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Occipital nerve stimulation for primary headaches

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Occipital nerve stimulation may be effective for primary headache disorders. Four studies, including two double-blind show, stimulation-controlled studies that were performed for chronic migraine showed evidence of benefit. A separate study suggested a benefit for combined supraorbital and greater occipital nerve stimulation. Anecdotal evidence suggests benefit in hemicrania continua. In chronic cluster headache, several case series have shown improvement, which, combined with the safety of occipital nerve stimulation relative to deep brain stimulation, have led to published reports supporting this as the preferred surgical technique for chronic cluster headache. A few case reports suggest a possible benefit in short-lasting unilateral neuralgiform headache attacks with conjunctival injection tearing and short-lasting unilateral neuralgiform headache.

KEY WORDS: Chronic headache - Cluster headache - Occipital lobe.

The term "primary headache disorder" refers to a headache that is not attributable to another condition, such as an infection or tumor. Primary headache disorders may have triggers and exacerbating factors, which do not cause the condition. Migraine, cluster headache, and hemicrania continua are three primary headache disorders that are generally acknowledged to be severe and often disabling; tension-type headache is a common primary headache disorder that is not severe or disabling.

Migraine is the most common disabling primary headache disorder. Migraine headaches are typically unilateral and throbbing and are associated with nausea, vomiting, and sensitivity to light, sound, and head movement. Approximately 15% to 20% of migraine patients experience auras (usually visual).

Migraine can be episodic (<15 headache days per month) or chronic (≥15 headache days per month >3 months). While various definitions have been used in studies, discussion of these subtleties is outside of the scope of this article. The FDA, in its approval of onabotulinum toxin for chronic migraine (CM), simply used the frequency and duration numbers above and "a link to migraine" rather than specify the exact number of days a full or partial definition of migraine is attained. CM is a highly prevalent and disabling neurologic disorder affecting approximately 2.0% of the general population.[1, 2] According to the International Headache society, CM is characterized by at least 15 headache days per month of which at least 8 days meet diagnostic criteria for migraine without aura or respond to a migraine-specific acute medication.[3] Compared with those with episodic migraine, individuals with CM experienced significantly greater disability, economic burden, and impairments in health-related quality of life (HRQoL) and overall quality of life.[4-7]

Migraine is a neurovascular pain syndrome. The migraine prodrome is present in 60% of patients. It occurs hours to days before the pain, and symptoms may include mood changes, yawning, fluid retention, nausea, and photophobia. It is thought to be

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related, at least in part, to hypothalamic activation. The aura of migraine most commonly involves positive and negative visual phenomena that increase in size and migrate across a hemifield. It is due to a spreading wave of neural hyperactivity with neuroelectrical quiescence and decreased blood flow following in its wake. The aura activates meningeal nociception, possibly by triggering a reflex mediated by parasympathetic nerves. The pain of migraine is caused by neurogenic inflammation at the meninges and intracranial blood vessels. Neurogenic inflammation causes peripheral and ultimately central sensitization, which respectively explain the throbbing pain of migraine and eventually the cutaneous allodynia that accompanies at least 60% of migraine headaches.

In adults, migraine pain occurs commonly in the occipital area and the neck. Tenderness in the occipital notch may reflect allodynia and muscle tenderness, and trigger points may also represent the central sensitization that occurs in migraine.

Occipital nerve stimulation for treatment of intractable CM

Four studies of CM have been performed. Schwedt studied a mixed group of 15 patients, eight of whom had CM.[10] Statistics were calculated based on all 15 subjects, and data for CM alone within this group are unavailable. Nonetheless, the number of headache days went from 89 to 63 of 90, and median severity from 7.1 to 4.7 on the 11-point verbal rating scale. There was also statistically significant improvement in the Migraine Disability Assessment Score (MIDAS), HIT-6, and Beck Depression Inventory (BDI) scores. Lead migration was the most common adverse event.

Popeney and Alo [9] prospectively studied 25 CM patients for an average of 18 months. Pain scores prior to stimulation averaged 9.3 (on the 11-point verbal pain scale) in 76 headache days over three months. After stimulation, the average severity dropped to 5.7 and the number of headache days to 37.5. Eighty-eight reported a 50% or greater decrease in frequency or severity.

