Treatment of chronic neuropathic pain by motor cortex stimulation: Results of a bicentric controlled crossover trial

Jean-Paul Nguyen, MD\textsuperscript{a}, Francisco Velasco, MD\textsuperscript{b}, Pierre Brugières, MD\textsuperscript{c}, Marcos Velasco, MD, PhD\textsuperscript{b}, Yves Keravel, MD\textsuperscript{a}, Bernardo Boleaga, MD\textsuperscript{d}, Francisco Brito, MD\textsuperscript{b}, Jean-Pascal Lefaucheur, MD, PhD\textsuperscript{e}

\textsuperscript{a}Service de Neurochirurgie, Hôpital Henri Mondor, Assistance Publique–Hôpitaux de Paris, Créteil, France
\textsuperscript{b}Department of Stereotactic and Functional Neurosurgery, General Hospital of Mexico, and Department of Medical Research in Neurophysiology, National Medical Center, Mexico City, Mexico
\textsuperscript{c}Service de Neuroradiologie, Hôpital Henri Mondor, Assistance Publique–Hôpitaux de Paris, Créteil, France
\textsuperscript{d}Department of Magnetic Resonance Imaging, Clinica Londres, Mexico City, Mexico
\textsuperscript{e}Service de Physiologie-Explorations Fonctionnelles, Hôpital Henri Mondor, Assistance Publique–Hôpitaux de Paris, Créteil, France

Background
Chronic motor cortex stimulation (MCS) with surgically implanted epidural electrodes has been proposed as a treatment for neuropathic pain refractory compared with medical treatment. However, no prospective controlled trial has been published to provide convincing evidence of MCS analgesic efficacy.

Objective
To compare MCS analgesic efficacy between “ON”- and “OFF”-stimulation conditions in a double-blinded crossover trial.

Methods
Ten patients with chronic neuropathic pain of either peripheral or central origin underwent MCS implantation in two centers (Créteil, France, and Mexico City, Mexico). At the end of the second postoperative month, patients were randomly assigned into two groups. In the first group, the stimulator was switched “OFF” for two weeks and then was switched “ON” for the next 2 weeks. The opposite sequence was applied in the second group. Preoperative and postoperative assessment (until 1 year after surgery) was performed using visual analogue scale (VAS), verbal scale (VS), Wisconsin brief pain
questionnaire (WBPQ), McGill pain questionnaire (MPQ), McGill quality of life scale, and medication quantification scale.

Results
During the crossover trial, VAS, VS, WBPQ, and MPQ scores were significantly reduced in the “ON”-compared with the “OFF”-stimulation condition. One year after surgery, all clinical scores were significantly reduced compared with preoperative values. In particular, MCS decreased the affective MPQ subscore relative to the sensory MPQ subscore. Six of the 10 patients clearly benefited from MCS treatment.

Conclusions
These results were in favor of real analgesic effects produced by MCS with no loss of benefit over time. The differential changes in MPQ subscores suggested that MCS relieved pain by acting predominantly on its affective aspect. The decrease in pain intensity was associated with improved daily living activities and quality of life and reduced consumption of analgesic medication.

Materials and methods

Patients
This study was conducted in the Departments of Neurosurgery of Henri Mondor Hospital (Créteil, France) and Mexico General Hospital (Mexico City, Mexico). Five consecutive patients were enrolled in each center. The inclusion criteria for the patients included the following: ages between 18 and 80 years, chronic neuropathic pain resistant for more than a year to at least three different types of analgesic medical treatments, and average pain level 60 or greater on a 0-100 visual analogue scale (VAS) over 7 days of self-assessments. The exclusion criteria included the following: pregnancy, malignant disease, history of epileptic seizures, and unable to comply with study procedures and follow-up visits because of cognitive impairment.

The patients were six men and four women, aged from 29-75 years (mean [SD]: 54.7 [18.1] years). Three patients had central poststroke pain located at one hemibody or one hemiface (patients 1, 3, and 8), three patients had facial pain secondary to trigeminal nerve lesion (patients 2, 4, and 5), two patients had postherpetic cervical or thoracic pain (patients 6 and 7), and two patients had complex regional pain syndrome type 1 (CRPS) located at the upper limb (patients 9 and 10) (Table 1). Pain duration ranged from 1-14 years (mean [SD]: 5.3 [3.4] years). The protocol was approved by the local Ethics Committee in the two centers. All patients signed an informed consent form after reading a document that provided detailed information about the protocol.

