result	Follow-up and long-term result
1	M.Z	f	64	atypical facial pain tramadol DBS	8 years **VAS 9**	03.2005 one 4-contact electrode over dura parallel to the motor strip after DBS	40% reduction **VAS 6**	**VAS 9** no improvement after 2 years
2	D.W.	m	42	brachial injury pain tramadol SCS	15 years **VAS 9**	01.2008 one 4-contact electrode over dura parallel to the motor strip after SCS	40% reduction **VAS 6**	**VAS 9** no improvement after 2 years
3	B.S.	m	63	thalamic syndrome gabapentin, oxcarbamazepine	4 years **VAS 7**	06.2004 one 4-contact electrode over dura parallel to the motor strip	50% reduction **VAS 4**	**VAS 5** 40% after 6 years
4	Z.P.	m	58	thalamic syndrome tramadol	6 years **VAS 9**	07.2008 two electrodes: over dura parallel to the motor strip and under dura	80% reduction **VAS 2**	60% after 1 year **VAS 4** 50% after 5 years

Table 1. Characteristics of patients (cn.)

	Initials	Sex	Age	Dgn and previous treatment	Duration of pain and preoperative intensity	Date (month, year) of surgery and sort of electrode	Early post--operative result	Follow-up and long-term result
5	J.G.	m	60	thalamic syndrome in MS tramadol gabapentine oxcarbamazepine	10 years **VAS 9**	05.2009 one 8-contact electrode over dura parallel to the motor strip	90% reduction **VAS 1**	90% after 1 year **VAS 2** 70% after 4 years
6	W.M	f	64	half body pain in syringomielia metadon gabapentin	25 years **VAS 9**	09.2008 two 4-contact electrodes perpendiculary over dura 08.2010 insertion of new IPG	80% reduction **VAS 3**	**VAS 7** 40% after 1 year 30% after 5 years
7	M.S.	f	62	thalamic syndrome carabamazepine	15 years **VAS 8**	01.2006 one 4-contact electrode over dura parallel to the motor strip	80% reduction **VAS 3**	50% after 1 year **VAS 7** 30% after 5 years
8	M.S.	m	58	thalamic syndrome oxcarbamazepine valproic acid, clozapine	6 years **VAS 8**	04.2010 one 4-contact electrode over dura parallel to the motor strip	80% reduction **VAS 1**	**VAS 2** 80% after 3 years
9	H.L.	f	58	atypical facial pain tramadol	6 years **VAS 8**	07.2008 one 4-contact electrode over dura perpendiculary 11.2010 new IPG 06.2013 new IPG	80% reduction **VAS 2**	80% after 1 year **VAS 4** 60% after 5 years
10	M.M	f	32	thalamic syndrome fentanyl patch	6 years **VAS 9**	05.2011 two 4-contact electrodes: over dura parallel to the motor strip and under dura	80% reduction **VAS 2**	**VAS 4** 50% after 2 years
11	A.M	m	41	brachial injury pain tramadol morphine sulfate	For 7 years **VAS 8**	10.2011 one 8-contact electrode over dura parallel to the motor strip	70% reduction **VAS 3**	**VAS 2** 80% after 1 and **2 years**
12	J.Sz	m	40	brachial injury pain pregabaline amitryptyline	4 years **VAS 9**	09.2012 one 8-contact electrode over dura parallel to the motor strip	40% reduction **VAS 5**	**VAS 5** 40% **after 1 year**
13	D.J.	m	42	phantom pain metadon gabapentin	24 years **VAS 9**	03.2013 4-contact electrode parallel to the motor strip	60% reduction **VAS 4**	**VAS 5** 40% **after 3 months** – infection IPG
14	MI	m	52	thalamic pain tramadol, carbamazepine	11 years **VAS 9**	07.2013 four 4-contact electrodes perpendiculary	70% reduction **VAS 3**	VAS 6 after 1 year

