

Neuromodulation for cephalgias

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Abstract

Headaches (cephalgias) are a common reason for patients to seek medical care. There are groups of patients with recurrent headache and craniofacial pain presenting with malignant course of their disease that becomes refractory to pharmacotherapy and other medical management options. Neuromodulation can be a viable treatment modality for at least some of these patients. We review the available evidence related to the use of neuromodulation modalities for the treatment of medically refractory craniofacial pain of different nosology based on the International Classification of Headache Disorders, 2nd edition (ICHD-II) classification. This article also reviews the scientific rationale of neuromodulation application in management of cephalgias.

Key Words: Deep brain stimulation, migraine, cluster headache, occipital neuralgia, peripheral nerve stimulation, spinal cord stimulation

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INTRODUCTION

The term “cephalgia” refers to a condition of pain in the craniofacial region or recurrent headache. Headache may be divided into primary, as endogenously generated disorder, or secondary, as a consequence of exogenous factors, such as trauma, tumor, or infection, causing activation of cranial nociceptors and inducing pain in the head. Diagnostic criteria of primary and secondary headaches as well as cranial neuralgias are summarized in the second edition of the International Headache Classification.^[49]

First-line approaches for treating cephalgias include medications, physical therapy, biofeedback, psychotherapy, and regional nerve blocks. However, despite progress in growing variety of pharmacological medications, some patients with headache disorders are refractory to medical treatment. For example, 15-20% of patients with chronic cluster headache (CCH) do not adequately respond to pharmacologic monotherapy.^[44]

About 3-14% of migraine patients will progress to chronic migraine, with more than half of the days of each month in pain.^[62] Refractory headaches are a well-recognized occurrence in clinical practice. Around 3-10% of migraine and 20% of cluster headache sufferers progress to chronic state, with significant number of patients eventually becoming resistant to conventional multimodal and multidisciplinary therapies. Patients with refractory headaches fail adequate trials of conventional drugs due to lack of significant therapeutic effect, intolerable side effects, or contraindication for use.^[43]

An accurate estimate of the economic impact of refractory headache is difficult to ascertain. Almost 40 million Americans suffer from intractable migraine, CCH, cervicogenic and secondary headache syndromes including occipital neuralgia (ON).^[137] The Global Burden of Disease Study rates severe migraine at the highest of the 10 disability classes, along with psychosis and dementia, adding significant socioeconomic burden on patients and society, with estimated annual loss of

157 million workdays at an annual cost of \$17 billion.^[71,101] Moreover, annual medical treatment costs for migraine in the United States have been estimated to exceed 1 billion health care dollars.

Recurrent headache that is refractory to pharmacological and other conservative measures brings significant disability to the patients: It could ruin the patient's social, family, and professional life, and may push some of them to commit suicide. About 5% of patients with daily cephalgias will experience a significant loss of quality of life related to narcotic dependence, restriction in daily activities, failed personal and career objectives and overwhelming sense of despair and hopelessness.^[170]

Variety of conditions with recurrent, refractory craniofacial pain such as migraine, cluster headache, SUNCT syndrome, hemicrania continua, trigeminal neuropathic pain (TNP) require nonpharmacological options. Historically, various neurosurgical destructive procedures were tried with poor results in pain relief.^[39] Examples include radiofrequency lesions, glycerol injections or balloon compressions of the Gasserian ganglion, stereotactic radiosurgery, root sectioning of the trigeminal nerve, trigeminal tractotomy, lesioning of the nervus intermedius or the greater superficial petrosal nerve, blockade or radiofrequency lesions of the pterygopalatine ganglion, and microvascular decompression of the trigeminal nerve combined with nervus intermedius section.^[86] These destructive procedures impose an irreversible lesion to the brain or nerve tissue and could lead to serious complications such as keratitis and anesthesia dolorosa (AD). In addition, none of them consistently gave long-term satisfactory results. The development of nondestructive implantable interventions known as “neuromodulation” provides viable alternative for effective control of craniofacial pain in refractory cephalgias.

NEUROMODULATION CONCEPT

Electrical neuromodulation refers to adjustable manipulation of central or peripheral pain pathways with electrical current for the purpose of reversible modification of the nociceptive system function using implantable devices. Many targets for treating craniofacial pain via neuromodulation have been described, including trigeminal nerve and ganglion, vagus nerve, sphenopalatine ganglion (SPG), peripheral (occipital) nerves, cervical spinal cord, periaqueductal gray (PAG) matter, hypothalamus, and motor cortex.

NOCICEPTIVE SYSTEM OF FACE/HEAD PAIN

Application of different neuromodulation modalities is based on our knowledge of anatomy and function of the nociceptive system of the head known as the trigemino-thalamo-cortical system. The pain-producing

