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Precentral stimulation for chronic pain

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Many chronic pain conditions may become refractory to conventional medical therapies. In 1991, Tsubokawa et al [1] first reported their experience in 12 patients with deafferentation pain treated with epidural motor cortex stimulation (MCS). A chronic stimulating electrode was placed epidurally such that stimulation of the underlying cortex produced motor contractions in the painful region. Previous experience by the same group revealed that stimulation of the postcentral gyrus exacerbated the pain [2]. Other experimental work by the same authors demonstrated that transection of the spinothalamic tracts in animals could inhibit thalamic hyperactivity [3]. Since then, multiple groups from around the world have reported on their success with MCS [4–18].

Mechanism

The precise mechanism of action of epidural cortical stimulation remains uncertain. The central idea underlying the therapeutic effect of MCS is activation of nonnociceptive sensory neurons, which are believed to exert an inhibitory effect on their nociceptive counterparts. This type of interaction may be present at multiple levels of the somatosensory pathway along the peripheral and central nervous systems. Further, induction of motor contractions in the area of the pain often may result in pain relief.

In deafferentation pain, the flow of afferent nervous impulses mediating noxious stimuli may be partially or completely interrupted, resulting in the development of aberrant connections. Although these interactions are thought to be disrupted at the level of the lesion, it is proposed that they are preserved rostrally. Thus, stimulating nonnociceptive sensory neurons at a rostral cortical level may bypass the aberrant connections and exert an inhibitory effect on the nociceptive system.

Further, it may be more accurate to refer to this therapy as precentral stimulation as opposed to MCS [6,19,20]. We explored this notion via electric field modeling. The methodology previously applied to electric field modeling in the spinal cord and subdural cortical arrays was applied to a model of an extradural electrode array [21–30]. A cortical patch model, including cortex, white matter, cerebrospinal fluid (CSF), dura, and extradural connective tissue as well as the current density patterns, was generated for a representative Resume four-contact electrode array (Medtronic, Minneapolis, MN) (Fig. 1). The relative effectiveness of the stimulus current was estimated from calculating activating functions (the second spatial derivative of the voltage along the presumed direction of the nerve fiber) at different distances from the cathode in orthogonal directions.

The model demonstrated that the CSF has a large shunting effect on the effectiveness of the stimulus current. The effective stimulus amplitude (activating function peak) depends strongly on the thickness of the CSF layer between the dura and cortex. Essentially, the activating function at the

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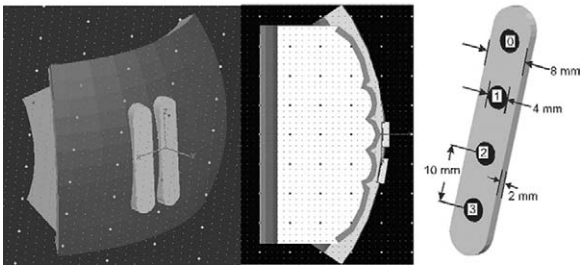

Fig. 1. A generic brain model was created to study the interaction of the electrode (Medtronic Resume Lead; Medtronic, Minneapolis, MN) and the underlying cortical structures. The following measurements were chosen for the development of the model: gyri (white) = 1 cm wide, cortex (gray) = 2 mm thick, dura (red) = 0.2 mm thick, and cerebrospinal fluid (blue).

depth of the sulci is minimal. Given that most cells comprising the motor cortex proper reside within the depths of the sulci rather than in the crown of the gyrus, this analysis shows that this is not the predominant cell type affected by epidural stimulation. Therefore, it may be more correct to use the term *precentral stimulation* to reflect the fact that the primary target is not motor cortex per se but the precentral gyrus.

Also noted was the fact that these model results were sensitive to the particular geometry (gyral anatomy or electrode) modeled. Specifically, we have analyzed the effects of contact spacing and interelectrode distance and, as expected, seen minimal interaction of the electric fields for the Resume electrode. Furthermore, the positional variability likely overshadows any small variations in electrode size and spacing as noted by the mentioned shunting effect of the CSF. These findings will have relevance to the refinement of the technique in the future.

