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Supplement Article

Vagus Nerve Stimulation and Headache

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Neuromodulation is an emerging area in headache management. Through neurostimulation, multiple brain areas can be modulated to alleviate pain, hence reducing the pharmacological need. In this review, we discuss the recent development of the vagus nerve stimulation (VNS) for headache management. Early case series from epilepsy and depression cohorts using invasive VNS showed a serendipitous reduction in headache frequency and/or severity. Noninvasive VNS (nVNS), which stimulates the carotid vagus nerve with the use of a personal handheld device, also demonstrated efficacy for acute migraine or cluster headache attacks. Long-term use of nVNS seemed to exert a prophylactic effect for both chronic migraine and chronic cluster headache. In animal studies, nVNS modulated multiple pain pathways and even lessen cortical spreading depression. Progression in nVNS clinical efficacy over time suggests an underlying disease-modifying neuromodulation. Noninvasive VNS appears to be as effective as the invasive counterpart for many indications. With an enormous potential therapeutic gain and a high safety profile, further development and application of nVNS is promising.

Key words: cluster headache, headache, migraine, vagus nerve, vagus nerve stimulation

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Neuromodulation is a growing field in headache management. Technology ranges from invasive deep brain stimulation (DBS) of the posterior hypothalamus, to minimally invasive percutaneous electrode implantation for occipital nerve stimulation, and noninvasive transcranial magnetic stimulation and transcranial direct current stimulation.[1–3] Neurostimulation can be particularly useful to those who failed triptans or other prophylactic treatments.[4] The European Headache Federation positioned that a neurostimulation device should only be used in medically intractable headache patient who has been evaluated at a tertiary headache center.[5] Vagus nerve stimulation (VNS), which has demonstrated its antinociceptive potential,[6] may also provide a relief of pain associated with headache.

VNS FOR HEADACHE MANAGEMENT

In several case reports and series in epilepsy and depression cohorts, chronic use of implanted VNS was associated with headache relief. In early 2000, Kirchner et al and Sadler et al each reported a case where headache improved significantly following VNS implantation.[7,8] Later, several small case series from other seizure cohorts found significant improvements in chronic migraine and chronic cluster headache.[9–11]

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Table.—Headache Trials Using tcVNS

Disorder	Cases	tcVNS	Results	Ref
Migraine				
Acute	19	Each attack	The mean pain intensity reduced from 6.63 to 3.95 after 2 hours.	15
Acute	30	Each attack	96 attacks treated. 43 (45%) complete remission; 42 (44%) no benefit; 11 (11%) uncertain in 2 hours.	16
Acute	30	Each attack	80 attacks treated. 12/54 (22%) 2 hour pain-free from moderate or severe attacks.	17
CM/MOH	15	Each attack	362 attacks treated. 33% pain-free at 2 hour.	18
CM	59	6 months	For prophylaxis, progressive improvement in headache days/month (1, 3, 6 days less at 2-, 4-, 6-monthvs baseline).	19
Cluster HA				
Acute/chronic	19	12 months	Among 11 chronic, 8 episodic cluster patients, 15 reported overall improvements (48% from baseline) remained the same.	20
Acute/chronic	93	4 week	Greater quality of life in VNS vs standard of care.	21
Acute	93	4 week	Reduced attacks per weeks in VNS (−7.6) vs standard of care (−2.0).	22
HC	2	24/32 week	Improvements in background pain (30%, 75%), and painful autonomic exacerbation (20%, 75%).	23
Mixed	13	0.7–6 week	13 patients (4 MWoA, 5 with MOH, 3 CM, 2 CH, 2 HC). Ten patients stopped VNS after 0.7–6 weeks because of lack of efficacy ($N = 9$) and/or side effects ($N = 6$).	24
Cluster-tic	1	12 week	Intensity and frequency of the cluster component decreased by 45%.	25

CM/MOH = chronic migraine with medication overuse headache; HC = hemicranias continua; MWoA = migraine without aura; tcVNS = transcervical vagal nerve stimulation.

A case series from a depression cohort found that VNS was beneficial in drug-refractory chronic daily headache.[12] Headache improvement occurred within 1–3 months postimplantation; in some cases, it took longer.[13] The effect on headache was independent of seizure control or the use of antiepileptic medication. VNS benefited a chronic cluster headache patient who failed to respond to DBS following head trauma; no electrical interference was observed from the two implants.[14] The antinociceptive benefit of chronic invasive VNS in headache sufferers was associated with potential surgical risks, leading to the evaluation of Noninvasive VNS (nVNS) in headache management.

Noninvasive VNS has been studied in several primary headache disorders (Table). To date, most headache-related nVNS clinical studies utilized the transcervical VNS (tcVNS) device (gammaCore). In 2012, Magis et al reported the first study examining tcVNS (90 seconds, 3 times/day) on 13 patients with different headache disorders (migraine, cluster headache, hemicranias continua, medication-overuse headache). Ten patients stopped the device after 0.7–6 weeks due to adverse side effects or lack of efficacy. However, this ineffectiveness may have been due to improper stimulation of the VN.[24] Further studies showing potential efficacy on cluster headache and migraine are discussed below.

