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Deep brain stimulation for the treatment of intractable pain

Robert M. Levy, MD, PhD

Departments of Neurological Surgery and Physiology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

History of deep brain stimulation for chronic pain

The first attempts to modulate pain by electrical stimulation of brain structures were those made by Heath and Mickle in the 1950s. The phenomenon of pain relief resulting from electrical stimulation of sites within the brain was first observed during the course of other neurosurgical procedures. Heath [1] in 1954 and Pool and coworkers [2] in 1956 reported successful pain relief on stimulation of the septal region, anterior and lateral to the anterior columns of the fornix, in patients with psychiatric disease. Pain relief with septal stimulation in patients without psychopathologic findings was subsequently reported by Heath and Mickle [3] in 1960. In 1966, Ervin and coworkers [4] reported pain relief after stimulation of the caudate nucleus. Gol [5] subsequently described limited success with stimulation of both the septal region and caudate nucleus.

Based on the prevailing rationale that neuropathic pain states arose because of the absence of sensory input into the somatosensory thalamic nuclei, interest developed in stimulating the somatosensory pathway at the level of its intrathalamic nuclei. This approach was first reported by Mazars et al [6] in 1960, who acutely stimulated the ventroposterolateral (VPL) thalamic relay nucleus. Subsequently, White and Sweet [7] reported control of pain in a patient suffering from facial postherpetic neuralgia by stimulation of the nucleus ventralis posteromedialis (VPM). Mazars et al [8] and Hosobuchi et al [9] in 1973 and Adams et al [10] in 1974 reported the first experience with chronic stimulation in the sensory thalamic relay nuclei and internal capsule for the treatment of neuropathic pain. Several other authors have reported their long-term success with somatosensory thalamic stimulation [11–18].

Other thalamic targets have been investigated for the treatment of chronic pain states. The dorsal medial nucleus (DM), the parafascicular nucleus (Pf), and the centromedian thalamic nuclei (CM) have been stimulated largely because of their proximity to the periventricular gray matter (PVG) and their initially inadvertent stimulation either by current spread from the PVG or by small errors in targeting the PVG [19]. A postmortem anatomic study by Boivie and Meyerson [20] of five patients who underwent PVG stimulation suggested an association between the location of the electrode in the DM and the Pf and successful pain relief. Stimulation that effectively inhibited pain in these patients included the ventromedial aspect of DM or the border of the PVG/Pf with at least one pole of the bipolar stimulation. Young and Rinaldi [21] analyzed the trajectory of their PVG implants and suggested that in successfully treated patients, the PVG electrode tip was situated within the endymalis nucleus. Some of their patients have experienced pain relief with DM stimulation.

It has been postulated that the CM nucleus plays a role in the integration and perception of pain, and it has been the focus of much attention in animal research [19,22,23]. Andy [24] reported successful pain relief with electrical stimulation of the centromedian parafascicular complex for chronic pain associated with dyskinesia.

Katayama and colleagues [25,26] have described electrical stimulation of the parabrachial

E-mail address: rml99@northwestern.edu

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region in cats. Associated with the parabrachial region is the Kolliker-Fuse nucleus, and it has been found to be the major source of catecholamines projecting into the feline spinal cord [27]. This nucleus was stimulated by Hodge and his colleagues in cats, and they reported inhibition of dorsal horn neuronal activity [28]. Pretreatment with reserpine antagonized this effect, thus suggesting a catecholaminergic mechanism in this inhibition. Young et al [29] have also reported stimulating the Kolliker-Fuse nucleus for pain relief in a limited number of patients.

The concept of PVG/periaqueductal gray matter (PAG) stimulation was introduced by Reynolds [30] in 1969. His group reported profound analgesia in rats on PAG stimulation. This work subsequently led to the discovery of opioid receptors in the human brain and to the discovery of endogenous opioid peptides. Capitalizing on these discoveries, Richardson and Akil in 1977 [31,32] and Hosobuchi and coworkers [33] reported effective pain relief after acute and chronic stimulation of the PAG and the PVG at the level of the posterior third ventricle in human patients. Several additional studies have subsequently confirmed this phenomenon [33–47].

