Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature

Clinical article

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Object. The authors systematically reviewed the published literature to evaluate the efficacy of and adverse effects after motor cortex stimulation (MCS) for chronic neuropathic pain.

Methods. A search of the PubMed database (1991–2006) using the key words “motor cortex,” “stimulation,” and “pain” yielded 244 articles. Only original nonduplicated articles were selected for further analysis; 14 studies were identified for critical review. All were series of cases and none was controlled. The outcomes in 210 patients were assessed and expressed as the percentage of patients that improved with the procedure.

Results. A good response to MCS (pain relief ≥ 40–50%) was observed in ~ 55% of patients who underwent surgery and in 45% of the 152 patients with a postoperative follow-up ≥ 1 year. Visual analog scale scores were provided in 76 patients, revealing an average 57% improvement in the 41 responders. A good response was achieved in 54% of the 117 patients with central pain and 68% of the 44 patients with trigeminal neuropathic pain. Adverse effects were reported in 10 studies, including 157 patients. Infections (5.7%) and hardware-related problems (5.1%) were relatively common complications. Seizures occurred in 19 patients (12%) in the early postoperative period, but no chronic epilepsy was reported.

Conclusions. The results of the authors’ review of the literature suggest that MCS is safe and effective in the treatment of chronic neuropathic pain. Results must be considered with caution, however, as none of the trials were blinded or controlled. Studies with a better design are mandatory to confirm the efficacy of MCS for chronic neuropathic pain. (DOI: 10.3171/2008.6.17602)

Key Words • adverse effect • motor cortex stimulation • neuropathic pain • pain • stroke pain • surgery

Motor cortex stimulation has been proposed since the early 1990s as a potential treatment for medically refractory neuropathic pain, but its true efficacy remains unknown. Reports published so far vary considerably in terms of surgical technique, origin of the pain syndromes, and the methods used to assess clinical outcome. In addition, the lack of randomized controlled studies makes it difficult to evaluate the actual efficacy of MCS or to compare it with other therapeutic modalities.

Authors of previous case series1,3–5,8–12,14,15,17–20,22,24,25,27,28,33–36 have reported satisfactory results in 40–75% of patients; yet reports of overall success in > 70% contradict the daily clinical practice of most surgeons, who anecdotally suggest that MCS results are not consistent, and are often disappointing. We conducted a critical review of the literature to assess the outcome of MCS for the treatment of intractable neuropathic pain.

Methods

The online PubMed database of the National Library of Medicine was searched using the key words “motor cortex,” “stimulation,” and “pain” for articles published between January 1991 and December 2006. This produced a total of 244 references. We reviewed the abstracts and articles for study design, content, and outcomes.

Study Selection

To be included in our review, articles had to: 1) clearly describe the clinical characteristics of pain; 2) provide

Abbreviations used in this paper: MCS = motor cortex stimulation; VAS = visual analog scale.
quantitative postoperative outcome; and 3) clearly state that patients had failed all other conventional treatments, except for deep brain stimulation. Abstracts from proceedings of meetings, review articles, non-English publications, textbook chapters, single case reports, and descriptions of surgical technique were excluded from our analysis.

Twenty-two studies met our initial inclusion criteria. These were most commonly retrospective, but some were prospective, case series. None of the studies were controlled, although in 1 series a double-blinded “on-off” stimulation trial was used to select whether patients would be candidates to receive a pulse generator.

Some of these series included patients who had been reported on previously in smaller studies by teams at the same surgical centers (Table 1). For this reason, we selected only 1 series per center, according to the following criteria: 1) highest number of cases; 2) longest follow-up; and 3) most detailed evaluation of pain or pain relief. The selected study was often the most recently published. Ultimately, 8 of the original 22 studies were excluded based on these criteria, and only 14 articles were selected for analysis.

Pain Evaluation

There was a lack of consistency across studies regarding the methods used to evaluate outcome. Only a few published series reported pre- and postoperative VAS scores for each patient. The authors of most studies only reported the percentage of pain relief after surgery or classified outcomes as “excellent,” “good,” “fair,” “poor,” or “failure.” In some cases, however, the definitions of these groups were different across studies. For example, 40% pain relief was considered a good outcome to some authors, while others required a > 50% improvement to include patients in this category.

