Motor cortex stimulation for deafferentation pain

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Object. The authors tested a modified motor cortex stimulation (MCS) protocol for the treatment of deafferentation pain in 15 patients: eight patients with poststroke pain, four with brachial plexus injury, two with phantom limb pain, and one with spinal cord injury.

Methods. Preoperative pharmacological tests were performed with phentolamine, lidocaine, ketamine, thiopental, morphine, and a placebo. In 12 patients we placed a 20- or 40-grid electrode in the subdural space to determine the best stimulation point for pain relief over a few weeks and therefore the optimum position for a permanent internal device. In four patients, the MCS devices were implanted in the interhemispheric fissure to reduce lower-extremity pain. In one patient, the MCS device was placed within the central sulcus, and a 20-grid electrode was placed on the brain surface. In two patients with pain extending from the upper extremity to the hyperbody, dual-electrode devices were implanted to drive two electrodes. In 10 of the 15 patients MCS-induced pain reduction was achieved (four with excellent, two with good, and four with fair alleviation of pain). The result of pharmacological testing indicated that patients with ketamine sensitivity seem to be good candidates for MCS.

Conclusions. Test stimulation with a subdural multigrid electrode was helpful in locating the best stimulation point for pain relief.

KEY WORDS • motor cortex stimulation • thalamic pain • phantom limb pain • brachial plexus injury

Deafferentation pain, including poststroke pain, brachial plexus injury–related, SCI-related, and phantom limb pain, has been the most difficult type of pain to control with medication.22 Thalamic stimulation is reported to relieve deafferentation pain in some cases, and although electrode implantation is a complicated procedure, the efficacy rate has not been unsatisfactory.7,10,11,23 As an alternative treatment to thalamic stimulation, Katayama, et al.,9 have reported the use of chronic MCS which they found relieved pain in approximately 50% of their patients with thalamic pain. Meyerson, et al.,13 have demonstrated that facial deafferentation pain also can be decreased using MCS. We have reported the effective use of MCS for treating peripheral deafferentation pain (brachial plexus injury and phantom limb pain).20

In several previous reports concerning MCS, the stimulation point was determined by epidural test stimulation after administering a local anesthetic.9,15,24 Limited operative time, however, can interfere with determining the most effective point for reducing pain. Epidural electrodes may require relatively high voltage for pain relief when the stimulated cerebral hemisphere is atrophic. Thus, we used a different protocol in which, after induction of general anesthesia, a 20-grid electrode is placed in the subdural space overlying the motor and sensory cortices. Various stimulation patterns are tested over a few weeks, after which patients in whom MCS-induced pain relief has been demonstrated undergo implantation of a permanent MCS system at the position determined most effective at yielding pain relief. In one patient with SCI, we implanted the device within the central sulcus.

In some prior reports of preoperative pharmacological tests of pain relief the authors have suggested that thiopental- and ketamine-responsive and morphine-resistant patients receive a lasting benefit from chronic MCS.26 We examine correlations between pharmacological testing results and the efficacy of stimulation by using a slightly different protocol.

CLINICAL MATERIAL AND METHODS

Patient Population

Fifteen patients with central and peripheral deafferentation pain were treated with MCS at Osaka University Hospital and Osaka Rosai Hospital between January 1996 and May 2001 (Table 1). There were 13 men and two woman...
patients who ranged in age from 50 to 68 years. Six patients had suffered thalamic hemorrhage; one, putaminal hemorrhage; one pontine hemorrhage; four, brachial plexus injury; one, SCI; and two experienced phantom limb pain. In the patients in whom hemorrhages had occurred posthemorrhagic lesions were clearly identifiable on MR imaging or computerized tomography scanning. The interval between hemorrhage and the onset of pain ranged from 0.5 to 4 years. The patients had been treated with various medications including nonsteroidal antiinflammatory drugs, anticonvulsants, and antidepressants. These drugs in various combinations failed to alleviate pain sufficiently.

All patients with central pain also suffered varying degrees of hemiparesis. They complained of intense spontaneous pain in the extremities or trunk, with a burning or tearing sensation. Various degrees of pinprick hypesthesia were demonstrated in all patients except those with phantom limb pain. No patients in whom psychological assessment showed severely depressive or neurotic tendencies were included in the study.