Saper *et al.*.[11] reported on a multicenter, prospective, randomized, single-blind, feasibility study of ONS for chronic migraine and to evaluate potential study outcome measures. No primary endpoint was prespecified. In this trial the neurologist was blinded, the implanter was unblinded, and the implanted subjects were blinded. Using the MIDAS at the beginning of the study, all patients had severe disability (Grade 4). At the completion of the study, 15 had little or no disability (Grade 1). Seventy-five of 110 subjects were assigned to a treatment group with either adjustable stimulation or preset stimulation. Ultimately 28 were implanted and completed their calendars in the adjustable stimulation group, 16 in the preset group, and 17 in the medically managed. The difference between adjustable stimulation, preset stimulation, and the medically managed group was not statistically significant. Overall pain intensity declined by 1.5 points in the adjustable stimulation group and 0.5 and 0.6 in the preset stimulation and medically managed groups.

A responder was a person who achieved a 50% or greater reduction in the number of headache days or a 3-point or greater reduction in overall pain intensity compared to baseline. Using this definition 39% of patients achieved this endpoint, compared to 6% in the preset stimulation group (P=0.032) and 0% in the medically managed (P=0.003). A total of 51 patients were successfully implanted.

There were 56 adverse device events in 36 patients. Twelve of 51 subjects (24%) had lead migration during the 3-month study period. During the open-label followup period an additional eight lead migrations occurred. The three serious adverse events were implant site infection, lead migration, and postoperative nausea leading to hospitalization. Nine percent of the adjustable stimulation subjects, 41% of the preset stimulation subjects, and 24% of the medically managed subjects reported worsened migraine during the study.

Silberstein *et al.*.[8] studied 157 patients of which 105 were randomized to the active stimulation group and 52 to the control group for 12 weeks, followed-up by an open-label phase for up to one year. At 12 weeks the number of headache days decreased 7.3 days per month in the active group (36.6% of days) and 4.2 days in the control group (25.6% of days) (P=0.015).

Other endpoints were measured. The MIDAS decreased 40.8% in the active group and 13.4% in the control group (P=0.001). The total Zung pain and distress score decreased 13.3 points in the active group and 5.5 points in the control group (P=0.001). At the end of 12 weeks subjects were asked to rate pain relief as excellent, good, fair, poor, or unable to decide. The groups differed significantly (P<0.001):

44.4% of active stimulation subjects rated their headache relief as excellent or good compared to 17.3% of the control group. Conversely 20.0% of the active group and 61.5% of the control group rated their control as poor.

At one year, 111 patients still had stimulators. The control group had received active stimulation for 40 weeks. There was a statistically significant mean reduction of the combined group of 7.1 days per month (P<0.001, intention to treat analysis).

Combining occipital nerve stimulation (ONS) with supraorbital nerve stimulation, Reed *et al.*.[19] championed combined occipital and supraorbital neurostimulation for the treatment of CM. He compared stimulation of ONS with combined stimulation, demonstrating greater benefit with the combined approach. During the trial period, one of his patients reported greater than 50% subjective response to occipital stimulation alone, while seven of eight reported 80% to 100% improvement. These seven patients had permanent implantation. At followup, all patients benefitted more from combined stimulation than ONS alone. While this study was unblinded and did not use standardized outcome measures, it does suggest that improved outcomes can be obtained with combined occipital and supraorbital nerve stimulation.

Hemicrania continua

Hemicrania continua (HC) is a primary headache disorder characterized by continuous unilateral headache and by intermittent unilateral cluster-like autonomic features such as, ptosis, lacrimation, or rhinorrhea. By definition, it responds to indomethacin, although continuous high doses of this drug necessary to relieve the headache, the medicine may not be tolerated.

Schwedt *et al.*[12] described a patient with a 12-year history of HC who had to discontinue indomethacin because of intolerance. She had a unilateral bion device implanted that resulted in significant improvement in pain, and she became pain-free at baseline. However, she experienced persistent autonomic features in the absence of head pain. Schwedt *et al.*[10] reported two additional HC patients treated with ONS. One patient had unilateral stimulation and the other bilateral. At 21 months, the 3-month headache frequency had dropped from 90 days in both patients to 10 and 12 days, while the pain severity had reduced from VRS 7.5 down to VRS 3-7. Both patients had lead migration and one had infection.

Burns *et al.*[13] prospectively studied six patients with HC in accordance with the IHC classification (including responsiveness to indomethacin). Subjects received a stimulator ipsilateral to the headache. The device was in for three months, off for one month, and on again for long-term followup. At a mean of 13.5 months, five of six patients reported sufficient improvement to recommend this treatment for other similar patients. Four of six reported 80-95% estimated improvement, one patient reported 30% improvement, and one was worse by 25%. The pain got worse when the device was switched off and improved again when it was switched back on.

Chronic cluster headache

Several case series of chronic cluster headache patients have been reported. Burns *et al.*[15] described eight patients with medically intractable chronic cluster headache. The median followup was 20 months. Improvements occurred gradually over several months. Two patients reported a 90% to 95% improvement in the number of attacks, three reported moderate (25%) improvement, and two were not improved. The first patient developed cluster attacks contralateral to the side of stimulation; all subsequent patients were given bilateral stimulation.