Indications

Clinical experience has proven efficacy in many patients with a variety of refractory pain syndromes. MCS has been described in patients with thalamic or subcortical pain, poststroke pain, phantom limb pain, complex regional pain syndrome, and trigeminal and atypical facial pain. For a patient to be a candidate for MCS, it is essential that cortical stimulation be possible in the homuncular region corresponding to the painful area. Patients who have suffered large cortical strokes and have significant encephalomalacia in the corresponding region of the cortex are not optimal candidates. Tsubokawa and his colleagues [2,31] have also suggested a predictive value in noting a positive response to barbiturates and a negative response to opioids. Moreover, there should be no significant weakness in the painful area. Severe hemiparesis or hemiplegia in the painful region has been shown to be a significant negative predictor for pain relief [32]. A thorough evaluation by a neuropsychologist familiar with chronic pain is useful in identifying emotional and psychiatric overlays that may influence response to therapy. Moreover, this aids in screening patients with significant secondary gain issues.

Technique

The patient is evaluated before surgery and a high-resolution MRI scan is obtained for the purpose of frameless neuronavigation. Herregodts et al [33] introduced MRI guidance to improve localization of the motor cortex. Similarly, at the Cleveland Clinic Foundation, the MRI scans are transferred to a proprietary guidance platform for image analysis using interactive three-dimensional volume rendering. This enables the central sulcus to be identified for the purposes of planning the craniotomy and scalp incision (Fig. 2). The patient is given antibiotics 30 minutes before the skin incision as well as a bolus dose of phenytoin for seizure prophylaxis. Monitored anesthesia care (MAC) is performed with an oral airway to allow for the possibility of awake stimulation should the motor threshold not be obtainable during surgery.

The patient is placed in the Mayfield three-pin headholder (OMI, Cincinnati, OH) after generous infiltration of the skin with 1% lidocaine. Note that the Mayfield headholder is gently allowed to rest on the bed without fixating to the bed and serves as a means to fixate the reference arm rigidly (Fig. 3). Registration of the scalp fiducial markers is performed, and a horseshoe incision is planned centered on the central sulcus. Some

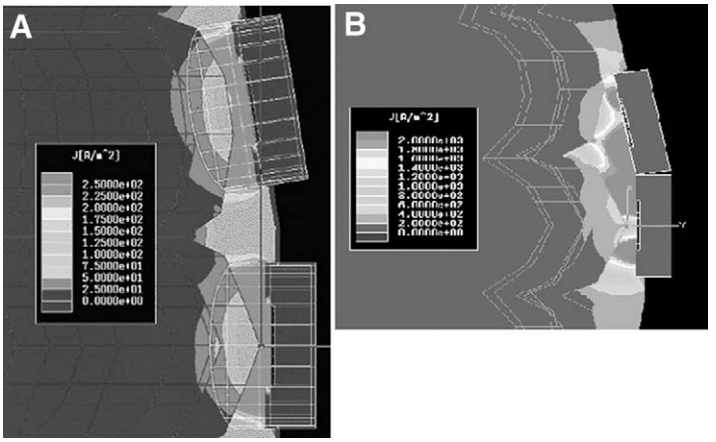

Fig. 2. The edges of the stimulating electrodes are about 4 mm apart (8 mm center to center) (*A*) or about 2 mm apart (6 mm center to center) (*B*). A higher concentration of current density between electrodes is achieved with closer spacing of the electrodes; however, a large cerebrospinal fluid shunting effect is still apparent.

strategic points should be considered when planning the incision. The incision should be large enough to allow for the placement of at least a 4 × 4 electrode grid so as to permit mapping of the cortex. For a patient with facial pain, one must distinguish between V1, V2, or V3 distribution of pain, remembering that the V3 region is furthest lateral and closest to the Sylvian fissure. Similarly, to ensure V1 coverage, not only should facial contractions be elicited, but there should be a concerted effort to obtain hand contraction given the organization of the cortical homunculus. Coverage of the lower extremity may prove problematic given the extremely medial location of this cortical region. Our group has had success in placing the electrode array parallel to the sagittal sinus (rather than parallel to the gyrus) approximately 1 cm from the midline.

