Topical review

Motor cortex stimulation for central and neuropathic pain: current status

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1. Historical background

The idea that central pain syndromes can be treated by manipulation of the motor cortex derives from the landmark observations of Penfield (Lende et al., 1971). While re-operating on patients on whom he had previously resected a portion of the post central gyrus for epilepsy and whose seizures recurred, Penfield observed that stimulation of the corresponding primary motor cortex elicited sensory responses (Lende et al., 1971). Sweet and White achieved only 13% pain relief with post central gyrectomy and recommended abandoning the operation (White and Sweet, 1955). Based on their observations of Penfield’s work and on the failure of post central gyrectomy alone, (Lende et al., 1971) treated three patients with facial neuropathic pain by resecting both the post central and corresponding pre central gyri, providing them long-term pain relief. No other reports of this aggressive technique have been published.

The use of central electrical stimulation to treat various pain problems is beyond the scope of this review. Most of the early work (deep brain stimulation, DBS) involved stereotaxic placement of electrodes into well-defined targets using stereotaxic techniques, including the sensory thalamus and midbrain periaqueductal or periventricular gray. Because there was insufficient data to support efficacy and safety of these procedures, DBS for pain was largely abandoned in the United States.

2. Scientific basis for motor cortex stimulation

Lenz et al. (1989) found that, in patients with pain derived from spinal cord injury, thalamic neurons are hyperactive compared to similar neurons in control patients. Tasker et al. (1987) discovered that if patients with central pain and symptoms of hyperpathia or allodynia, undergo intraoperative stimulation of the lateral thalamus, painful sensations are elicited. These sensations are comparable to those that the patients experienced clinically. Control patients with dyskinesias or tremor who undergo similar stimulation do not experience such pain. Also, spontaneously firing cells, called ‘bursting cells’, were present in all patients with central pain in whom thalamic microelectrode recording was performed. The sites of painful stimulation were not the same sites that demonstrated bursting cells. Finally, an altered thalamic somatotopy, a consequence of deafferentation, was identified, consisting of ‘empty’, displaced or reorganized receptive fields. These altered fields may represent plasticity of the axonal sprouting pattern (Gorecki et al., 1989). This body of work, performed throughout the 1980’s established the role of the human thalamus in central deafferentation pain (Lenz et al., 1987; Rinaldi et al., 1991).

During the same period Patrick Hardy postulated that stimulation of sites in the projections to the internal capsule, caudate nucleus, thalamic centromedian-parafascicular nucleus and midbrain pain pathways may also alleviate pain. Studies in rats and monkeys demonstrated frontal, cortical projections to the periaqueductal gray and adjacent regions. Maximum seizure sub threshold stimulation of prefrontal cortex in rats significantly increased nociceptive response latencies as measured by hot plate and tail flick techniques (Hardy, 1985). Prefrontal cortical stimulation, when applied simultaneously with a noxious stimulus, abolished the midbrain neuronal response to pain (Hardy and Haigler, 1985).

In an effort to identify a more effective and safe site for stimulation-induced analgesia, Tsubokawa and colleagues used their cat model of spinothalamic tractotomy. They observed thalamic hyperactivity, of low threshold mechanoreceptor neurons 3 weeks after tractotomy and found that
motor cortex stimulation profoundly inhibited the abnormal firing. Sensory cortical stimulation was without effect (Rinaldi et al., 1991; Tsubokawa et al., 1991a,b).

3. Clinical indications

A large number of clinical studies have been published summarizing the results of the treatment of a variety of central and neuropathic pain syndromes. Pain syndromes that have been treated by motor cortex stimulation in published series include many forms of neuropathic and central pain such as anesthesia dolorosa and other forms of trigeminal deafferentation pain, central pain secondary to stroke, postherpetic neuralgia, peripheral deafferentation pain syndromes such as brachial plexus or sciatic nerve injury, spinal cord injury, phantom limb and stump pain (Table 1). More data are available for central and facial pain than for other deafferentation syndromes.

