Motor Cortex Stimulation

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ABSTRACT

Motor cortex stimulation represents a paradigm shift in our understanding of the options available for treatment of both motor and somatosensory syndromes including central and neuropathic pain, weakness after stroke, Parkinson’s disease, and tinnitus. Extensive clinical information over the past 15 years is now available on the beneficial effects on intractable central and neuropathic pain, especially facial pain. More recently, there is preclinical and clinical evidence of its benefit in treating Parkinson’s disease. Clinical applications of epidural cortical stimulation in conjunction with rehabilitation to enhance recovery from motor weakness after stroke now exist. There is potential benefit suggested in the treatment of intractable tinnitus with implanted cortical electrodes. Non-invasive transcranial magnetic stimulation may also be useful to screen patients for treatment by electrode implantation in these entities. This article reviews the current status of applications of cortical stimulation in each of these areas.

Key Words. Motor Cortex Stimulation; Neuropathic Pain; Parkinson’s Disease; Herpes Zoster

Introduction

Motor cortex stimulation has become of interest in a number of clinical applications since its introduction into practice 15 years ago. In this article, the use of motor cortex stimulation will be reviewed first for its benefit in the treatment of central and neuropathic pain syndromes—areas that have been most extensively studied. Other emerging areas of use include its effect on recovery from stroke, improvement from symptoms of Parkinson’s disease and, most recently, in reduction of symptomatic tinnitus, which will also be discussed. Finally, the use of transcranial magnetic stimulation will be touched on as well.

Motor Cortex Stimulation for Pain

Motor cortex stimulation has been used for the treatment of central and neuropathic pain syndromes since 1991. It is a form of neuromodulation that is indicated most commonly for thalamic, putaminal, and lateral medullary infarction, traumatic trigeminal neuropathy, postherpetic neuralgia, brachial plexopathy, and neuropathic spinal cord or phantom limb pain. In the initial publication, Tsubokawa et al. achieved good to excellent pain relief in seven patients with medically intractable thalamic pain [1]. Ensuing articles have since clarified the indications, operative techniques, and results from motor cortex stimulation surgery as now performed worldwide [2].

Indications

Motor cortex stimulation is best indicated for medically unresponsive central and neuropathic pain. Candidates for this surgery have all failed extensive efforts at medical treatment. Trigeminal nerve injury at the level of the peripheral nerve branches, ganglion, or root is a common indication. Postherpetic facial neuralgia and central pain after thalamic or lateral medullary stroke are indications for treatment, as well as phantom limb pain and neuropathic spinal cord injury pain that may be one-sided or bilateral. Trigeminal neuralgia is not an indication, although other forms of neuropathic trigeminal pain are indications for treatment. Brachial plexus injury is an indication, but there have only been scattered case reports...
regarding motor cortex stimulation for complex regional pain syndromes or for failed spinal cord stimulation.

Cortical stimulation is not indicated when there is epilepsy present or if there is significant risk from discontinuing anticoagulation therapy for surgery. Personality disorders such as severe depression or psychotic disorders need to be screened for by a preoperative neuropsychological evaluation. Inabilities to adequately communicate the nature of the pain because of a stroke or dementia are also contraindications.

**Surgical Technique**

All centers now use neuronavigational techniques for placement of electrodes. Some centers are also able to integrate functional magnetic resonance imaging (MRI), especially for hand localization [3–7]. The target is selected on the primary motor cortex based on somatotopic anatomic landmarks. The target for facial pain is located anterior to the central sulcus at the level of the inferior frontal sulcus as seen on the sagittal MRI or computerized tomography (CT), for example (Figure 1). A light, general endotracheal anesthesia is induced in preparation for a 4 x 4-cm craniotomy that is centered on the target site. After completing the craniotomy, the central sulcus at the level of hand function may be identified using median nerve somatosensory evoked potentials and determination of N20–P20 phase shift. Cortical mapping is then performed. Electromyographic recordings during cortical stimulation in the target muscles of the region of pain determine the site of maximal electromyographic response to stimulation. One or two four-plate electrode paddle arrays are sutured to the dura, parallel or perpendicular to the central sulcus, overlying the primary motor cortex. Often, patients have residual pain relief from the intraoperative stimulation that persists for hours after emerging from anesthesia. The electrode leads are tunneled to a subclavicular exit pocket where leads that are able to be externalized are connected.

