Peripheral Neuromodulation for Migraine Headache

Damien J. Ellens[a] · Robert M. Levy[a–c]

Departments of [a]Neurological Surgery, [b]Physiology and [c]Radiation Oncology, Feinberg School of Medicine, Northwestern University, Chicago, Ill., USA

Abstract

Extremely high prevalence among general population along with the high percentage of treatment-refractory cases makes migraine headaches one of the potentially largest indications for neuromodulation. Cranial peripheral nerve stimulation targeting the occipital nerve(s) alone or in combination with others appears to be both safe and efficacious for the treatment of medically intractable migraine headaches. Although initial reports of occipital nerve stimulation for migraine headaches were very encouraging, this clinical benefit was not clearly confirmed in larger-scale prospective randomized trials. Moreover, the exact mechanism of neuromodulation effect in migraine treatment remains unclear. Significant further investigation needs to be performed to optimize our knowledge concerning patient selection, stimulation targets and parameters and device programming, and further improve clinical results. At present, neurostimulation for migraine headache pain is performed in the United States on an 'off-label' basis, but based upon our experience and the increasing evidence in the medical literature, we look forward to its approval by the FDA in the near future so that patients suffering from severe, medically intractable headache pain may gain access to these potentially important therapies.

Almost 40 million Americans suffer from intractable migraine, chronic daily headache, cervicogenic and secondary headache syndromes including occipital neuralgia [1]. About 5% of these patients suffer daily or near daily headaches, including transformed migraine and chronic daily headaches, resulting in significant loss of quality of life related to narcotic dependence, restriction in daily activities, failed personal and career objectives and an overwhelming sense of despair and hopelessness [2].

The term 'chronic daily headache' refers to a group of nonparoxysmal headaches, including those associated with overuse of pain-relieving medications, that present on a daily or near daily basis with a duration of greater than 4 hours a day and lasting longer than 6 months [3]. Roughly 2.2 million Americans, about 0.5–6% of the population, are afflicted by chronic daily headaches [4]. Episodic migraine headaches cost

American employers 13 billion USD a year from absenteeism, with direct treatment costs running over USD 1 billion annually [5].

Pharmacotherapy for migraine headaches includes those medications that offer acute pain relief (abortives) and those used for migraine prevention. Pharmacologic options for acute pain relief include nonsteroidal anti-inflammatory agents, triptans, opioids, ergot compounds and sedatives. Medications effective in headache prevention include anticonvulsants, antidepressants, beta-blockers and serotonin antagonists. Since migraines are often triggered by environmental or emotional factors, recognition and avoidance of precipitating agents like caffeine, stress and a number of foods can provide significant relief and decrease the need for medications. Alternative nonpharmacological migraine treatment options include acupuncture, biofeedback, massage and diet control.

Ablative and decompressive neurosurgical techniques have been tried in patients with migraine headaches. In the past, neurosurgeons performed occipital neurolysis and neurectomy for the treatment of headache pain. Such techniques may result in delayed neuropathic pain in the sensory distribution of the affected occipital nerve(s). Ganglionectomy at the second cervical level was reported to be 80% effective at a 3-year follow-up in posttraumatic second cervical pain syndromes [6]. Nontraumatic pain in this region was not, however, significantly relieved by ganglionectomy, and the procedure is not without risk. Second cervical nerve decompression was also reported to be nearly 80% effective in providing pain relief at 2 years [7]. Posterior rhizotomy at the first, second or third cervical level performed by ventrolateral dorsal root entry zone lesioning is sometimes effective but is highly invasive and has a significant risk [8]. Neurolysis of the greater occipital nerve is often effective initially in controlling pain, but patients commonly report significant recurrence within 2 years [9]. Peripheral nerve stimulation using a cuff electrode was found to be effective in 6 patients with occipital neuralgia [10]. Direct stimulation of the greater occipital nerve has also been shown to be very effective in relieving painful peripheral neuropathy [11].

The use of implanted neurostimulation for the treatment of migraine headache is a relatively recent development. When Weiner and Reed [12] first reported their use of percutaneously implanted occipital nerve stimulation electrodes, the stated indication for this treatment was that of occipital neuralgia. However, subsequent evaluation of 8 of these patients by positron emission tomography demonstrated patterns most consistent with chronic migraine headaches [13]. Subsequently, other reports found occipital nerve stimulation efficacious for the treatment of several headache disorders including migraine headaches [14, 15], cluster headache [16, 17], hemicrania continua [18] and true occipital neuralgia [19].