innervation of cranium projects through branches of the trigeminal and upper cervical nerves to the trigeminocervical complex within brainstem and upper cervical spinal cord from where nociceptive pathways project to the higher centers via anterior trigeminothalamic tract, which serves as pain, temperature, and crude touch pathway from the face, head, and neck. It receives input from trigeminal nerve, sensory portion of the facial nerve, glossopharyngeal nerve, and vagus nerve. Three pairs of occipital nerves (i.e., the greater, lesser, and third occipital nerves) provide sensory innervation of the back of the head on either side. The central projections of the first order trigeminal neurons enter the pons and then descend to the medulla, forming the spinal trigeminal tract, and synapse in the spinal trigeminal complex. Nociceptive fibers project to the upper cervical spinal dorsal horns that are contiguous with the trigeminal nucleus caudalis, where nociceptive fibers of the trigeminal nerve synapse. Taken together, the upper cervical dorsal horns of C1 to C3 and trigeminal nucleus caudalis form the trigeminocervical complex, which is a functional rather than anatomical entity. From here the nociceptive information is transmitted to higher centers in the brain. Nociceptive and nonnociceptive information is transmitted also to brainstem relay sites such as dorsolateral pontomesencephalic tegmentum, rostral ventromedial medulla, and PAG matter, all of which form pain-modulatory circuits that relay antinociceptive inhibitory descending projections back to the trigemino-cervical complex. Axons of the second order neurons cross the midline and terminate in the ventral posterior medial thalamus to mediate conscious sensation of pain and temperature from the face, head, and neck. The third order neurons in the thalamus then connect to the sensory of the postcentral gyrus. The affective/motivational component of craniofacial pain is mediated by connections to reticular formation, midbrain, and the midline nuclei of the thalamus. The third order neurons of the midline nuclei then synapse to the cingulate and insular cortex.

SCIENTIFIC BASIS FOR NEUROMODULATION

Experimental studies

Multidisciplinary research has led to clarification and refinements in our knowledge of pathophysiology of craniofacial pain in different cephalgias. Laboratory and neuroimaging studies as well as case reports on early neurosurgical management of refractory cephalgic conditions laid foundations for development of neuromodulation procedures. Understanding of trigemino-cervical complex has been illustrated through a series of animal studies. Although an anatomical overlap of trigeminal and cervical afferents through the trigemino-cervical complex from the level of the caudal trigeminal nucleus to at least C2 segment was first

suggested by Kerr,^[65] a direct coupling between meningeal afferents and cervical afferents in the spinal dorsal horn has not been described until recently.^[5] In the cat model, stimulation of superior sagittal sinus produced activation of the most caudal part of the trigeminal nucleus caudalis and dorsal horns of the C1 and C2 cervical segments.^[45,63,67] The activation of Fos-like protein immunoreactivity, a marker of proto-oncogene expression, by neuronal perturbation was demonstrated in the trigemino-cervical complex in the same distribution as is seen with metabolic mapping in cats.^[64] These results were also seen in nonhuman primates.^[41] When activated, the trigemino-cervical complex neurons project to activate neurons in the ventrolateral PAG matter.^[54] Stimulation of the great occipital nerve in cats increases metabolic activity in the dorsal horn at the cervical spinal level C1 and C2 and the caudal trigeminal nucleus.^[42] Nociceptive inflow to secondary order neurons in the spinal cord and trigemino-cervical complex is modulated by descending inhibitory projections from the brainstem structures such as the PAG, nucleus raphe magnus, and rostroventral medulla.^[7,29,128] Stimulation of these regions produces profound antinociception.^[30] Anatomical-physiological studies in rats have demonstrated a direct connection between the posterior hypothalamus and the trigeminal nucleus caudalis thought to be the trigemino-hypothalamic tract.^[82] Peripheral information from trigeminally innervated areas reaches the hypothalamus via this tract. Further studies point out to the role of the posterior hypothalamus as a physiologic modulator of trigeminal nucleus caudalis.^[21,52] Vagal nerve nuclei have widespread ascending central connections to brainstem and diencephalon, including nucleus of tractus solitarius, nucleus parabrachialis, locus coeruleus. Through these connections the vagus nerve may influence cortico-associative and limbic circuits and affect nociceptive information processing.

Neuroimaging studies

Positron emission tomography (PET) in the cluster headache,^[89,90,145] PET studies in paroxysmal hemicranias,^[87] and functional magnetic resonance imaging (MRI) studies in SUNCT^[16,91] have demonstrated posterior hypothalamic activation. Deep brain stimulation (DBS) of the posterior hypothalamus has been the first therapeutic application of functional neuroimaging study data to plan neuromodulation application. Further PET study of cluster headache patients implanted with DBS showed that neuromodulation activated several areas of pain neuromatrix in addition to implanted hypothalamic area.^[92] Similar results have been shown with FDG-PET (fluorodeoxyglucose positron emission tomography) study of patients with cluster headache treated with occipital nerve stimulation (ONS). In all patients, several areas of the pain neuromatrix showed hypermetabolism: Ipsilateral hypothalamus, midbrain and ipsilateral lower pons – all of which normalized after ONS.^[80] The technique of ONS was first described by Weiner and

Reed in patients who suffered from ON.^[171] However, a later clinical review and PET assessment of this patient cohort showed that most of them actually had chronic migraine.^[85] This study also showed that activity of an area in the dorsal rostral pons, known to be activated during migraine attack, was modulated proportionally to the pain level, and that thalamic activation was seen when the pain improved.

