Electrical Stimulation of the Brain for Relief of Intractable Pain Due to Cancer

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Seventeen patients with intractable pain due to progressive malignancies were treated by electrical stimulation of the brain after more conventional pain therapies applied in the University of California, Los Angeles Cancer Pain Clinic had failed. Electrodes were stereotactically implanted under local anesthesia in the periaqueductal gray (PAG) or periventricular gray (PVG) in 11 patients. In six patients electrodes were placed in both PAG-PVG targets and in the sensory thalamic nuclei. Thirteen of the 17 patients achieved virtually total pain relief and 2 others achieved partial pain relief. At the hospital discharge only 4 of 17 patients required narcotic analgesics for pain relief. Follow-up periods ranged from 1 to 21 months and 6 patients remain alive. Fourteen patients eventually required narcotics for pain relief, usually in the terminal few weeks of their lives. Pain relief was achieved in spite of the fact that all patients were tolerant to large doses of systematically or intraspinally administered narcotics at the time of electrode placement. No complications related to brain stimulation were identified. Brain stimulation is a safe and effective method for treatment of intractable pain due to malignancy in certain patients.


Narcotic analgesics are the mainstay in therapy of intractable pain due to malignancy.1 Oral administration and more recently, intraspinal administration of opiates2 achieves pain relief frequently. Unfortunately large doses of narcotics eventually may be required, resulting in undesirable side effects, namely somnolence and mental confusion, which seriously detract from the quality of life. Additionally, tolerance to opiate analgesia frequently develops, such that effective pain control cannot be achieved at any dose short of that producing near anesthesia. For localized pain, certain neuroablative procedures, eg, rhizotomy, cordotomy, thalamotomy, etc, may prove effective.1 Several forms of intractable pain due to malignancy are not well treated by ablative procedures, however. These include pain due to diffuse metastases, pain in midline structures such as the spine and pelvis, bilateral leg pain, pain due to brachial and lumbar-sacral plexus invasion, and recurrent pain of the head and neck. The use of chronic intraspinal opiate administration has improved the therapy of certain midline and bilateral pain problems in the lower trunk and legs, but opiate tolerance also may develop, making this form of therapy unsuccessful as well.

Although electrical stimulation of the brain for treatment of chronic, noncancer-related pain dates at least from 1956, the discovery of the phenomenon of so-called “stimulation-produced analgesia” (SPA) by electrical stimulation of the medial brainstem3 and the identification of naturally occurring opiate-like polypeptides (the endorphins) in the mid 1970s4 provided an apparent anatomic and pharmacologic foundation for an expanded use of this method for treatment of chronic pain.

The method of deep-brain stimulation (DBS) has been applied mainly to therapy of chronic noncancer-related pain5-12 but has had little application to therapy of pain due to malignancy.13-18 Since DBS in man was believed to produce pain relief by release of endogenous opiate compounds18,19-21 it was thought unlikely to be effective in patients with chronic pain due to malignancies, most of whom are tolerant to exogenous opiates. Some recent studies, however, cast doubt on the theory that DBS provides pain relief by an endogenous opiate mechanism.12,22-25
Because of failure of all other available modes of therapy, we began to utilize DBS to treat chronic pain due to malignancy in certain patients, with surprisingly successful results. This report describes our experience with DBS in the treatment of seventeen patients with intractable pain due to cancer between 1978 and 1984.

### Patient Selection

All patients were treated in the University of California, Los Angeles (UCLA) Multidisciplinary Cancer Pain Center before consideration for DBS. Previous therapies included cancer-directed modalities such as surgery, chemotherapy, radiotherapy, and pain-directed therapies such as pharmacologic tailoring, temporary and neurolytic blocks. Noninvasive pain treatment methods such as hypothesis, biofeedback, transcutaneous electrical stimulation, acupuncture, and physical and psychological therapy also had been applied where appropriate. All patients with pain confined to the pelvis and/or lower extremities had undergone a test injection of 2 to 8 mg of morphine sulfate into the subarachnoid space to test possible efficacy of chronic intraspinal opiate administration for pain relief. Three patients eventually treated by DBS had undergone placement of various catheter systems and had been receiving chronic intraspinal opiates for up to 4 months without benefit. If the above-described therapeutic measures were unsuccessful in providing pain relief satisfactory to the patient, DBS was offered as an alternative.