Surgical procedure
The surgery was performed as previously described. The first stage was a craniotomy of approximately 4 cm in diameter centered on the precentral motor cortical area corresponding to the painful zone, as defined by magnetic resonance imaging (MRI)- or computed tomographic (CT)-guided neuronavigation. The second stage was neurophysiologic monitoring aimed at locating (1) the central sulcus, by recording the phase reversal of the somatosensory cortical-evoked potentials to median nerve stimulation; and (2) the target for chronic MCS, by recording motor responses in the painful zone to cortical stimulation. The third stage was the placement of a Resume quadripolar lead (model 3587A, Medtronic Neurological, Minneapolis, Minnesota) over the target for chronic stimulation. In all cases, the lead was placed in the epidural space and sutured onto the dura mater. Finally, an Itrel II pulse generator (Medtronic Neurological) was implanted subcutaneously in the pectoral region. In most cases, bipolar montage was used for chronic stimulation, a contact placed over
the motor cortex serving as a cathode and a contact situated immediately behind (over the central sulcus or the postcentral cortex) serving as an anode. The parameters of stimulation were initially set as follows: amplitude 2 V, rate 40 Hz, pulse width 60 microseconds, full-time mode. These are classical parameters used in chronic MCS therapy for neuropathic pain.6 For the first two postoperative months, these parameters have been readjusted on empirical bases in some patients, with respect to the clinical effects observed within a few days after the time of programming. After this 2-month period of optimization, stimulation parameters were kept constant in all cases until the end of the study.

Study design

The evaluation of the patients, based on clinical scores, described later in this text, was performed 30 days before surgery (Pre) and then 30, 60, 75, and 90 days after surgery (M1, M2, M2.5, and M3). Long-term evaluation was performed at 6 and 12 months postoperative (M6 and M12). Clinical evaluation was conducted by a medical examiner, who was trained in the management of chronic pain and blinded for the parameters of stimulation. Analgesic treatment was optimized in the preoperative period, and changes were authorized during the whole postoperative period, including the randomized ON/OFF trial.

At M2, the patients were randomly assigned into two groups. In the first group (five patients), the stimulators were switched “OFF” until M2.5 (OFF-period), and then switched “ON” from M2.5-M3 (ON-period). The opposite sequence was applied in the five patients of the second group: stimulators being switched “ON” from M2-M2.5 (ON-period) and then switched “OFF” from M2.5-M3 (OFF-period). This procedure was double-blinded: neither the patient nor the clinical examiner was informed about the sequence. During the ON/OFF trial, changes in pain medication were not the result of the examiner’s decision not to interfere with the double-blind process. However, all patients and raters knew that the general design of the trial included 2 weeks “ON” and 2 weeks “OFF” in a randomized order.

Clinical scores

At each interview, patients rated the intensity of their ongoing pain on a 0-100 VAS (0, no pain, to 100, highest imaginable pain)8 and on a 6-point verbal scale (VS: 0, no pain; 1, mild pain; 2, uncomfortable pain; 3, strong pain; 4, terrible pain; and 5, unbearable pain).9 Pain assessment was also carried out using short versions of the Wisconsin Brief Pain Questionnaire (WBPS)10 and McGill Pain Questionnaire (MPQ).11 The WBPS provides information on the degree to which pain interferes with seven different functions or daily living activities (general activity, mood, walking ability, normal work, relations, sleep, and enjoyment of life). Interference was rated for each item on a 0-100 scale (0, pain does not interfere, to 100, pain completely interferes) and the averaged value was taken for analysis. The MPQ consists of 20 descriptors that fall into four subscores: sensory (descriptors 1-10), affective (11-15), evaluative (16), and miscellaneous (17-20). The pain rating index (MPQ-PRI) was calculated as the sum of the rank values for each descriptor (based on its position in the word set). In addition, to determine the respective impact of MCS on affective and sensori-discriminative aspects of pain, a ratio (MPQ-ratio) was calculated by dividing affective MPQ subscore by sensory MPQ subscore.

The patients also rated their quality of life according to a modified version of the McGill Quality of Life Scale (MQoL),12 taking into account only the first eight items of this scale (regarding physical and psychologic domains, but not the existential one as chronic pain could not be considered as a life-threatening condition). An averaged score on an 11-point scale (0-10) was calculated, a higher score reflecting a greater impact of pain on the quality of life.