Brief overview of neurosurgical experience

In the first century A.D., the physician Scribonius Largus used the electric fish *Torpedo marmorata* to reduce head pain of Claudius, the Roman emperor. The first reports on surgical management of refractory cephalgic conditions were focused on the peripheral components of nervous system and consisted of resection of the greater petrosal nerve, nervus intermedius, occipital nerves and superior cervical ganglia (by means of neurectomy and ganglionectomy), SPG block by anesthetic or radiofrequency lesion, and trigeminal nerve interventions, including posterior fossa trigeminal sensory rhizotomy or percutaneous radiofrequency trigeminal gangliorhizolysis.^[37,59,104,116,124,127,150,158] Successfully treated intractable facial pain was reported with posteromedial hypothalamotomy confirming involvement of posterior hypothalamus in pain control in humans.^[129] First trial of percutaneous neuromodulation of peripheral branches of cranial nerve V were performed by Drs. Wall and Sweet on themselves by inserting electrodes into their own infraorbital foramina.^[167] Even before that, Shelden used high-frequency stimulation of the mandibular nerve to treat neuropathic trigeminal pain.^[135] ONS was introduced in the 1970s but became popular only after Weiner and Reed's paper in the late 1990s.^[171] Short-term percutaneous electrical stimulation of SPG during acute episode of cluster headache can be effective in relieving acute craniofacial pain.^[2,154] Vagal nerve stimulation (VNS) has been approved by US Food and Drug Administration as an adjunctive treatment for drug-refractory depressive disorder and epilepsy. Migraine is often comorbid with both epilepsy and depression. Several case reports at have suggested that VNS may markedly improve both the epilepsy and migraine;^[126] it has also been shown to be effective in controlling episodic migraine in depressed patients.^[100]

Neuromodulation classification

Current neuromodulation taxonomy of existing range of procedures includes:

1. Brain stimulation
 - a. Cortical stimulation
 - b. Deep brain stimulation
2. Spinal stimulation
 - a. Dorsal column
 - b. Nerve root
 - c. Dorsal root ganglion
3. Peripheral neurostimulation
 - a. Peripheral nerve stimulation (PNS)
 - b. Peripheral nerve field stimulation (PNFS).^[75]

With recent developments in the field it needs to be updated to include Gasserian ganglion stimulation (Trigeminal ganglion stimulation (TGS)), which is cranial nerve ganglion and SPG stimulation, which is an example of peripheral nervous system ganglion. PNS related to craniofacial pain may include cranial nerve stimulation, including that of trigeminal nerve branches with supraorbital (SONS), infraorbital (IONS) and mandibular nerves, and the vagus nerve, and spinal nerves stimulation—occipital nerves (ONS). Combination of cranial nerve and ONS has also been described

Mode of action of different neuromodulation modalities

Theoretical mechanism of neuromodulation for cephalgias involves signal modification of intrinsic electrical impulses within pain neuromatrix by exogenous application of electrical current via implantable system. Due to different neuroanatomical targets neuromodulation mechanisms would vary depending on location of stimulating electrode.

PNS in its pure sense refers to a modality where electrical impulses are delivered to peripheral branches of trigeminal or occipital nerves via minimally invasive procedure with electrodes implanted in the epifascial layer. When stimulation applied, the paresthesias are felt in the distribution of sensory representation of the stimulated nerve. In case of PNS of head and neck stimulation depolarizes trigeminal and occipital nerves and antegrade impulses travel via the sensory fibers toward central nervous system (CNS). The beneficial effect of PNS for cephalgias treatment suggests a nonspecific pain relief mechanism and appears to involve the following elements:

- subcutaneous electrical conduction
- dermatomal stimulation
- myotomal stimulation
- sympathetic stimulation
- local blood flow alterations
- peripheral nerve excitation
- peripheral and central neurochemical mechanisms
- trigemino-cervical complex.

Orthodromic stimulation of nonnociceptive Ab nerve fibers in accordance to the “gate-control” theory of Melzack and Wall results in inhibition of interneurons in trigemino-cervical complex and interrupts or decreases transmission of pain signals.^[95] At the level of trigemino-cervical complex a spatial specificity is lost; therefore ONS may have an antinociceptive effect in the trigeminal distribution.

High cervical spinal cord stimulation may be influencing processing and transmission of nociceptive information in the trigemino-cervical complex from first to second level neurons of trigemino-thalamo-cortical system

by modulating excitatory and inhibitory influences at segmental level.

DBS of hypothalamus modulates direct hypothalamic-trigeminal connections. Mechanism of hypothalamic stimulation is complex; it is not just the result of simple inhibition of hypothalamic neurons, since there is a latency of clinical response of chronic stimulation and inability of acute stimulation to interrupt or abort craniofacial pain. There is no physiological or clinical marker for the right positioning of DBS electrodes and no specific neuronal firing pattern on microelectrode recording.

The analgesic effect of PVG (periventricular gray matter) and/or PAG stimulation is thought to be mediated by an increase in the release of endogenous opioids, and this effect can be reversed by administration of the opioid antagonist naloxone.^[55] However, an increase in endogenous opioid release was not confirmed in all patients with DBS of PVG and/or PAG, implying existence of opioid-independent mechanism for pain control.^[175]

Thalamic DBS is based on the Head and Holmes’s theory that the thalamus is the main organ for integration of nociceptive information and pain processing.^[48] Electrical stimulation of the ventral posterolateral nucleus of thalamus modulates (a) the integration of sensory information transmitted via lemniscal and extralemniscal system, (b) the propagation of sensory information along the corresponding spinal tracts which regulates neuronal activities in the dorsal horns, and (c) activation of long-loop polysynaptic pathways involving the sensorimotor cortex, basal ganglia and medial thalamus.^[165] An opioid-independent mechanism is likely responsible for the analgesia by thalamic DBS.^[174]

VNS has the capability to influence parasympathetic nervous system and has been shown to change blood flow in several brain structures such as posterior cingulate gyrus, hippocampus, amygdala, temporal cortex, thalamus, putamen, postcentral gyrus, insula, and cerebellum.