Pharmacological Tests

In an attempt to clarify the pathophysiological mechanisms and determine drug-related responses in these patients, we performed preoperative pharmacological tests including administration of phentolamine (0.17 mg/kg/hr for 3 hours), lidocaine (0.5 mg/kg, given as an initial dose, then 1 mg/kg/hr of continuous administration for 3 hours), ketamine (0.17 mg/kg/hr for 3 hours), thiopental (0.5 mg/kg twice, 30 minutes apart), morphine (3.3 mg/hour continuously for 3 hours), and placebo (saline solution, 5 ml as the initial dose, then 0.1 ml/kg/hr for 3 hours). In the patient in Case 2, morphine was contraindicated because of asthma, and fentanyl citrate was substituted. To evaluate the analgesic effects of these drugs on ongoing pain, we had the patients respond to a VAS hourly for 6 hours except after the administration of thiopental. In this case, the VAS was used before and soon after administration of the drug. If the VAS score indicated that pain was reduced to 60% or less of the preinfusion level, pain was considered significantly reduced.

Pain Assessment

Changes in pain level were evaluated in each patient by a physician at a pain clinic not affiliated with our department. More than 20 different stimulatory patterns were evaluated with use of the grid electrodes to determine the optimum stimulation point for pain relief. Each patient was asked to describe pain intensity by responding to a VAS and the McGill Pain Questionnaire. The effects of stimulation were classified into four categories, based on reduction in pain from the prestimulation level: excellent, 80 to 100% reduced; good, 60 to 79% reduced; fair, 40 to 59% reduced; and poor, less than 40% reduced. The pain level was evaluated after a 30-minute stimulation period enacted no more than three times a day during the test period.

Surgical Procedures

The location of the central sulcus was approximated by performing preoperative MR imaging. After induction of general anesthesia, a skin incision was made in a location appropriate to the pain site. A craniotomy was performed over a 5 × 6-cm area, overlying the motor and sensory cortices, except in four patients complaining of leg pain in whom craniotomy was performed in the area overlying the superior sagittal sinus. In 11 patients, a 20-grid electrode was placed subdurally (4 × 5 array; 0.3-cm-diameter electrode; 0.7-cm separation; Unique Medical Co., Tokyo, Japan). In one patient with thalamic pain (Case 4) a 40-grid electrode was placed. In one patient another device was placed in the central sulcus (Fig. 1). The four patients with leg pain underwent placement of an electrode in the interhemispheric fissure (0.4-cm-diameter, 0.6-cm separation; Medtronic, Inc., Minneapolis, MN). The devices were placed in the interhemispheric fissure from the parietal or prefrontal directions, depending on the development of cortical veins. In cases in which the 20-electrode grid was implanted, locations of pre- and postcentral gyri were confirmed from phase reversal of the

### Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age (yrs)</th>
<th>Disease</th>
<th>Pharmacological Tests (positive drugs)</th>
<th>Result of Test Stimulation</th>
<th>Outcome* (mos)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>M, 68</td>
<td>thalamic hemorrhage</td>
<td>thiopental</td>
<td>poor</td>
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<tr>
<td>2</td>
<td>M, 60</td>
<td>putaminal hemorrhage</td>
<td>lidocaine, ketamine, fentanyl</td>
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<td>thalamic hemorrhage</td>
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<td>fair</td>
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<td>none</td>
<td>poor</td>
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<tr>
<td>6</td>
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<td>none</td>
<td>fair</td>
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<tr>
<td>8</td>
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<td>thalamic hemorrhage</td>
<td>lidocaine, ketamine, thiopental</td>
<td>excellent</td>
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<tr>
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<td>10</td>
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<td>brachial plexus injury</td>
<td>morphine, ketamine, thiopental</td>
<td>good</td>
<td>poor (36)</td>
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<tr>
<td>11</td>
<td>M, 62</td>
<td>phantom limb pain</td>
<td>morphine, ketamine, thiopental</td>
<td>excellent</td>
<td>excellent (40)</td>
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<tr>
<td>12</td>
<td>M, 64</td>
<td>brachial plexus injury</td>
<td>morphine</td>
<td>excellent</td>
<td>excellent (36)</td>
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<tr>
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<td>morphine</td>
<td>fair</td>
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<td>morphine</td>
<td>fair</td>
<td>fair (36)</td>
</tr>
<tr>
<td>15</td>
<td>M, 66</td>
<td>brachial plexus injury</td>
<td>morphine</td>
<td>poor</td>
<td>NA</td>
</tr>
</tbody>
</table>