A local field block is performed with 0.5% bupivacaine diluted 1:1 with saline, 1% lidocaine is injected at the planned incision site for additional anesthesia, and a routine craniotomy exposure is performed. Care should be taken when nearing the toxic dosage of lidocaine with and without epinephrine (7 mg/kg and 5 mg/kg, respectively) and bupivacaine with and without epinephrine (3.2 mg/kg and 2. 5 mg/kg, respectively). A craniotomy is performed, and dural tack-up sutures are generously used to ensure epidural hemostasis, because the presence of blood between the dura and the electrode can significantly alter stimulation thresholds (see Fig. 3).

An electrode grid is placed on the dura and registered into the neuronavigation system for the purpose of mapping the cortex. The neurophysiology team monitors somatosensory evoked potentials (SSEPs), looking for N20 to P20 wave phase reversal across the central sulcus (Fig. 4). Once located, the central sulcus is marked epidurally with blue ink, and two Resume TL (Medtronic, Minneapolis, MN) electrode arrays are placed. One electrode is placed over the central sulcus, and the other is placed immediately anterior to it, predominantly over the precentral gyrus. Extender cables are attached and thrown off the field for test stimulation so as to obtain motor contraction thresholds in the region of the pain. Once contractions are apparent at the lowest thresholds in the proper body region, the electrodes are sutured to the dura with nonabsorbable suture, the field is copiously irrigated, absolute hemostasis is achieved, and the craniotomy is closed in a standard manner. The extension cables are tunneled toward the inferior aspect of the craniotomy after exiting through a burr hole that has been leveled to prevent any acute angulation of the exiting lead. Care should also be taken to leave some excess loop above the craniotomy to serve as strain relief (Fig. 5). The extension cables should be positioned to allow relatively easy access for the planned second stage, which will require tunneling to the chest.

After surgery, the patient is taken to the epilepsy monitoring unit, where extensive trial stimulation is performed. Skull radiographs are obtained to document the position of the electrode arrays. We first attempt to determine the threshold for motor contraction in the painful

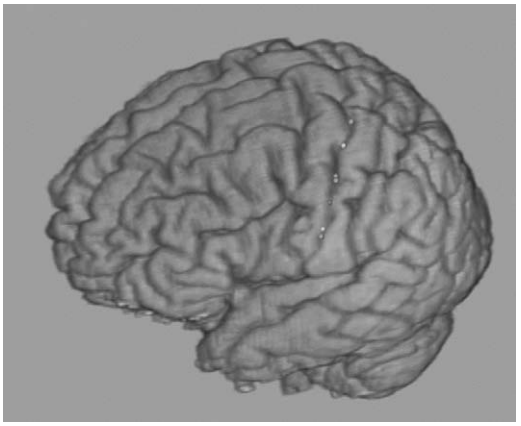

Fig. 3. High-resolution T1-weighted MRI is obtained before surgery for neuronavigation. (MPRAGE, T1-weighted inversion recovery prepared with rapid three-dimensional gradient echo coronal acquisition: field of view = 256 mm, 256 × 256 matrix, 256-mm slab thickness, 128–256 partitions, repetition time = 9.7 milliseconds, echo time = 4 milliseconds, and fip angle = 10°). Additionally, a functional MRI study is conducted to allow localization of the region of interest (light area represents activation resulting from lips performing kissing movements). The central sulcus is identified and marked (dots). The anticipated electrode position is noted in the four small multicolor dots. (Image provided courtesy of Eric Lapresto.) The Mayfield head frame is placed after administration of local anesthetics and sedation to allow rigid fixation of the neuronavigation registration arm to the head. (Note that the Mayfield head frame is not rigidly fixed to the bed, allowing the patient to move the head once awake.) A large C-shaped incision is marked above the Sylvian fissure, with the anterior limb directed toward the coronal suture to allow for the placement of a grid permitting extensive motor mapping. (Note that a posterior exit site has been prepared for the lead extensions.)

