

Special Article - Pain Management

Neurostimulation for the Treatment of Cluster Headache

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Abstract

Neurostimulation procedures have been introduced quite recently as an alternative treatment of intractable chronic headaches mainly because they are less invasive than the surgical ablative techniques used in the past years. We review the current neurostimulation approaches to the management of chronic cluster headache which is an extremely severe and debilitating trigeminoautonomic pain syndrome. The results of hypothalamic deep brain stimulation, occipital nerve stimulation and sphenopalatine ganglion stimulation are promising, but we do not know which is more effective, because these procedures are still investigational. Many other target are being used and new devices are being developed.

Keywords: Cluster headache; Neurostimulation; Deep brain stimulation; Occipital nerve stimulation; Sphenopalatine ganglion stimulation; Hypothalamus

Abbreviations

CH: Cluster Headache; hDBS: hypothalamic Deep Brain Stimulation; ONS: Occipital Nerve Stimulation; SPGS: Sphenopalatine Ganglion Stimulation; drCCH: drug-resistant Chronic Cluster Headache; SCN: Suprachiasmatic Nucleus; CCH: Chronic Cluster Headache; SONS: Supraorbital Nerve Stimulation; VNS: Vagal Nerve Stimulation; tVNS: transcutaneous Vagal Nerve Stimulation; SCS: Spinal Cord Stimulation

Introduction

Cluster Headache (CH) is a severe and painful condition that is characterized by short-lasting, severe, strictly unilateral pain along the distribution of the first branch of the trigeminal nerve, accompanied by prominent cranial, parasympathetic, autonomic features with circadian and circannual regularity [1]. The diagnosis is still clinical and a recent study highlighted a male prevalence [2]. 10-20% of patients seem to be resistant to all pharmacological treatments [3]. Many ablative techniques, such as radiofrequency lesioning or gamma-knife lesioning of the trigeminal nerve or of sphenopalatine ganglion, trigeminal tractotomy, have been used to treat these patients with varying results and with permanent and severe complications. Neurostimulation techniques have been introduced fairly recently to treat completely drug-resistant Chronic Cluster Headache (drCCH). Treatment with these techniques remains investigational, but it represents a valid alternative to destructive surgical procedures. Hypothalamic Deep Brain Stimulation (hDBS), Occipital Nerve Stimulation (ONS), Sphenopalatine Ganglion Stimulation (SPGS) and some others seem to be a nondestructive, reversible and adaptive way of helping drCCH patients.

Anatomy of trigeminal system and pathophysiology of cluster headache

The trigeminal system provides the primary sensory innervation of the face, innervates the dura mater and cranial blood vessels, where its fibers endings can promote an inflammatory response by releasing vasoactive peptides that are involved probably in the generation of headache [4]. The trigeminal nerve originates from the lateral Pons

and it divides into three branches: the ophthalmic, the maxillary and the mandibular one. The posterior region of the head is innervated by the greater, lesser and third occipital nerves, that arise from the spinal nerve of the occipital plexus [5]. Goadsby and Hoskin demonstrated that there is a connection between the cervical and trigeminal system [6]. This anatomical and functional relation might explain the nociceptive frontal activation from the cervical region. From this theory, the neuromodulation of occipital nerves and nerves that supply the face might provide improved relief from headache pain not only in the territories that it innervates itself, but also in those innervated by the trigeminal nerve [7]. The hypothalamus plays an important role in the pathophysiological mechanisms behind CH [8,9]. Neuroimaging has suggested an abnormality or dysfunction of the posterior hypothalamus, especially of the Supra Chiasmatic Nucleus (SCN) [10,11]. The SCN is responsible for controlling the circadian rhythmicity of hormone release and sleep-wakefulness cycles. It has also projections to the pineal gland, responsible for melatonin production [12,13]. It has been demonstrated that the circadian pattern of melatonin and cortisol are altered in CH patients [14]. PET studies showed significant activation of the ipsilateral, posterior, hypothalamic gray matter only in CH patients inside a cluster period, suggesting a specific role for the hypothalamus in CH. Moreover a voxel-based, morphometric, magnetic resonance study found a significantly increased density and volume of the gray matter region corresponding to the inferior posterior hypothalamus [15,16].

