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Narrative Review

Intracranial Neurostimulation for Pain Control: A Review

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Intracranial neurostimulation for pain relief is most frequently delivered by stimulating the motor cortex, the sensory thalamus, or the periaqueductal and periventricular gray matter. The stimulation of these sites through MCS (motor cortex stimulation) and DBS (deep brain stimulation) has proven effective for treating a number of neuropathic and nociceptive pain states that are not responsive or amenable to other therapies or types of neurostimulation. Prospective randomized clinical trials to confirm the efficacy of these intracranial therapies have not been published. Intracranial neurostimulation is somewhat different than other forms of neurostimulation in that its current primary application is for the treatment of medically intractable movement disorders. However, the increasing use of intracranial neurostimulation for the treatment of chronic pain, especially for pain not responsive to other neuromodulation techniques, reflects the efficacy and relative safety of these intracranial procedures. First employed in 1954, intracranial neurostimulation represents one of the earliest uses of neurostimulation to treat chronic pain that is refractory to medical therapy. Currently, 2 kinds of intracranial neurostimulation are commonly used to control pain: motor cortex stimulation and deep brain stimulation. MCS has shown particular promise in the treatment of trigeminal neuropathic pain and central pain syndromes such as thalamic pain syndrome. DBS may be employed for a number of nociceptive and neuropathic pain states, including cluster headaches, chronic low back pain, failed back surgery syndrome, peripheral neuropathic pain, facial deafferentation pain, and pain that is secondary to brachial plexus avulsion.

The unique lack of stimulation-induced perceptual experience with MCS makes MCS uniquely suited for blinded studies of its effectiveness.

This article will review the scientific rationale, indications, surgical techniques, and outcomes of intracranial neuromodulation procedures for the treatment of chronic pain.

Key words: Motor cortex stimulation, deep brain stimulation, pain, neurostimulation

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Neurostimulation involves the use of electrical pulses to activate neuronal targets in the central or peripheral nervous system usually via an implanted power source and lead(s). The therapy is most commonly employed to manage intractable chronic pain, and it offers an important treatment alternative to ablative surgery or the long-term use of analgesic medications, including opioids.

Intracranial neurostimulation is somewhat different than other forms of neurostimulation in that its current primary application is for the treatment of medically intractable movement disorders. However, the increasing use of intracranial neurostimulation for the treatment of chronic pain, especially for pain not responsive to other neuromodulation techniques, reflects the efficacy and relative safety of these intracranial procedures. First employed in 1954, intracranial

neurostimulation represents one of the earliest uses of neurostimulation to treat chronic pain that is refractory to medical therapy. Currently, 2 kinds of intracranial neurostimulation are commonly used to control pain: motor cortex stimulation and deep brain stimulation.

Motor Cortex Stimulation

Motor cortex stimulation (MCS) has shown particular promise in the treatment of trigeminal neuropathic pain and central pain syndromes such as thalamic pain syndrome. Chronic stimulation of the precentral cortex for the treatment of pain was first reported by Tsubokawa in 1991 (1,2). Interestingly, stimulation of the motor cortex gave better results than stimulation of the sensory cortex, the latter of which caused some patients' pain to worsen. A number of reports have followed describing the use of MCS for intractable pain syndromes including post-stroke pain, phantom limb pain, spinal cord injury pain, postherpetic neuralgia, and neuropathic pain of the limbs or face (3). The majority of studies involving MCS focus on its use in post-stroke and trigeminal neuropathic pain, for which there are few other treatments (1,2,4-13). Post-stroke pain responds well to MCS, with approximately two-thirds of patients achieving adequate relief. Several studies have documented the excellent results of using MCS for the treatment of trigeminal neuropathic pain, with 75% to 100% of patients achieving good to excellent pain relief (7,9,14-16).

Surgical Technique for MCS

Prior to the surgical procedure, a functional MRI (fMRI) is performed to precisely localize the site of the motor cortex that will be activated to treat a region affected by pain (17-20). Some investigators prefer to use an MRI without the addition of functional information to provide anatomic guidance (4,9,18,21-24). Most investigators have chosen to perform a small craniotomy for electrode placement (7-9,15), either under local (5-9,13-16,20,25-27) or general anesthetic (4,10,11,18,19, 21,24,28). Image-guided neuronavigation is used to precisely identify the motor cortex intraoperatively (9,18-21). Then a linear incision, approximately 10 cm long, is made, followed by a circular craniotomy approximately 5 cm in diameter.