Similar finding were observed during PET studies with motor cortex stimulation (MCS) – blood flow has been increased in the ipsilateral thalamus, cingulate gyrus, orbito-frontal cortex, and brainstem. The degree of analgesia correlates with the increase blood flow in cingulate and improves the suffering component of chronic pain.^[35,36,113] The mechanism of action of MCS is now thought to involve excitation of fibers running parallel to the cortical surface in the precentral gyrus, and modulation of various neural structures distant from the site of stimulation, such as the sensory thalamus or the limbic nervous system. Restoration of defective intracortical GABAergic inhibition may also be involved in the therapeutic effect of MCS.^[106]

Cranial parasympathetic autonomic outflow originates in superior salivary nucleus within the pons, which is activated by trigemino-cervical complex during pain attack. It exits the brainstem via pathway to SPG. Therefore, SPG may be used as peripheral target for neuromodulation of autonomic activation.

METHODS

The goal of this article is to provide an overview of the current status of neuromodulation of craniofacial pain. We conducted literature search for “neuromodulation, neurostimulation, craniofacial pain, facial pain, headache.” Two reviewers (SYR and KVS) assessed the abstracts and decided which complete publications should be evaluated. Most of the literature on this topic is presented as case series. Some of the information is incomplete as neuromodulation for craniofacial pain is frequently a part of bigger studies on pain control.^[163] We tried to compare efficacy of different neuromodulation modalities for control of craniofacial pain of different nosology based on ICDH-II classification.^[49] Technical and surgical aspects of different neuromodulation techniques are described elsewhere.^[76,143,157,161,169]

Part one: The primary headaches

Migraine

Chronic migraine (IHS ICHD-II code 1.5.1; WHO ICD-10NA code [G43.3])

Migraine is a common disabling primary headache disorder. Recurrent headaches may manifest in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine

physical activity and association with nausea and/or photophobia and phonophobia. Most cases of chronic migraine start as migraine without aura. Chronicity may be regarded as a complication of episodic migraine. Chronic migraine description: migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse. As chronicity develops, headache tends to lose its attack-wise (episodic) presentation although it is not been always the case.

PNS is the main approach of neuromodulation for intractable chronic migraine treatment. Globally, several hundreds of patients with migraine have been treated with ONS.^[112] The exact number of implanted and treated patients is difficult to estimate since they have been included in multiple bigger series on neurostimulation for pain, or authors have been including patients with migraine under craniofacial pain.^[25] Efficacy of neuromodulation for headaches treatment is recorded as percentage of patients with more than 50% decrease in frequency or severity of headaches or both. For ONS it has ranged from 39% to 88% in published case series.^[107,117,125,130,133,136,156] Stimulation of peripheral branches of trigeminal nerves alone^[139] or in combination with ONS provided >50% pain relief in 83% to 100% of patients.^[28,121,125] Lead migration and infection are major complication of procedures [Table 1].

We found three articles on VNS in treatment of migraines. A total of 10 patients exhibited 25-100% efficacy of this mode of neuromodulation.^[15,53,88] A separate paper described improvement of migraines in an epilepsy patient treated with VNS.^[126] Side effects

Table 1: Chronic migraine

Neuromodulation mode	Author	Year	Number of patients	Efficacy	Complications
ONS	Popeney <i>et al.</i>	2003	25	88%>50% decrease frequency or severity	36% had lead migration 12% had infection
	Oh <i>et al.</i>	2004	10	100%>50% relief	
	Schwedt <i>et al.</i>	2007	8	50%>50% decrease of severity	100% had lead migration at 3 years follow-up
	Trentman <i>et al.</i>	2009	3	2/3 excellent	None reported
	Silberstein <i>et al.</i>	2011	105	53% good or excellent	
	Saper <i>et al.</i>	2011	29	39% had>50% decrease frequency or decrease severity over 3 points	24% had lead migration 14% had infection
	Royster <i>et al.</i>	2011	1	100%>50% relief	None reported
ANS	Simopoulos <i>et al.</i>	2007	1	>3 point reduction in severity	
ONS+SNS	Reed <i>et al.</i>	2010	7	100%>50% decreased severity	14% had lead migration
	Royster <i>et al.</i>	2011	2	100%>50% relief	None reported
PNS	Ellens and Levy	2011	45	83%	66% lead migration or fracture
VNS	Hord <i>et al.</i>	2003	4	75%>50% relief	
	Mauskop	2005	4	25% had>50% decreased frequency	
	Cecchini <i>et al.</i>	2009	2	100%>50% relief	

reported in initial trials for epilepsy included postsurgical infection, transient left vocal cord or lower facial muscle paralysis and mild to moderate dyspnea and voice alteration at various level of stimulation.^[38,131]

Cluster headache and other trigeminal autonomic cephalalgias
The trigeminal autonomic cephalalgias (TAC) share the clinical features of headache and prominent autonomic features. Experimental and human functional imaging suggests that these syndromes activate a normal human trigeminal-parasympathetic reflex with clinical signs of cranial sympathetic dysfunction being secondary.

Chronic cluster headache (IHS ICHD-II code 3.1.2; WHO ICD-10NA code [G44.02])

CCH refers to attacks of severe, strictly unilateral pain, which is orbital, supraorbital, temporal, or in any combination of these sites, lasting 15-180 minutes and occurring from once every other day to eight times a day. The attacks are associated with one or more of the following (all of which are ipsilateral): conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, eyelid edema. Most patients are restless or agitated during the attack.