Bearing these facts in mind, outcome in this analysis is primarily reported as proportions of patients whose pain improved by > 70, 50, 40, and 30%.

Results

Overall, data from 210 patients reported in 14 studies were evaluated (Table 1). Remarkably, if we consider 26 additional patients reported as single cases or in small case series that did not fulfill our inclusion criteria, only 236 patients with neuropathic pain who have undergone MCS treatment have been reported in the literature between 1991 and 2006. The postoperative follow-up period varied from several weeks to 10 years (mean 30.5 months in 10 series providing this information). Only 152 of the 210 patients had a follow-up period > 1 year.

Overall Results

Considering all patients who underwent surgery, 56.7%

<table>
<thead>
<tr>
<th>Series</th>
<th>Corresponding Redundant Series†</th>
<th>No. of Patients</th>
<th>FU (mos)</th>
<th>Pain Relief &gt;70%</th>
<th>Pain Relief &gt;50%</th>
<th>Pain Relief &gt;40%</th>
<th>Pain Relief &gt;30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsubokawa et al., 1993</td>
<td>Tsubokawa et al., 1991</td>
<td>11</td>
<td>&gt;24</td>
<td>—</td>
<td>—</td>
<td>6 (54.5)</td>
<td>—</td>
</tr>
<tr>
<td>Meyerson et al., 1993</td>
<td>none</td>
<td>10</td>
<td>12.7</td>
<td>2 (20)</td>
<td>5 (50)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hosobuchi, 1993</td>
<td>none</td>
<td>6</td>
<td>9–30</td>
<td>—</td>
<td>3 (50)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Herregodts et al., 1995</td>
<td>none</td>
<td>7</td>
<td>12.7</td>
<td>2 (28.6)</td>
<td>5 (71)</td>
<td>5 (71)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Katayama et al., 1998</td>
<td>Katayama et al., 1994, &amp; Yamamoto et al., 1997</td>
<td>31</td>
<td>&gt;24</td>
<td>—</td>
<td>15 (48.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nguyen et al., 1999</td>
<td>Nguyen et al., 1997 &amp; 2000, &amp; Drouot et al., 2002</td>
<td>32</td>
<td>27.3</td>
<td>15 (46.9)</td>
<td>—</td>
<td>—</td>
<td>23 (71.9)</td>
</tr>
<tr>
<td>Carroll et al., 2000</td>
<td>Smith et al., 2001, &amp; Nandi et al., 2002</td>
<td>10</td>
<td>21–31</td>
<td>3 (30)</td>
<td>4 (40)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Saitoh et al., 2001</td>
<td>Saitoh et al., 1999 &amp; 2000</td>
<td>15</td>
<td>24.1</td>
<td>—</td>
<td>—</td>
<td>7 (46.7)</td>
<td>—</td>
</tr>
<tr>
<td>Sol et al., 2001</td>
<td>Roux et al., 2001</td>
<td>3</td>
<td>27.3</td>
<td>2 (66.7)</td>
<td>2 (66.7)</td>
<td>2 (66.7)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Velasco et al., 2002</td>
<td>none</td>
<td>9</td>
<td>12</td>
<td>4 (44.5)</td>
<td>—</td>
<td>6 (66.7)</td>
<td>6 (66.7)</td>
</tr>
<tr>
<td>Brown &amp; Pilitsis, 2005</td>
<td>none</td>
<td>10</td>
<td>10</td>
<td>4 (40)</td>
<td>6 (60)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nuti et al., 2005</td>
<td>Mertens et al., 1999</td>
<td>31</td>
<td>49</td>
<td>3 (9.7)</td>
<td>7 (22.6)</td>
<td>16 (51.6)</td>
<td>21 (67.7)</td>
</tr>
<tr>
<td>Pirotte et al., 2005</td>
<td>none</td>
<td>18</td>
<td>29.7</td>
<td>10 (55.6)</td>
<td>11 (61.6)</td>
<td>11 (61.6)</td>
<td>11 (61.6)</td>
</tr>
<tr>
<td>Rasche et al., 2006</td>
<td>Ebel et al., 1996</td>
<td>17</td>
<td>49.7</td>
<td>1 (5.9)</td>
<td>4 (47)</td>
<td>5 (29.4)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>total‡</td>
<td>—</td>
<td>210</td>
<td>44/147 (29.9)</td>
<td>62/143 (43.4)</td>
<td>81/143 (56.6)</td>
<td>53/85 (62.4)</td>
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</tr>
</tbody>
</table>