Finally, analgesic drug consumption was quantified using the Medication Quantification Scale (MQS).13 In this scale, a score is calculated for each medication by multiplying a consensus-based detriment weight for a given

---

**Table 1 Clinical data**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Origin of pain</th>
<th>Location of pain</th>
<th>Duration of pain (y)</th>
<th>Sensory disturbances in the painful zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>70</td>
<td>Stroke (hemorrhage)</td>
<td>Right hemibody</td>
<td>5</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>75</td>
<td>Trigeminal neuropathy</td>
<td>Right hemiface</td>
<td>5</td>
<td>Alldynia</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>57</td>
<td>Stroke (ischemia)</td>
<td>Right hemibody</td>
<td>5</td>
<td>Hypoesthesia</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>57</td>
<td>Trigeminal neuropathy</td>
<td>Left hemiface</td>
<td>6</td>
<td>Hypoesthesia</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>31</td>
<td>Trigeminal neuropathy</td>
<td>Right hemiface</td>
<td>3</td>
<td>Hypoesthesia</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>75</td>
<td>Postherpetic neuralgia</td>
<td>Left intercostal T5-T6</td>
<td>4</td>
<td>Alldynia</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>68</td>
<td>Postherpetic neuralgia</td>
<td>Right cervical C2-C3</td>
<td>4</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>52</td>
<td>Stroke (ischemia)</td>
<td>Left hemiface</td>
<td>1</td>
<td>Alldynia</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>29</td>
<td>CRPS</td>
<td>Left upper limb</td>
<td>14</td>
<td>Alldynia</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>33</td>
<td>CRPS</td>
<td>Left upper limb</td>
<td>6</td>
<td>Alldynia</td>
</tr>
</tbody>
</table>

CRPS: complex regional pain syndrome.
pharmacologic class by a score for dosage. The total MQS score was calculated as the sum of the scores for each medication.

Statistical analyses

Nonparametric tests were used because not all data passed the normality test as assessed by the Kolmogorov-Smirnov method. In all cases, a $P$ value of less than .05 was considered as significant. First, clinical scores (VAS, VS, WBPQ, MPQ-PRI, MPQ-ratio, MQoL, and MQS) collected before and after MCS implantation (Pre, M1, M2, M6, and M12) were compared by using nonparametric repeated measures analysis of variance (ANOVA) (Friedman test). Dunn’s multiple comparison post hoc tests were used to compare selected pairs of columns (preoperative vs postoperative; M1 vs M12). Regarding the randomized ON/OFF period, comparisons were performed by using Wilcoxon matched-pairs signed-ranks test (ON-period vs OFF-period; ON-period vs M2; ON then OFF vs OFF then ON).

Results

Overall results

All patients completed the study without any adverse events. In particular, no seizure and no infection at the level of the implanted devices were observed. All clinical scores (VAS, VS, WBPQ, MPQ-PRI, MPQ-ratio, MQoL, and MQS) varied significantly in the follow-up (Friedman test, $P < .05$) (Figure 1). Post hoc analyses showed a significant decrease of all scores between preoperative evaluation and any postoperative evaluation from 1-12 months after surgery (Dunn test, $P < .05$). In contrast, no significant differences were observed between 1-month and 1-year postoperative assessments (Dunn test, $P > .05$).

Results of the randomized ON/OFF period

All patients completed the randomized ON/OFF trial between M2 and M3. Sequence order (ON- then OFF-period vs OFF- then ON-period) did not significantly influence the results (Wilcoxon test, $P > .05$ for all scores). The following scores were lower in the ON-period than in the OFF-period (Wilcoxon test, $P < .05$): VAS (mean: 53.5 vs 78.0), VS (2.1 vs 3.3), WBPQ (36.0 vs 53.0), and MPQ-PRI (33.9 vs 60.1) (Figure 2). The other scores did not change between the conditions ($P > .05$): MPQ-ratio (mean: 0.58 vs 0.58), MQoL (4.6 vs 5.4), and MQS (20.3 vs 26.3).

Both VAS scores and MPQ-PRI increased in the ON-period compared with the prerandomization period (M2) (Wilcoxon test, $P < .05$), but did not return to preoperative values (Figure 2). In the OFF-period, all clinical scores rose to the range of preoperative values (Figure 2). At 6-month postoperative, beyond the period of randomization, clinical scores returned to the range of values observed at 2-month postoperative (Figure 2).