Review of the literature

Neuromodulation involves the exogenous application of electrical current as a method of influencing pain signals for the purpose of reversible modification of the nociceptive system function, using implantable electrodes and generator devices [17]. The publication of the "Gate Control Theory" by Melzack and Wall in 1965 offered a theoretical foundation for considering direct electrical stimulation of the spinal cord and peripheral nerves as a potential treatment for chronic pain [18]. Its use in headache disorders increased in the 1990s with Weiner and Reed, who first described a percutaneous approach for Occipital Nerve Stimulation (ONS) in presumed occipital neuralgia [19].

Table 1: Hypothalamus deep brain stimulation for drCCH patients.

Study	Number of patients	Implantation site	Response rate (improvement of > 50%)
Leone et al [20] Broggi et al [21]	16	14 Unilateral 2 Bilateral	13 of 16 patients = 81%
Schoenen et al [22]	6	Unilateral	3 of 6 patients = 50%
Bartsch et al [23]	6	Unilateral	3 of 6 patients = 50%
Sillay et al [24]	8 (data only for 5 patients)	Unilateral	5 of 8 patients = 63%
Fontaine et al [25]	11	Unilateral	6 of 11 patients = 55%
Owen et al [26] Brittain et al [27]	3	Unilateral	3 of 3 patients = 100%
Hidding and May [28]	1	Unilateral	0 of 1 patient = 0%
Seijo et al [29]	5	Unilateral	5 of 5 patients = 100%

Many neuromodulation targets for treating Chronic Cluster Headache (CCH) are described in literature. The following discussion will outline some of these targets.

Hypothalamic Deep Brain Stimulation (hDBS) in CCH (Table 1): The above mentioned evidence of hypothalamic involvement in CH pathophysiology led to the use of hypothalamic DBS in drCCH patients. A lead is positioned in the posterior, inferior hypothalamus, ipsilaterally to the side of the facial pain. Leone and Broggi treated 16 drCCH patients, 14 with an unilateral DBS, 2 with a bilateral implant. The mean duration of chronic CH phase was of three years. The response rate (defined by improvement of > 50%) was 81% - the best available result - with ten patient's pain free and three patients with sporadic attacks [20,21]. Schoenen performed unilateral hDBS in six patients with a response rate of 50%. This was a pilot study [22]. The result was equaled by Bartsch with six patients treated unilaterally [23]. Sillay treated eight patients, but the data available were only for five patients. He performed an unilateral hDBS with a response rate of 63% [24]. Fontaine performed the first sham-trial involving unilateral hDBS in drCCH patients. This was a randomized, prospective, crossover study involving eleven patients, although the crossover period was too short (only one month) to appreciate significant changes in headache attacks. The response rate was of 55% [25]. Brittain and Owen treated 3 patients with an unilateral HDBS with a 100% response rate [26,27]. Hidding and May reported a single unilateral hDBS case, after which a frontal bilateral headache arose and disappeared when stimulator was turned off [28]. Seijo performed five unilateral hDBS on a modified target to avoid hemorrhagic complications due to the proximity to the third ventricle. The response rate was 100%, but three patients had permanent euphoria and myosis [29].

Occipital Nerve Stimulation (ONS) in CCH (Table 2): Occipital nerve stimulation is a neuromodulation technique in which electrodes are placed in the subcutaneous tissue at the C1 level of the spinal cord [30]. The main targets of stimulation are the distal branches of the C2-C3 roots where electrodes should produce a field of paresthesias.

Burns enrolled fourteen drCCH patients and performed bilateral ONS with a response rate of 36%, because only five patients of fourteen improved 50% [31]. Magis enrolled fifteen patients to subject to unilateral ONS. The response rate was 80% with 60% of patients becoming pain free for prolonged periods [32]. Schwedt treated two patients with bilateral ONS and one patient with unilateral ONS with a 67% of response rate [33]. A case report of an unilateral ONS by the same author found a 100% improvement [34]. Müller enrolled seven patients receiving bilateral ONS. Six of seven patients were responders (86%) with a reduction in acute medication [35]. De Quintana-Schmidt reported a study with four patients improved with bilateral ONS [36]. Fontaine et al. performed bilateral ONS in thirteen patients with a response rate of 77% [37]. Strand used an implantable rechargeable microstimulator unilaterally and report of three patients, two of whom were responders (67%) [38].