Table 1 describes our patient population. There were nine men and eight women (mean age, 50 years). Pain duration was 3 months to 2 years (mean, 9 months). In 13 patients, pain was due to generalized metastatic disease, and in 4 patients it was due to local tumor recurrence. In five patients, associated neurologic deficits in one extremity were shown to be due to brachial plexus or lumbosacral plexus invasion by tumor, and in one patient it was due to trigeminal nerve involvement.

### Electrode Implantation

Stimulating electrodes were placed stereotactically under local anesthesia via a burr hole using conventional methods. If pain was associated with neurologic deficit due to deafferentation as a result of peripheral nerve destruction by tumor, electrodes were placed in both the periaqueductal grey (PAG)–periventricular grey (PVG) region, and in the somatosensory thalamic relay nucleus contralateral to the side of the pain (six patients). For facial pain, thalamic electrodes were placed in the nucleus ventralis posteromedialis (VPM), and for extremity pain, in the nucleus ventralis posterolateralis (VPL). If the pain was not associated with neurologic deficits, electrodes were placed only in PAG–PVG (11 patients). In one patient a single electrode was placed contralateral to the side of pain in PAG–PVG but in all others, bilateral PAG–PVG electrodes were placed. The electrode leads were externalized via a small stab wound in the scalp and screening stimulation was carried out for several days to
One patient did not obtain pain relief from stimulation and the electrode was not internalized. One patient, in whom screening stimulation produced total pain relief, had recurrent pain after permanent electrode implantation while still hospitalized. Two others experienced partial pain relief. Thus, of the original 17 patients, 13 (76%) experienced excellent pain relief and were no longer utilizing narcotics at discharge (Tables 2 and 3). The two patients with partial pain relief from stimulation utilized about 50% less narcotics at discharge than on hospital admission.

Follow-up periods ranged from 1 to 21 months (mean, 5.8 months). Six patients remain alive at present, a mean of 10 months postimplantation. Of the ten patients who died, all had persisting pain relief until death, although all required narcotics in the terminal few weeks of their lives. Other than for terminal care, only 1 patient of the 15 discharged postoperatively required hospital readmission for pain control. In this patient, spinal instability was treated by Harrington rod fixation and effective pain relief was again produced.

No complications occurred either intraoperatively or postoperatively. The two patients who died postoperatively without leaving the hospital and the other eight who died later all died from disseminated malignancy.

Case Reports

Two case reports are presented to illustrate the utilization of DBS for pain control.

Case 1

A 62-year-old man had undergone prostatectomy and orchiectomy for treatment of carcinoma of the prostate. Lumbar laminectomy and radiotherapy were carried out subsequently for treatment of upper lumbar spinal epidural metastases, with cauda equina compression. Neurologic deficit was resolved but back pain persisted. The patient was treated with systemic opiates and later with placement of a catheter in the spinal epidural space for narcotic administration. Pain relief was not effected and an infusion pump attached to a subarachnoid catheter was implanted for opiate administration. Pain relief was not obtained. The patient was transferred to UCLA Hospital after nearly 5 months of continuous hospitalization elsewhere.

Bilateral PVG electrodes were placed and excellent pain relief
was obtained. Narcotic withdrawal symptoms occurred for 4 to 5 days when narcotic dosage was reduced and finally discontinued, but these resolved. The patient was discharged home, ambulating for the first time in almost 6 months, with excellent pain relief by alternate side electrode stimulation for 30 minutes three times per day.

About 6 months later the patient again began to note upper lumbar back pain inspite of stimulation and studies disclosed spinal instability at the site of metastatic disease with vertebral collapse. Harrington rods were placed to provide spinal stability and the patient again had good pain relief and was discharged.

Thirteen months after DBS implant the patient experienced increasingly diffuse pain and multiple new metastases in bones and lungs were identified. Deep-brain stimulation provided only partial relief for this new pain. Narcotics gave only minimal pain relief and the patient deteriorated and died in 1 month.

Case 2

A 46-year-old woman had undergone mastectomy, radiotherapy, and chemotherapy for treatment of metastatic breast carcinoma. She began to complain of pain and progressive loss of neurologic function in her right arm. Evidence of recurrent metastatic tumor involving the right brachial plexus was obtained by plain x-rays, computerized tomography (CT) scan, and electromyography. Oral and parenteral therapy with narcotics provided minimal pain relief and the patient required hospitalization. Hypnosis, biofeedback, acupuncture, transcutaneous stimulation, and spinal cord stimulation also failed to provide pain relief.