Surgical Procedure

The standard surgical procedure for occipital nerve stimulation has been significantly refined since its first description [12]. Multiple authors have contributed to the

technical development of neurostimulator electrode placement describing the use of both cylindrical and paddle-type leads [14, 15, 20, 21].

For the stimulation trial procedure, percutaneous-type cylindrical leads are used almost exclusively. Trial lead placement is performed with the patient in the supine position with the head turned sharply away from the side of pain. After the injection of local anesthetic at a point 1 cm caudal and 1 cm medial to the tip of the mastoid process, a bent Tuohy needle is advanced under fluoroscopic guidance into the subcutaneous space toward the posterior cervical midline. The needle is advanced until the tip of the needle projects over the odontoid process of C2 on antero-posterior fluoroscopic images. The stylet of the needle is removed and replaced with a multi-contact cylindrical lead; centering the contacts over the expected location of the occipital nerve(s). A purse-string suture is placed around the exit site of the Tuohy needle through the skin and the needle is carefully withdrawn and removed. Physiologic testing is then performed and the lead position is adjusted until the patient reports stimulation-induced paresthesias throughout the distribution of the nerve. The purse-string suture is then secured around the exit of the lead through the skin and the wound is dressed.

If trial stimulation is successful, permanent surgical implantation is usually undertaken. The surgical technique using percutaneous-type cylindrical neurostimulation leads involves making a vertical incision about 2 cm long down to the cervicodorsal fascia, either 1 cm caudal and 1cm medial to the tip of the mastoid process (for the lateral to medial approach) or at the posterior midline at the level of C1 (for the medial to lateral approach). For the former approach, the patient is positioned supine with their head turned sharply away from the side of their pain; for the latter approach, the patient is placed in the prone position. A subcutaneous pocket above the fascia is developed to accommodate the fixation hardware and for placement of a redundant loop of the electrode wire.

A Tuohy needle is gently bent to a curve similar to the curvature of the neck, and is then passed under fluoroscopic guidance transversely into the subcutaneous plane across the course of the occipital nerve(s) to the posterior cervical midline. At this level, the greater and lesser occipital nerves are located within the cervical musculature and overlying fascia. Single (for unilateral) or dual (for bilateral) four or eight electrode leads may be used; these can be placed from midline toward either side, or across the entire cervical curvature from one side to the other, or by using bilateral incisions.

Once the lead is adequately positioned, the lead is fixed to the underlying fascia using two silicone anchors secured with nonabsorbable suture material [22]. A strain relief loop is made in the lead wire to help prevent migration by decreasing electrode traction during normal patient movement. The lead is then tunneled to a pulse generator implanted over the chest wall.

While many authors prefer this transverse lead orientation which provides the possibility of stimulating the greater, lesser and potentially third occipital nerves,

some favor a vertical lead trajectory which allows for stimulation along the peripheral branches of the occipital nerve. Another variation in technique employs subcutaneous placement of paddle-type leads, with the electrode contacts oriented down towards the fascia, which provide unidirectional stimulation and greater current densities.

Mechanism of Action

There are two prevailing theories with respect to the potential mechanism of action of peripheral nerve stimulation in the relief of migraine headache pain. The first of these invokes modulation of the same gait-control mechanism implicated in the mechanism of action of spinal cord or peripheral nerve stimulation for somatic neuropathic pain [23]. The second suggests that retrograde activation of the C2 and C3 nerve roots, resulting from occipital nerve stimulation, modulates the brainstem nuclei involved in the trigeminal-vascular system thus inhibiting or aborting migraine headaches. The group of Goadsby and Weiner [13] evaluated 8 patients with chronic migraine treated with bilateral suboccipital stimulation using positron emission tomography (PET). Patients underwent PET imaging during three phases: (1) with their stimulators at optimum pain relief settings with the patients experiencing stimulation-induced paresthesias, (2) with the stimulator off and the patient experiencing pain without stimulation induced paresthesias, and (3) with the stimulator partially active with intermediate levels of pain and paresthesia. Significant blood flow changes were seen in the dorsal rostral pons, anterior cingulate cortex and cuneate nucleus; this pattern suggested stimulation induced modification of the brainstem trigeminal vascular system implicated in migraine headaches. Interestingly, the areas of activity during stimulation were, in fact, similar to the pattern seen in episodic migraine.