CCH attacks occur for more than 1 year without remission or with remissions lasting less than 1 month. CCH may start *de novo* or evolve from the episodic subtype. Some patients may switch from chronic to episodic cluster headache.

Several neuromodulation options are available for patients with CCH including ONS,^[13,22,23,32,66,69,79,81,99,134,149] trigeminal nerve stimulation,^[83,103,160] cervical SCS (spinal cord stimulator),^[168] stimulation of SPG,^[57,115] VNS,^[88] and hypothalamic DBS.^[6,8,9,10,19,33,51,68,72,84,108,110,114,118,132,138,146] Efficacy and complication data are shown in Table 2. Clinical outcome data of more than 60 patients with ONS in the literature proved it to be useful in 50-90% of patients with more than 50% improvement in severity or frequency of cluster attacks. Stimulation of peripheral trigeminal branches achieved similar results in all five patients reported. Somewhat similar effect was achieved with neuromodulation of cervical spinal cord, SPG with and without ONS, and VNS, however, number of patients is low and most are published as case reports. As of July 2012, more than 60 total cases of hypothalamic DBS for cluster headache have been reported. Hypothalamic DBS is generally ineffective in ameliorating acute attacks and is therefore used to reduce attack frequency with continuous stimulation effective in 33-100% of implanted patients. Like all deep brain electrode implantation procedures, hypothalamic DBS is associated with a small risk of intracerebral hemorrhage and is currently performed in few centers (Italy, USA, Germany, Belgium, UK, France) by expert neurosurgical teams. Other side effects of this mode of neuromodulation include panic attacks and transient diplopia. Diplopia occurs when the

stimulation amplitude is increased too rapidly. A single report described a patient who underwent treatment with hypothalamic DBS and subsequent VNS as a rescue treatment after an episode of trivial head and neck trauma triggered loss of hypothalamic DBS efficacy.^[34] Due to the fact that PNS has equal or better outcome and is less invasive, this mode of neuromodulation is considered a first-line surgical treatment and hypothalamic DBS is viewed as a last resort.

Chronic paroxysmal hemicrania (IHS ICHD-II code 3.2.2; WHO ICD-10NA code [G44.03])

Chronic paroxysmal hemicrania (CPH) presents with attacks with characteristics of pain and associated symptoms and signs similar to those of cluster headache, but they are shorter-lasting, more frequent, occurring more commonly in females and responding absolutely to indomethacin. CPH usually occurs for >1 year without remission or with remissions lasting <1 month.

Neuromodulation for treatment CPH is indicated only if patient cannot receive indomethacin and is refractory to other medical therapies.^[73] Among a total of four patients reported by two authors [Table 3], three were treated with ONS with efficacy of 66%^[40] and one patient underwent hypothalamic DBS with initial pain relief.^[166]

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) (IHS ICHD-II Code 3.3; WHO ICD-10NA code [G44.08])

This syndrome is characterized by short-lasting attacks of unilateral pain that are much briefer than those seen in any other TAC and very often accompanied by prominent lacrimation and redness of the ipsilateral eye.

Out of only five patients reported in literature [Table 4], three underwent PNS^[40,160] and two had hypothalamic DBS.^[74,77]

Other primary headaches

Hypnic headache (IHS ICHD-II code 4.5; WHO ICD-10NA code [G44.80])

Hypnic headache is a rare, primary headache disorder that exclusively occurs regularly during sleep presenting as attacks of dull headache that always wake up the patient from sleep.

One case of a 64-year-old female with 4-year history of right occipital headache that regularly awakened her from sleep, successfully treated with ONS has been reported^[144] [Table 5].

Hemicrania continua (IHS ICHD-II code 4.7; WHO ICD-10NA code [G44.80])

Hemicrania continua is usually an unremitting, persistent, strictly unilateral headache responsive to indomethacin.

A total of nine patients have been reported in the literature [Table 6]. All of them underwent ONS.^[14,23,134]

Table 2: Chronic cluster headache

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
ONS	Schwedt <i>et al.</i>	2006	3	66%	None reported
	Burns <i>et al.</i>	2007	8	37%	62% had lead migration or power loss
	Dodick <i>et al.</i>	2007	14	36%	
	Magis <i>et al.</i>	2007/2011	14	85%	12% had unbearable paresthesia
	Lainez <i>et al.</i>	2008	5	80%	
	de Quintana-Schmidt <i>et al.</i>	2010	4	50%	
	Lara <i>et al.</i>	2011	6	66%	
	Fontaine <i>et al.</i>	2011	13	76%	
	Mueller <i>et al.</i>	2011	10	90%	10% had infection 10% reoperation for due to scar tissue formation around connector
	Strand <i>et al.</i>	2011	4/3	50%	50% neck pain and/or cramping with stimulation at high amplitudes 25% revision for a faulty battery
SONS	Narouze and Kapural	2007	1	100%	None reported
	Vaisman <i>et al.</i>	2012	3	100%	
SONS+IONS	Vaisman <i>et al.</i>	2012	1	100%	Skin erosion
ONS+SONS+IONS	Mammis <i>et al.</i>	2011	1	100%	
Cervical SCS	Walter <i>et al.</i>	2008	1	100%	Intolerable paresthesia with continuous stimulation and 1 revision required
SPG	Ibarra	2007	1	100%	Stimulation failure
ONS+SPG	Piedimonte <i>et al.</i>	2011	2	100%	50% lead migration
VNS	Mauskop	2005	2	100% had significant MIDAS decrease	None reported
hDBS	Schoenen <i>et al.</i>	2005	6	50%	Fatal hemorrhage; panic attack; oculomotor disturbances
	D'Andrea <i>et al.</i>	2006	3	66%	
	Leone <i>et al.</i>	2006	16	62%	Lead infection; arterial hypotension; diplopia; weight loss; electrode replacement; electrode migration; asymptomatic 3 rd ventricular hemorrhage
	Benabid <i>et al.</i>	2006	1	75%	
	Rasche <i>et al.</i>	2006	1	100%	Diplopia, tachycardia, panic attack
	Starr <i>et al.</i>	2007/	8	62%	Perioperative TIA, diplopia, ophthalmoplegia, skew deviation, dizziness
	Sillay <i>et al.</i>	2010			
	Owen <i>et al.</i>	2007/	3	100%	
	Brittain <i>et al.</i>	2009			
	Mateos <i>et al.</i>	2007	2	100%	
	Black <i>et al.</i>	2007	2	100%	
	Bartsch <i>et al.</i>	2008	6	50%	
	Lanteri-Minet <i>et al.</i>	2008	8	50%	
	Piacentino <i>et al.</i>	2008	4	100%	
	Fontaine <i>et al.</i>	2010	11	55%	
	Hidding <i>et al.</i>	2011	1	100%	
Pascual <i>et al.</i>	2011	5	100%		
hDBS+VNS	Franzini <i>et al.</i>	2009	1	100%	