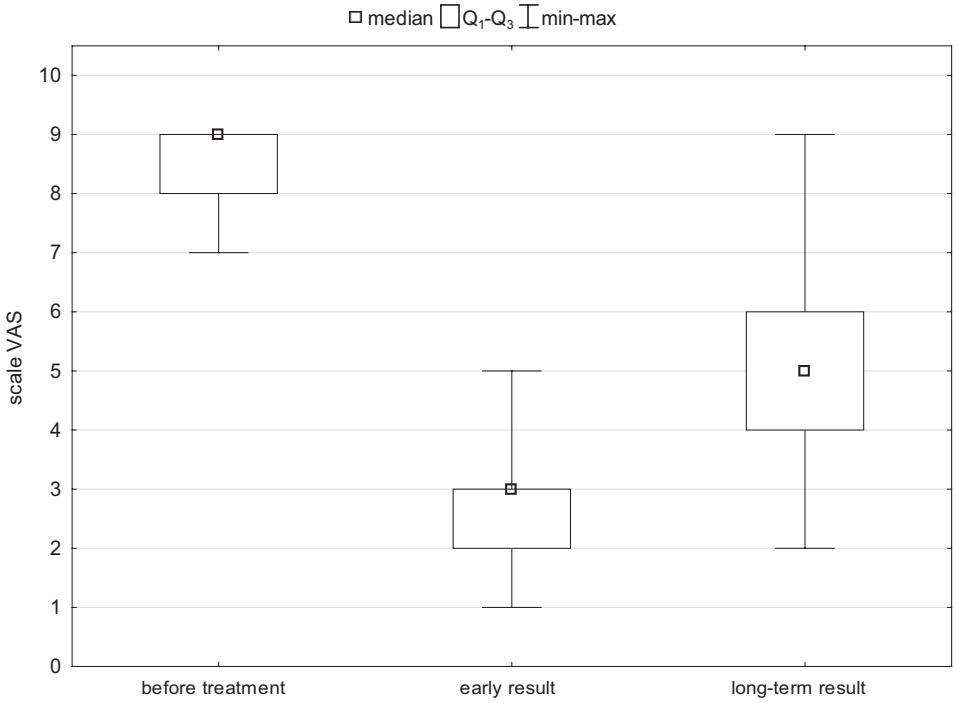

Fig. 1. Statistical significance in diffference between VAS score before treatment and early result ($p = 0.0009$), early result and long-term result ($p = 0.0051$), and before treatment and long-term result ($p = 0.0036$) according to Wilcoxon test

Table 2. VAS results before and after treatment

	The level of pain on a VAS scale							
	n	**$\bar{x}$**	**SD**	**min**	**Q_1**	**Me**	**Q_3**	**max**
Before treatment	14	8.6	0.6	8	7	9	9	9
Early result	14	2.8	1.1	2	1	3	3	5
Long-term result	13	4.9	2.4	2	4	5	6	9

the Mann-Whitney *U* test, the Wilcoxon test and Spearman's rank correlation coefficient. A p value < 0.05 was accepted as the level of statistical significance. All calculations were performed using STATISTICA software (version 10, StatSoft, Inc., Tulsa, Oklahoma, USA).

Surgical Management

The surgical procedure was performed under general anesthesia without muscle relaxation, with a small craniotomy over the motor cortex using neurosurgical navigation. Intraoperative electrophysiological tests using electrodes for somato-sensory evoked potential (SSEP) enabled the central sulcus to be to localized by the typical SSEP phase reversal. For the localization of the motor strip, electrodes for motor evoked potential (MEP) were used, which enabled the representative cortex for the upper and lower extremities and for the face to be found (Fig. 2). Stimulating electrodes were placed perpendicularly or along the motor strip over the dura (Fig. 3, 4). The dura was opened when the electrodes were placed in the interhemispheric fissure in order to stimulate the motor cortex for the lower extremities. Subdurally, a collagen sponge coated with human fibrinogen and thrombin (TachoSil, Takeda, Japan) was applied to fix the electrode to the cortex.

Leads from the electrodes were passed under the skin to a pulse generator positioned on the chest wall in a subcutaneous pocket in the subclavian region. Stimulation was usually set in a cycling mode of 1–3 off and 10–3 on, with a low frequency from 40–50 Hz, pulse wave ranging from 90 to 240 ms, and a variable amplitude A = from 0.5 to 8.0.