For migraine attack management, Moscato et al studied 19 chronic migraine subjects in high intensity crisis receiving tcVNS (two 120 seconds, 15 minutes apart). After 2 hours, the mean pain intensity (visual analog scale [VAS] 1-10) reduced from 6.63 to 3.95 ($P < .05$); 9 patients no longer had pain, 6 had reduced pain, and 4 showed no variation.[15] Grazzi

et al studied 30 patients with episodic migraine without aura and treated a total 96 attacks with right tcVNS (120 seconds): 43 (44.8%) resolved completely in 30 minutes; 42 (43.7%) did not show any benefit in the first 2 hours; and, in 11 (11.4%), the results were uncertain.[16] Rainero et al examined the effect of tcVNS on 15 patients of chronic migraine with medication overuse headache. During the 6-month study period (including 5-day inpatient detoxification period), a total of 362 migraine attacks were recorded. At 2 hours, a pain-free response was observed in 121/362 patients (33.4%). Average initial pain was 1.66 ± 0.7 and dropped to 1.1 ± 0.9 at 2 hours ($P < .01$). A significant response to tcVNS was observed in 50% of treated patients.[18] Goadsby et al also applied tcVNS (two 120 seconds, 15 minutes apart) to a total of 80 migraine attacks from 30 episodic migraine patients. For attacks with a baseline of moderate or severe headache, 12 of 54 (22%) attacks were pain free at 2 hours, while 23 of 54 (43%) attacks showed pain relief (43%). On 10 of 26 (38%) attacks with mild pain, they reported being pain free at 2 hours. The results were comparable to similarly tolerated triptans and the device was well-tolerated.[17]

TcVNS also exhibits a prophylactic effect in chronic migraine. In a double-blinded, randomized-controlled pilot trial, Silberstein et al compared the efficacy of tcVNS (two 120 seconds stimulation sessions, 3 times/day) with a sham device. During the 2-month randomization phase (tcVNS vs sham; $n = 49$), more subjects from the tcVNS group had >25% reduction in headache days; only tcVNS subjects had reduction of >50% or >75%. Following a 6-month open-label phase, tcVNS was associated with a mean reduction of 4 headache days among completers ($n = 26$). During the study period, there was no significant difference in pain medication use between tcVNS and sham groups. The adverse effects were mild and the device was well-tolerated. Interestingly, similar to the findings in the VNS-treated epilepsy patients, the neuromodulatory effect on headache seemed to improve over time.[19]

Long-term tcVNS also reduces the severity of cluster headache. Nesbitt et al studied 19 cluster headache patients (11 chronic, 8 episodic) with tcVNS applied for over 12 months. Fifteen patients reported an overall improvement in their condition as using the device, stating a mean estimated subjective improvement of 48% from baseline. Prophylactic use of the device resulted in a substantial reduction in estimated mean attack frequency from 4.5/24 hours to 2.6/24 hours posttreatment.[20] Gaul et al compared tcVNS (120 seconds, twice daily plus optionally for rescue treatment) with the standard of care in 93 chronic cluster headache patients. Number of attacks per week was significantly reduced in subjects treated with tcVNS vs standard of care only (-7.6 vs -2.0; $P < .05$). Prophylactic use of tcVNS was associated with less use of rescue medications and demonstrated a favorable safety/tolerability profile.[22] The use of tcVNS was associated with greater improvement in quality of life in these subjects.[21] Recently, Kinfe et al also reported a case with 11 years of cluster-tic syndrome that underwent right tcVNS (two 120 seconds, 15 minutes apart; additional treatment at the onset of each attack). At about the 24th day of treatment, a significant reduction of the cluster component and gradual amelioration of the tic component was reported. By 12 weeks, the intensity and frequency of the cluster component decreased by approximately 45% and the patient described a slight reduction in the sharpness of tics, even though there was no change in analgesic use. Migraine Disability Assessment scores dropped from 171 to 81.[25] These studies clearly demonstrated the antinociceptive potential of tcVNS in cluster headache patients.

The underlying mechanism for tcVNS in headache treatment is likely similar to invasive VNS. In particular, the involvement of locus coeruleus, dorsal raphe nucleus, periaqueductal gray, ventral posteriomedial nucleus, and cingulate cortex from VNS clearly reflects the role of norepinephrine, serotonin, and central sensitization underlying the pathophysiology of different headache disorders. However, very few studies have addressed the mechanism of tcVNS. Oshinsky et al applied tcVNS for 2 minutes on a rat allodynia model and observed an extended inhibitory effect lasting more than 3 hours. TcVNS also suppressed the glutamate increase in the nucleus of the trigeminal nerve

(TNC) triggered by glycerol trinitrate application. No change was seen in GABA, glycine, 5-HT, or norepinephrine.[26] Chen et al found that 4 minutes of tcVNS can reduce cortical spreading depression (the generally accepted mechanism of the migraine aura) for at least 2 hours.[27] No functional imaging study is available to date. Although there is no consensus on where the tcVNS mechanism of action takes place, its timing is better understood as evidenced by a rather sustaining effect beyond the actual stimulation period. Current studies suggest a possible underlying neuromodulatory process for headache management.

CONCLUSION

Early studies demonstrated the potential of invasive VNS and nVNS in the management of distinct types of headache disorders. VNS may be effective for both acute and prophylactic treatment of headache. Chronic use of VNS seems to be associated with a better outcome that improves over time. The mechanism of action, particularly from nVNS on headache, remains to be studied. A clearly effective double-blinded, sham-controlled study that has a strongly positive primary endpoint for various types of headache is needed. With a good safety profile and the strong suggestion of efficacy in previous trials, nVNS may constitute an effective headache treatment. More trials are underway.

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