* FU = follow-up.
† Indicates series published by the same group of authors but not included in our review.
‡ Values are not calculated out of 210 because evaluations were not the same across different studies and data on pain relief over the defined thresholds were not extractable in all studies.
Motor cortex stimulation for chronic neuropathic pain

had a “good postoperative outcome” (defined as a pain relief ≥ 40 or ≥ 50%, depending on the studies) and ~ 30% had ≥ 70% improvement with MCS (Table 1). When only the 152 patients with a follow-up ≥ 1 year were considered, 69 (45.4%) had a “good postoperative outcome.” In the 2 studies with the longest follow-up period (49 months in both), 472 and 22.6%20 of the patients experienced a long-term pain relief of ≥ 50%.

Of all the studies included in our analysis, individual pre- and postoperative VAS scores were either provided or could be calculated in only 76 patients.1,2,3,19 In these patients, the mean preoperative score was 8.3. Forty-one patients (53.9%) responded to the procedure with an average 56.6% improvement after MCS (pre- and postoperative mean VAS scores were 7.6 and 4.3).

Placebo Effect

Motor cortex stimulation usually does not induce perceptible sensations; this provides an ideal scenario for crossover placebo-controlled and blinded evaluations. Nonetheless, none of the studies included in our analysis were controlled. The only possible exception was an article in which the authors mentioned a double-blinded “on-off” evaluation but did not provide clear results.17 Few patients experienced pain recurrence after discontinuation of the stimulation either due to malfunction of the hardware (in 11 patients), the patient being unaware that the device was off,1,19 or to system removal (in 2 patients) after obvious infection.22,23

Rasche et al.22 used a double-blinded “on-off” stimulation trial after the electrodes were implanted to select patients who would receive a pulse generator for chronic stimulation. Of 17 patients, 3 showed no improvement in any condition (on or off), 6 experienced a similar degree of pain relief when the electrodes were on or off, and 8 were improved only during stimulation. In that context, a placebo effect was suggested to occur in 35% of the cases.

Results According to Origin and Location of Pain

Outcome according to the etiological diagnosis of pain is described in Table 2. To date, MCS has been used more commonly in patients with central pain (117 of 210 cases) after ischemic or hemorrhagic stroke in most cases, and for multiple sclerosis or trauma in rare cases. Another common indication was trigeminal neuropathic pain (44 patients). Far less frequently, MCS was offered to patients with spinal cord injuries (11 cases), plexus avulsions (13), phantom limb pain (10), postherpetic neuralgia (3), or pain resulting from other peripheral nervous system lesions (12). As can be appreciated in Table 2, conditions that improved the most were trigeminal neuropathic pain, phantom limb pain, and spinal cord injury. When a ≥ 1-year follow-up was considered, ~ 50% of patients responded to MCS independent of the condition treated.

Although the somatotopic positioning of the motor cortex electrodes over the cortical area corresponding to the location of the pain has been suggested to be important, the true value of this strategy is not known. Nevertheless, patients with lower limb pain are said to have a worse outcome with MCS, which has been attributed to the technical difficulties associated with implanting electrodes on the medial surface of the brain. In fact, only 12 patients who underwent treatment mainly for inferior limb pain were reported on in the studies pooled in our analysis.3,18–20,25 Six electrodes were implanted subdurally over the paracentral lobule, and 6 were epidural (close to the sinus). In contrast to what has been suggested, 50% of patients (6 of 12) with lower limb pain treated with MCS improved by > 40–50%. The causes of pain in these patients were poststroke pain (in 6), phantom limb pain (in 3), spinal cord injury (in 2), and peripheral nerve lesion (in 1 patient).