Results

In the study group, a statistically significant reduction in the intensity of pain was achieved in patients treated with MCS (before surgery, median VAS = 9, early result, median VAS = 3, long-term result, median VAS = 5) (Table 2, Fig. 1). In the long term, with follow-ups ranging from 1 to 6 years, there were two cases with no improvement postoperatively (15%), unsatisfactory/poor control

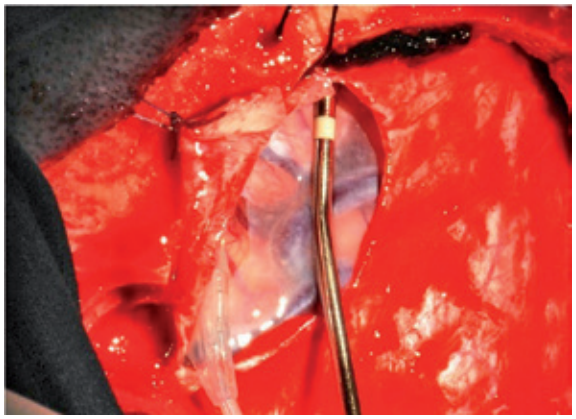

Fig. 2. Electrode placed under dura directly on the motor cortex

of pain (less than 50%) was noted in 31% of the cases; satisfactory reduction of pain (50–80%) was achieved in 23% of the patients; and excellent results (over 80% reduction of pain) were observed in 31% of the patients (Table 3b). Significantly better improvement was observed in the early post-operative period (Table 3a).

In patients with thalamic pain syndrome, there were 2 cases with excellent long-term results and 3 cases with satisfactory results; in the other 2 the effect was unsatisfactory. This means that 5/7 patients (71%) with thalamic pain have a satisfactory effect after MCS. In the cases of atypical facial pain (n = 2), there was 1 satisfactory and 1 unsatisfactory result. In the cases of pain following brachial plexus injuries (n = 3), there was one satisfactory result, one unsatisfactory/poor result and no improvement in 1 case. In the case of phantom pain (n = 1), as well as in the case of central pain in the course of syringomyelia (n = 1), the results were unsatisfactory/poor. In this study group the highest efficacy of MCS was observed in post-stroke or post-hemorrhagic thalamic pain.

Tables 3A and 3B. Postoperative and long-term results

Long-term result		
	no.	**%**
No relief > 30%	2	15
Unsatisfactory 50–30%	4	31
Satisfactory 80–50%	3	23
Excellent < 80%	4	31

Early post-operative result		
	no.	**%**
No relief > 30%	2	14
Unsatisfactory 50–30%	1	7
Satisfactory 80–50%	4	29
Excellent < 80%	7	50

Fig. 3. Two electrodes in thalamic pain of upper and lower contralateral extremities

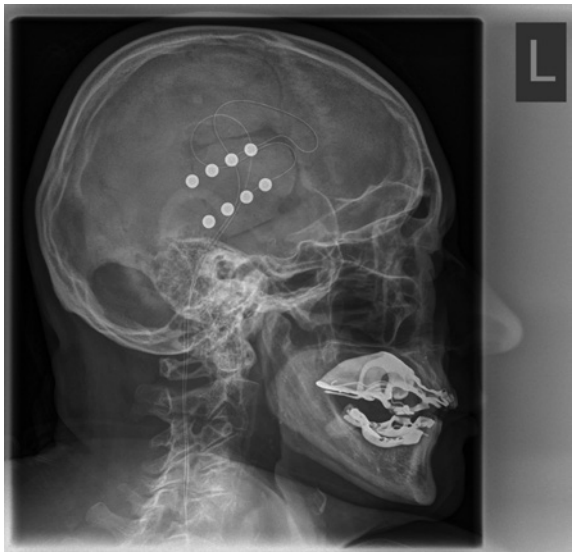

Fig. 4. Four electrodes in contralateral thalamic and facial pain

Complications included 2 incidents of transient seizures during intraoperative stimulation and one incident after the operation (21%); one case (7%) of infection of the wound, managed by IPG removal; 1 case (7%) of electrode lead fracture documented by increased impedance and an X-ray scan (Fig. 5.)