At this point, electrophysiologic monitoring and stimulation are performed. The central sulcus is identified by recording brain surface electrical activity using an epidural grid electrode. A waveform is seen approximately 20 msec after stimulation; the inflection of this waveform reverses from negative to positive at the central sulcus (an effect known as the N20/P20 waveform phase reversal). The cortex is stimulated and both somatosensory-evoked potentials and EMG are monitored to precisely locate the area of the motor cortex that corresponds to the pain region. Electrode strips are then placed over the center of this target. Nearly all investigators place the electrodes epidurally, although subdural placement has been described (22,29). Some investigators prefer to place the electrode strips across the precentral gyrus while others prefer a longitudinal orientation; no clear evidence exists to favor one technique over another. The use of 2 side-by-side 4-contact electrode strips is preferred by some investigators. Other investigators have been exploring the use of an implantable electrode grid designed specifically for MCS (Keravel, personal communication). Motor threshold testing is often carried out in the operating room (4,5,8,12,30), and, in awake patients, pain relief is sometimes sought.

In light of the homonucular representation of the body on the motor cortex, coverage of facial and arm pain over the cortical convexity is straightforward. With the representation of the leg extending medially into the interhemispheric fissure, however, coverage of leg pain is more challenging. Some investigators place the lead epidurally as close to midline as possible and rely upon increased stimulation intensities to drive current deeper into leg motor cortex. Others have placed leads subdurally within the interhemispheric fissure to directly contactthe leg motor cortex. (11)

After closure of the craniotomy, the electrode cable is externalized for trial stimulation. Patients then undergo a period of trial stimulation usually lasting 3 to 7 days. Unlike other forms of neurostimulation, patients experience no stimulation-induced sensory phenomenon during MCS; only a degree of pain relief is noted. There is considerable variation in the stimulation parameters used by various investigators. Reported amplitudes range from 0.5 V to 10 V, rates from 5 Hz to 130 Hz, and pulse widths from 60 μsec to 450 μsec (31). Once the pulse width and frequency have been optimized, most investigators will increase stimulus intensities during the trial using a percentage of the motor threshold as a guide. Many investigators begin by increasing the intensity by 20% of the motor threshold and then increase by 20% increments thereafter to

80% of motor threshold. Others use fixed stimulus intensities in their trials. If patients obtain sufficient pain relief, they are returned to the operating room and the electrode is connected to an implanted pulse generator, usually placed subcutaneously over the pectoralis muscle.

Complications of MCS

While a majority of studies have reported no adverse events with MCS (1,2,17,27,29,32-34), serious complications have been reported. The surgical risks of MCS include intracranial bleeding, infection, and permanent neurological deficits (4,7,9,11,12,15,18,19,21,22). Seizure induction has been reported following MCS programming and during chronic MCS (5,10,11,14,16,18-20). While seizure induction does not necessarily lead to the development of epilepsy, there is at least one patient who developed severe epilepsy after long-term motor cortex stimulation (35).

Efficacy of MCS

Successful treatment of facial neuropathic pain with MCS has been uniformly reported (7-9,14,15). A review of the literature has corroborated these results, showing that 29 of 38 (76%) reported patients with neuropathic facial pain achieved ≥ 50% pain relief with MCS (21). Post-stroke pain responds nearly as well, with almost two-thirds of patients obtaining good to excellent relief (8,9).

MCS Conclusions

MCS thus appears to hold great promise for patients with trigeminal neuropathic pain, post-stroke pain, and pain which has failed to respond to other less invasive forms of neurostimulation. MCS for intractable pain has not, however, been rigorously studied in a prospective fashion. There are differing opinions in the literature regarding surgical technique, programming, and patient selection. Nonetheless, MCS appears to be a relatively safe and effective neuromodulation procedure for appropriately selected patients.

Deep Brain Stimulation

Heath (36) in 1954 and Pool and coworkers (37) in 1956 first reported successful pain relief with stimulation of the septal region nuclei in patients with psychiatric disease. Mazars et al (38) and Hosobuchi et al (39) in 1973 and Adams et al (40) in 1974 reported the first experience of using chronic stimulation in the sensory thalamic nuclei to treat neuropathic pain. Several other authors have reported their long-term success with somatosensory thalamic stimulation (41–48). Richardson and Akil (49,50) and Hosobuchi and coworkers (51) reported pain relief in patients undergoing chronic stimulation of the periaqueductal gray (PAG) and the periventricular gray (PVG) at the level of the posterior 3rd. This phenomenon has been subsequently confirmed in several additional studies (51–65).