Magis *et al.*[14] prospectively evaluated eight patients with unilateral ONS implantation ipsilateral to the cluster attacks for a mean of 15 months. Two patients became pain-free, three had a 90% decrease in frequency, and two patients had 40% improvement. All but one patient was able to reduce preventive medications.

DeQuintana-Schmidt *et al.*[16] reported four patients with chronic cluster who were treated with bilateral greater occipital nerve (GON) stimulation. The mean reduction in attack frequency at six months was 56%, and the mean reduction of attack intensity was 48.8%. All patients reported improved quality of life and all reported that they would recommend the procedure to others in a similar clinical situation (Table I).

In an editorial in *Cephalalgia*, Ambrosini[20] pointed out that the clinical effect of ONS is slightly inferior to and slower than that of deep brain stimula-

TABLE I.—*Treatment modality – occipital nerve stimulation.*

Author	Diagnosis	Number Treated	Design	Efficacy	Significant adverse events
Silberstein *et al.*[8]	CM	105	DB, R, B, CT	Headache days decreased 36.6% vs 25.6, p<0.015	Skin erosion 3.8%, infection 5.7%, or lead migration 12.8%
Popeney *et al.*[9]	CM	25	P	88% had >50% decreased frequency or severity	36% had lead migraine/12% had infection
Schwedt *et al.*[10]	CM	8	Re	50% had >50% decreased severity	20% had lead migration
Saper *et al.*[11]	CM	75	M, R, B, CT	39% responders (>50% decreased frequency >50 or a decreased severity over 3 points)	24% had lead migration/14% had infection
Schwedt *et al.*[12]	HC	2	Re	100% had >50% decreased frequency/ severity	None reported
Burns *et al.*[13]	HC	6	U	66% had >50% decreased severity	None reported
Schwedt *et al.*[10]	CCH	3	Re	66% had >50% decreased frequency or severity	None reported
Magis *et al.*[14]	CCH	8	P	63% had >50% decreased frequency	12% had unbearable paresthesia
Burns *et al.*[15]	CCH	8	U, P, C	37% had >50% decreased frequency or severity	None reported
Dequintana-Schmidt *et al.*[16]	CCH	4	P	50% had >50% decreased frequency or severity	None reported
Goadsby[17]	PH	3	Re	2 of 3 responded well	None reported
Goadsby[17]	SUNCT	2	Re	1 had near complete resolution	None reported

Modified from Jenkins et al.[18]
B: blinded; C: crossover; CCH: chronic cluster headache; CM: chronic migraine; CT: controlled trial; DB: double-blind; HC: hemicrania continua; M: multicenter; P: prospective; PH: paroxysmal hemicrania; R: randomized; Re: retrospective; SUNCT: short-lasting unilateral neuralgiform headaches with conjunctival tearing and injection; U: unblinded.

tion, but that the safety and adverse effects favored ONS. Although controlled trial exists, she concluded it was reasonable to propose ONS for patients with drug resistant chronic cluster before considering deep brain stimulation.

Other TACs (SUNCT and SUNA)

Matharu *et al.*[21] reported on seven patients with medically intractable short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and one patient with short-lasting neuralgiform headache attacks with autonomic symptoms (SUNA) who had failed multiple preventive treatments. They were treated with bilateral ONS. At a median follow up of 24 months, four patients had a substantial improvement (95-100%), one a moderate benefit (50%), one a temporary marked benefit (50%) for 6 months, and one failed to respond. The onset of the benefit was rapid (within 2 weeks), with attacks recurring rapidly when the stimulator was switched off or malfunctioned. No major adverse events were reported.

Studies of "occipital neuralgia"

Werner originally reported good results from ONS in eight patients with occipital neuralgia. Matharu *et al.*[22] reinterviewed these patients and established that they actually met criteria for CM. When Anthony [23] first described occipital neuralgia, he based his diagnosis on whether or not patients who would otherwise be classified as having migraine improved when they had surgical section of the GON or were treated by local anesthetic blocks of the GON injection of long-lasting steroids into the region of the GON. Patients with "occipital neuralgia" had more localized pain and dysesthesias as opposed to those with "occipital irritation" and were treated with occipital neurectomy. The majority of patients in both groups responded to GON injection with depomedrol. Forty-two of 60 patients responded to occipital neurectomy for a mean of 244 days. By today's criteria, these patients had migraine that responded to various neuromodulating techniques involving the occipital nerve. Although compression of theGON by the occipital artery has been hypothesized, no study has established that this as a common cause

of headache.[24] It is wise to assume that true occipital neuralgia is, at best, very rare and that persons with migraine who respond to nerve blocks, neurolysis, or GON stimulation, have migraine responsive to neuromodulation.