The potential of cortical stimulation for pain relief has also been investigated. Cortical resection was initially investigated as a potential treatment for thalamic pain syndrome [48]. Tsubokawa and colleagues [49] reported pain relief from chronic subthreshold epidural stimulation of the motor cortex in patients suffering from deafferentation pain. In this series, 5 of 12 patients had complete pain relief at 1 year. These results have been replicated by several investigators; most recently, Keravel and Nguyen have implanted more than 200 patients with trigeminal neuropathic pain or poststroke pain with greater than 60% long-term success (personal communication, 2002).

Spinothalamic projections to the cortex have been demonstrated, and Talbot et al [50] demonstrated significant cortical activation after painful stimuli using positron emission tomography (PET). Studies using functional MRI (fMRI) are beginning to define cortical responses to pain [51]. Using fMRI, Apkarian and coworkers (personal communication, 2002) have demonstrated prefrontal regions that receive projections from motor cortex, which appear to have a primary role in pain perception. Thus, motor cortex stimulation may act indirectly by anterograde activation of these prefrontal pain regions. The role of the motor cortex in pain perception and modulation is still not clearly understood, and further studies are required to determine the potential role of motor cortex stimulation for pain relief.

Scientific rationale and mechanism of action

Neuropathic pain

Neuropathic pain occurs in the setting of damage to the central nervous system. It has been defined by the International Association for the Study of Pain (IASP) Task Force as "pain initiated or caused by a primary lesion or dysfunction of the nervous system." This damage can occur anywhere along the neuraxis and is thought to result from the loss of innervation of central pain pathways. Neuropathic pain may be constant and steady, lancinating, or intermittent and is usually described as burning, dysesthetic, shooting, or tingling in nature. Medical therapy, including nerve blocks, neuroablation, and pharmacologic management, is frequently only partially successful, although the newer anticonvulsant agents, such as gabapentin (Neurontin) or oxcarbazepine (Trileptal), have been significant advances in neuropathic pain therapy. Neuropathic pain seems to be particularly responsive to somatosensory thalamic stimulation. Although often considered a central analogue to spinal cord stimulation, the mechanism of pain relief from somatosensory thalamic stimulation is not fully understood. Studies in monkeys suggest that VPL stimulation produces inhibition of spinothalamic tract neurons in the dorsal horn of the spinal cord [52,53]. Stimulation of the VPL in the rat has been shown to inhibit neuronal activity in the CM-Pf complex [54]. This suggests an intrathalamic mechanism of pain relief that may be similar to the gate control model of pain suppression in the spinal cord. Lenz et al [55] have described abnormal activity of somatosensory thalamic neurons in patients with neuropathic pain. Hirayama and coworkers [56] found abnormal firing in the ventrocaudalis region of the thalamus in patients with chronic pain. Rinaldi et al [57] have recorded abnormal bursting patterns in the medial and intralaminar thalamic nuclei in chronic neuropathic pain patients. In addition, they also demonstrated an increased number of bursting neurons in medial and lateral thalamic nuclei in deafferented rats compared with controlled rats and an associated increase in the number of neurons lacking receptive fields. Lenz [58] proposed that this abnormal bursting of thalamic cells may be mediated

by NMDA-regulated calcium-binding protein changes and may be involved in the development of central pain syndromes.

Nociceptive pain

Nociceptive pain results from the appropriate activation of peripheral nociceptors and subsequent activation of an intact central somatosensory pathway by a potentially tissue-damaging stimulus. It is usually described as sharp or aching in nature and, unlike neuropathic pain, is often responsive to opioid analgesics.

The relief of chronic nociceptive pain with DBS has its origin in the work of Reynolds [30], who described analgesia in rats after PAG stimulation, a phenomenon referred to as stimulation-produced analgesia (SPA). SPA is at least partially reversible by naloxone, a specific opiate receptor antagonist, and cross-tolerance can develop with opioid analgesics. Third ventricular cerebrospinal fluid has been sampled after PAG/PVG stimulation by Hosobuchi and coworkers [35,37] and by Akil et al [38]; both groups demonstrated a rise in endogenous opioid peptide levels. Subsequent studies, however, suggested that this rise might have been artifactual and in fact reflect the cross-reaction of contrast agents used for ventriculography with the reagents used in radioimmunoassay for opioids [59,60]. Young and his colleagues [40,61,62] demonstrated that levels of β-endorphin and met-enkephalin do rise after PAG stimulation, whereas no change was seen after VPL stimulation. These data strongly support the hypothesis that PVG stimulation-induced pain relief is mediated through endogenous opioid peptides.