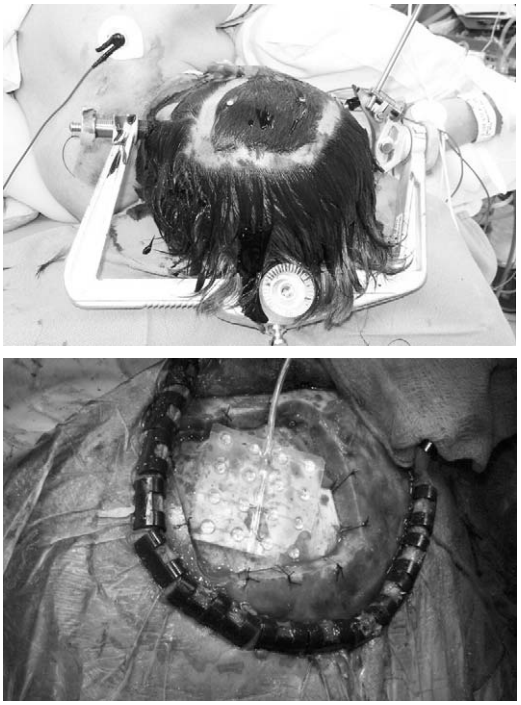

Fig. 4. Somatosensory evoked potentials are recorded with the following parameters: sampling at 30 to 40 K, bandpass at 30 to 2000 Hz, stimulation pulse wave of 200 microseconds with supramotor threshold, and two sessions of 200 to 500 trials. A clear phase reversal of N1 and P1 is recognized. After the central sulcus is identified, bipolar cortical stimulation through the dura is conducted with a biphasic pulse with decay, pulse duration of 50 to 450 microseconds, and frequency of 30 to 150 Hz to confirm facial or extremity contraction.

region. The stimulation amplitude is then set at 80% of this level while electrode montages and other parameters (eg, pulse width, frequency) are adjusted. Unlike movement disorders, the optimal stimulation parameters vary widely from patient to patient, and testing requires time and effort to find the settings that provide the most pain relief with the minimum energy use. The stimulation is often cycled (20 minutes on/1 hour off) to prevent the development of tolerance. If the patient has breakthrough pain, the off period may be reduced. The beneficial effects of stimulation persist after the stimulator is deactivated. In fact, many patients do well even if the stimulator is off twice as often as it is on. This helps to conserve battery life, because the voltage requirements of this therapy are usually high (>5 V).

Patients who have successful trials (>50% pain relief) return to the operating room within 3 to 5 days for internalization of the electrode system. Those who have failed the trial have the arrays removed. The procedure is performed under general anesthesia. An extension is used to connect the leads to the neural pulse generator, and the connector must be fixed rostral to the mastoid process to prevent eventual lead or extension fracture. The distal end of the extension is attached to the pulse generator, which is sutured to the pectoralis fascia. All wounds are closed in multiple layers.

The patient typically remains in the hospital for an additional day for permanent programming. The patient returns to clinic in 10 to 14