Several days of trial stimulation then proceed. When pain relief is substantial or at least greater than 50%, the pulse generator is implanted in a second procedure. Stimulation below the threshold for muscle activity relieves pain. Stimulation parameters vary, but are usually at a low frequency (40 Hz), low pulse width (90 ms), and low amplitudes (2–10 V). Some centers target stimulation amplitude at a percentage of motor threshold [8]. More difficult to treat pain syndromes (such as anesthesia dolorosa) often require higher energy delivery.

Programming of motor cortex stimulation is different from the programming commonly done for spinal neurostimulation. Because the stimulation parameters are subthreshold and based on the motor system, there are no detectable paresthesias to guide one to the best level of stimulation. Optimal stimulation is that level of stimulation that provides the best pain relief, yet does not cause a seizure, pain from dural stimulation, or electromyographic activity. Empirical starting parameters for amplitude are 2–4 V.

Stimulation may be intermittent or continuous. To preserve battery life, some patients turn the pulse generator off while sleeping. Pain recurs shortly after stopping stimulation, making rechargeable systems appropriate in the chronic conditions being treated.

Tsubokawa and colleagues first published their series of 11 patients with central pain treated with motor cortex stimulation at 2-year follow-up in 1991. More than 80% pain relief was maintained in 5 of the 11 patients [9]. Meyerson was later able to relieve more than 50% of pain in 5 out of 10 patients in his series, but only in those patients who had trigeminal neuropathic pain. He noted that the patients with good pain relief also had reduced allodynia, dysesthesia, and hyperaesthesia.
during periods of stimulation [10]. Katayama et al. treated four patients with motor cortex stimulation who no longer benefited from deep brain stimulation of the ventroposterolateral thalamic relay nucleus for their pain relief. These patients then reported 40–60% pain relief. Another patient whose ventroposterolateral nuclear stimulation was unsuccessful went on to receive relief with motor cortical stimulation [11].

Later studies have improved upon the surgical technique and led to better treatment results. Nguyen et al. mapped the epidural stimulation sites that led to the best pain relief, correlating them with their somatotopic location. In 12 patients with medically intractable neuropathic facial pain, Nguyen et al. achieved good to excellent pain relief in 75% of patients [11,12]. Pain relief was also obtained in 10 out of 13 patients (77%) with central pain. Most series focused on a unidimensional pain analysis to report their results. When a multidimensional index of pain was used, pain was observed to decrease by a mean of 55% in 10 patients with neuropathic facial pain treated with motor cortex stimulation and evaluated for a mean period of 10 months. Concurrently, pain medication requirements diminished by 50% in this group of patients with an average pain duration before surgery of 6 years [13].

The precise mechanism for the effectiveness of motor cortex stimulation in relieving pain remains unknown. Studies have demonstrated that motor cortex stimulation leads to an increase in cerebral blood flow in the ipsilateral thalamus, cingulate gyrus, orbitofrontal cortex, and midbrain. The extent of pain relief correlates best, however, with anterior cingulate gyrus blood flow. Functional MRI studies suggest that the cingulate gyrus is involved in the suffering element of chronic pain and this target may be the source of pain relief with cortical stimulation [14,15]. Recently, laboratory studies have also examined the effect of motor cortex stimulation on the somatosensory system. They show that selective reduction occurs in spinal cord dorsal-horn neurons’ responsiveness to pinch but not to brush stimuli. When stimulation is stopped, the effect on dorsal spinal cord neurons ceases. Two mechanisms for this diminished responsiveness are hypothesized. There may be either direct activation of inhibitory interneurons in the spinal cord or indirect inhibition during stimulation [16]. Additionally, in their series of 31 patients, Nuti et al. found that the level of pain relief, as evaluated in the first month following implantation, to be the strongest predictor of long-term relief [17]. There was no correlation with the presence of motor function as had been suggested by Katayama et al. [18].