Individual results

The clinical outcome was classified into two categories according to the percentage of VAS score reduction between preoperative and 1-year postoperative values. These categories were good outcome (satisfactory to excellent results, >40% pain reduction) and poor outcome (<40% pain reduction). The outcome was judged as good in six patients and poor in four patients (Table 2). Considering the small number of patients, the possibility of a bias related to the center could not be relevantly analyzed. There were four of five responders in center 2, but two of five responders in center 1. However, one patient from center 1 was totally relieved from pain (patient 4), whereas one patient of each center did not experience any pain improvement on VAS (patients 5 and 6).

Two of the four oldest patients (68-75 years old) greatly improved in the long term. Significant improvement was also observed whether the interval between pain onset and surgery was the shortest (1 year) or the longest (14 years). The treatment failed in two of three patients with poststroke pain, in one of three patients with trigeminal neuropathic pain, and in one of two patients with postherpetic thoracic neuralgia. The treatment has been efficacious in the two patients with complex regional pain syndrome (CRPS). Three of four patients with facial pain and all three patients with cervical or upper limb pain benefited from MCS. In contrast, the three patients with pain located at thoracic level or affecting the whole hemibody did not respond.

Postoperative evolution was similar for all scores in four patients (patients 7-10) but was more variable in the others. In patient 1, VAS and MQoL scores decreased by 16-20%, MPQ, WBPQ and MQS scores decreased by 30-35%, and VS score decreased by 60%. In patient 2, all scores decreased by more than 50%, whereas the WBPQ score curiously remained constant. Patient 3 showed high VS and WBPQ scores reduction but only a little change in the MQS score. Patient 4 was totally relieved from pain but analgesic drug consumption was only reduced by 32%. Patients 5 and 6 did not experience any pain relief on VAS score and MQS.

Discussion

Chronic MCS with surgically implanted epidural electrodes had been proposed to treat refractory neuropathic pain 15 years ago, but controlled trials were still lacking. This crossover study showed significant clinical improvement in
ON-stimulation condition compared with OFF-stimulation condition during a period of randomization that took place between 2 and 3 months after implantation. This result was in favor of a real analgesic effect and not a placebo effect of MCS. The fact that patients did not feel any subjective sensation when MCS was switched “ON” allowed a double-blind design. However, patients were not asked whether they were able to discern their devices were turned on.

Figure 1 Evolution of the clinical scores (mean, SEM) in a series of ten patients treated by chronic MCS. MPQ-PRI, MPQ-ratio: McGill pain questionnaire—pain rating index, ratio between affective and sensory subscores; MQoL: McGill quality of life scale; MQS: medication quantification scale; VAS: visual analogue scale; VS: verbal scale; WBPQ: Wisconsin brief pain questionnaire.

ON-stimulation condition compared with OFF-stimulation condition during a period of randomization that took place between 2 and 3 months after implantation. This result was in favor of a real analgesic effect and not a placebo effect of MCS. The fact that patients did not feel any subjective sensation when MCS was switched “ON” allowed a double-blind design. However, patients were not asked whether they were able to discern their devices were turned on.
“OFF” because the pain returned. This was a potential limitation of this study.

Differences between ON- and OFF-stimulation conditions were significant on various scales assessing pain level or repercussion (VAS, VS, MPQ, and WBPQ). However, the mean VAS score change between ON- and OFF-stimulation periods was only about 25 of 100, which was not so relevant. Probably because of the short duration of the period of randomization, the impact of switching “ON” MCS was not significant on scales assessing quality of life and medication use (MQoL and MQS). The short duration of each period of the ON/OFF trial was related to an ethical issue (we were asked to limit the duration of the OFF-period). However, considering the present results and that a posteffect had been often observed with MCS, the duration of the randomized period should be prolonged to a least 1 month in future studies to better appraise the impact of MCS on various aspects of the chronic pain syndrome.

Clinical improvement was significant at 1- and 2-month postoperative compared with preoperative baseline. When MCS was switched “OFF” during the period of randomization, clinical scores returned to the range of preoperative values. Clinical scores also deteriorated in the ON-stimulation condition, at least for the VAS score and MPQ-PRI. These scores did not return to preoperative values but exceeded prerandomization values. This was likely due to the uncertainty of the patients about the status of the stimulation during the period of randomization.