Independent Clinical Trials

In a study of 13 occipital neuralgia patients implanted with percutaneous occipital leads followed for 18 months to 6 years, 12 patients continued to report good to excellent response and required minimal oral analgesic medications [12]. Upon independent evaluation of the clinical vignettes of these patients, it was suggested that these patients rather suffered from migraine headaches. In a subsequent report of 25 patients with occipital neuralgia treated with occipital percutaneous neurostimulation leads, with an average follow-up of 18 months, 88% showed a positive response, with an overall 50% reduction in headache days [14]. Slavin et al. [19] reported 10 patients with occipital neuralgia treated with percutaneous occipital stimulation; 70% reported good pain control at 22 months, with between 60

and 90% pain relief; patients also decreased their use of analgesics and continued employment.

Oh et al. [15] reported 20 patients suffering from transformed migraine headaches treated with occipital paddle type neurostimulation leads. All patients had greater than 75% pain relief at 1 month. 80% reported greater than 75% pain relief at 6 months, and 95% reported both improvement in their quality of life and their willingness to undergo the procedure again.

Eight patients with drug-resistant chronic cluster headaches were treated with suboccipital neurostimulation on the side of the headache and reported by Magis et al. [17]. At a mean follow-up of 15 months, 2 patients were pain free, 3 had 90% reduction in headaches, and 2 patients had 40% improvement. In another study, 10 of 14 patients with intractable chronic cluster headache treated with bilateral occipital nerve stimulation reported significant improvement [16].

Industry-Sponsored Clinical Trials

As of 2010, neurostimulation for the treatment of migraine headache is not approved by the Food and Drug Administration. As such, it is used by physicians on an 'off label' basis. While this is both reasonable and appropriate, industry is not allowed to market or promote the use of their products for 'off-label' indications. In light of this limitation, and the significant potential of neuromodulation for the treatment of migraine headache, all three of the major equipment manufacturers in this sector (Medtronic, Minneapolis, Minn., St. Jude Medical, Plano, Tex., and Boston Scientific, Valencia, Calif., USA) have sponsored research trials to investigate the safety and efficacy of their neurostimulation products for the treatment of migraine headaches. Thus far, these corporate sponsored trials have been the largest and best designed studies of neuromodulation for headache.

Medtronic
The Occipital Nerve Stimulation for the Treatment of Intractable Migraine (ONSTIM) trial, sponsored by Medtronic, was a preliminary study to determine whether a well designed placebo controlled trial could provide insights into the potential risks and benefits of occipital nerve stimulation in patients with migraine headache. These insights could then be used for the design of a phase III pivotal trial which, if it met its primary endpoint(s), might lead to FDA approval of this therapy. This trial collected electronic diary data from patients enrolled at 9 centers over 3 months who reported 15 or more headaches per month and were not responsive to conventional medical therapies. Patients were randomized into three groups: in one group, patients received a neurostimulator and had the ability to control the level of stimulation, in the second group, patients received a neurostimulator as part of a device control group, and the third group received standard medical management. A positive response was defined

as at least 50% reduction in the number of headache days per month, and/or a 3 or more point reduction in pain intensity on a 0- to 10-point pain scale. The ONSTIM trial further collected three years of safety data on enrolled patients.

The results of this multicenter, randomized, blinded controlled feasibility trial were recently published [24]. Of note is that all subjects eligible for the trial received an occipital nerve block and randomization required a positive response to the nerve block. Seventy-five of 110 enrolled subjects were assigned to a treatment group and complete data were available for 66 of these patients. Three-month responder rates were 39% for the group receiving active occipital nerve stimulation, 6% for the surgical control group, and 0% for the group receiving medical management only. There were no adverse device events reported while lead migration occurred in 12 of 51 (24%) of subjects.

St. Jude Medical
St. Jude Medical Neuromodulation has sponsored an Investigation Device Exemption pivotal trial to evaluate occipital nerve stimulation in chronic migraine patients. 150 patients were randomized from 15 centers, with success defined as a 50% reduction in pain and no increase in headache frequency or duration. Other headache measures included the Migraine Disability Assessment (MIDAS) questionnaire, Headache Index, Pain and Distress Score and patient satisfaction. Patients were randomized in a 2:1 ratio to either a stimulation trial followed by device implantation and active stimulation for 12 weeks or a stimulation trial followed by device implantation but sham stimulation for 12 weeks. After 12 weeks, subjects were unblinded but continued to be followed for 1 year. Data collection from this study has been completed and we await publication of the data.