Surgical Technique for DBS

The use of PAG/PVG stimulation for the treatment of nociceptive pain and ventroposterolateral/ventroposteromedial (VPL/VPM) thalamic stimulation for neuropathic pain has been the general recommendation of many authors (66). While several authors have reported that rigid adherence to this rule is not mandatory, a meta-analysis of all reported cases suggests that successful long-term DBS is, in fact, target-specific for the type of pain to be treated. Most patients in clinical practice, however, present with combined pain syndromes that have both neuropathic and nociceptive components; the most common example being patients with failed back surgery syndrome. Frequently, these patients complain of nociceptive low back pain and radicular neuropathic leg pain. It is the usual practice to implant both PAG/PVG and sensory thalamic electrodes simultaneously in these patients and to internalize one or both of these electrodes based upon the results of trial stimulation (67).

DBS electrodes are implanted using stereotactic guidance. While frameless approaches have been reported, the majority of surgeons use frame-based stereotaxy for electrode implantation. After the frame is applied, patients undergo high resolution stereotactic MRI. Surgery is performed under local anesthesia supplemented as needed by intravenous sedation. A parasagittal frontal burr hole is created through a small incision. Intraoperative physiological stimulation is required to define the exact target for stimulation, which is only approximated by the stereotactic MRI. Thus, the stereotactic coordinates represent only starting points for localization of the physiological targets. Microelectrode recording, microstimulation, and macrostimulation can all be used in the process of localization (44,67-70). Microelectrode recording can help locate targets based on their particular electrophysiologic activity (71). Once the physiologic targets have been defined with stimulation, permanent electrodes are introduced to those sites, and the leads are externalized through a separate stab wound in the scalp for trial stimulation.

Typically, a postoperative CT scan or MRI is obtained to confirm electrode placement and to assess possible intracerebral hemorrhage. After postoperative recovery and resolution of any peri-electrode edema, test stimulation is initiated to evaluate the patient's pain relief. All possible stimulation combinations are explored during a trial stimulation period that generally lasts 5 to 9 days. If satisfactory pain relief is obtained, the patient is returned to the operating room and the electrodes are connected to an implantable pulse generator.

Complications of DBS

The potential complications of DBS have been well elucidated (61-63,65-67,72,73). Intracranial hemorrhage is the most significant complication of DBS. It can occur at the time of the insertion or removal of the electrode. The reported incidence of hemorrhage ranges between 1.9% and 4.1%. Using contemporary coaxial DBS electrodes, there has been a significant decrease in the incidence of intracranial hemorrhage. Permanent neurological deficits have occurred in 14 of the 649 reported patients, with the incidence of such complications ranging from 2.0% to 3.4%. The deficits most commonly resulted from intracranial hemorrhage. Mortality is rare from DBS; mortality rates have been reported ranging from 0 to 1.6%. Of the 4 total deaths associated with DBS for pain, 3 have resulted from complications of intracranial hemorrhage.

The incidence of infectious complications from DBS ranges between 3.3% and 13.3%. These complications included meningitis, encephalitis, and infection of the scalp or IPG site. No correlation was found between the time that the electrode was externalized and the occurrence of infection (72). The majority of cases required wound debridement and removal of all hardware in addition to systemic antibiotics for successful resolution of the infection.

Minor complications of DBS (72) include transient headache (51.5%). The majority of these headaches was believed to be a direct result of the intracranial operation and had resolved by the time of patient discharge from the hospital. PAG/PVG stimulation can cause other transient side effects, including diplopia (14.2%), nausea (10.6%), vertical gaze palsies (9.9%), blurred vision (9.2%), horizontal nystagmus (4.3%), and persistent oscillopsia (3.5%).

In summary, even historical series of DBS patients have shown acceptable complication rates. Mortality from DBS is rare. Technical advances may already have reduced the morbidity and mortality of DBS.

Efficacy of DBS

A meta-analysis of studies was performed to determine the efficacy of DBS for the treatment of chronic pain. Thirteen series with long-term outcome reports for a total of 1,114 patients were evaluated (48,61-63,65-67,72-75). Of the patients, 561 (50%) had long-term successful pain relief with DBS. The rates of long-term success ranged from 19% to 79%, and it appears that there is a falloff in success as the length of follow-up increases. Overall, 711 patients had neuropathic pain, of which 296 (42%) had success at long-term follow-up. Of the 443 patients with nociceptive pain, 272 (61%) experienced long-term success.

