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Neurostimulation for Primary Headache Disorders

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Abstract

Neurostimulation has emerged as a potential treatment option for patients with chronic, disabling, intractable primary headache disorders. Although safety and efficacy data are limited in quantity, there is accumulating experience with the use of peripheral nerve stimulation for the treatment of intractable occipital neuralgia, cluster headache, migraine, and less common headache disorders. Deep brain stimulation has been used to treat intractable chronic cluster headache and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing. This article discusses the theorized mechanisms of action of these novel treatment modalities and summarizes current knowledge regarding safety and efficacy of neurostimulation for the treatment of headache.

Introduction

Neurostimulation may be a useful treatment for the most refractory and disabling primary headache disorders. Peripheral nerve stimulation—in most cases involving branches of the occipital nerve or supraorbital nerve—has been used to treat occipital neuralgia, chronic migraine, cluster headache, hemicrania continua, and other craniofacial pain. Deep brain stimulation (DBS) of the posterior hypothalamus has been used to treat short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and cluster headache. Given the invasive nature of these modalities, neurostimulation is reserved for patients with chronic headache disorders that result in significant disability and are intractable to conventional therapies. Although it is difficult to determine the number of patients meeting criteria for refractory headache, unfortunately such patients are not rare. For example, 15% to 20% of patients with chronic cluster headache do not adequately respond to pharmacologic monotherapy [1]. Some of them will respond to polypharmacy, but many will not and may thus benefit from surgical treatment. Another example is that some patients with hemicrania continua do not tolerate or have contraindications to indomethacin. Because other medications may provide limited or no benefit, there may be a role for neurostimulation. Similarly, some patients with chronic migraine, occipital neuralgia, and other cranial pain are severely disabled from their refractory headache disorders and may thus benefit from interventional approaches.

This article discusses the proposed mechanism by which neuromodulation treats headache as well as the safety and efficacy of such treatment.

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Peripheral Nerve Stimulation

Mechanism of action

Electrical stimulation of peripheral nerves results in pain modulation by direct effects on the stimulated nerve as well as secondary effects on the central nervous system.

The theorized mechanism by which peripheral nerve stimulation reduces pain in the periphery is based upon the ideas of Melzack and Wall [2]. The Melzack–Wall gate-control theory suggests that there is an inverse relationship between activity in small-diameter nociceptive afferents and large-diameter nerve fibers. Stimulation of large-diameter fibers leads to suppression of small-diameter fiber nociceptive input and elevation of pain thresholds. Thus, for example, electrical stimulation of large-fiber C2–C3 nerve branches (occipital nerve stimulation [ONS]) is expected to decrease activity in small-diameter nociceptive fibers, resulting in pain relief. Although the gate-control hypothesis suggested that this interaction occurred in the dorsal horn of the spinal cord, additional studies have shown alteration of peripheral nerve activity prior to the first spinal cord synapse [3].

Stimulation of peripheral branches of the occipital nerves also has central nervous system effects. This finding is not unexpected given our current understanding of the trigeminocervical pain pathway, a pathway that plays an essential role in migraine and other headaches. Animal and human studies have shown that the trigeminocervical pathway is multidirectional, with activation of one part of the system resulting in activation of other components. For instance, mechanical and electrical stimulation of the superior sagittal sinus results in activation of cells that extend from the trigeminal nucleus caudalis to C1 and C2 dorsal horns [4,5]. Furthermore, stimulation of the greater occipital nerve has been shown to increase metabolic activity in the dorsal horn at C1 and C2 as well as in the trigeminal nucleus caudalis [6]. Positron emission tomography studies of eight patients with chronic migraine effectively treated with bilateral ONS demonstrated central effects of stimulation, including alteration in thalamic activation that correlated with improvement in head pain [7]. Thus, pain modulation via ONS produces beneficial effects for headache via the peripheral and central nervous systems.