In an attempt to better understand the mechanism of action of DBS, Rezai et al [64] have examined the safety and potential utility of fMRI in patients undergoing thalamic DBS. They demonstrated that fMRI can safely detect the activation of cortical and subcortical neuronal pathways during stimulation and that stimulation does not interfere with imaging. This approach might provide a potentially powerful tool for conducting further studies that will further enhance our understanding of the mechanism of DBS.

Patient selection and preoperative evaluation

DBS is generally used only in patients with chronic incapacitating pain states that have not responded to more conventional treatment modalities. Important factors to consider in the decision to attempt DBS for chronic pain include the cause of the pain, its nature and distribution, and the response of the pain to prior therapeutic interventions [65].

Patients considered for DBS should have a history of pain lasting at least 6 months. In fact, a minimum of 6 months should be allowed for aggressive treatment of the pain in a multidisciplinary pain clinic setting. Most patients undergoing DBS have suffered the pain for several years and failed all other therapies short of destructive neuroablative procedures. To be considered candidates for DBS, patients must have a clearly defined cause for the pain. Failure of more conservative pain control measures should be established.

The presence of a major psychiatric disorder is a contraindication to DBS; thus, patients with severe psychopathologies, including severe untreated depression, are excluded from consideration for DBS [66]. Tests like the Minnesota Multiphasic Personality Inventory (MMPI) can be used for psychologic assessment before treatment [67]. Patients with marked elevations of the hypochondriasis and hysteria scales on the MMPI and with low scores on the depression scale, the so-called "conversion-V pattern," are associated with a worse outcome after pain surgery [68]. Such patients with a strong psychologic component to their pain should undergo further psychologic treatment before the consideration of DBS. Patients with a prior history of frequent surgical procedures for equivocal indications and patients with excessive neurotic concerns with bodily functions and disease processes are poor candidates for implantation. It should be mentioned that most patients with chronic pain have mild psychologic disturbances, such as reactive depression, anxiety and somatization; however, these conditions are not necessarily contraindications for implantation.

As a means of selecting patients for PVG or PAG stimulation, Hosobuchi [47] recommended the morphine naloxone test, in which increasing doses of morphine sulfate are given intravenously until pain relief occurs. Previous studies [33,63,69] suggested that the response to opioids predicted the efficacy of DBS, but a later study [62] did not confirm that a response to opiates predicted successful PVG stimulation. In this paradigm, if the patient demonstrated pain relief in response to morphine infusion, the pain was classified as nociceptive and the patient was considered for

PVG implantation. Young and Kroening [70] abandoned this test after their study showed no difference in outcome between patients who did and did not undergo screening. They studied morphine screening in 129 patients: 59 patients studied using preoperative morphine screening and 70 using no screening. There was no statistically significant difference in the rates of successful DBS between the two groups. Of historic interest only in the setting of DBS is l-tryptophan, which was used as part of the morphine test and for patients with possible tolerance to DBS. Patients who could not be classified based on their morphine-naloxone tests were given daily treatments of tryptophan as opioids were withdrawn over a 1-month period. The morphine-naloxone test was then repeated. Those responding positively were classified as having nociceptive pain and treated with PVG implants [63]. l-tryptophan is no longer used because of the equivocal nature of the results and because of the potentially fatal eosinophilia-myalgia syndrome now occasionally associated with its use [70].

Some authors have recommended termination of pain medications for variable periods before implantation because of the belief that opioid analgesics may cause cross tolerance to DBS, especially during PAG/PVG stimulation [33–37,46,71]. There is a great deal of variability in the approach to opioid-dependent patients considered for DBS. Some authors discontinue opioids completely, others recommend tapering of opioids as tolerated, and still others, including Young and Rinaldi [21], have observed successful treatment in patients taking large doses of narcotics at the time of treatment.

Kumar et al [69] recommend preoperative CT or MRI to rule out encephalomalacia in the thalamus, which might make thalamic stimulation ineffective. If this area is large and there is little to no remaining thalamic tissue, alternate sites for stimulation, such as the posterior limb of the internal capsule, are considered. In our experience, it is often valuable to attempt thalamic electrode implantation even in this setting, because appropriate thalamic target cells are identified at least 25% of the time.