When the VPL was stimulated for neuropathic pain, 228 of 409 patients achieved long-term success (56%), but when sensory thalamic stimulation was used for nociceptive pain, 0 of 51 patients achieved long-term success. A total of 35 out of 155 patients (23%) achieved long-term success when the PVG was stimulated for neuropathic pain whereas 172 out of 291 patients (59%) achieved long-term success when this same site was used to treat nociceptive pain. These results support the hypothesis that PVG stimulation is the preferred site for nociceptive pain states while the sensory thalamic stimulation is preferable for neuropathic pain.

It is important to note that many of these patients were treated early in the development of DBS and prior to the clarification of patient selection and target criteria. Thus, it is expected that contemporary experience should be better than that which is reflected in this literature.

DBS appears to be more effective for certain pain states than others. Long-term success was achieved more frequently for pain resulting from cervical or brachial avulsion, peripheral neuropathy, and failed low back surgery syndrome. DBS, however, appears to be less effective for the treatment of thalamic pain syndrome and paraplegia pain. For other pain states, outcomes reported in the literature are mixed.

Contemporary DBS Literature

While over 1,000 cases of DBS for chronic pain were performed between the early 1970s and 1986, the procedure was then virtually abandoned in the United States when its approved status was rescinded by the Food and Drug Administration (FDA). The FDA commissioner demanded that further comprehensive safety and efficacy trials be performed. Due to the small number of patients available for, and the significant expense

of these trials, DBS for intractable pain remains investigational in the United States. Only after the approval of DBS hardware for the treatment of movement disorders in 1996 and its market introduction in 1997 were neurosurgeons able to perform DBS for chronic pain on an "off label basis."

In part as a result, there has been a resurgence of interest in DBS for chronic pain over the past decade. In 2003, Katayama, Yamamoto, and colleagues (76) reported their contemporary DBS experience in patients with pain following cerebrovascular accidents. Using a target in the thalamic posterior nucleus ovalis, 70% of patients experienced good relief. Thalamic nucleus Vc (ventralis caudalis) or internal capsular stimulation was much less effective and gave disappointing results.

Bittar, Aziz, and coworkers (77) reported their contemporary experience with DBS for chronic pain in the United Kingdom. Three patients with phantom limb pain were treated; all underwent PVG stimulation, and in one patient, a sensory thalamic electrode was placed as well. The patients reported 55% to 70% pain relief at a mean follow-up of 13.3 months. The authors of this study also performed a meta-analysis of the contemporary literature. They observed that stimulation efficacy was correlated with the stimulation target. PAG/PVG stimulation produced good to excellent results in 79% of patients; the addition of sensory thalamic or internal capsule stimulation increased the success rate to 87%. Sensory thalamic stimulation alone, however, produced statistically significantly poorer results (58%). They further observed that success rates varied by diagnosis. Patients with failed back surgery syndrome obtained satisfactory relief 80% of the time, while lower percentages of patients with post-stroke pain (58%) and phantom limb pain or peripheral neuropathies (60% to 75%) experienced such results. Interestingly, the authors found that nociceptive pain responded better to DBS than neuropathic pain (63% vs. 47%; $P < 0.01$).

Hamani, Lozano, and coworkers (78) recently reported their contemporary experience with DBS for pain control. They performed DBS trial stimulation in 21 patients and internalized 13 of them (62%), with 13 patients undergoing Vc thalamic stimulation and 8 patients undergoing PAG/PVG stimulation. Of particular interest is that 9 patients (43%) experienced pain relief as a result of electrode insertion alone; one patient obtained lasting complete relief without permanent implantation. Of the 13 implanted patients, 8 patients failed to get satisfactory results and were explanted while 5 patients had long-term pain relief (38%). Contrary to Bittar et al's (77) experience, 80% of the successfully treated patients had Vc thalamic stimulation.

Franzini and coworkers (79) reported that DBS of a posterior hypothalamic target resulted in complete and long-term pain relief in 5 patients with medically intractable cluster headaches. Schoenen et al (80). subsequently reported their experience of using hypothalamic DBS for cluster headache. Of their patients, 3 of 6 had a good result; one patient died perioperatively from an intracerebral hemorrhage along the lead insertion tract. Green and coworkers (81) reported their experience with using DBS for neuropathic cephalgias. A total of 7 patients were treated with PAG/PVG and/or VPM thalamic stimulation. All patients experienced greater than 50% improvement in their pain with associated improvements demonstrated on the McGill Pain Inventory and Short Form 36. The use of hypothalamic DBS for cluster headaches appears to be highly successful over the longer-term (G. Broggi, personal communication).