Supraorbital nerve stimulation likely exerts its effects in a fashion similar to ONS. The supraorbital nerve, a terminal branch of the frontal nerve, is derived from the first division of the trigeminal nerve. Stimulation of the supraorbital nerve may thus have effects not only in this peripheral nerve but also centrally via the trigeminocervical complex.

Occipital nerve stimulation

ONS has been used for several headache disorders, including occipital neuralgia, migraine, cluster headache and other trigeminal autonomic cephalalgias (TACs), and hemicrania continua. Although the number of patients with intractable headache disorders treated with ONS remains small, early data on efficacy suggest that ONS is beneficial in each of these headache disorders. A comprehensive systematic review of ONS for the treatment of chronic headache has been recently published [8].

At this time, ONS is considered only for the treatment of chronic intractable headache disorders that result in significant disability. Medication overuse headache should be ruled out prior to consideration for ONS. Although a positive but transient response to occipital nerve blockade has frequently been used as a prerequisite to an ONS trial, evidence suggests that it may not be a good predictor [9]. Most centers use a 5- to 7-day percutaneous stimulator trial to test efficacy and tolerability before permanent implantation. Although such a trial may be a decent predictor of tolerability, its predictive value for efficacy of permanent implantation is unknown. Furthermore, it is not clear if this trial provides benefits

beyond testing at the time of stimulator placement followed by permanent implantation as indicated. Given data suggesting that ONS may not be beneficial until after several months of stimulation, the predictive value of both methods is questioned.

Occipital neuralgia—Several groups have reported using ONS to treat occipital neuralgia. Weiner and Reed [10] presented 13 patients with intractable occipital neuralgia treated with ONS. All of them had received transient relief from occipital nerve blocks, and seven had failed ablative procedures prior to ONS. At last follow-up, ranging from 1 year to 6 years (mean, 2 years), two-thirds of the patients had greater than 75% pain relief and one-third had 50% to 75% pain relief. The need for medication was reduced significantly. One revision for lead migration and one electrode replacement due to breakage and infection were required. The stimulator was removed from one patient after symptoms resolved.

Sixteen subjects were prospectively enrolled in a study of ONS for the treatment of C2-mediated occipital headaches [11]. Of the 14 undergoing a stimulator trial, 11 had at least a 50% reduction in visual analogue scale (VAS) scores and thus underwent permanent implantation. Twelve weeks after implantation, there were significant reductions in scores on the Short-Form McGill Pain Questionnaire (24.6 to 8.9; $P = 0.0013$), VAS (9.3 to 3.1; $P < 0.0001$), and Present Pain Index (3.6 to 1.2; $P = 0.0009$). Seventy-three percent of patients subjectively reported excellent or good relief, and 27% felt their response was poor. Two subjects had adverse events: one required intervention for a loose connection and one for lead migration.

Similarly promising results have been reported in other case series. Slavin and colleagues [12] reported on 10 patients who were treated with ONS and followed for a mean of 22 months. At last follow-up, five patients were pain free and three continued to have significant benefit. One patient required stimulator explantation because of chronic infection, and one required surgical intervention for lead migration and then explantation due to lack of efficacy and muscle spasms. A series of six patients showed significant reductions in VAS score (8.66 to 2.5; $P < 0.0001$) and Pain Disability Index (49.8 to 14.0; $P < 0.0005$) 3 months after implantation and reported no adverse events [13]. Of 10 patients undergoing ONS in a series by Oh et al. [14], seven reported greater than 90% pain relief and one reported 50% to 74% pain relief 6 months after implantation. Two patients requested removal of the stimulator due to worsening pain. In a series by Johnstone and Sundaraj [15], seven of eight patients undergoing a stimulator trial had greater than 50% pain reduction and thus underwent permanent implantation. At an average of 25 months of follow-up, five of seven patients had reductions in VAS scores and the total quantity of required pain medications was reduced. Two patients suffered from stimulator-related infection requiring explantation and reimplantation.

Cluster headache—Several groups have published safety and efficacy data on ONS for the treatment of chronic cluster headache.