Electrodes were placed in the left PVG and left thalamic nucleus VPL about 6 weeks after hospital admission. Immediate pain relief was effected, and the patient was easily tapered off opiates without withdrawal symptoms. The electrodes were permanently placed and she was discharged 11 days after the implant. Initially both PVG and thalamic electrodes provided complete pain relief. Gradually the PVG electrode was less effective and the patient required nearly continuous thalamic stimulation at ever increasing stimulus strengths. Later, recurrent use of oral narcotics provided good pain relief when combined with thalamic stimulation. She remained at home until she died, nearly 5 months after electrode implantation.

Discussion

Exogenous opiates remain the primary approach of most oncologists for therapy of intractable pain due to malignancy.1 Adjunctive noninvasive methods such as psychological or pharmacologic therapy (especially of depression), transcutaneous electrical stimulation, hypnosis, acupuncture, etc., may enhance or obviate the need for opiates. Temporary nerve blocks with local anesthetics or permanent blocks with neurolytic chemicals for localized pain also may be useful.

Ispite of application of all of these therapies a certain proportion of patients will not receive satisfactory pain relief. Increasing dosages of narcotics may provide ineffective pain relief due to the development of opiate tolerance and undesirable opiate side effects; usually sedation may occur. In such situations surgical intervention may be considered.

The traditional neurosurgical approach to cancer pain has employed ablative lesions designed to interrupt anatomical pain pathways.1 Standard operative procedures have included rhizotomy, cordotomy, myelotomy, and thalamotomy, among others. Such procedures have a number of disadvantages including the following (1) loss of normal sensory function in some part of the body; (2) the need for extensive surgical procedures, often requiring general anesthesia; (3) the limited application of many procedures to regional pain such as that in one leg, one side of the body or, one side of the face; (4) the occurrence of secondary pain syndromes due to the procedure itself, eg, postcordotomy dysesthesias; and (5) complications resulting in loss of nonsensory neurologic function, eg, weakness or paralysis of the extremities, interference with respiratory function, sphincter function, or sexual function.

For pain of midline or bilateral distribution, most ablative procedures either are ineffective or produce significant loss of normal neurologic function in a large number of patients. The intraspinal administration of opiates is useful for treatment of pain in the midline of the lower body or in the legs bilaterally,2 but opiate tolerance may develop in such patients, making such therapy ineffective. For midline or bilateral head and neck or upper body pain, little effective therapy is available. Likewise, when neurogenic pain due to invasion of large nerve trunks by malignant disease is present, neither ablative procedures nor intraspinal opiates usually are effective.

For patients in whom the usual cancer or pain therapy is not suitable or ineffective, DBS offers a viable alternative. The procedure is performed under local anesthesia via a burr hole only.12 We have experienced no complications in our series of 17 cancer patients, however, we have reported a number of mild, reversible complications in a larger series of patients undergoing DBS for treatment of primarily noncancer-related pain.12 These complications include electrode infection requiring removal and technical malfunction of hardware, which usually is corrected easily. Occasional problems previously experienced with diplopia or unintended motor activation during stimulation now are avoided by adjustments in final electrode targets.

Periaqueductal grey–periventricular grey stimulation is effective for treatment of chronic nondeafferentation pain due to cancer when the pain is bilateral, midline, or in
the upper body, neck, or head. Several others previously reported similar success in a small series of cancer patients. Patients experienced little or no induced sensation during PAG–PVG stimulation, and stimulation for 20 to 30 minutes three to four times per day often provided 24-hour pain relief.

Previous laboratory and clinical results have suggested that PAG–PVG stimulation relieves pain by causing release of naturally occurring opiate-like peptides (the endorphins) into the cerebrospinal fluid, thus accounting for the ability of PAG–PVG stimulation to relieve pain diffusely throughout the body. The endorphins are hypothesized to activate a descending pain-inhibitory system from the central brainstem to the dorsolateral quadrant of the spinal cord and down to the spinal dorsal horn where suppression of pain transmission neurons occurs. Animal studies have shown suppression of nociceptive neuronal activity in the spinal dorsal horn, as well as apparent analgesia evoked by electrical stimulation in the PAG and by microinjection of morphine into the same area. The development of tolerance to such stimulation, the demonstration of cross-tolerance with morphine and antagonism of the effects of such stimulation by the opiate antagonist naloxone led to the concept that SPA was dependent on an endogenous opiate mechanism.

However, some recent reports suggest, that neuronal inhibition induced by PAG stimulation may not be reliably antagonized by naloxone in animals. The hypothesis that pain relief due to PAG–PVG stimulation in man is opiate-mediated is based on the demonstration of elevated levels of endorphins in ventricular cerebrospinal fluid (CSF) after stimulation and antagonism of stimulation produced analgesia by the narcotic antagonist naloxone.