How does occipital nerve stimulation work?

The exact mechanisms of action of ONS are unknown. Dural (trigeminal) cervical nociceptive nerve synapse on the same second order neurons in the trigeminal nucleus caudalis. Mustard oil applied on the dura sensitizes trigeminal nucleus caudalis neurons with convergent input from trigeminal and cervical afferent. This can be modulated by cervical stimulation.[25] The gate-control theory of pain (which proposes that the activation of large-diameter afferent nerve fibers inhibit transmission in small-diameter primary afferent nociceptive fibers) probably does not account for all of the relief.[26] Additional mechanisms include activation of supraspinal mechanisms; alteration of putative neurotransmitter levels; and blockade of sympathetic mechanisms.

In eight successfully treated patients, Matharu *et al.*[22] studied changes in regional cerebral blood flow (rCBF) using PET in three states: during stimulation when the patient was pain free; during pain with the ONS switched off; and during partial stimulation and varying levels of pain and paresthesia. Stimulation evoked local paresthesia; it suppressed the headache within

30 minutes and pain recurred within 20 minutes of switching off the device. There were significant changes in rCBF in the dorsal pons, anterior cingulate cortex, and cuneus correlated with pain. However, in the anterior cingulate cortex and cuneus, rCBF correlated with paresthesias. The dorsal rostral pons may have a role in neuromodulation. Stiller *et al.*[27] performed microdialysis studies on transmitter release in the periacqueductal gray (PAG) of rats receiving spinal cord stimulation. As GABA neurons in the PAG exert a tonic depressive effect on the activity in descending pain inhibitory pathways, a decreased GABA level in this region might indicate increased pain inhibition.

Allodynia and hyperalgesia are important centrally mediated symptoms of chronic and episodic pain syndromes thought to be due to sensitization of secondary neurons in the dorsal horn. Oshinsky *et al.*[28] quantified the effects of ONS on trigeminal sensitization in rats following a noxious stimulation of the dura. They quantified the response to brush and nociceptive pinch stimuli before and after capsaicin sensitization on the dura using single cell extracellular recordings of second order wide dynamic range (WDR) neurons in the trigeminal nucleus caudalis (TNC). Brush stimuli evoked more action potentials in the WDR neurons following the application of capsaicin (with or without stimulation); thus capsaicin sensitized the WDR neurons. In the capsaicin only group, there was no change in the number of evoked action potentials following the nociceptive pinch stimulus. In contrast, there was significant inhibition of the pinch response in the capsaicin with stimulation group. ONS stimulation following sensitization of WDR neurons by capsaicin reduced the response to subsequent nociceptive but not to brush stimuli. Microdialysis in the TNC during sensitization demonstrated an increase in GABA only in the ONS stimulation group accounting for the inhibition of sensitization.

Magis *et al.*[29] studied 10 patients with medically intractable chronic cluster headache (CCH) treated with ONS and 39 drug-free healthy volunteers using 18-fluorodeoxyglucose PET. The 10 patients with CCH underwent an 18-fluorodeoxyglucose PET scan after ONS, at delays varying between 0 and 30 months. All were scanned with ongoing ONS and with the stimulator switched off. After 6-30 months of ONS, three patients were pain-free and four had a reduction of attack frequency of at least 90% (patients who responded). In all patients compared with controls, several areas of the pain matrix showed hypermetabolism, including the ipsilateral hypothalamus, midbrain and ipsilateral lower pons. Except for the hypothalamus, all normalized after ONS. Switching the stimulator on or off had little influence on brain glucose metabolism. The perigenual anterior cingulate cortex was hyperactive in patients who responded to ONS compared with those who did not respond. These results may support the hypothesis that ONS exerts its beneficial effects via slow neuromodulatory processes in the central pain matrix. The finding of a possible selective perigenual anterior cingulate cortex in patients who responded raises the possibility that ONS activates descending pain control systems in a top-down manner and restores an equilibrium in antinociceptive opioidergic pathways. The study also reported persistent hypermetabolism of the ipsilateral posterior hypothalamus outside of an attack, which might be a hallmark

of cluster headaches and also explains why attacks rapidly recur after interruption of ONS.

Conclusions

ONS is emerging as a promising treatment modality for medically intractable primary headache syndromes, including migraine, cluster headache, HC and SUNCT/SUNA.[30] In CM, two randomized controlled trials and two case series show meaningful efficacy, and ONS is considered the preferred surgical treatment of intractable chronic cluster headache.

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