Burns et al. [16••] and Magis et al. [17] reported their experiences with eight subjects in each of their series. Subjects were stimulated bilaterally in the series by Burns et al. [16••] and unilaterally in the series by Magis et al. [17]. In the series by Burns et al. [16••], the median follow-up was 20 months. Subjective self-assessment of benefit was graded as substantial (90%) by two patients, moderate (40%) by three, mild (25%) by one, and nonexistent by two. Notably, five of eight patients continued to have daily attacks of cluster headache, and six of eight patients reported that they would recommend the use of ONS to similarly afflicted patients. There were no complications in four patients and six complications in the other four: excessive pain at incision site (1), electrode migration (3), electrode fracture (1), and shocklike sensation due to kinking of wires (1). As expected,

battery depletion was reported in four, which required surgery for replacement. In the series by Magis et al. [17], at a mean follow-up of 15.1 months, two of eight patients were pain free, three had an approximate 90% reduction in headache frequency, two had an approximate 40% reduction, and one experienced no benefit. The cluster attacks shifted sides in two patients, requiring suboccipital steroid injections. One patient had electrode migration, one had lead displacement after a fall, two had thoracic discomfort or tingling, four had battery depletion, and in one the stimulator was turned off due to lack of efficacy and unbearable paresthesias (some patients had more than one complication).

In a report by Lainez et al. [18], three of five patients with chronic cluster headache obtained excellent responses, one obtained a partial response, and one was unresponsive 24 months after initiation of bilateral ONS. No adverse events were reported. A study of three cluster patients with a mean follow-up of 20 months reported less benefit [19]. Headache frequency was unchanged in two subjects and increased in one, and headache severity decreased in two and was not changed in one. Two patients required revisions for lead migration. Prospective analysis of four chronic cluster patients treated with ONS by Vargas et al. [20] found that three had positive responses. Two patients had stimulation-related neck pain, and one required surgery for a faulty battery.

The beneficial effects of ONS for the treatment of cluster headache are often delayed, reaching their maximum after several months of stimulation [16•,17,18]. This observation must be considered if one is using a beneficial response to a short trial with a percutaneous stimulator as a prerequisite for permanent implantation, when determining the role for continued stimulation in an individual patient, and for setting outcomes in prospective clinical trials.

Migraine—ONS outcomes for the treatment of intractable transformed migraine have been reported in 25 patients by Popeney and Alo [21] and in 10 patients by Oh et al. [14]. At a mean follow-up of 18.3 months, 88% of the patients studied by Popeney and Alo [21] received significant benefit, defined as greater than 50% reduction in headache frequency or severity. There were significant reductions in headache frequency (75.6/90 days to 37.5/90 days; $P < 0.001$), severity (9.32 to 5.72 on a pain scale from 1 [mildest pain] to 10 [most severe pain]; $P < 0.001$), and headache-related disability (Migraine Disability Assessment [MIDAS] score 121 to 15). There were six traumatic and three spontaneous lead migrations and one infection. In the series by Oh et al. [14], seven patients reported greater than 90% pain relief and two reported 75% to 90% relief 6 months after stimulator implantation. One patient was lost to follow-up. Of two patients with infection, one required stimulator explantation. All 10 patients were satisfied with stimulation, reporting that they would have the surgery again.

ONS outcomes for chronic migraine have been reported in another 16 patients [7,19]. Matharu et al. [7] reported that at a mean follow-up of 1.5 years, four of eight patients had an excellent response (headaches completely suppressed with only rare breakthrough headaches), two had a very good response (breakthrough headaches about 10 days per month), and two had less benefit (continued constant headaches but with severity reduced 50%–75%). All patients significantly reduced or discontinued use of headache medications. Complications included four lead migrations and one abdominal hematoma developing immediately postoperatively at the site of the implantable pulse generator. In a separate study of eight patients with chronic migraines, at a mean follow-up of 17.8 months ONS resulted in significant reductions in headache days (90/90 days to 60/90 days; $P = 0.04$), headache severity (6.75/10 to 4.5/10; $P = 0.009$), headache-related disability (MIDAS score, 170 to 116; $P = 0.048$; HIT-6 version of the Headache Impact Test, 73 to 61; $P = 0.02$), and depression scores (Beck Depression Inventory, 19 to 11.5; $P = 0.07$) [19]. Adverse events

included three lead migrations, one implantable pulse generator malfunction, one case of neck stiffness, and one case of incision site pain.