Boston Scientific
Boston Scientific performed a prospective, randomized, double-blind, placebo-controlled trial of occipital nerve stimulation for drug refractory migraine named the PRISM (Precision Implantable Stimulator for Migraine) trial. The results of the PRISM study were presented at the 14th Congress of the International Headache Society and the 51st Annual Scientific Meeting of the American Headache Society in September, 2009 [25]. 132 patients who met the 2004 International Classification of Headache Disorders (ICHD-2) criteria for migraine were enrolled. All patients had failed therapy with a least two acute and two preventive medications, and all had 6 days or more per month of migraine headaches lasting 4 or more hours with moderate to severe pain. Prior to permanent implant, all subjects underwent percutaneous trial stimulation.

During the 12-week blinded period, patients were randomized in a 1:1 ratio to receive bilateral active stimulation or sham stimulation. At 12 weeks, all patients were converted to active stimulation. The primary endpoint of the study, change from baseline in migraine days per month, was evaluated at 12 weeks 125 subjects; there

was no significant difference between groups (−5.5 vs. -3.9 days/month; p = 0.29). In patients who responded positively to a percutaneous trial, however, stimulation reduced migraine days per month by 8.8 days, as compared with 0.7 days in those whose trial failed to provide relief (p < 0.001). Two-year follow-up data showed that the most frequent adverse events were device infection, non-target area sensory phenomena and pain at the implant site.

The Northwestern Experience

Having a similar experience to that reported in the ONSTIM trial, with only about 40% of migraine headache patients having a significant response to occipital nerve stimulation, we began several years ago to look for possible explanations and alternative solutions. In our experience, patients whose pain was located within the sensory distribution of the occipital nerve(s), or those who identified that their headache pain originated from the occipital nerve(s) tended to respond overwhelmingly to occipital nerve stimulation. Those patients whose migraine pain fell outside these areas, however, tended to respond poorly. We thus began to question the hypothesis that occipital nerve stimulation was helping migraine headache pain by retrograde modulation of the trigeminal vascular system. We proposed that neurostimulation for migraine headache pain acted in a manner similar to that of peripheral nerve stimulation for somatic pain; that is, through a 'pain gate control' mechanism [23] where the degree of pain relief correlates directly with the degree of overlap of the pain with stimulation induced paresthesias [26].

To further investigate this proposal, we began to carefully map out the topography of patient's usual migraine headache pain. We then identified those specific cranial and peripheral nerves whose sensory distribution covered these areas of pain and proposed cranial peripheral nerve stimulation of any and all of those involved nerves. These nerves have included the greater and lesser occipital nerves as well as the supraorbital, auriculotemporal, infraorbital, supratrochlear and infratrochlear nerves. We then embarked on a trial of cranial peripheral nerve stimulation in patients who had failed aggressive medical therapy including comprehensive pharmacologic trials, selective nerve root blocks, and psychological therapies.

In a prospective, nonrandomized group of 50 patients, 45 of whom were diagnosed with chronic daily headache or chronic migraine, data collected by non-interested third parties revealed that 83% of patients reported a good to excellent relief at two year follow-up with an additional 9% reporting satisfactory pain relief of 30% or more. All 92% of these patients indicated their retrospective willingness to have the device implanted based upon their 2-year experience and their unwillingness to have the devices removed [unpubl. data]. This approach is not without its complications. While infection and lead erosion are uncommon problems, lead migration or fracture occurred in up to 66% of patients [unpubl. data]. Fewer lead revisions have been

seen in patients after adopting more aggressive fixation techniques and with the use of larger percutaneous leads, but this remains a problem that suggests the need for hardware specifically designed for this application.

Conclusion

Cranial peripheral nerve stimulation, whether of the occipital nerve(s) alone or in combination with others, appears to be both safe and efficacious for the treatment of medically intractable migraine headache. Significant further investigation needs to be performed to optimize our knowledge concerning patient selection, stimulation targets and parameters and device programming and further improve clinical results. At present, neurostimulation for migraine headache pain is performed in the United States on an 'off-label' basis, but based upon our experience and the increasing evidence in the medical literature, we look forward to its approval by the FDA in the near future so that patients suffering from severe, medically intractable headache pain may gain access to these potentially important therapies.

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Robert Levy, MD, PhD
Department of Neurological Surgery
Feinberg School of Medicine, Northwestern University
676 North St. Clair Street Suite 2210, Chicago, IL 60611 (USA)
E-Mail rml199@northwestern.edu