Noninvasive vagus nerve stimulation in the management of cluster headache: clinical evidence and practical experience

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***Abstract*:** The efficacy of invasive vagal nerve stimulation as well as other invasive neuromodulatory approaches such as deep brain stimulation, occipital nerve stimulation, and ganglion sphenopalatine stimulation has been shown in the treatment of headache disorders in several studies in the past. However, these invasive treatment options were quite costly and often associated with perioperative and postoperative side effects, some severe. As such, they were predominantly restricted to chronic and therapy refractory patients. Transcutaneous vagal nerve stimulation now offers a new, noninvasive neuromodulatory treatment approach. Recently published studies showed encouraging results of noninvasive vagus nerve stimulation (nVNS), especially with respect to cluster headache, with high tolerability and a low rate of side effects; however, randomized controlled trials are needed to prove its efficacy. Further data also indicate therapeutic benefits regarding treatment of migraine and medication overuse headache. This review summarizes current knowledge and personal experiences of nVNS in the treatment of cluster headache.

Keywords: acute treatment, cluster headache, noninvasive vagus nerve stimulation, nVNS, prophylactic treatment

Introduction

Cluster headache (CH) is a rare primary trigeminal autonomic cephalalgia (TAC) which is characterized by excruciating unilateral headache attacks accompanied by primarily ipsilateral cranial autonomic symptoms (CAS) such as lacrimation, rhinorrhea or nasal congestion. During the CH attacks, which last between 15 and 180 minutes, patients are usually agitated. More men than women are affected. Headache attacks occur in most cases in 'bouts', meaning that episodes of headache attacks ('inside bout') take turns with pain free episodes ('outside bout') that might last even several years. A minority of patients suffer from chronic CH, which is defined by a lack of headache free times >1 month within a year. [Fischera *et al.* 2008; Gaul *et al.* 2012; Headache Classification Committee of the International Headache Society (IHS), 2013].

Acute attack therapy usually consists of 100% oxygen (8–15 l/min over 20 minutes) [Cohen, *et al.* 2009; Nesbitt and Goadsby, 2012], subcutaneous sumatriptan (6 mg) or nasal spray (20 mg), zolmitriptan nasal spray (5 mg) [Francis *et al.* 2010; Law *et al.* 2013; Nesbitt and Goadsby, 2012] and lidocaine nasal spray (1 ml of 10%). Steroids can be used for bout termination; verapamil and lithium can be applied as prophylactic treatment. Although many patients can be treated sufficiently with these existing therapeutic options, some patients do not respond satisfactorily or suffer from displeasing side effects of the medication which often leads to abortion of drug therapy.

In the past, invasive neuromodulatory approaches such as deep brain stimulation, occipital nerve stimulation, and ganglion sphenopalatine stimulation have been shown to be effective in CH, but because of sometimes severe side effects these invasive approaches were restricted to the most serious chronic CH subtypes and therapy refractory cases [Leone and Cecchini, 2015; Mueller *et al.* 2011; Schoenen *et al.* 2013].

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A newer approach to neuromodulatory treatment is noninvasive vagus nerve stimulation (nVNS). This approach is based on the pathophysiological role of the parasympathetic nervous system in headache and pain disorders, which is indicated by accompanied cranial autonomic symptoms (CAS) activation of the main parasympathetic ganglion (the sphenopalatine ganglion). The exact underlying mechanism of nVNS is still not completely understood. Previous studies suggest that multiple peripheral and central mechanisms might be involved in nVNS-mediated antinociception [Yuan and Silberstein, 2015a]. Animal studies showed that gamma aminobutyric acid (GABA)-mediated inhibition might play a crucial role [Krahl, 2012; Krahl and Clark, 2012; Ruffoli *et al.* 2011]. Oshinsky and colleagues showed that two minutes of nVNS in rats with chronic allodynia lead to an alleviation of trigeminal allodynia and pain for 3.5 hours [Oshinsky *et al.* 2014]. The authors showed that clinical improvement was associated with a block or reverse of high glutamate levels in the trigeminal nucleus caudalis (TNC) and suppression of extracellular glutamate levels. GABA, glycine, norepinephrine and 5-hydroxytryptamine (5-HT) levels stayed unchanged. Further experimental data showed potential antinociceptive effects of invasive and noninvasive vagal nerve stimulation which were not restricted to trigeminal pain or headache [Busch *et al.* 2013; Kirchner *et al.* 2000; Lyubashina, *et al.* 2012; Multon and Schoenen, 2005]. These data were supported by case series showing effects on primary headaches in patients with epilepsy treated with invasive vagal nerve stimulation [Lenaerts, *et al.* 2008; Mauskop, 2005; Sadler *et al.* 2002]. However, invasive therapies are difficult to apply, show individual risk of side effects and are expensive.