Surgical Technique

Surgical techniques vary considerably among surgical centers. In all studies a quadripolar electrode was placed over the precentral gyrus, either perpendicular to the central sulcus (8 studies) or parallel to it (3 studies). In 1 series, electrodes were implanted in both directions, and in another article the details on the surgical technique were not reported. Electrodes were epidural in 12 studies and subdural in 1.24–26 In 1 study, electrodes were implanted epidurally in most cases, except in patients with lower limb pain who received subdural electrodes.25 Electrodes were implanted either through a bur hole (7 studies) or

<table>
<thead>
<tr>
<th>TABLE 2: Long-term outcome of MCS according to the cause of pain*</th>
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<tbody>
<tr>
<td>Pain Syndrome/Etiology</td>
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<tr>
<td>------------------------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>central pain</td>
</tr>
<tr>
<td>TNP</td>
</tr>
<tr>
<td>spine injury</td>
</tr>
<tr>
<td>plexus avulsion</td>
</tr>
<tr>
<td>phantom limb</td>
</tr>
</tbody>
</table>

* Conditions for which < 10 patients underwent treatment are not listed in this table. Central pain includes patients with central poststroke pain and those with central pain due to multiple sclerosis or traumatic injury. Note that not all values are calculated out of the total number of patients per study because not all information was available in every study. Abbreviation: TNP = trigeminal neuropathic pain.
a small craniotomy (6 studies). In 1 series, the authors initially implanted MCS electrodes through bur holes but changed their technique due to adverse effects (2 epidural hematomas).

Preoperative and intraoperative localization of the motor cortex was usually achieved through a combination of techniques including: 1) neuronavigation in 7 studies; 2) functional MR imaging in 3; 3) perioperative somatosensory evoked potentials in 12; and 4) intraoperative cortical stimulation inducing contralateral motor responses in 14 studies. Because the technical aspects to target the motor cortex varied significantly across centers, we were not able to show any significant correlation between surgical technique and outcome.

Stimulation Parameters and Electrode Location

Stimulation parameters used for MCS varied considerably not only across studies, but also among patients treated in the same center. The most commonly used settings were 2–3 V (range 0.5–9.5 V), 25–50 Hz (range 15–130 Hz), and 200 μsec (range 60–450 μsec). It was not possible to establish a correlation between stimulation parameters and outcome because individual settings were not reported in several of the articles included in our analysis. Stimulation parameters were not systematically studied in all studies, and stimulation settings in nonresponders were rarely reported.

Chronic stimulation was usually conducted in a bipolar configuration. Two series with electrodes implanted perpendicular to the central sulcus reported that cathodes were placed over the precentral gyrus. The exact location of the electrodes assessed by postoperative MR imaging or CT scans was only reported in 3 studies (10 patients). In 7 patients, postoperative imaging studies were obtained because the patients did not benefit from the procedure and the authors wanted to rule out electrode misplacement. In other patients, electrodes were supposed to be located in a region corresponding to that targeted preoperatively with an image-guided system and confirmed with intraoperative cortical stimulation. The anteroposterior placement of the active contacts relative to the central sulcus was not provided.

Adverse Effects

Adverse effects were systematically reported in 10 series, in which 157 patients were treated with MCS (Table 3). The most common adverse effects were hardware-related problems (in 5.1%) and infections (in 5.7%), and usually required the removal of parts of or the entire MSC system. Seizures, occurring during the operation or the postoperative stimulation trial, were reported in 19 patients (12%). It is important to note however, that no seizures or epilepsy have been reported after long-term follow-up. Two patients developed transient postoperative neurological complications (1 speech disorder and 1 motor deficit), and 2 had speech disturbances that lasted several months and finally resolved. Two epidural and 2 subdural hematomas were also reported.

Three patients died during the follow-up period. One had a pulmonary embolism following the evacuation of a subdural hematoma that occurred after an MCS electrode was revised 6 months after the original surgery. Two patients with poststroke pain died of intracerebral hemorrhages several months after MCS (the relationship between these events and the surgical procedure is unclear).

Discussion

According to the main studies published in the literature to date, MCS appears to be relatively safe and effective in the treatment of medically refractory neuropathic pain in certain patients. Overall ~ 56.7% of patients had a “good outcome” (≥ 40–50% improvement) after surgery. These results, however, must be considered with caution for several reasons. First, the total number of studies including nonrepetitive clinical series was relatively low. In addition, in each of these series the authors only reported results in 3–31 patients. This could be especially problematic when the interpretation of MCS results for less frequent indications is considered (such as phantom limb pain or plexus avulsion). Another caveat of the studies pooled for analysis in our review was that almost all of them were retrospective series of cases with no controlled arms. This lack of controlled trials might contribute to an overemphasis on the proportion of patients who responded to the procedure. Rasche and colleagues suggested that under double-blinded “on-off” stimulation conditions, a placebo response with > 50% improvement in pain scores might occur in 35% of patients undergoing treatment with MCS. Moreover, one could speculate that small series with negative results might not have been submitted or were less likely to have been accepted for publication due to a potentially negative bias against such results. Another feature that deserves consideration is the relatively short follow-up period in most studies, which may also have led to an overestimation of the results. In the 152 patients with ≥ 1-year follow-up, 45% of patients had a good outcome with MCS, in contrast to the 57% of patients having similar results with the procedure. Long-term loss of efficacy has occasionally been observed in patients who had an initial good outcome.