More recent publications suggest that the original reports of elevated endorphin levels after PAG–PVG stimulation may have been artifactual due to interference of the radioiodinated contrast material, employed in ventriculography utilized to select electrode placement sites, with the radioimmunoassay methods used to detect endorphins. Others have not been able to correlate CSF endorphin levels with pain relief after DBS. In addition, attempts by others to reverse PAG–PVG-induced pain relief by naloxone sometimes have been unsuccessful.

The basis for pain relief by PAG–PVG stimulation is clinically important for patient selection. We and others previously have used preoperative opiate responsiveness as a criteria for selecting patients for PAG–PVG electrode implantation and have believed that patients already tolerant to opiates would not respond to stimulation. The patients reported here clearly refute such an idea. All patients had pain either unrelieved by opiates or had developed tolerance to the analgesic effect of opiates. Inspite of this, excellent pain relief was achieved.

We believe that the endogenous opiate hypothesis to explain pain relief by PAG–PVG stimulation in man is open to serious question. Several recent reports have suggested that other neurotransmitters, particularly serotonin or norepinephrine, may be responsible for pain relief elicited by PAG–PVG stimulation. Our results clearly show that patients in whom pain is unresponsive to opiates or in whom opiate tolerance has developed may benefit from PAG–PVG stimulation.

When pain is due to invasion or destruction of major nerve trunks by malignancy, deafferentation pain results and PAG–PVG stimulation alone rarely provides effective pain relief. In such patients stimulation in thalamic sensory nuclei may provide pain relief either alone or in combination with PAG–PVG stimulation. Although the mechanism of pain relief by thalamic stimulation is unknown, several reports have described inhibition of nociceptive neurons in the spinal dorsal horn by stimulation of thalamic sensory nuclei. An endorphinergic mechanism has not been suggested for pain relief by thalamic stimulation. Considerable success has been reported in the relief of noncancer-related deafferentation pain by thalamic stimulation.

Patients experience paraesthesias in the body regions which correspond to the thalamic nuclear region stimulated and usually achieve effective pain relief only during actual stimulation. Pain relief which outlasts the period of stimulation for 2 to 4 hours or more, as is often seen with PAG–PVG stimulation, rarely occurs with thalamic stimulation. The paraesthesias induced by stimulation are not bothersome to the patient and are not associated with any loss of function. Patients may self-stimulate their thalamus for many hours or days without any known deleterious effect. The use of thalamic stimulation makes possible effective treatment of pains secondary to brachial and lumbosacral plexus invasion and recurrent head and neck cancers, which are not effectively treated by other methods.

Sixteen of our 17 patients experienced excellent pain relief after electrode implantation. One patient, while still hospitalized, became rapidly tolerant to the analgesic effect of PAG–PVG stimulation. This patient had pain due to lumbosacral plexus invasion, and eventually underwent bilateral cordotomy, which resulted in complete pain relief but loss of sphincter control and inability to ambulate. Two other patients had partial pain relief but required some narcotic usage at hospital discharge but neither patient has increased narcotic usage over follow-up periods.
up to 12 months. Thirteen patients (76%) no longer required narcotics for pain relief at hospital discharge. Eleven of these patients did use narcotics to some extent later in the course of their illness, most commonly in the terminal phases. Even in these patients, however, their quality of life was markedly improved. Five patients who had been hospitalized for periods up to 5 months, solely for attempted pain control, could be discharged from the hospital with excellent pain relief due to stimulation alone.

**Conclusion**

We believe that electrical stimulation of the brain offers an excellent alternative for relief of intractable pain due to recurrent or metastatic malignancies. Pain relief may be achieved in a large proportion of patients, even those unresponsive or tolerant to the analgesic effects of opiates. This pain relief can be achieved by a safe surgical procedure, performed under local anesthesia, without interference with normal neurologic function.

**REFERENCES**

34. Meyerson BA. Electrostimulation procedures: Their effects, presumed rationale and mechanisms. In: Bonica JJ, Lindblom U, Igo A,


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**Erratum**

A correction should be noted in the article by Rodriguez-Cuevas _et al._, "High-altitude paragangliomas diagnostic and therapeutic considerations," (Cancer 1986; 57:672–676). On page 673, the last sentence of the third paragraph of the "Results" section should read, "In six cases (15%), the tumors bulged into the lateral wall of the oropharynx."