4. Clinical studies

Tsubokawa et al. described their first clinical experience using motor cortex stimulation to treat central pain syndromes in 1991. They treated seven patients with thalamic pain syndrome using motor cortex stimulation and observed ‘excellent or good’ pain relief. During stimulation there was increased cortical and thalamic cerebral blood flow, increased temperature in the region of pain and, interestingly, improved movement of the painful limbs and improved hemiparesis (Tsubokawa et al., 1991b).

The long-term efficacy of motor cortex stimulation firmly established its utility for the control of pain. Thus, eight of 12 treated patients continued to achieve benefit from stimulation after 1 year. No seizures were observed nor was there electroencephalographic evidence for any seizure activity. Pain relief occurred at stimulus intensities below the threshold for muscular movement. As in the cat, when the post central gyrus was stimulated, pain was either exacerbated or unchanged. Motor cortex stimulation was now a viable therapy for central pain (Tsubokawa et al., 1991a).

Tsubokawa et al. (1991a) then published a series of 11 patients with central pain after putaminal or thalamic hemorrhage, eight of whom underwent implantation of a stimulation system after a 1-week trial. Greater than 80% pain relief was maintained for 2 years in five of 11 patients.

Meyerson et al. (1993) began treating a series of patients in 1990, publishing his results in ten patients in 1993. All five of his patients with trigeminal neuropathic pain achieved greater than 50% pain relief and greater than 75% pain relief in two patients. Stimulation was used at intervals of 20–30 min for one to six times daily. Allodynia, dysesthesia and hyperesthesia were carefully measured in one patient and were markedly diminished during stimulation. When the sub-threshold stimulation was turned off without telling one patient who was studied, there was no reduction in dysesthesia or allodynia, suggesting the absence of placebo effect. Brief seizures were induced in several instances during test stimulation, but no lasting motor effects occurred.

Katayama extended the indications for surgery to include lateral medullary infarction. Four patients with Wallenberg syndrome treated by ventroposterolateral (VPL) thalamic nucleus stimulation reported increased pain. Three patients were then treated by motor cortex stimulation, and two reported greater than 60% pain reduction and one reported greater than 40% reduction. This latter patient had previously undergone unsuccessful VPL stimulation. Motor weakness and dysarthria also improved with stimulation (Katayama et al., 1994).

Positron emission tomography (PET) studies show that motor cortex stimulation increases cerebral blood flow in the ipsilateral thalamus, cingulate gyrus, orbito-frontal cortex and brainstem (Peyron et al., 1995; Garcia-Larrea et al., 1997, 1999). The degree of analgesia correlates with the increase in cingulate blood flow. The authors suggest that stimulation improves the suffering component of chronic pain. Activation of the brainstem periaqueductal gray area is also a possible consequence of stimulation. The somatosensory cortex or immediate subcortical zones are not activated by motor cortex stimulation. Electrophysiological studies by the same group showed that stimulation also attenuates nociceptive spinal pain reflexes (Garcia-Larrea et al., 1999). These results suggested that an intact corticospinal tract neuronal system originating from the motor cortex is required for effective pain relief. Katayama et al. (1998) observed that pain relief was satisfactory in 73% of patients who had mild or absent motor weakness. When motor weakness was present and moderate to severe, then there was benefit in only 15% of the 13 patients. When motor contractions could not be induced, only 9% of patients ($P < 0.01$) achieved pain relief.

An intriguing observation made by Yamamoto and Tsubokawa was that pain reduction by infused pharmacologic agents could predict successful pain relief by electrical stimulation of the motor cortex. In their report, patients who were likely to benefit from the procedure experienced at least 40% pain relief with intravenous thiamylal when given in increments of 50 mg every 5 min to a maximum dose of 250 mg. They were less likely to respond to intravenous morphine when given in 0.3-mg increments every 5 min to a maximum of 18 mg (Yamamoto et al., 1997). This response deserves further study, as methods to predict a successful outcome from this relatively invasive procedure would be of great clinical significance.