Preliminary results from the first prospective, single-blind, randomized study of ONS for intractable chronic migraine were reported at the annual scientific meeting of the American Headache Society in June 2008 [22]. The primary aim was to test feasibility and safety, and a secondary goal was to test efficacy. Thus, many measures of efficacy were explored without a priori selection of primary end points and without statistical correction for multiple comparisons. Sixty-six subjects completed the study. The overall response rate, defined as a 50% or greater reduction in headache days per month or a three-point or greater reduction in overall pain severity, was 39% (13 of 33) in the treatment group (ONS with adjustable stimulation), 0% in the medically managed group (control), and 6% in the “implanted control group” (ONS with preset stimulation parameters). In the treatment group, headache frequency at 3 months was reduced by 27% (22.4 to 15.7 d/mo) and headache severity by 1.4 points (5.2 to 3.8). Lead migration occurred in 24% of the subjects who received implants. Other “expected” adverse events were stated to have occurred but were not discussed.

Other headache disorders—ONS has been used in a few cases of hemicrania continua, paroxysmal hemicrania, and SUNCT. Significant benefit from ONS has been reported in two patients with hemicrania continua who were intolerant of indomethacin [19]. At a mean follow-up of 17 months, headache frequency dropped from 90 of 90 days to 10 and 12 days, and there were reductions in headache severity, headache related-disability, and depression scores. Goadsby [23] reported that two of three patients with paroxysmal hemicrania and one of two patients with SUNCT treated with ONS had significant benefit.

Table 1 summarizes the efficacy and safety of ONS.

Supraorbital nerve stimulation

A few cases of supraorbital nerve stimulation have been reported. In one retrospective case series, 10 subjects had permanent implantation of a supraorbital nerve stimulator for the treatment of chronic, intractable frontal and frontotemporal headaches unresponsive to medication [24]. Sixteen patients were selected for a trial of supraorbital nerve stimulation after diagnostic supraorbital and supratrochlear nerve blocks and cryodenervation or pulsed radiofrequency of the supraorbital and supratrochlear nerves. Patients who had transient positive responses underwent a 5- to 7-day stimulator trial. Ten subjects, each having at least a 50% improvement in headache score, then underwent permanent implantation. Permanent implantation resulted in significant reductions in pain and use of opiate pain medications. Three subjects required lead revisions, two of whom had superficial infections responsive to oral medications. Single case reports of supraorbital nerve stimulation for supraorbital neuralgia and for the treatment of cluster headache have been published [25,26]. Slavin et al. [27] reported on five patients undergoing supraorbital nerve stimulation for craniofacial pain. Further studies are required to determine the safety and efficacy of supraorbital nerve stimulation for treating headache disorders.

Deep Brain Stimulation

DBS of the periventricular and periaqueductal gray matter, thalamus, and internal capsule has been used to treat medically intractable chronic pain disorders. Hypothalamic DBS has been applied for the treatment of cluster headache and SUNCT. Given the inherent risks of DBS for the treatment of headache, it is reserved for patients with treatment-resistant chronic and disabling headache disorders. Patient selection criteria for DBS in chronic cluster headache have been proposed [28].