Noninvasive vagus nerve stimulation application

For headache treatment with nVNS the gammaCore® device is used primarily, which displays a 1 ms pulse of kHz sine waves for stimulation of the cervical branch of the vagal nerve. The patient is able to determine the stimulation intensity himself (up to 24V a 60mA). The recommended duration of stimulation is 2 minutes. Stimulation can be repeated several times (up to 12 times). Patients report a painless A-fiber mediated mild facial twitching.

nVNS in cluster headache

Up to now, nVNS has been studied as a treatment tool in two large clinical studies:

The PREVA study was the first randomized, prospective, controlled trial which investigated the efficacy of nVNS for prevention and acute treatment of chronic CH [Gaul *et al.* 2015]. The study was performed in a parallel-group design and conducted in 10 European centers. After a 2-week baseline, patients were treated for 4 weeks with standard of care alone (control group) or standard of care and nVNS (intervention group). After that a 4 week extension phase followed where all study participants received nVNS treatment. nVNS intervention parameters were chosen according to previous study results [Nesbitt *et al.* 2015].

Ninety-seven patients suffering from chronic CH according to the diagnostic criteria of the International Headache Society (ICHD-2) [Headache Classification Subcommittee of the International Headache Society, 2004] were randomized into the two treatment groups (nVNS, $n = 45$; control, $n = 48$) (intent-to-treat population). The treatment group showed a significantly greater reduction in the number of CH attacks per week compared with the control group (−5.9 *versus* −2.1, respectively). The mean therapeutic gain was a mean reduction of 3.9 CH attacks per week ($p = 0.02$). A total of 30 participants continued or started nVNS during the extension phase. They reported a further reduction of CH attacks by two attacks per week (randomized treatment phase, 9.6; extension phase 7.6.; $p < 0.001$). More patients in the nVNS treatment group achieved a ⩾50% response rate compared with the control group (48.6% *versus* 8.5%, respectively; $p < 0.001$). The amount of abortive medication use was significantly reduced in the treatment group compared with the control group, especially regarding administration of subcutaneous sumatriptan and inhalation of oxygen. However, nVNS did not significantly reduce duration or pain intensity of CH attacks. No serious side effects regarding the application of the nVNS occurred and most of the reported adverse events appeared to be mild or moderate. The acceptance of the device for CH treatment was high (65% would recommend nVNS to others, >75% evaluated nVNS as easy to use, and >50% were to some degree satisfied with nVNS).

Table 1. nVNS intervention and endpoints of the PREVA study.

Study characteristics	Description
Patient population	Chronic cluster headache according to ICHD-2
nVNS parameters	Low-voltage electrical signal (25 Hz); max: 24 V and 60 mA output current (adjustment by the user)
nVNS stimulation site	Right site of the neck (right vagal nerve)
Prophylaxis	Three 2-minute stimulations (= 3 doses) 5 minutes apart twice daily (= 6 doses/day); **1. Treatment:** within 1 hour of waking **2. Treatment:** 7–10 hours after first treatment
Acute treatment	Optional three additional nVNS doses at pain onset; Prophylactic treatment should not be administered within two hours after acute treatment; If acute nVNS was not working sufficiently, intake of acute abortive medication was allowed after 15 minutes
Primary endpoint	Reduction in the mean number of cluster headache attacks per week (number of attacks during the last week of the 4 weeks) during randomized intervention phase minus number of atatcks during baseline
Secondary endpoints (selection)	• ⩾50% responder rate • Abortive medication use • Duration and intensity of cluster headache attacks • HIT-6™ (headache impact test) • EQ-5D-3L (assessment for health-related quality of life)
Most common adverse events	• Headache • Nasopharyngitis • Dizziness • Oropharyngeal pain • Neck pain

nVNS, noninvasive vagus nerve stimulation.