DBS Conclusions

Long-term pain relief with DBS for a number of indications has been widely documented (41-48,51-65). A meta-analysis of the literature has shown that 50% to 60% of DBS patients report at least moderate levels of pain relief and/or have continued stimulator use at one year follow-up (82). Recent data moderately supports the use of DBS for refractory pain associated with cephalgia and failed back surgery syndrome and suggests that the therapy may have a value for treating post-stroke pain, central pain syndromes, and peripheral deafferentation pain (77,81). Some investigators have reported an "insertion effect" in which the placement of DBS leads provides pain relief even when the leads are not activated (78). DBS has had its best success in treating cluster headaches and nociceptive syndromes such as chronic low back pain (80,83,84); thalamic pain syndrome (probably due to the frequent loss of the target cells for stimulation), postherpetic neuralgia, and pain due to spinal cord injury are not well treated with DBS. DBS continues to play a role in the treatment of chronic pain when other less invasive treatment modalities have been exhausted.

Conclusions

Intracranial stimulation should only be considered after more conservative therapies have failed, including less invasive neurostimulation methods. Like other pain treatments, MCS or DBS must be employed in light of

the circumstances of individual cases and the morbidity associated with alternative treatments, particularly the long-term use of opioids.

MCS appears to be an appropriate treatment for neuropathic facial pain, post-stroke pain, or chronic pain conditions that do not respond to other types of neurostimulation. However, there may be occasions in which MCS is indicated without being preceded by such neurostimulation, as is the case in patients with complete deafferentation conditions. There is no compelling evidence that MCS is less effective than DBS for treating chronic pain.

DBS may be employed for a number of nociceptive and neuropathic pain states, including cluster headaches, chronic low back pain, failed back surgery syndrome, peripheral neuropathic pain, facial deafferentation pain, and pain that is secondary to brachial plexus avulsion. Due to the poor overall results reported by several investigators, DBS is not highly recommended for thalamic pain syndrome, post-herpetic neuralgia, and pain due to spinal cord injury. Implantation of 2 leads, one in the PAG/PVG and the other in the sensory thalamus, may optimize the chances of achieving satisfactory pain relief.

Areas for Future Research

Future research into intracranial stimulation should focus in part on customizing neurostimulation technology for MCS or DBS applications. For example, paddle leads that were originally designed for spinal cord stimulation are often employed in MCS, even though their length and intercontact distances can make them unwieldy. Additionally, these leads have a relatively narrow strip of electrodes that makes them poorly suited to cover multiple targets on the motor cortex. Implanters can attempt to use multiple leads to compensate for this shortcoming, but this may result in poor control over the stimulation field and possibly interference between the leads. Additionally, using a standard 4-contact paddle lead to stimulate the motor cortex, as often happens in clinical practice, is not a particularly discrete way of targeting the geography of motor cortex areas, and leads that allow more precise stimulation may be desired. Leads could be designed to allow for stimulation both parallel and perpendicular to the precentral gyrus, permitting the selection of the most effective stimulation targets in individual patients. Further research is required to determine the optimal stimulation parameters for MCS. Research should also focus on how to overcome the apparent habituation that some patients experience during the course of their MCS or DBS therapy.

While many case series have been published on the use of MCS or DBS for pain, no randomized, controlled trials exist to confirm the therapies' effectiveness. This lack of class I data may cause some observers to view the therapies skeptically in spite of their considerable history of clinical use. MCS is probably better suited to such studies than other forms of neurostimulation, in that effective stimulation evokes no perception on the part of the patient save for pain relief. This presents researchers with a unique opportunity to perform blinded studies in which placebo effects can be assessed. Such studies could employ crossover designs to encourage enrollment and address ethical concerns related to the implantation of leads into control patients.

The lack of randomized controlled trials may be due, in part, to the challenges of patient recruitment and monitoring and the need to assign patients to control groups, which by definition means subjecting patients to treatments that have already been unsuccessful in managing their pain. However, the risk of not performing these studies is great, because it means that both physicians and patients lack definitive information about the efficacy of intracranial neurostimulation therapies. This then will slow the further development of the therapies and limit the access of patients to them in the future.

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