Target site selection

The use of PAG/PVG stimulation for the treatment of nociceptive pain and VPL/VPM stimulation for neuropathic pain has been the general recommendation of many authors. Although several authors have reported that rigid adherence to this rule is not mandatory, a meta-analysis of all reported cases in the literature suggests that successful long-term DBS is target specific for the type of pain to be treated. Most patients in clinical practice, however, present with combined pain syndromes with both neuropathic and nociceptive components; the most common are 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 PAG/PVG and sensory thalamic electrodes simultaneously in these patients and to choose to internalize one or both of these electrodes based on the results of trial stimulation [21].

Another issue with regard to target site selection concerns whether the electrodes should be placed unilaterally or bilaterally. Animal models [30] have shown that analgesia from PVG stimulation is generally bilateral, but others have shown a somatotopic relation between stimulation sites in the PAG and analgesia. The choice of hemisphere in which to implant the PAG/PVG electrodes remains controversial. Young favors placing PAG or PVG electrodes contralateral to the side of unilateral pain or in the nondominant hemisphere for bilateral pain. Hosobuchi [72,73], however, implants bilateral PAG electrodes and has reported generally better results with the left hemispheric PAG stimulation. For somatosensory thalamic stimulation, effective pain relief is only achieved on the side contralateral to electrode placement; therefore, the somatosensory thalamic electrode is always placed contralateral to the site of pain or is placed bilaterally with bilateral pain.

Surgical technique and target localization

Using stereotactic guidance, the electrodes are implanted under local anesthesia supplemented as needed by intravenous sedation. After the stereotactic frame is attached to the head, a parasagittal frontal burr hole is placed through a stab wound incision. In the past, intraoperative positive-contrast ventriculography was used for electrode targeting [74,75]. The introduction of MRI promised to improve anatomic resolution and simplify electrode target selection. Some authors continue to suggest that ventriculography is more reliable than MRI in defining thalamic coordinates because of the potential for MRI error introduced by magnetic field distortion [76].

Ventriculography, however, is also prone to error as a result of magnification errors, changes in the size of the ventricles after drainage of cerebrospinal fluid, and parallax errors caused by x-ray beam misalignment. Additionally, there are occasional difficulties or complications of cannulating the ventricles and injecting contrast material. Young and Rinaldi [21] carefully compared target selection by standard ventriculography, CT, and MRI techniques and demonstrated the relative superiority of MRI. In that several validation studies have documented the reliability of high-resolution MRI as long as correction has been made for inhomogeneities in the MRI magnetic field, most contemporary neurosurgeons use perioperative stereotactic MRI alone for target selection.

Intraoperative physiologic stimulation is required to define the exact target for stimulation, which is only approximated by stereotactic MRI. Thus, the stereotactic coordinates represent only starting points for localization of the physiologic targets. Microelectrode recording, microstimulation, and macrostimulation can all be used in the process of physiologic localization. Microelectrode recording can help to locate targets based on their particular electrophysiologic activity [57]. The electrode used by Young and Rinaldi [21] consists of an inner fine tungsten rod microelectrode and an outer stainless steel tube insulated except for the distal 0.5 mm, which forms a ring around the end nearest the tip of the microelectrode. The fine recording electrode tip (1–5 μ) allows for microstimulation. Macrostimulation is accomplished with the uninsulated ring portion of the outer tube. Single cell recording in the thalamic nuclei allows for plotting of receptive fields [58].

Ventroposterolateral/nucleus ventralis posteromedialis

Turnbull and coworkers [77] have described the technique of macrostimulation in the sensory thalamus. High-frequency (50–60 Hz) stimulation with low voltage is undertaken in 2-mm steps beginning 10 mm above the intercommissural line and continuing for 6 mm below this line between the anterior and posterior commissures until paresthesias are felt in the region of the body involved with pain. Low-voltage stimulation should yield paresthesia of an area encompassing the entire painful region when the proper target site is reached. This is widely accepted to be the best confirmatory process for accurate placement in the sensory thalamus. The area of stimulation-evoked paresthesias is not always identical to the area of cellular receptive fields recorded from the same location in the thalamus. Furthermore, Young and Rinaldi [21] point out that if muscle contractions are elicited with low-frequency stimulation at the same amplitude, the electrode is in or near the posterior limb of the internal capsule and should be moved. Once the target has been localized, permanent quadripolar electrodes are placed at the same site.