Motor cortex stimulation improves motor function, not just pain control. Improved thalamic hand syndrome, spasticity, action tremor, intention myoclonus, advanced Parkinson’s symptoms, and motor functional recovery after stroke have been observed after intermittent or constant stimulation [19–24]. Discriminative sensation has also been seen to improve during cortical stimulation. This may occur because motor cortex stimulation inhibits the conduction block to sensory input created by the thalamic hyperactivity that develops with deafferentation [13].

Motor Cortex Stimulation for Stroke Recovery

Recent multicenter studies test the hypothesis that subthreshold cortical stimulation of primary motor cortex involved in producing residual motion in an impaired limb after a nonhemorrhagic cortical or subcortical infarction enhances motor recovery [24]. In the first successful case that was reported, a 65-year-old man with a subcortical ischemic infarct and right spastic hemiparesis occurring 19 months before treatment underwent subthreshold epidural motor cortex stimulation that was delivered during a rehabilitation program that constrained use of the most functional limb. Whereas, before stimulation, the patient’s stroke-affected arm rested in a flexion posture without the ability to flex or extend the fingers, and after stimulation and rehabilitation, he was able to grasp a pen and to write letters. The Fugl–Meyer motor scale score, a measurement of hand/arm function based on a 100-point scale, improved from 36 to 46. This improvement was sustained for 4 weeks after conclusion of the rehabilitation therapy, as far as the study evaluated function [24].

A prospective, randomized, multicenter study of safety of subthreshold motor cortical electrical stimulation of patients with motor deficit resulting from a stroke that occurred at least 4 months prior to enrollment has since been completed [25]. Patients in this study were randomized into two treatment groups. One group underwent an electrode implant and subsequent epidural electrical stimulation (at 50 Hz and 50% of the current needed to evoke gross motor movement) during 3 weeks of constrained limb rehabilitation. A control group of stroke patients received the same 3 weeks of rehabilitation but did not undergo
implantation. Before surgery, the site for hand function was identified on a functional MRI protocol. This activation site was integrated into a neuronavigational workstation. During surgery, a craniotomy was performed over the targeted site and transdural electrical stimulation was done to find electromyographic evidence for activation of the hand/finger sites. An electrode grid was sutured to the dura with the center of the grid over the point deemed to be the center of the MRI “hot spot.” The electrode lead was then tunneled to a supraclavicular exit site and the bone flap replaced. Rehabilitation began 1 week later. Control patients did not undergo device implantation but did complete the same rehabilitation protocol as the treatment patients.

During each rehabilitation session, stimulation was begun at 50% of the amplitude needed to reach the threshold for movement or 6.5 mA if no movement was obtained. The mean time since stroke was 18 ± 18 (9–33) months in the surgical group and ±38 (15–68) months in the control group. Of the eight patients completing surgical implantation and/or rehabilitation, the stimulation plus rehabilitation group improved significantly better than controls in the upper extremity Fugl–Meyer score (P = 0.003 overall), and the hand function score of the Stroke Impact Scale (P = 0.001 overall). The Fugl–Meyer scale is a scale of hand function based on a norm of 100. In an intention to treat analysis, scores were also analyzed using all available serially collected Fugl–Meyer data for all 10 patients entered into the study, including all available data from 2 patients who dropped out of the study due to infection. The difference between treatment groups remained significant (P = 0.027). Improvements persisted through the 12-week follow-up assessment (study week 16). In comparison, lesser improvements in control patients occurred within the first 2 weeks and then seemed to decrease over time.

This improvement in function may be because of cortical reorganization. Another explanation is that there is inhibition of regions that have developed hyperactivity after stroke, which then confound effective motor function or retraining. For example, Tsubokawa et al. noted an inhibitory effect from cortical stimulation on thalamic hyperactivity by motor cortex stimulation in a cat deafferentation model wherein the spinothalamic tract had been sectioned [1]. Garcia-Larrea et al. observed regions of increased blood flow when viewed with positron emission tomography during motor cortex stimulation of patients with central pain syndromes. The most significant increase in regional cerebral blood flow was seen in the ventral lateral thalamus. This may occur because of corticothalamic projections from motor areas [14]. It could reflect direct enhancement of motor output or secondary enhancement of this region from inhibition of other regions. How the hypothesis of thalamic inhibition during cortical stimulation fits in with these identified sites of increased regional cerebral blood flow is not known.