* NA = not available.
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Fig. 1. Schematic drawing showing a four-electrode array that was positioned within the central sulcus, in addition to a 20-grid electrode placed on the brain surface. Broken arrows indicate the most effective position for pain relief (VAS scores from 8 to 1). Narrow arrows indicate slightly effective (VAS scores from 8 to 5 or 6). Broad arrows indicate minimal effectiveness. The central sulcus was identified by surface anatomy visualization using MR imaging and intraoperative SSEP monitoring.

RESULTS

In 10 of the 15 patients various degrees of pain control in test stimulations were shown (Table 1). In the other five, more than 20 different patterns of stimulation on the 20-grid electrode were attempted without successful reduction of pain. Stimulation of the precentral gyrus within the central sulcus provided excellent pain relief in the patient in Case 9 (Fig. 1). When electrodes were placed in the interhemispheric fissure, possible electrode positions were limited. With the grid electrode, more than 20 different stimulatory patterns were evaluated in 12 patients to determine the best point for pain relief. In each patient in whom a response was successfully elicited, several stimulation points were effective, and pain relief was achieved even with stimulation of the sensory cortex. In the patients in Cases 2, 6, 11, and 13, the electrode grids were positioned in proximity to the motor cortex corresponding to the affected lower extremities.

In the patient in Case 10 the epidural electrode provided decreasing levels of relief over time. After approximately 6 months, the electrode was replaced in the subdural space just under the previous site, and the original degree of effectiveness returned when a lower voltage was delivered. Granulation tissue had proliferated under the epidural electrode. After a year, the patient complained that stimulation failed to alleviate his pain. Therefore, deep brain stimulation was performed, and the effect was described as good. In one patient (Case 4) a subdural effusion developed after implantation of MCS system but disappeared spontaneously.

Of the 15 patients, six in whom excellent or good MCS-induced pain relief was achieved had morphine (four cases [one was a fentanyl substitute] patients), ketamine (four cases), thiopental (three cases) or lidocaine (two cases) sensitivities. The nine patients with fair or poor pain relief had morphine (three cases), and thiopental (one case) sensitivities. No relations were found between morphine and MCS-induced pain relief, and in no case was a patient phentolamine sensitive. Based on these findings, a patient’s response to ketamine might be critical to anticipating the effectiveness of the MCS for deafferentation pain (Table 1).

The patient in Case 4 complained of pain extending from the upper extremity to the hip, and the patient in Case 13 suffered phantom foot pain and stump pain, a distribution difficult to treat completely using a single electrode. The Mättrix dual-electrode system was implanted after confirmation of the most effective stimulation points, and it brought relief of pain. The patient in Case 13 feared convulsions, and the stimulation system was removed after 6 months.

In the patients in Cases 8, 11, and 12 pain relief was demonstrated for 24 hours with 30 minutes’ stimulation. In contrast, in the patients in Cases 10 and 13 pain relief was sustained for only approximately 1 hour after stimulation. In the others pain relief was demonstrated for 3 to 5 hours. Follow-up study on an outpatient basis was conducted for 6 to 40 months. Two patients (Cases 4 and 12) suffered a cerebral hemorrhage: one patient (Case 4) is now in a vegetative state; and one patient (Case 12) died 36 months after implantation of the MCS system.

DISCUSSION

In previous reports numerous authors have described the implantation of an epidural MCS device over the pre-
Circumstances. We chose to test a two-stage procedure in which we typically placed a 20-grid electrode over the sensorimotor cortex to test various geometric patterns of stimulation to determine the optimum pattern for pain relief. In the first stage, the MCS device was implanted within the central sulcus in addition to the 20-grid electrode. The most effective stimulation site was found to be within the central sulcus. The second stage was implantation of the permanent system for chronic stimulation based on the results of the first stage.