In another open-label observational cohort study Nesbitt and colleagues investigated the efficacy of nVNS in 19 patients with CH [Nesbitt *et al.* 2015]. Eleven of them suffered from a chronic subtype (seven of them, therapy refractory) and eight reported an episodic course of disease. nVNS was used for acute treatment of CH attacks as well as for preventing CH attacks, whereupon first-line treatment as well as an adjunctive treatment was possible. The same stimulation paradigm as in the PREVA study was used [Gaul *et al.* 2015]. The majority of patients ($n = 15/19$) reported a general improvement from baseline, while 4 of 19 did not experience a change in their CH condition. The individual mean estimated improvement was 48% ± 9% at 12 months. Regarding acute treatment, the average abortion time for CH attacks after device use was 11 ± 1 minutes. The frequency of CH attacks was reduced from 4.5 to 2.6 per 24 hours ($p < 0.0005$) in chronic as well as episodic CH with no difference between both subtypes. In two patients the predicted length of the cluster episode was shortened by 4 weeks, in the other patients no bout shortening was observed. As in the PREVA study no serious adverse events occurred.

Furthermore, a small study including 13 patients with different headache diagnosis (two of them suffered from CH) did not show any efficacy of nVNS as 10 patients stopped therapy after 0.7–6 weeks because of insufficient treatment response ($n = 9$) or side effects ($n = 6$) [Magis *et al.* 2012].

Therefore, the advantage of nVNS lies in the safety of the technique and the low rate of associated side effects. The nVNS might be used not only as add-on prophylactic therapy in refractory chronic CH patients but also episodic subtypes.

nVNS in other headache disorders

nVNS has been studied in several other headache disorders in addition to CH such as migraine, hemicranias continua and medication overuse headache. As in CH, the gammaCore® device is

used for stimulation in almost all studies. Efficacy of nVNS regarding acute attack treatment has been shown regarding episodic and chronic migraine as well as medication overuse headache [Yuan and Silberstein, 2015b]. Significant pain relief was reached in up to half of the treated patients. Prophylactic treatment effects of nVNS have been shown in chronic migraine [Silberstein *et al.* 2015]. Effects on additional secondary endpoints like quality of life, depression and sleep disturbance could be shown in a recent prophylactic study of episodic and chronic migraine [Kinfe *et al.* 2015b].

In two patients with HC an improvement of background pain and reduction of painful autonomic exacerbation could be reached [Nesbitt *et al.* 2012]. Another case reported showed a reduction of intensity and frequency of the cluster component in a cluster-tic headache [Kinfe *et al.* 2015a].

Practical experiences and consequences for CH treatment

nVNS seems to be well tolerated and, compared to invasive treatment, less expensive than prophylactic treatment options in CH. Patients seem to be satisfied with therapy, especially regarding the low rate of side effects. It must be mentioned that the current nVNS device is only disposable and not rechargeable, which make it somewhat unattractive regarding eco-friendliness aspects. Furthermore, device costs are rather high at the moment.

Based on the authors' experiences, therapeutic benefit from prophylactic treatment is more convincing than from acute treatment of CH especially in chronic CH. nVNS might be used as an add-on and monotherapy, although its efficacy as a monotherapy seems to be not comparable with drug therapy. Therefore, adjunctive nVNS therapy seems to be appropriate in the majority of CH patients. Further controlled clinical trials are needed to prove the efficacy of this procedure. A sham stimulation procedure was recommended and used in ongoing clinical studies since the intervention procedure itself displays a high placebo effect. In addition, clinical conditions and features need to be identified that predict clinical response to nVNS in CH patients. Stimulation paradigms might also be optimized in the future.

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