Functional enhancement persists after withdrawal of cortical stimulation, as seen both in preclinical and clinical studies [26]. This suggests that the motor improvement represents more than direct enhancement of surrounding marginally functional cortical neurons. It also suggests that the improvement is not an indirect result of inhibition of confounding regions of hyperactivity. During intraoperative cortical mapping, individual finger contractions occurred, movements that were not present before stimulation through voluntary effort. The combination of rehabilitation and stimulation may enhance the plasticity of marginally effective circuits, leading to improved voluntary function. Thus, preliminary motor assessment data shows that intermittent cortical stimulation delivered during periods of rehabilitation activity enhances upper extremity functional recovery when compared with control groups of patients who receive only rehabilitation [25].

**Motor Cortex Stimulation for Parkinson’s Disease**

Recently, there has been evidence that motor cortex stimulation either by implanted epidural electrodes or transcranial magnetic stimulation may improve motor function in Parkinson’s disease. An early case report appeared in 2000 [27]. In a preclinical study of electrical interference in the primary motor cortex using a chronic MPTP primate model in which dopamine depletion was progressive as measured by using 18F-dihydroxyphenylalanine (DOPA) positron tomography, high-frequency motor cortex stimulation significantly reduced akinesia and bradykinesia. This behavioral benefit was associated with an increased metabolic activity in the supplementary motor area as assessed with an 18-F-deoxyglucose positron emission tomography (PET), a normalization of mean firing rate in the internal globus pallidus (GPI) and the subthalamic nucleus (STN), and a reduction of synchronized oscillatory neuronal activities in these two structures [22]. Several clinical series of epidural cortical stimulation for
Parkinson’s disease have been published. Most recently, 10 patients in one series received unilateral, subthreshold extradural motor cortex stimulation (2.8 Volt, 100–400 microsec., 20–120 Hz) by chronically implanted epidural electrodes. Patients were evaluated at 3–30 months after implantation. Findings included a reduction in levodopa dosage by 50%. Motor improvement as measured on the standard Unified Parkinson’s Disease Rating Scale (UPDRS) ranged from <25% to 75% in 9 out of 10 patients. Dyskinesias, motor fluctuations, and other secondary effect of levodopa administration psychiatric symptoms improved. Improvement was observed also in those with disabling motor fluctuation and dyskinesias. These could be abolished [28].

Motor Cortex Stimulation for Intractable Tinnitus

Tinnitus affects up to 15% of the population for whom no satisfactory treatment exists. Tinnitus may be an auditory phantom phenomenon similar to deafferentation pain. It is accompanied by a change in the map of the auditory cortical tones. There is a highly positive association between the subjective intensity of the tinnitus and the amount of shift in tinnitus frequency in the auditory cortex, a form of cortical reorganization that can be demonstrated by functional MRI. After transcranial magnetic stimulation screening, an epidural electrode was implanted in one patient over the contralateral primary auditory cortex using auditory functional magnetic imaging navigation. Tinnitus disappeared and remained absent 10 months later. Transcranial magnetic stimulation may also be a useful noninvasive way of screening surgical candidates [29].

Transcranial Magnetic Stimulation

Noninvasive approaches to cortical stimulation for stroke recovery enhancement have also been investigated. Transcranial direct current stimulation used in a double-blind protocol on motor regions of a stroke-affected hemisphere caused improvements in pinch force, hand function as measured by a well-validated test for functional motor assessment that reflects activities of daily living, and simple reaction times in the paretic hand. Improvements persisted beyond the stimulation period for at least 40 minutes. The improvements were associated with reduced cortical inhibition to transcranial magnetic stimulation. This raises the possibility of further study of noninvasive transcranial cortical stimulation to enhance stroke recovery [30–32].

Conclusion

Much has been learned in the 15 years since this relatively safe and simple technique was introduced in the treatment of central pain syndromes. Cortical stimulation represents a paradigm shift in our approach to the treatment of pain, motor, and even other somatosensory disorders. Much remains to be discovered. Motor cortex stimulation is directed toward disease entities for which there is otherwise limited or no treatment available at all. These patients deserve our future attention and research.

References

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