Sphenopalatine ganglion (SPG) stimulation in CCH (Table 3): The SPG (also known as pterygopalatine ganglion) is a neural structure situated extra cranially behind the maxillary sinus in the pterygopalatine fossa. It contains sensory, motor and autonomic fibers. Its role in the pathophysiology of CCH is well recognized [39]. The first report of SPG stimulation for the treatment of cluster headache was a case report published by Ibarra in 2007 [40,41]. Ansarinia demonstrated the acute benefits of SPG stimulation in six drCCH patients. An electrode was applied through a standard

Table 2: Occipital nerve stimulation for drCCH patients.

Study	Number of patients	Implantation site	Response rate (improvement of > 50%)
Burns et al [31]	14	Bilateral	5 of 14 patients = 36%
Magis et al [32]	15	Unilateral	12 of 15 patients = 80%
Schwedt et al [33]	3	2 Bilateral 1 Unilateral	2 of 3 patients = 67%
Schwedt et al [34]	1	Unilateral	1 of 1 patient = 100%
Müller et al [35]	7	Bilateral	6 of 7 patients = 86%
de Quintana-Schmidt et al [36]	4	Bilateral	/
Fontaine et al [37]	13	Bilateral	10 of 13 patients = 77%
Strand et al [38]	3	Unilateral	2 of 3 patients = 67%

Table 3: Sphenopalatine ganglion stimulation for drCCH patients.

Study	Number of patients	Implantation site	Response rate (improvement of > 50%)
Ansarinia et al [42]	6	Unilateral	/
Schoenen et al [43]	32 (only 28 patients completed the experimental period)	Unilateral	19 of 28 patients = 68%

infra zygomatic transcoronoid approach. About 61% of attacks achieved complete pain relief and 22% of attacks achieved partial pain resolution within 1-3 min of irritation of stimulation. The most common frequency to achieve pain resolution was 50 Hz, pulse width of 300 μ s and an amplitude below 2 V [42]. Schoenen conducted a multicenter, multiple CH attack study of an implantable on-demand SPG neurostimulator in thirty-two patients suffering from refractory CCH. Each CH attack was randomly treated with full, sub-perception or sham stimulation. Twenty-eight patients completed the randomized experimental period. Pain relief was achieved in 67,1% of full stimulation-treated attacks compared to 7,4% of sham-treated and 7,3% of sub-perception-treated attacks [43].

Supraorbital Nerve Stimulation (SONS) in CCH: The use of Supraorbital Nerve Stimulation (SONS) – one of the terminal nerves from the ophthalmic branch of the trigeminal nerve - both alone and in combination with ONS is a recent, newer emerging option of neuromodulation for CH. The first successful application of SONS for CH was published in 2009 by Narouze [44]. The effectiveness of SONS was confirmed in a retrospective study of five patients with CCH performed by Vaisman [45] [60]. Reed published an extended case series of combined ONS and SONS for chronic migraine headaches [46]. In a single-center study published, the 71% of fourteen patients treated with simultaneous occipital and supraorbital stimulation achieved > 50% decrease in pain severity [47]. A randomized, controlled trial describing a novel non-invasive device for SONS in headache – the transcutaneous stimulator Cefaly – included sixty-seven patients treated daily for three months [48]. The results showed a significant decrease of migraine days.

Vagal Nerve Stimulation (VNS) in CCH: Only smaller open case series exist. Sadler published a report describing the case of a patient whose migraine attacks were aborted following Vagal Nerve Stimulation (VNS) for intractable epilepsy [49]. Favorable response rate was confirmed in two reports detailing the use of VNS in patients with CCH [50,51]. Despite these promising results, the morbidity associated with the invasive implantation of VNS device limited its use to the patients with concomitant intractable headache, epilepsy and major depression.

However with the development of non-invasive transcutaneous VNS systems (tVNS) the stimulation of the vagal nerve was used as a treatment for CH. A case series described the results of using tVNS for fourteen intractable cluster headache patients. Thirteen of the fourteen patients experienced a subjective improvement of 60% following treatment over 14 weeks [52].

Spinal Cord Stimulation (SCS) in CCH: High cervical SCS is a neuromodulation technique similar to ONS except that the electrodes are placed within the epidural space in the upper cervical area. High cervical SCS was first used by Wolter in a CCH patient in 2004, decreasing from eight to one daily attack of CCH. The first series of high cervical SCS for CCH is made by Wolter. Seven patients with medically intractable chronic cluster headache were implanted with

high cervical epidural electrodes. After a median test phase of 10 days, an impulse generator was implanted subcutaneously. In all patients improvement occurred immediately after electrode implantation. The mean attack frequency decreased, as well as the mean duration and intensity of attacks. Also depression, anxiety and pain-related impairment scores decreased and medication intake was markedly reduced [53].