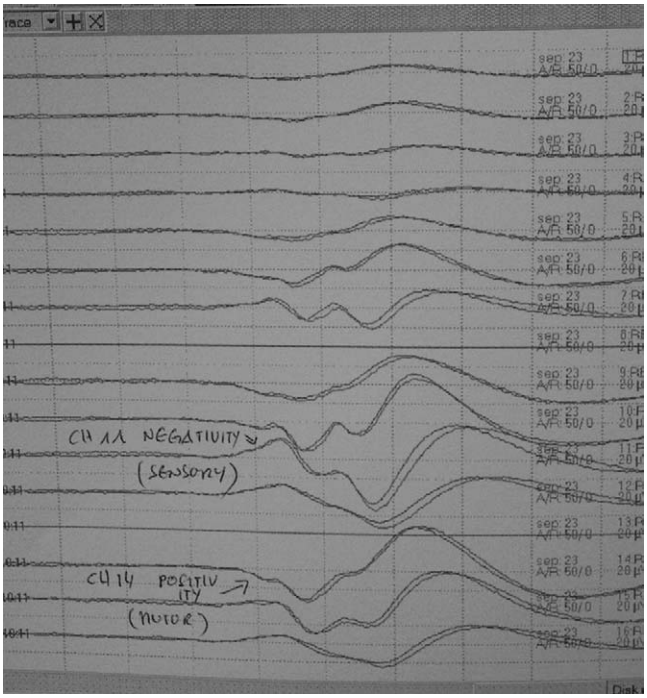

Fig. 5. Once ideal placement has been determined based on somatosensory evoked potentials and motor mapping, two Resume electrodes (Medtronic, Minneapolis, MN) are sutured to the dura. The anterior electrode is positioned on the precentral gyrus, and the posterior electrode is placed over the central sulcus. (Note that the Gelfoam is removed and tacking sutures are placed before closure and that absolute hemostasis is obtained, because it is believed that remaining blood beneath the electrodes might have a tendency to cause impedance over time.) The connectors are kept close to the incision to allow for easier access after the period of trial stimulation. The remainder of the wire is tucked beneath the galea.

days; at that time, the stitches are removed and the seizure medications are discontinued.

Analysis of the electric parameters used to achieve therapeutic benefits has been unrevealing. On occasion, however, 20% of the potential threshold and low-frequency stimulation was used. We have not observed a consistent correlation with the production of an occasional tingling sensation reported by some patients and pain relief. Most patients experienced pain relief soon after adjustment of the electric parameters.

Literature review

In Tsubokawa et al's initial reports [1,34], 6 of the 12 patients achieved complete resolution of their pain, whereas another 3 experienced at least a 60% reduction. Previous work of this same group [35] demonstrated that thalamic hyperactivity caused by severing the spinothalamic tracts (a model of chronic neuropathic pain) could be inhibited by stimulation of the motor cortex. Meyerson's group [11] soon followed with their report of 10 patients with a variety of pain syndromes. The best results were seen in those patients with facial pain. Importantly, both Tsubokawa's group and Meyerson's group noted that in those patients who benefited, satisfactory results could be obtained with intermittent rather than constant stimulation. In contrast, however, none of Meyerson's group's patients with thalamic pain syndromes achieved significant pain relief [1,11,34,36], and the indications, optimal stimulating parameters, and optimal electrode location remained undetermined. In general, the body of literature regarding this technique is plagued by a lack of controlled blind studies, large patient groups, and uniform objective rating scales.

Katayama and Yamamoto [10] have also reported satisfactory results in patients with brain stem infarcts. Nguyen et al's larger series [12] of 20 patients demonstrated the variability in outcomes with this technique. Although all 7 of the patients with trigeminal pain achieved greater than 80% relief, only half of the 10 poststroke patients even