According to results of the Mann-Whitney test, neither the patient's sex (p = 0.766), nor the patient's age (p = 0.946), nor the duration of pain (p = 0.946), nor the position and type of electrode (p = 0.460) are significant factors improving the outcome.

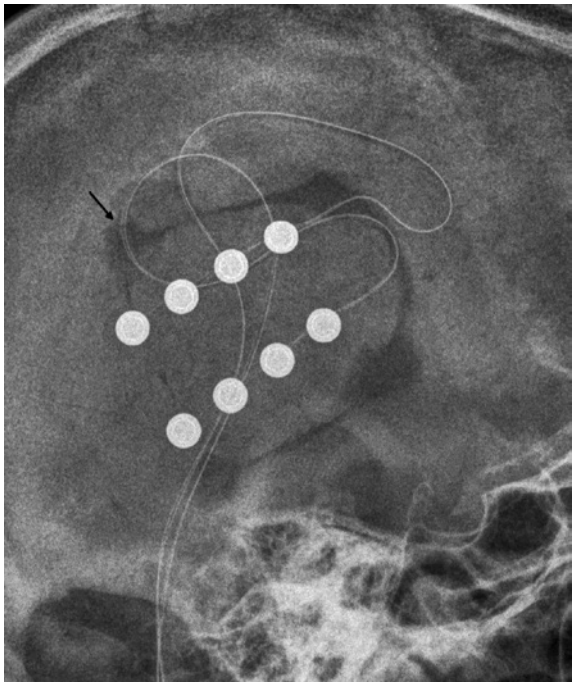

Fig. 5. Broken wire in an electrode lead

Discussion

Stimulation of the cerebral cortex (MCS) is frequently a treatment of a last resort for chronic central pain that is refractory to pharmacological treatment and that cannot be treated with other stimulation techniques, such as spinal cord stimulation (SCS). The present study included patients with diagnoses that are primary indicators for MCS: thalamic syndrome after a stroke or traumatic brain injury, central pain due to spinal cord injury, brachial plexus injury, neuropathic facial pain and phantom pain. In 2 cases patients previously treated with other neuromodulation therapies were qualified for MCS: a patient with brachial avulsion injury pain, in whom cervical SCS had been unsuccessful, and a patient with a poor response to deep brain stimulation (DBS) of the internal capsule in anesthesia dolorosa. In these 2 cases no improvement was observed after MCS.

Additional criteria for qualifying patients for MCS were also used in this study: chronic neuropathic pain lasting over 6 months, refractoriness to pharmacological treatment and age over 16 years old [16]. The present study group included patients with a long duration of pain before surgery (median 7.5 years); based on the statistical analysis, there was no relation between the duration of pain and the outcome.

Preoperatively, patients should undergo pain-intensity assessment and psychological tests. In the authors' clinic, all patients undergo preoperative psychological evaluation allowing patients with major depression, dementia, psychotic disorders or high levels of anxiety to be excluded, along with poorly motivated patients. The following psychological scales are used the Mini Mental State Examination (MMSE), the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI) and a structured clinical interview. The purpose of the interview is the elimination of psychological risk factors for poor surgical outcomes, such as substance abuse, marital dissatisfaction, pending legal action related to pain, pre-injury psychological problems, financial benefits due to temporary disability, job dissatisfaction, workers compensation or reinforcement of the disability by family members. Two patients with major depression were disqualified from the treatment on the basis of the psychological evaluation.

In MCS the precentral gyrus is stimulated in areas representing the contralateral extremities or the face. Electrodes are placed on the dura or under the dura in the interhemispheric fissure. MEPs and SSEPs are used, but actually in phantom pain and often in thalamic pain it is difficult or impossible to locate the motor strip. Intraoperative cortical stimulation triggers muscle spasms in the upper limb contra-laterally, which confirms the correctness of the position of the electrode. Electromyographic (EMG) stimulation is a routine method used to monitor the accuracy of the selected target [3–9]. In cases of phantom pain in an upper extremity, neighboring areas are localized, and electrodes are placed between the cortex for the lower extremity and the face. The most important factor in these cases is neurosurgical navigation.