Periventricular gray matter/periaqueductal gray matter

For PVG, four pole platinum electrodes are implanted directly, with the most distant pole 1 mm caudal to and 1 mm below the posterior commissure and 2 to 3 mm lateral to the lateral wall of the third ventricle (parafascicularis-centromedian complex). Stimulation at threshold amplitude at a frequency around 50 Hz and with pulse durations ranging from 0.2 to 1.0 milliseconds will produce a pleasant sensation of bodily warmth, floating, dizziness, and well-being. At higher amplitudes, PVG stimulation will evoke feelings of nervousness, anxiety, and diffuse burning. Stimulation of the ventral PAG will produce similar sensations but with less pronounced burning, nervousness, and anxiety. Dorsal PAG stimulation is not liked by patients, and it evokes sensations of fear, doom, severe anxiety, and agitation. Kumar et al [63] found that when the PVG was the target site for DBS, a feeling of warmth or cold felt contralaterally or all over the body was a good prognostic sign. This feeling was described as relaxing and pleasurable.

High-amplitude stimulation in both the PVG and the dorsal and ventral PAG can produce limitation in vertical gaze, complete gaze paralysis, and oscillopsia. These target areas are near the Edinger-Westphal and oculomotor nerve nuclei; therefore, the neurosurgeon must be conscious of the implication of these stimulation-induced complaints. Hosobuchi [73] has found the inhibition of conjugate upward gaze during stimulation to be the most reliable physiologic determinant to ensure correct placement of the electrode.

In addition to using bodily sensations and visual changes to localize PVG/PAG targets, there are characteristic cardiovascular changes that can help to locate the appropriate target [21,78]. These cardiovascular changes include a rise in heart rate

above prestimulation baseline and an increase in systolic and diastolic blood pressures. In Young's series of 120 patients, the heart rate rose by 32 ± 12 beats per minute, the mean systolic blood pressure rose by 72 ± 21 mm Hg, and the diastolic blood pressure rose by 47 ± 10 mm Hg. Pain relief occurred in 87% of the patients who exhibited such cardiovascular changes, whereas only 26% of patients who did not exhibit cardiovascular changes experienced pain relief.

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. The leads are connected to a handheld stimulator, which allows for patient-controlled trial stimulation. Modern DBS leads are quadripolar platinum-iridium electrodes, which allow for bipolar or monopolar stimulation. These electrodes employ a central stylet for easier introduction into the brain rather than the adjacent introducer method used with older electrodes. A plastic burr hole ring and silastic cap can be used to fix the electrode into place. The ring fits into a 15-mm burr hole and allows for alteration of the electrode position if required.

Typically, a postoperative CT or MRI scan is obtained to confirm electrode placement and to assess possible intracerebral hemorrhage. After postoperative recovery and resolution of any perielectrode edema, testing is initiated to evaluate effectiveness of stimulation for pain relief. An exploration of all possible stimulation combinations is performed during the trial stimulation period, which generally lasts 5 to 9 days. Once optimal stimulation parameters are defined, formal single- and double-blind testing for pain relief is performed. If satisfactory pain relief is obtained, the patient is returned to the operating room and the electrodes are either connected to a radiofrequency connector or, more commonly, to a fully implantable pulse generator, which is programmed and activated using an external programmer. If patients fail to obtain pain relief during the trial period, the electrodes may be removed.

Results

A meta-analysis of all studies including more than 15 patients that had been published after 1977 was performed to determine the efficacy of DBS for the treatment of chronic pain. In this analysis, all the data have been normalized with respect to the stimulation target sites, specific pain states, and definitions of success and failure. In a few of the studies, it was possible to assess outcome relative to the stimulation sites used. Success on long-term follow-up was defined based on one of the following: greater than 50% pain relief, continued use of the stimulator with greater than 1 year of follow-up, or one of the following descriptions of pain relief: good, excellent, total, moderate, and complete. Failure at long-term follow-up was defined based on one of the following criteria: less than 50% pain relief, discontinuation of stimulator use, or one of the following descriptions of pain relief: fair, poor, none, slight, and partial.