### TABLE 3: Reported complications of MCS in the treatment of neuropathic pain

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>infection</td>
<td>9</td>
</tr>
<tr>
<td>wound problem/hardware dysfunction</td>
<td>8</td>
</tr>
<tr>
<td>intraop or trial stimulation period seizure</td>
<td>19</td>
</tr>
<tr>
<td>long-term seizure/chronic epilepsy</td>
<td>0</td>
</tr>
<tr>
<td>subdural hemorrhage</td>
<td>2</td>
</tr>
<tr>
<td>epidural hemorrhage</td>
<td>2</td>
</tr>
<tr>
<td>transient neurological deficit (&lt;1 mo)</td>
<td>2</td>
</tr>
<tr>
<td>long-lasting neurological deficit</td>
<td>2</td>
</tr>
<tr>
<td>local pain/headache</td>
<td>5</td>
</tr>
</tbody>
</table>

* Data obtained in 10 studies in which 157 patients underwent MCS and complications were systematically reported.
Other potential sources of variability stem from the differences in surgical techniques across studies, and variable stimulation settings and electrode locations, not only across centers but also in patients treated in the same surgical center. This would not be a so much of a confounding factor if the electrode locations and the stimulation settings used at different centers, and consequently the current spreading, could be compared. Modeling studies have shown that the effect of electrical stimulation on the neuronal structures lying within the precentral gyrus and central sulcus varies widely according to the respective locations of the anode, cathode, and isopotential lines. These models suggest that the location of the electrodes over the motor/premotor cortices might be important to the efficacy of MCS. Unfortunately, this factor has been insufficiently studied in the past. Also lacking are predictive factors for a good outcome with MCS. Although in the past, pharmacological classification of pain, motor impairment, sensory changes in the painful zone, or response to repetitive transcranial magnetic stimulation have been proposed as potential predictive factors, none of these has been further confirmed in larger studies.

The efficacy of MCS must also be considered in the light of the severity of disease in the patients who underwent the procedure. Their pain was extremely severe, as reflected by a mean preoperative VAS score of 8.3/10, and the failure of all other treatment modalities in bringing any important and sustainable pain relief to these patients. In this context, it is difficult to establish what might be considered a “good outcome” (for example, a 30% decrease on VAS scores could be associated with a significant improvement in quality of life in some patients). As another example, Nuti et al. reported that 8 of 11 patients who had a poor result, namely pain relief of 10–39%, answered positively to the question “would you accept the surgery again?” In addition, it was possible to reduce medication doses in several of these patients. Few studies used multidimensional pain scales and none used scales measuring quality of life. Brown and Pilitsis reported that in 6 responders, the McGill Pain Questionnaire total pain-rating index was decreased by 55% at 10 months. In the study by Nguyen and colleagues, 43.7% of 31 patients treated with MCS reported improvement in activities of daily living.

Conclusions

Despite the multiple biases we discussed, our literature analysis shows that MCS may significantly improve symptoms in patients with severe and medically resistant pain, for whom no other treatment is currently available. Considering the encouraging results of previous series on one hand, and the invasiveness and cost of the procedure on the other, a double-blinded, placebo-controlled randomized study is now mandatory to evaluate the actual efficacy of MCS. The design of such a study will have to take into account the clinical characteristics of the MCS response, including: 1) the variable time intervals between turning on the electrodes and the onset of a clinical response; 2) the carry-over effect that might occur when the electrodes are turned off; and 3) the need for prerandomization stimulation trials to assess the most effective parameters for each patient. Potential prognostic factors will have to be studied to improve the selection of patients.

Disclaimer

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

References

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