A number of questions remain concerning mechanisms, indications, implantation strategies, and further technical developments in MCS. We estimated the location of the central sulcus by performing preoperative MR imaging and intraoperative SSEP assessments. Some differences were noted between the morphologically MR imaging–identified central sulcus and the site of N20 reversal. These discrepancies underscore the need for test stimulation with an electrode grid prior to placement of the permanent system for chronic stimulation.

Optimum placement and orientation of the MCS system in relation to the motor cortex has not yet been established. In our test stimulations, stimulation of the prefrontal cortex with grid electrode failed to reduce pain in all 10 cases, whereas stimulation of the sensory cortex was able to reduce pain slightly. In all 10 cases treated successfully by stimulation, the best stimulation site for pain relief was on the precentral gyrus and within the central sulcus. In our series, the duration of pain relief with a 30-minute period of stimulation was from 1 to 24 hours. This wide variation in the period of pain relief may be explained by several factors, including the results of pharmacological tests, the original pathological entities, and the stimulation point.

A VAS was used to evaluate the stimulation effect in our study. In the test stimulation with a grid electrode, patients were repeatedly and randomly asked to score the effect according to the VAS at stimulation, and the results were fairly consistent. The patients described whether the pain was better or worse than that before stimulation, and they rated the intensity and quality of the pain according to the McGill Pain Questionnaire before and after stimulation. The VAS–indicated changes for each patient seemed to be reliable. Testing with an grid electrodes can control for psychological effects.

Several groups have favored epidural placement of electrodes for MCS because it is thought to minimize invasiveness. In one of our patients, however, an epidural electrode lost its effectiveness over a 6-month period. When the electrode was moved to the subdural space during a second operation, epidural granulation tissue was found beneath the electrode. After moving the electrode, pain could again be reduced and with a lower voltage than that used in the original electrode position. One patient’s surgery was complicated by subdural effusion. No other procedure-related complications were noted.

Yamamoto, et al., have reported that thiopental- and ketamine-responsive and morphine-resistant patients, long-lasting pain reduction is demonstrated with long-term use of MCS. Unfortunately, our patient population was too small to confirm an apparent correlation between pharmacological responses and the effectiveness of MCS. Based on our pharmacological tests, ketamine might be a critical drug to use for anticipating the effectiveness of MCS for deafferentation pain. Two of four patients with excellent pain relief, however, did not respond to any drug. Our pharmacological tests are different from those used in previous protocols. A uniform method of pharmacological testing is needed.

Evaluation of our present results suggests that MCS can be effective for both peripheral and central deafferentation pain. Although it has been reported effective for facial deafferentation pain, it has been rarely studied in phantom limb pain or brachial plexus avulsion. Phantom limb pain is a very rare symptom for which several medical and surgical approaches have been pursued. Postcentral stimulation of appropriate areas actually can exacerbate phantom limb pain in some patients. Even after excision of cortical or thalamic areas, phantom limb pain tends to recur in time. Resection of a dorsal root entry zone lesion reportedly is effective in 60 to 70% of cases with brachial plexus avulsions. Motor cortex stimulation, however, is less invasive than the latter procedure. Notably, the patient in Case 10 did not respond after resection of the dorsal root entry zone but responded well to MCS.

Motor cortex stimulation has been effective in approximately 50% of the patients with central deafferentation pain in the largest published series, together with many other reports. Our success rate is similar to that reported by others. In one of our patients with SCI whose pain did not respond to any drug in drug challenge tests, stimulation of prefrontal gyrus within the central sulcus was very effective for relieving upper-extremity pain. We plan to continue using and evaluating chronic MCS within the central sulcus. This strategy may improve the success rate for treatment of patients with deafferentation pain.

References

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Manuscript received July 9, 2001. Accepted in final form August 15, 2001. Address reprint requests to: Youichi Saitoh, M.D., Ph.D., Department of Neurosurgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871 Japan. email: saitoh@silver.ocn.ne.jp.