It was noted that patients who have severe weakness in the area of pain are less likely to achieve clinical improvement. It appears that intact cortico-spinal tracts are necessary for effective control of pain [6]. In phantom pain these tracts are present, but in cases of central pain due to spinal cord injury they are interrupted, and the results of the current study show that in these cases the effects are poor. The efficacy of stimulation of the cerebral cortex can be enhanced by placing subdural electrodes in the sulcus of Roland or in the interhemispheric sulcus in the case of localized pain in a lower limb [12]. The present study included 2 cases of MCS with electrodes placed subdurally. Velasco et al. and Nguyen et al. found that it is more effective to use electrodes applied perpendicularly to the axis of the motor cortex [8, 11]. In the present study electrodes were placed along the motor strip in 11 cases, perpendicularly in 3 cases and in the interhemispheric fissure in 2 cases.

Less impressive results are achieved in cases of pain due to brachial plexus injury. Some researchers suggest that MCS is suitable in chronic,

permanent pain but not in paroxysmal pain, when DREZotomy should be used [7, 19].

In all kinds of central pain, although the results are not excellent in the majority of subjects, the patients usually demand reimplantation of the internal pulse generator (IPG) when the battery is depleted, to restore effective stimulation that reduces their pain level, allows them to decrease doses of analgesic medication, improves their quality of life and functional ability. Pain inhibition occurs at intensities below the threshold for the induction of muscle contraction. When satisfactory pain inhibition is achieved, the patients report a slight tingling or mild vibration during stimulation projected in the same area of distribution as their pain. This situation occurs in neuropathic trigeminal pain; in thalamic syndrome, patients generally report no sensations. The experience of other researchers indicates significant improvements in the effectiveness of MCS after changing the stimulation parameters [20, 21]. In order to overcome habituation, the authors change the mode from cycling to continuous stimulation or *vice versa*, and in cycling mode the off period is prolonged or shortened. In the literature, there are also reports of a lack of efficacy of the treatment of neuropathic pain in the face and upper extremities that is refractory to medication.

Transcranial magnetic stimulation (TMS) has been shown to correlate with a good response to MCS [22], but it is not available at the authors' center, and it is therefore not used as a selection tool for patients with central pain. The authors don't use trial-period testing to avoid subjecting patients to a second surgical procedure: in cases of failed trial periods, the electrodes must be removed from the dura, and when the trial period is successful it is necessary to implant a permanent IPG.

Potential complications of MCS are mainly infections (5.7%), hardware–related problems (5.1%) and seizures; rarely, hematomas, speech disorders or paraesthesias may occur [5, 12]. The complication rate is low, amounting to less than 10% [8]. In the present study, there was one case of purulent infection (7%) which necessitated the removal of the infected IPG. Epileptic seizures were observed in 3 cases (21%); after a reduction of the amplitude of stimulation current these symptoms subsided.

The authors' experience has shown that MCS is a promising treatment in thalamic pain. It is difficult to predict in which cases MCS will work the most effectively. According to Nuti at al. the only strong predictor of long-term relief was pain relief in the first month after implantation. The interval between pain onset and surgery, the pain characteristics, the type of lesion, SSEP status and preoperative motor status were found not to be significant predictors [23]. Satisfactory long-term results are observed in 50% of all patients with MCS. The best pain control is achieved in thalamic central pain. In the present study, it was more difficult to attain satisfactory pain relief in neuropathic facial pain and pain due to brachial plexus injury. Meticulous adjusting of the stimulation parameters (frequency, pulse width, amplitude, mode) improves treatment outcomes. Most patients notice a lack of analgesic stimulation when the battery is depleted and demand reimplantation of depleted IPGs.

MCS significantly reduces the intensity of neurogenic pain. Better results are noted in the early post-operative period. In the present study the best long-term results were achieved in patients with thalamic syndrome. No significant predictors of a final successful outcome were found. The authors consider the appropriate selection of patients, accurate placement of electrodes (neuronavigation and neuromonitoring) and periodic adjusting of the stimulation parameters to be important factors increasing the efficacy of MCS.

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Conflict of interest: None declared

Received: 27.10.2013
Revised: 1.09.2014
Accepted: 19.03.2015