Mechanisms of action

The posterior hypothalamus plays a role in the pathophysiology of the TACs and hemicrania continua. Both metabolic and structural brain imaging have implicated the hypothalamus as a player in cluster headache. Functional imaging studies have revealed metabolic activation of the ipsilateral ventroposterior hypothalamus during nitroglycerin-induced and spontaneous cluster headache attacks [29,30]. Brain morphometric imaging has shown increased hypothalamic gray matter density in subjects with cluster headache [31]. The posterior hypothalamus also has been shown to play a physiologic role in SUNCT, paroxysmal hemicrania, and hemicrania continua [32–34]. Activation of the posterior hypothalamus is thought to be specific to the TACs and hemicrania continua and not simply a component of all headache pain pathways. Thus, the posterior hypothalamus has been the focus for neuromodulatory therapy in treatment-resistant chronic cluster headache and SUNCT.

Although the posterior hypothalamus plays a key role in the TACs, the method by which the hypothalamus may generate cluster headache and the methods by which stimulation of this structure alters headache patterns have yet to be determined. DBS may provide an analgesic effect by reducing the cluster headache-triggering activity of the hypothalamus, increasing pain thresholds, or altering activity in neuronal pain-processing pathways [35,36]. Because the posterior hypothalamus is activated in cluster headache and has been proposed as a cluster headache generator, it is plausible that reducing activity in the posterior hypothalamus via DBS directly leads to reduction in the frequency of cluster attacks. Benefit from DBS could also be attributed to an increase in pain thresholds. Quantitative sensory testing has suggested that hypothalamic DBS results in increased pain thresholds. Schoenen and colleagues [37] found increased extracephalic pressure and electrical pain thresholds in four patients being treated with DBS. Leone and colleagues [38] found that stimulated patients had increased cold pain thresholds in the ophthalmic division of the trigeminal nerve ipsilateral to stimulation. Hypothalamic DBS has been shown to modulate both local (hypothalamus) and distant brain structures. The effects of bilateral hypothalamic DBS on pain-processing pathways were investigated by positron emission tomography in 10 subjects with cluster headache [35]. Stimulator-induced activations were identified not only in the ipsilateral posterior inferior hypothalamic gray but also in the thalamus, somatosensory cortex, precuneus, anterior cingulate cortex, trigeminal nucleus, and trigeminal ganglion. Deactivations were identified in the middle temporal gyrus, posterior cingulate cortex, inferior temporal gyrus bilaterally, and the contralateral anterior insula. These findings suggest that the beneficial effects of hypothalamic DBS are due to modulation of multiple components of the pain pathway. Thus, hypothalamic DBS may exert its therapeutic effects by direct modulation of the posterior hypothalamus, which may act as a TAC “generator,” as well as by modulation of distant structures involved in pain processing.

Safety and efficacy

Several authors have reported on the safety and efficacy of DBS to treat medically intractable chronic cluster headache [37,39••,40–45]. Leone and colleagues [39••] reported outcomes of 16 patients at a mean of 23 months (range, 1–52 months) after initiation of DBS. All patients met International Headache Society criteria for chronic cluster headache. They had suffered from chronic cluster for a mean of 3 years (range, 1–10 years) and experienced five to eight attacks per day. They had normal evaluations for secondary causes of cluster headache and were intractable to multiple conventional therapies prior to DBS. Two patients were treated with bilateral stimulation due to attacks that alternated sides. Fifteen of the 18 (83.3%) implants (13 of the 16 patients) resulted in abolition or major improvement in pain. Eleven (61.1%) implants (10 patients) resulted in complete cluster headache relief, and four implants resulted in near-complete relief with remaining sporadic

attacks. The remaining three implants resulted in a reduction in frequency, intensity, and duration of attacks but with less exuberant response. Five patients remained on prophylactic medications. The mean duration of time until stable benefit was 42 days (range, 1–86 days). The benefit was noted to occur gradually over time and to require multiple amplitude adjustments. Transient diplopia was noted in most patients when the amplitude was increased too quickly, and one patient had a small nonsymptomatic third ventricular hemorrhage following the operative procedure.