Table 1
Review of major series on motor cortex stimulation for pain

Authors and year	No of cases	Diagnosis (No of patients)	Follow-up period	Pain reduction
Tsubokawa et al, 1990	25	Poststroke pain	7 months	75% response rate
Katayama et al, 1991	8	Persistent vegetative state		
Hosobuchi et al, 1993	6	Poststroke pain (5), after resection of left parietal arteriovenous malformation (1)	2–3 months	4 will excellent relief, 1 with 30% 1 with 0% 9–30 month's follow-up: 3 with excellent relief
Meyerson et al, 1993	10	Poststroke pain (4), neuropathic pain (6)	4–28 months	6 of 6 with 50% relief
Tsubokawa et al, 1993	11	Poststroke pain	2 years	5 with/ satisfactory relief
Katayama et al, 1994	7	Poststroke pain	NS	2 with/ satisfactory relief
Canavero and Bonicalzi, 1995	2	Cervical syringomyelia (1) post, stroke pain (1)	2 years	30%–50% initial pain relief with 50% pain spread to contralateral side at 2 year no response in second patient
Herregodts et al, 1995	7	Central poststroke pain (2) trigeminal neuralgia (5)	9–22 month	At least 50% relief in 5 of 7, no relief at 4 months/in 1 of 2, 1 with anesthesia dolorosa: 20% relief at 6 weeks and no relief at 13 months
Peyron et al, 1995	2	Poststroke pain	22 months	1 with pain relief for 22 months, the other for 3 weeks
Ebel et al, 1996	7	Tigeminal neuralgia	5–24 months	6 initially responded: 3 with good to excellent pain relief and 3 with decreased positive effects
Fujii et al, 1997	7	Poststroke pain	3 months	5 with fair relief
Garcia-Larrea et al, 1997	9	Poststroke pain (6), brachial plexus pain (3)	NS	3 with >80% pain relief 2 with 40%–50% relief 4 with <40% relief
Nguyen et al, 1997	20	Trigeminal neuralgia (7), poststroke pain (10), peripheral neuralgia (1), spinal cord lesions (2)	14–39 months	14 had 40%–100% main relief 7 of 7 and 1 of 1 had 80% pain relief 5 of 10 and 1 of 2 had excellent relief
Rainov et al, 1997	2	Chronic facial pain	18 months	Satisfactory relief
Yamamoto et al, 1997	28	Poststroke	>12 months	13 (76%) had positive response
Canavero et al, 1998	29	5 with central pain, 3 with neuropathic pain, 11 with atypical facial pain	2 months	1 of 5 had response at 2 months, others had no long-term response
Katayama et al, 1998	31	Poststroke pain	2 years	15 had device implantation with good pain relief, 8 had gradual increase in pain
Canavero et al, 1999	1	Poststroke pain	6 weeks	No relief
Franzini et al, 2000	1	Thalamic hand syndrome	2 years	Complete recovery
Nguyen et al, 2000	32	13 with central pain, 12 with neuropathic facial pain, 3 with postparaplegic pain, 1 with plexus avulsion, 1 with intercostal herpes zoster	27.3 months	10 of 13 and 9 of 12 had substantial relief, 1 of 3 clearly improved, no satisfactory improvement in the other 2

Table 1 (*continued*)

Authors and year	No of cases	Diagnosis (No of patients)	Follow-up period	Pain reduction
Saitoh et al, 2000	8	4 with thalamic pain, 4 with peripheral deafferentation pain	NS	6 with pain relief (2 excellent, 2 good, 2 fair + E21)
Roux et al,	1	Phantom limb pain	NS	70% reduction
Smith et al, 2001	12	Poststroke (6), brain stem gunshot injury (1), peripheral neuropathic pain (5)	2 weeks–36 months	3 of 6 had 50%–100% pain relief, 1 of 1 had 50%–60% pain relief, 2 of 5 had 0–75% pain relief

Abbreviation: NS, not significant.

achieved 40% pain reduction. Many of these patients had been followed longer than 2 years at the time of final evaluation. Nevertheless, these investigators and others [6,32,36] have remarked about the loss of efficacy of stimulation in some patients over time. Frequently, it is difficult or impossible to recapture the same amount of pain relief once it has been lost. The reason for this is unknown, but some investigators speculate that epidural granulation between the electrode and the dura may be the issue.

As previously stated, significant hemiparesis/hemiplegia in the painful region is considered a relative contraindication, as only 1 or 11 patients experienced greater than 60% pain control. This is based on Ebel et al's study [6], Katayama et al's study [32], and Tsubokawa et al's study [36], in which only 1 of 11 patients with significant weakness achieved greater than 60% pain control. Sensory symptoms in the painful region were not a significant predictor of response. Table 1 lists a more complete summary of the available literature.

Complications

The complications have been previously described[2,11,12,14,37]. Most commonly, they have included infections requiring removal of the entire system; bleeding complications, including epidural hemorrhage related to the tack-up sutures; a change in the electrode impedance, requiring re-exploration; hardware malfunction from lead breakage; increased pain at either the painful site or related to the stimulation; and seizures. Seizures in these patients are almost always directly related to the high energies used to obtain pain relief. They respond rapidly to a reduction in stimulation voltage and usually do not require chronic anticonvulsant coverage. Patients who develop seizures should be evaluated for the presence of a subdural collection. We have only had one patient who was forced to deactivate the stimulators permanently because of seizures.

Summary

A decade of clinical experience has suggested that precentral stimulation is an option for patients with deafferentation as well as other chronic pain syndromes. Permanent complications are uncommon. More scientific evidence is warranted to understand the precise mechanism for this treatment modality. A larger organized clinical trial is desired to establish the efficacy of precentral stimulation.

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