Table 3: Chronic paroxysmal hemicrania

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
ONS	Goadsby PJ	2007	3	67%	None reported
hDBS	Walcott <i>et al.</i>	2009	1	Initial relief, follow-up pending	None reported

Part two: The secondary headaches

Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures

Cervicogenic headache (IHS ICHD-II code 11.2.1; WHO ICD-10NA code [G44.841])

Diagnostic criteria:

- Pain is referred from a source in the neck and perceived in one or more regions of the head and/or face
- Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache
- Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following:
 - a. Demonstration of clinical signs that implicate a source of pain in the neck
 - b. Abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo- or other adequate controls
- Pain resolves within 3 months after successful treatment of the causative disorder or lesion

Current literature shows that PNS (namely, ONS) could be used for successful relief of pain in selected patients^[123,141,159,176] [Table 7].

Part three: Cranial neuralgias, central and primary face pain and other headaches

Cranial neuralgias and central causes of facial pain.

Supraorbital neuralgia (IHS ICHD-II code 13.6; WHO ICD-10NA code [G44.847])

Supraorbital neuralgia (SN) is an uncommon disorder characterized by pain in the region of the supraorbital notch and medial aspect of the forehead in the area supplied by the supraorbital nerve.

Neurostimulation of supraorbital nerve could provide significant pain relief in cases refractory to medical treatment.^[1,3] [Table 8].

Occipital neuralgia (IHS ICHD-II code 13.8; WHO ICD-10NA code [G44.847])

ON is a paroxysmal jabbing pain in the distribution of the greater or lesser occipital nerves, or of the third occipital nerve, sometimes accompanied by diminished sensation or dysesthesia in the affected area. It is commonly associated with tenderness over the nerve concerned.

ONS is neuromodulation mode of choice in refractory cases.^[61,140,142] Cervical SCS appears to be effective in less than 30% of patients^[155] [Table 9].

Table 4: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
ONS	Goadsby	2007	2	50%	None reported
SONS	Vaisman <i>et al.</i>	2012	1	100%	Skin erosion, superficial infection
hDBS	Leone <i>et al.</i>	2005	1	100% had pain freedom	
	Lyons <i>et al.</i>	2009	1	100% had >50% decrease frequency	Erectile dysfunction

Table 5: Hypnic headache

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
ONS	Son <i>et al.</i>	2012	1	100%	Electrode migration and revision

Table 6: Hemicrania continua

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
ONS	Schwedt <i>et al.</i>	2006	1	100%	
	Dodick <i>et al.</i>	2007	2	100%	
	Burns <i>et al.</i>	2008	6	66%	

Table 7: Cervicogenic headache

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
ONS	Rodrigo-Royo <i>et al.</i>	2005	4	100%	
ONS+SONS	Vadivelu <i>et al.</i>	2011	18	61%	31% device related-complications requiring additional surgeries
	Zhou <i>et al.</i>	2011	15	100%	
PNS	Slavin	2006	3	?	

Postherpetic neuralgia (IHS ICHD-II code 13.15.2; WHO ICD-10NA code [G44.847])

Herpes zoster affects the trigeminal ganglion in 10-15% of patients with the disease, and the ophthalmic division is singled out in about 80% of those patients. Herpes zoster may also involve the geniculate ganglion, causing an eruption in the external auditory meatus. The soft palate or areas of distribution of upper cervical roots may be involved in some patients. Ophthalmic herpes may be associated with third, fourth, and/or sixth cranial nerve palsies while geniculate herpes may be accompanied by facial palsy and/or acoustic symptoms.

Postherpetic neuralgia (PHN) is facial pain persisting or recurring more than 3 months after the onset of herpes zoster. PHN is more often a sequel of herpes zoster as age advances, afflicting 50% of patients contracting zoster over the age of 60 years. Hypoesthesia or hyperalgesia and/or allodynia are usually present in the territory involved.