Schoenen and colleagues [37] reported the outcomes of six patients with chronic cluster headache treated with ipsilateral ventroposterior hypothalamic DBS. Four patients successfully underwent implantation and stimulation. Two were free of pain at last follow-up (12 and 17 months after implantation), and nitroglycerin no longer triggered a cluster headache. One had a significant reduction in headache frequency, and the fourth had periodic remissions with headache recurrence. The procedure was stopped in a patient who had anxiety, polypnea, tachycardia, and hypertension during the implantation. After implantation, another patient developed a massive intracerebral hemorrhage and died. The four patients with successful implantation reported diplopia and dizziness with high stimulus intensities.

Bartsch and colleagues [40] treated six chronic cluster patients with posterior hypothalamic DBS. At last follow-up, ranging from 9 to 24 months, three patients had a good or excellent response (reduction from one to three attacks per day to no more than one attack per month). Three patients had poor response or no response. Transient vertigo and diplopia, the most frequent side effects, were noted with initiation and reprogramming of DBS.

Further study is necessary to determine the safety and efficacy of posterior hypothalamic DBS for the treatment of cluster headache. Published reports suggest that most patients undergoing implantation benefit from significant or complete relief. Although complication rates have been low, serious complications are certainly possible and have included intracranial hemorrhage and death.

A single case of posterior hypothalamic DBS for the treatment of medically intractable SUNCT was reported in a 66-year-old woman with a 14-year history of SUNCT with a mean of 70 attacks per day [46]. She had a normal diagnostic evaluation ruling out secondary causes and received no benefit from multiple prophylactic medications. Many adjustments in stimulator parameters were required after implantation, and the patient had a fluctuating headache response in relation to these changes. At last follow-up, 17 months after placement of the stimulator, DBS and 100 mg of lamotrigine daily were providing complete headache relief. Transient diplopia was frequently encountered when the stimulation amplitude was increased. Otherwise, stimulation was well tolerated.

Table 2 summarizes the efficacy and safety of DBS.

Conclusions

Neurostimulation is a promising modality for the treatment of chronic, disabling, intractable headache disorders. Additional safety and efficacy data are required to determine the exact role of peripheral nerve stimulation and DBS. Such information will have to be obtained through prospective controlled clinical trials. Several prospective trials of ONS are enrolling patients in North America and Europe, and a prospective multi-center double-blind study of DBS for intractable chronic cluster headache is under way [47].

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Table 1

Efficacy and safety of occipital nerve stimulation *

Subjects	Excellent/good result (%)	Fair/poor result (%)	Complications			
			Equipment revision	Infection	Stimulator-related pain	Other
Occipital neuralgia [10–15]	56	47 (84)	4	4	1	0
Cluster [16•,17–20]	28	16 (57)	9	0	7	0
Migraine [7,14,19,21,22]	83	56 (67)	29	3	2	1: hematoma
SUNCT [23]	2	1 (50)	NR	NR	NR	NR
Hemicrania continua [19]	2	2 (100)	2	0	1	0
Paroxytmal hemicrania [23]	3	2 (67)	NR	NR	NR	NR

* Although outcomes have been reported using different measures, “excellent/good” generally refers to 50% reduction in headache frequency or severity and “fair/poor” to 50% reduction in headache frequency and severity. Complications are reported as the number of events—not the number of patients having the complication. Battery depletion was not considered as a complication because it is an expected occurrence.

NR—not reported; SUNCT—short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

Table 2

Efficacy and safety of deep brain stimulation*

	Subjects	Excellent/good result (%)	Fair/poor result (%)	Complications
Cluster [37,39••,40–45]	38	27 (71)	11 (29)	5: intracranial hemorrhage (2); patient death (1); intolerability (no implantation) (1); intraoperative TIA (1)
SUNCT [46]	1	1 (100)	0 (0)	0

* Although outcomes have been reported using different measures, “excellent/good” generally refers to 50% reduction in headache frequency or severity and “fair/poor” to 50% reduction in headache frequency and severity. Complications are reported as the number of events, not the number of patients having the complication.

SUNCT—short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; TIA—transient ischemic attack.