Figure 2  Evolution of the clinical scores (mean, SEM) in a series of ten patients treated by chronic MCS, before, during, and after a period of randomized crossover trial. The stimulator was switched “ON” and “OFF,” respectively, for 2 weeks from M2-M3 after surgery. The dotted horizontal line corresponds to mean preoperative baseline value for each score. Significance of the Wilcoxon test is presented above the M2-M3 ON-period bar for comparisons made between M2 and M2-M3 ON-period and above the M2-M3 OFF-period bar for comparisons made between M2-M3 ON-period and M2-M3 OFF-period. ns: Not significant (P > .05). *Significant (P < .05).
Beyond the period of randomization, the initial improvement was restored in both groups. On average, clinical scores were found quite similar before (M1-M2) and after (M6-M12) the crossover trial. The efficacy of MCS was in the same range in the short-term (1 month) and the long-term (1 year) follow-up. We did not notice any loss of benefits over time, in contrast to previous reports. Another study showed that the level of pain relief in the first month postoperative was a strong predictor of long-term clinical outcome.16

Regarding individual results, the reduction of pain level ranged from satisfactory to excellent in 6 of 10 patients (60%). This rate of MCS responders was in the average of previous reports when all indications are pooled. The interval between pain onset and surgery or the age of the patient did not seem to influence the clinical outcome. This surgical treatment appeared to be safe even in elderly patients, at least until age 75 years. Considering the small number of patients, the current study could not provide relevant information on the influence of various clinical parameters (for example, origin, location, or duration of pain, existence, and type of associated sensory disturbances) on MCS efficacy. Nevertheless, it could be noticed that the two patients with CRPS experienced a very good improvement. CRPS is a rare and maybe underestimated indication of MCS treatment. In contrast, the two patients with hemibody pain did not benefit from MCS. It was likely that the implantation of only one 4-contact electrode array was not enough to reduce pain in one hemibody.

Various aspects of MCS efficacy have been analyzed in this study. The decrease in pain intensity provided by MCS was concomitant with an improvement in daily living activities and quality of life, as shown by WBPQ and MQoL postoperative changes in the long term. Pain relief was also accompanied by a reduction in analgesic drug consumption, as shown by MQS evolution. Finally, one interesting observation was the significant postoperative decrease of the MPQ-ratio (affective/sensory MPQ subscores). MCS could have induced functional changes in the neural networks that are involved in the affective and not the sensory-discriminative aspect of pain. Previous clinical studies, even from our group, have reported that MCS could improve sensory perception in the painful zone. However, functional imaging showed that MCS could also act on neural structures involved in the emotional appraisal of pain (perigenual cingulate and orbitofrontal cortical areas).

In conclusion, this controlled study showed that MCS was an effective method to improve various types of drug-resistant chronic neuropathic pain, of either peripheral or central origin. These results need to be confirmed and extended in larger series of patients.

J.-P. Nguyen thanks M. Sobel and H. Ollat for editing the English language content of the manuscript and T. Bianchi for his assistance in the review of the literature.

References


Table 2 Parameters of chronic stimulation and percentage of reduction of various clinical scores at 1-year postoperative compared with preoperative baseline in each patient

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Stimulation parameters: amplitude (V), rate (Hz), pulse width (µsec)</th>
<th>VAS</th>
<th>VS</th>
<th>WBPQ</th>
<th>MPQ</th>
<th>MQoL</th>
<th>MQS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2, 60, 60</td>
<td>16%</td>
<td>60%</td>
<td>35%</td>
<td>34%</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>
| 2              | 1.4, 35, 60                                                    | 85% | 80%| −1%  | 77% | 50%  | 100%
| 3              | 2.5, 40, 90                                                    | 38% | 60%| 51%  | 37% | 25%  | 13%
| 4              | 2.1, 35, 60                                                    | 100%| 100%| 100% | 100%| 80%  | 32%
| 5              | 3, 40, 60                                                     | 0%  | 40%| −45% | −43%| −20% | 39%
| 6              | 6, 60, 90                                                     | 0%  | 0% | 41%  | 0%  | 0%   | 37%
| 7              | 6.5, 40, 60                                                   | 63% | 67%| 90%  | 70% | 43%  | 58%
| 8              | 3.5, 40, 60                                                   | 80% | 80%| 98%  | 98% | 63%  | 55%
| 9              | 5, 40, 60                                                     | 80% | 80%| 46%  | 87% | 44%  | 46%
| 10             | 5, 40, 90                                                     | 70% | 60%| 72%  | 74% | 56%  | 73% |

MPQ: McGill pain questionnaire–pain rating index; MQoL: McGill quality of life scale; MQS: medication quantification scale; VAS: visual analogue scale; VS: verbal scale; WBPQ: Wisconsin brief pain questionnaire.