Thirteen such series with long-term outcome reported for 1114 patients were evaluated [18,21,44,45,47,69,79–83]. Of these 1114 patients, 561 (50%) had long-term successful pain relief with DBS. Long-term success ranged from 19% to 79%, and it seems that there is a drop off in success rates as the length of follow-up increases. Seven hundred of the 1114 patients had neuropathic pain, of whom 296 (47%) had long-term success at long-term follow-up. Of the 443 patients with nociceptive pain, 272 (61%) experienced long-term success with their stimulators at long-term follow-up. It is important to note that many of the patients were reported from early in the course of development of DBS and the clarification of patient selection and target criteria. Thus, it is expected that contemporary experience should be better than that reflected in this developmental literature.

Long-term success rates relative to target site selection and the nature of the treated pain syndrome are outlined in Tables 1 and 2. When VPL was stimulated for neuropathic pain, 228 of 409 patients achieved long-term success (56%), but when sensory thalamic stimulation was used

Table 1
Deep brain stimulation for nociceptive pain

Electrode site	No.	Long-term success	Percentage
Overall	419	247	59%
VPL/VPM	51	0	0%
PAG/PVG	291	172	59%

Abbreviations: PAG, periaqueductal gray matter; PVG, periventricular gray matter; VPL, ventroposterolateral; VPM, nucleus ventralis posteromedialis.

Table 2
Deep brain stimulation for deafferent pain

Electrode site	No.	Long-term success	Percentage
Overall	644	349	54%
VPL/VPM	409	228	56%
PAG/PVG	155	35	23%

Abbreviations: PAG, periaqueductal gray matter; PVG, periventricular gray matter; VPL, ventroposterolateral; VPM, nucleus ventralis posteromedialis.

for nociceptive pain, none of 51 patients achieved long-term success.

Thirty-five of 155 patients achieved long-term success (23%) when PVG was stimulated for neuropathic pain, whereas 172 of 291 patients achieved long-term success (59%) when this same site was used for nociceptive pain. These results support the hypothesis that PVG stimulation is the preferred site for nociceptive pain states, whereas sensory thalamic stimulation is preferable for neuropathic pain.

DBS proved 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, seems 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.

Apparent tolerance to DBS has been reported to occur, and the loss of effectiveness of DBS over time remains a vexing clinical problem. Thus, tolerance is suggested when patients achieve excellent pain relief during trial stimulation and shortly after permanent electrode implantation only to have their pain become refractory to stimulation at a later time, usually within a year of the original implant. Whether this is true pharmacologic tolerance or rather a result of synaptic reorganization leading to alternative routes for pain transmission is unclear. A number of methods have been employed to overcome the development of apparent tolerance. In some patients, alteration of stimulus parameters, such as pulse duration, frequency, amplitude, and scheduled on/off times, has proved effective. Although ramping of the stimulation was suggested as a method to overcome tolerance, this has not been proven effective [63]. Kumar et al [63] also suggested insertion of a second electrode to overcome tolerance, but this remains unproved.

Complications

The potential complications of DBS have been well elucidated [21,44,45,47,69,79,81,83]. Intracranial hemorrhage is the most significant complication of DBS. It can occur at the time of insertion or removal of the electrode. The reported incidence of hemorrhage ranges between 1.9% and 4.1%. The newer DBS electrodes, which do not require a small adjacent leukotomy for placement, have resulted in a significant decrease in the incidence of hemorrhage.

As with the implantation of any foreign body, infection is a potential concern. The incidence of infection of any sort ranges between 3.3% and 13.3%. No correlation was found between the time of externalization of the electrode and the occurrence of infection [79]. Furthermore, no difference was found in the rate of infection between the early postoperative period (less than 30 days after surgery) and the late postoperative period (30 days or more after surgery). Most cases required wound debridement and removal of all hardware in addition to systemic antibiotics for successful resolution of the infection. It has been suggested that treatment with parenteral antibiotics and removal of an involved electrode while leaving uninvolved electrodes and hardware in place may be a viable treatment option.