PHN is often quite resistant to pharmacological treatment. Almost all modes of neuromodulation has

been tried to alleviate pain in this condition [Table 10], however, only PNS^[24,60,148] and DBS^[46,47,119] modality showed some efficacy in single case reports. TGSs,^[153] cervical SCS,^[155] and MCS^[12,26,162] have been used for this condition. MCS failed to relieve painful condition in one report^[26] but achieved pain control in all three patients from two other centers.^[12,162]

Central causes of facial pain

Anesthesia dolorosa (IHS ICHD-II code 13.18.1; WHO ICD-10NA code [G44.847])

AD is often related to surgical trauma of the occipital nerves or trigeminal ganglion, evoked most frequently after a rhizotomy or thermocoagulation has been performed for treatment of classical trigeminal neuralgia. It presents as a persistent and painful anesthesia or hypoesthesia in the distribution of the trigeminal nerve or one of its divisions, or of the occipital nerves.

We found five articles related to this indication, which used different modes of neuromodulation [Table 11]. However, the number of patients is too small to make any recommendations. MCS achieved more than 50% pain relief in all patients,^[26] whereas DBS of thalamus

Table 8: Supraorbital neuralgia

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
SONS	Asensio-Samper <i>et al.</i>	2008	1	100%	
	Amin <i>et al.</i>	2008	16	62%	

Table 9: Occipital neuralgia

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
ONS	Slavin <i>et al.</i>	2006	14	50%	3 points hardware removed due to loss of beneficial effect or occurrence of infection
	Johnstone <i>et al.</i>	2006	8	63%	
	Skaribas <i>et al.</i>	2011	1	100%	Infection required explantation of the lead
Cervical SCS	Tomycz <i>et al.</i>	2011	7	28.6%	

Table 10: Post-herpetic neuralgia

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
SNS	Duntevan	2002	2	100	Lead migration required reimplantation
	Johnson <i>et al.</i>	2004	4	40%	
	Stidd <i>et al.</i>	2012	1	100%	
TGS	Taub <i>et al.</i>	1997	4	0%	
Cervical SCS	Tomycz <i>et al.</i>	2011	2	0%	
DBS (VPL and PVG)	Green <i>et al.</i>	2003	1	100%	None reported
		2005	1	100%	
	Rasche	2006	2	50%	
MCS	Ebel <i>et al.</i>	1996	1	0%	
	Brown and Pilitsis	2005	2	100%	
	Velasco <i>et al.</i>	2008	1	100%	

achieved pain relief in 80% of patients^[56] and DBS of VPM/PVG was effective in half of the patients.^[119] TGS was effective in only 60% in an American center^[173] and none in Canadian center.^[153]

Central Poststroke Pain (IHS ICHD-II Code 13.18.2; WHO ICD-10NA code [G44.810])

Unilateral pain and dysesthesia associated with impaired sensation involving part or the whole side of the face, not explicable by a lesion of the trigeminal nerve, may be attributed to a lesion of the trigeminothalamic pathway, thalamus or thalamocortical projection. Symptoms may also involve the trunk and/or limbs of the affected or contralateral side. Facial pain following a thalamic lesion is part of a hemisindrome. With lateral medullary lesions hemifacial pain may occur in isolation, but it is more often accompanied by crossed hemi-dysesthesia. The facial pain and dysesthesia are usually persistent.

Stimulation of Gasserian ganglion (TGS) was used in six patients and provided more than 50% relief of pain in five of them.^[153] There was no efficacy of cervical SCS^[155] or DBS for PVG.^[102,109] MCS was also ineffective in two patients in a study from UK^[109] and in one patient from an American center,^[12] but three of four patients in a study from Japan^[151] and one patient from Mexico^[162] achieved pain reduction more than 50% [Table 12].

Facial pain attributed to multiple sclerosis (IHS ICHD-II code 13.18.3; WHO ICD-10NA code [G44.847])

This refers to a unilateral or bilateral facial pain, with or without dysesthesia, attributed to a demyelinating lesion

of the central connections of the trigeminal nerve, which commonly remits and relapses. Pain may be tic-like or continuous. Trigeminal neuralgia occurring in young people or affecting one and then the other side should arouse the suspicion of multiple sclerosis.

Two patients reported with cervical SCS,^[4,27] five with DBS,^[17] and another two with MCS.^[58,152] In all of them, neuromodulation achieved more than 50% pain relief [Table 13]. All patients with hypothalamic DBS reported a reduction of paroxysmal pain attacks within the ophthalmic branch after surgery; three of them had beneficial effect within 24 h from the procedure. However, three patients complained of recurrent pain in the II and III branch (but, importantly, not in the first) and underwent thermorhizotomy. The other two patients reported relief of pain in all three trigeminal branches by combining stimulation with analgesics and did not require further surgical procedures.

Persistent idiopathic facial pain (IHS ICHD-II code 13.18.4; WHO ICD-10NA code [G44.847])

This condition refers to a persistent facial pain that does not have the characteristics of the cranial neuralgias and is not attributed to another disorder. Pain may be initiated by surgery or injury to the face, teeth, or gums, but persists without any demonstrable local cause. Pain at onset is commonly in the nasolabial fold or side of the chin, and may spread to the upper or lower jaw or a wider area of the face and neck. In neurosurgical literature, this condition is frequently referred to as “trigeminal neuropathic pain”.