Motor cortex stimulation has also proven beneficial for trigeminal neuropathic pain (Herregodts et al., 1995; Ebel et al., 1996; Nguyen et al., 1997; Rainov et al., 1997; Nguyen et al., 2000). Nguyen et al. (1997), reported on seven patients with neuropathic facial pain followed for
more than 2 years. All had some pain control and four patients had greater than 60% pain relief. In a later study ten of 13 patients with central pain (77%) and nine of 12 with neuropathic facial pain (75%) had experienced substantial pain relief (Nguyen et al., 2000). A possible explanation for these particularly excellent results in trigeminal neuropathic pain syndromes is that the facial somatotopic representation on the motor cortex is large compared to that of other body regions.

From Tsubokawa’s first publication on the treatment of central pain with motor cortex stimulation, anecdotal observations of the beneficial effect of stimulation on motor function have been made. Eight patients, 19% of their patient population, treated by Katayama et al. (1997) for
central deafferentation pain had improved motor performance that was independent of pain control. Improvements in symptoms from thalamic hand syndrome, action tremor, intention myoclonus and advanced Parkinson’s disease have been reported after motor cortex stimulation (Franzini et al., 2000; Nguyen et al., 1998; Canavero et al., 2003; Franzini et al., 2003). The significance of these observations awaits further study.

5. Surgical technique

A variety of techniques for accurately placing epidural electrodes over the motor cortex are used, but these techniques have not been systemically compared. The original procedure used by Tsubokawa for epidural electrode placement has been refined. Nguyen and Keravel pioneered a planning technique using localization by superficial computed tomography reconstruction of the central region combined with neuronavigation. They confirm the position of the central sulcus with intraoperative median nerve somatosensory evoked potentials. The somatotopic organization of the motor cortex is established intraoperatively by studying motor responses with transdural cortical mapping (Nguyen et al., 2000). More recently, neurosurgeons have used magnetic resonance imaging (MRI) combined with neuronavigation (Franzini et al., 2003). Several centers have integrated functional MRI into the targeting plan (Roux et al., 2001). The stimulation frequencies used for motor cortex stimulation range between 40 and 100 Hz and amplitudes range from 1.5 to 10 volts. Pulse width may range from 90 to 450 msec. Subdural electrode placement is also used, especially for treatment of leg pain and when epidural stimulation has ceased to be effective (Saitoh et al., 2000). In virtually all reported studies, an empirical approach is used: frequency, amplitude and pulse width are adjusted according to patient reports of side effects and pain relief.

6. Risks

In no published cases has neurologic injury occurred with this procedure. Morbidity reported includes intraoperative seizures, stimulator-pocket infection, epidural hematoma, subdural effusion and dehiscence of the stimulator pocket. Chronic seizures have not been observed. Bezard et al. (1999) studied the effect of cortical stimulation in three monkeys. Using frequency and pulse duration of 40 Hz and 90 msec, (comparable to that used in humans) and an intensity set just below the threshold for eliciting muscle twitch, seizures did not occur. When stimulus intensity was increased it was possible to induce reversible epileptic seizures; however, the threshold for these seizures did not change despite repeated events.

7. Summary

Motor cortex stimulation represents a paradigm change in the neurosurgical approach to the treatment of complex central and neuropathic pain disorders. With cortical stimulation the therapeutic target has expanded from the tip of the cone to the top of the cone, from the target of fiber projections to their wider and more superficial base of origin (Brown, 2003). Although the scientific basis for pain relief with this technique is not known, the available literature suggests that at least part of the effect is via inhibition of thalamic pain pathways. Projections to brainstem nuclei involved in pain modulation are another potential site of action. The clinical studies published to date are retrospective reviews. Motor cortex stimulation is used most often for pain originating from central and trigeminal system causes-pain entities for which no other effective surgical option is available. It represents a remarkable advance in treatment that deserves further study. Prospective studies will help to clarify the full benefit of this technique.

References