Foreign body reactions characterized by inflammation, local pain, and erythema with occasional systemic generalization of an immunologic reaction have been reported in only six patients. These patients had marked eosinophilia. In all but one of these patients, it was necessary to remove the DBS equipment completely to treat the complication adequately. Interestingly, with advancements in materials technology and hardware design, such foreign body reactions have not been seen by the author in more than a decade.

Permanent neurologic deficits occurred in 14 of the 649 reported patients, with an incidence ranging from 2% to 3.4%. Such deficits most commonly resulted from intracranial hemorrhage. Three patients experienced permanent dysconjugate gaze in Hosobuchi's series [73]. This complication has been subsequently avoided by not advancing the tip of the electrode a few millimeters caudal to the iter of the aqueduct of Sylvius [69].

When bulky hardware is implanted underneath a scalp that has already been thinned by multiple operations, erosion through the scalp can occur. This complication has been reported in 12

patients. Erosion was treated with electrode reimplantation or complete removal [79].

Mechanical complications have occurred with decreasing frequency as newer and better electrodes have become available. The incidence of electrode displacement ranged from 2% to 9.9%. Levy et al [79] and Hosobuchi [47] reported that newer concentric multipolar electrodes made completely from platinum have largely eliminated this complication. In older series, hardware failure was reported with an incidence ranging between 4.9% and 13.3%. With new technical innovations, the incidence of this problem has also decreased over time. More modern numbers are not available because of the US Food and Drug Administration (FDA)–imposed hiatus for DBS between 1987 and 1997 and the lack of more contemporary series.

Mortality is rare from DBS; mortality rates have been reported ranging from 0% to 1.6%. Of the four total deaths associated with DBS for pain, three resulted from complications of intracranial hemorrhage.

Minor complications of DBS [79] include transient headache (51.5%). Most of these headaches were believed to be a direct result of the intracranial operation and had resolved by the time of patient discharge from the hospital. Air or positive-contrast ventriculography and 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 have reported acceptable complication rates. Overall complication rates are usually 8% or less, and most of these complications are amenable to therapy. Mortality from DBS is rare. Technical advances may already have reduced the morbidity and mortality of DBS.

Discussion

DBS has been employed in the treatment of more than 1000 patients suffering from chronic pain within the past 30 years. It offers real hope for patients who have failed other more conservative forms of therapy and those incapacitated by their pain. Implantation of electrodes in both the PVG or PAG and the thalamic somatosensory nuclei (VPL for body pain and VPM for facial pain) with postoperative determination of the most efficacious electrode is the most commonly accepted method for selecting the optimal target for chronic stimulation. The reported success rate for DBS at long-term follow-up averages roughly 60%. Patients with chronic low back pain, painful peripheral neuropathy, deafferentation pain, and pain secondary to brachial plexus avulsion seem to respond well to DBS. In contrast, those syndromes that do not apparently respond well to DBS include thalamic pain syndrome (probably because of the frequent loss of the target cells for stimulation), postherpetic neuralgia, and pain caused by spinal cord injury. Most complications are mild, transient, and amenable to therapy. The mortality rate of DBS is less than 2%.

It is important to note that DBS for chronic pain is currently performed in the United States as an "off-label" procedure. DBS, a widely accepted and once-approved neurosurgical procedure, was reclassified as an experimental procedure roughly 15 years ago; the FDA expressed concerns that inadequate safety and efficacy data had been collected before approval. After this decision, an FDA-approved protocol was established with industry support to supplement the existing data. Unfortunately, a combination of slow patient accrual and economic concerns resulted in the discontinuation of this study. Fortunately, identical electrodes and pulse generators were approved for thalamic stimulation for the control of tremor, and product release followed FDA approval in 1997. Using physician discretion (off-label use) or physician-based investigational new device (IND) applications, DBS has again become available to the practicing neurosurgeon for the past 5 years.

Perhaps as a result of the ruling of the FDA, the number of modern reports of DBS has been sparse. Despite this limitation, DBS continues to play an important role in the treatment of chronic pain when other less invasive treatment modalities have been exhausted. DBS is an apparently safe and effective treatment option for this select group of patients. Further research into the mechanisms of pain relief by DBS and careful prospective outcomes studies will help to define better the optimal techniques for DBS and clarify which patient populations may be best helped by this interventional procedure.

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