Table 11: Anesthesia dolorosa

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
DBS (thalamus)	Hosobuchi <i>et al.</i>	1993	5	80%	
DBS (VPL/VPG)	Rasche <i>et al.</i>	2006	6	50%	
	Green <i>et al.</i>	2005	1	0%	
TGS	Young <i>et al.</i>	1995	5	60%	
	Taub <i>et al.</i>	1997	3	0%	
MCS	Ebel <i>et al.</i>	1996	6	100%	

Table 12: Central post-stroke pain

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
TGS	Taub <i>et al.</i>	1997	6	83%	
Cervical SCS	Tomycz <i>et al.</i>	2011	1	0%	
PVG	Owen <i>et al.</i>	2006	2	0%	
	Nandi <i>et al.</i>	2002	1	0%	
MCS			2	0%	
	Brown and Pilitsis	2005	1	0%	
	Velasco <i>et al.</i>	2008	1	100%	
	Tanei <i>et al.</i>	2011	4	75%	

Fifty-four TNP patients were treated with MCS with various degree of efficacy.^[12,50,98,105,120,164] In critical review of MCS, a good response was achieved in 68% of the 44 patients with TNP.^[31] European Federation of Neurological Societies published guidelines on neurostimulation therapy for neuropathic pain, which provides summary of efficacy and safety of MCS in facial pain based on a case series of 60 patients.^[18] Satisfactory pain relief of more than 50% was reported in 43-100% of cases with mean of 66% of patients obtaining satisfactory pain relief. Most common complications were battery failure, seizures, wound infection, and sepsis. Overall, 20% of patients experienced one or more complication induced by MCS, in general of benign nature, but extradural hematoma was also reported [Table 14].

In recent years with progress of PNS techniques for other indications several authors successfully applied it for treatment of TNP with almost 100% response rate.^[20,60,122,141,148,172] [Table 15].

DBS and VNS fail to achieve > 50% pain reduction when used for TNP.^[15,108,111] Only two out eight patients with DBS and none with VNS were able to achieve pain reduction of more than 50%. However, cervical SCS was effective in 80% of patients with TNP and in 70% of patients with trigeminal deafferentation pain^[155] [Table 16].

More than 400 patients who underwent TCS for treatment of TNP with different degree of efficacy are reported in literature [Table 17].^[11,70,78,93,94,96,97,147,153,173] In the biggest series from Germany, average efficacy of this procedure was 52%.^[94]

CONCLUSION

There is an increasing interest of medical community in various neuromodulation modalities for treatment of severe intractable cephalgias. Encouraging new data about efficacy and safety of surgical neuromodulation procedures provides a new hope for desperate patients. Neuromodulation appears to be the most advanced

Table 13: Multiple sclerosis

Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
Cervical SCS	Barolat <i>et al.</i>	2008	1	100%	
	Eldridge <i>et al.</i>	2003	1	100%	
hDBS	Gordella <i>et al.</i>	2009	5	100%	
MCS	Tanei <i>et al.</i>	2010	1	100%	
	Isagulyan and Shabalov	2011	1	100%	

Table 14: Persistent idiopathic facial pain – MCS

Type of neuropathic pain (Burchiel classification)	Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
TNP (neuropathic)	MCS	Meyerson <i>et al.</i>	1993	2	50%	
TDP (deafferentation)				5	100%	
		Herregodts	1995	5	?	
		Rainov <i>et al.</i>	1997	2	100%	1 Seizure in 1 patient
?		Nguyen <i>et al.</i>	2009	33	75%	
?		Brown and Pilitsis	2005	7	57%	
TNP		Jan Vesper <i>et al.</i>	2011	1	100%	

Table 15: Persistent idiopathic facial pain – PNS

Type of neuropathic pain (Burchiel classification)	Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
TNP	PNS (SONS or IONS)	Johnson and Burchiel	2004	6	100%	
	PNS (SONS, or IONS, or ONS, or SONS + ONS, or IONS + ONS)	Slavin <i>et al.</i>	2006	3	?	
					13	?
	PNS	Deogaonkar	2011	15	100%	
		Reverberi and Dario	2011	4	100%	
?		Yakovlev <i>et al.</i>	2011	1	100%	
TNP	SNS + INS	Stidd <i>et al.</i>	2012	2	100%	

Table 16: Persistent idiopathic facial pain – DBS/VNS/SCS

Type of neuropathic pain (Burchiel classification)	Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
TNP	DBS (VPL/PVG)	Green <i>et al.</i>	2005	5	40%	
?		Pereira <i>et al.</i>	2007	3	0%	
TNP	VNS	Cecchini <i>et al.</i>	2009	2	0%	
	Cervical SNS	Tomysz <i>et al.</i>	2011	5	80%	
TDP				10	70%	

Table 17: Persistent idiopathic facial pain – TGS

Type of neuropathic pain (Burchiel classification)	Neuromodulation mode	Author	Year	Number of patients	Efficacy (with at least 50% improvement)	Complications
TDP	GGS	Meyerson and Hakansson	1980	5	100%	
		Meglio	1984	5	100%	
		Steude	1984	10	30%	
		Meyerson and Hakansson	1986	14	79%	
		Broggi <i>et al.</i>	1987	8	38%	
		Lazorthes <i>et al.</i>	1987	21	14%	
		Young	1995	16	56%	
		Taub <i>et al.</i>	1997	19	23%	
		Machado <i>et al.</i>	2007	10	30%	
		Mehrkens and Steude	2007	321	52%	

minimally invasive surgical treatment for patients with pharmacologically resistant craniofacial pain. However, there is a need of collaborative effort among neuromodulation community to support clinical trials and improve data reporting.

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