Discussion

Cluster headache is an severe trigeminoautonomic pain syndrome characterized by pain localized in orbital, supraorbital and temporal regions, lasting for 15-180 min and occurring from once every other day to several times a day. Conventional medical treatment comprises acute, intermediate, and prophylactic drugs. Also with maximal therapy a substantial proportion of patients do not experience a satisfactory pain relief. Hypothalamic Deep Brain Stimulation (hDBS), Occipital Nerve Stimulation (ONS), Sphenopalatine Ganglion Stimulation (SPGS), Supraorbital Nerve Stimulation (SONS), Vagal Nerve Stimulation (VNS) and Spinal Cord Stimulation (SCS) are described in literature such as possible neuromodulation treatment of drug-resistant Chronic Cluster Headache (drCCH). Long-term hDBS has generally proven to be without lasting side effects [54]. However in drCCH patients the response rate is approximately 60% [1]. We do not know with certainty whether the stimulated area is the posterior hypothalamus or the adjacent mesencephalic gray, although the proposed cluster generator might be located in the same way in the posterior hypothalamus, the SCN, the mesencephalic gray. Based on this, failure of hDBS may not necessarily be explained by a misplaced electrode. In line with this observation, a neuro imaging study showed that the anatomical location of the stimulating electrodes did not differ significantly between responders and non-responders [55]. Oculomotor disturbances, intra operative transient ischemic attack and subcutaneous infection are reported as adverse effects of hDBS. Heart rate, blood pressure and respiratory rate are not influenced by hDBS when amplitude is increased slowly; however sudden increase in amplitude can provoke autonomic and oculomotor disturbances [56]. Nowadays it is evident that acute hypothalamic stimulation does not abort acute CH attacks and it takes time for a prophylactic effect to develop, probably due to brain plasticity [57]. Compared to hDBS, ONS seems safer and complications are fewer and milder [58-61]. Local neck stiffness and discomfort are common [59]. In ONS lead migration and battery depletion are the main problems that require surgical revision or replacement of the device [30]. Such as for hDBS, ONS requires weeks or months to achieve a therapeutic effect, suggesting that a complex neuromodulation process is responsible for bringing about pain relief, rather than direct inhibition of pain pathways. Also evident is the fast relapse in both hDBS and ONS in which turning off the stimulator pain and headache attacks return to baseline levels. These data are not yet available on SPG stimulation, probably because the studies are few and not all are randomized and controlled. Its rate of device-related complications was quite low, most frequently sensory disturbances and pain. Local sensory impairment

seems to be a mild complication compared to the severe cluster attacks [25,43]. The very limited experience and the small series of studies about the use of SONS, VNS, SCS in drCCH patients prevents to have clear data about their safety and effectiveness. Adverse effects such as lead migration, battery depletion and local infections are the same of the other neuromodulatory approaches. However the rate reported in high cervical SCS seems exceedingly high, with a risk of permanent neurological deficit, and resulted in repeated surgical procedures, mostly lead revision for breakage or dislocation [53,62].

Conclusion

Neurostimulation has emerged as a viable treatment option for drug refractory chronic cluster headache: stimulation of the posterior hypothalamus, the occipital nerve and the sphenopalatine ganglion have mostly investigated while only a few reports are found in the literature regarding the use of supraorbital nerve stimulation, vagal nerve stimulation and spinal cord stimulation. hDBS is invasive, expensive and probably non-specific technique that must be employed with caution and only carefully considered for the most severely affected patients with drug-resistant chronic cluster headache when other treatment strategies have been employed and failed. ONS is attractive because is less invasive than hDBS. Both hDBS and ONS offer prophylactic benefit but the precise mechanisms underlying for the two techniques are yet to be determined. The response reflects a reduction in trigeminal activation and mobilization of central pain modulatory centers. SONS is used in combination with ONS. SPG stimulation could be an alternative in patients with episodic forms of the disorder for which there is no response to preventive treatments and in patients with contra indications or poor tolerability to acute treatments. VNS and tVNS are considered in patients with concomitant intractable headache, epilepsy and major depression. SCS may be indicated in case of unsuccessful ONS, although it remains invasive, no risk-free neuromodulatory procedure. However the greatest limitation for clinical use of neurostimulation techniques in drCCH is the lack of proper controlled studies.

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