Chapter 14
Peripheral Neuromodulation on the Refractory Headache Disorders

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Introduction

The medical treatment of patients with chronic primary headache syndromes is particularly challenging, and, in many cases, even higher doses of preventive medication are ineffective, and adverse side effects frequently complicate the course of medical treatment. In these cases, patients can profit from the emerging diversity of invasive and noninvasive neuromodulatory techniques. Practical application of noninvasive neuromodulation reportedly dates to Roman times when Galen used marbled electric rays to treat headache, pain, and epilepsy [1]. Various forms of neuromodulation have been used in the past 50 years for different indications, like occipital nerve stimulation (ONS) in presumed occipital neuralgia in the late 1990s and deep brain stimulation (DBS) of the posterior hypothalamic area in cluster headache in 2001 [2]. This development involves some advantages for the affected patients; neuromodulation is in principle reversible, it allows dynamic adjustment of stimulation parameters, and, unlike the mostly transient benefit from pharmacological nerve blocks, it can exert prolonged effects. In this chapter, the most used peripheral neurostimulation techniques in primary headaches are reviewed, with special regard to their advantages and downsides.

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A. Özge et al. (eds.), *Peripheral Interventional Management in Headache*,
Headache, https://doi.org/10.1007/978-3-030-10853-3_14

14.1 Occipital Nerve Stimulation (ONS)

The ONS mechanisms involved in ONS efficacy are multiple. Spinal and supraspinal actions are probably involved. Modulation at the level of the spinal cord via convergence of trigeminal nerve and upper cervical afferents (C2/C3) in the trigemino-cervical complex is hypothesized as a nexus to explain efficacy of chronic stimulation of the occipital nerve [3].

Central mechanisms are also involved. Suboccipital stimulation modulates the activity in the left pulvinar and anterior cingulate cortex and produces an activation of the dorsal rostral pons. Experimental evidence also suggests a contribution of descending pain modulating pathways in mediating the analgesic effects of peripheral nerve stimulation. Peripheral nerve stimulation is a potential minimally invasive way to control pain [4].

Open-label data in 91 medically intractable chronic cluster headache (CCH) patients treated with ONS have shown favorable outcomes with a reduction of more than 50% of attacks in around 70% of patients with cluster headache [5]. Magis et al. implanted ONS in 15 patients with refractory CCH, followed for up to 5 years. One patient was explanted due to infection, 11 (80%) had 90% improvement, with 60% becoming pain-free for prolonged periods, while 2 patients did not respond or described mild improvement. Side shift with infrequent contralateral attacks occurred in 36%, and/or isolated ipsilateral autonomic attacks were described without pain in 36% [6].

Burns et al. retrospectively reviewed outcomes from 14 patients over 17.5 months on average. The first patient was implanted unilaterally and improved, but then the attacks shifted side; hence, all subsequent patients were implanted bilaterally. Ten of 14 patients reported improvement, 3 had improvement of 90%, 3 had moderate improvement 40%, and 4 had mild improvement (20–30%) [7]. Another study by Fontaine et al. also showed similar encouraging results in 13 patients implanted bilaterally, as 10/13 patients had an improvement of about 50% [8]. Brewer et al. reported success in 4/5 patients. One patient had a 50% improvement, one a 70% improvement, and one an 80% improvement, one was "doing very well," and ONS did not work for one [9]. Mueller et al. implanted ONS in 10 patients with CCH and found a frequency and/or intensity improvement in 90% of them [10], and Strand et al. used a unilateral microstimulator (Bion) in three develop drug-resistant CCH (drCCH) patients also showing a long-term benefit for up to 5 years [11]. Our team implanted bilateral ONS in 16 drCCH patients; follow-up range was 1–8 years. Eight patients were asymptomatic, two patients changed to episodic attacks, four patients had improvement of >50%, one patient had no improvement, and one patient shifted to contralateral CH. Complications were two electrode migrations, three battery replacements, and three explants due to infection. ONS is safe, but the rate of complications is high in the long-term follow-up [12].

ONS has also been described as effective in hemicrania continua (HC) and SUNCT. Lambru et al. described the outcome of nine medically intractable SUNCT

(n = 6) and SUNA (n = 3) patients treated with bilateral ONS. All but one patient showed substantial improvements. Four patients became pain free, two almost pain free, and two had a remarkable reduction in attack frequency and severity [13]. Two case series in patients suffering from chronic migraine found a reduction of attack frequency or headache severity of more than 50% along with relevant improvements of migraine-associated disability in more than 85% of the participants. Despite these promising initial findings, larger studies have yielded ambiguous results. And three larger randomized clinical trials have failed to show meaningful and conclusive improvements in their experimental period in patients with chronic migraine [14, 15].

In practice, the greater occipital nerve (GON) is stimulated using a subcutaneous electrode crossing the nerve trajectory, to obtain paresthesias in the GON territory. ONS can be set up bilaterally or unilaterally, but because of the lower invasiveness of the procedure, and the risk of switching sides, bilateral stimulation of the occipital nerve is recommended.

Large number of patients successfully treated in unblinded studies with good efficacy in trigeminal autonomic cephalgias and moderate efficacy in open-label studies/case series on patients with chronic migraine. As bilateral implantations are now standard in most centers, it is the method of choice for non-side-locked trigeminal autonomic cephalgias. The side effects reported for ONS are usually mild but frequent, especially in the long-term. Electrode migration rates needing surgical revision are highly variable between groups, from 0% to 30%. Another technical problem is the use of high current intensities, leading to frequent battery depletion, which can potentially be avoided by the implantation of rechargeable batteries. Infection is also described in 3–5%. The patient's self-reported intolerance to paresthesias and tension feeling in the cable joining the electrode to the battery can be significant for some. One important consequence not collected as an adverse event, but important in the patient daily life, is limitation of physical activity to avoid electrode migration [14, 15].

14.2 High Cervical Spinal Cord Stimulation (hcSCS)

High cervical stimulation of the dorsal column was studied prospectively in a small sample of refractory chronic cluster headache patients (n = 7) with a mean follow-up of 23 months. Continuous stimulation (except for one patient with intermittent use) led to an impressive and immediate reduction of mean attack frequency from 6.0 to 1.4 with a responder rate of 86%. However, dislocation of electrodes, rapid depletion of batteries, and lead breakage occurred in five out of seven patients with frequent revisions. As in other unilateral approaches, two patients reported a side shift of attacks. Although the underlying concept is intriguing and hcSCS is probably more effective than ONS, the high rate of complications strongly argues against its clinical use [16].

14.3 Sphenopalatine Ganglion Stimulation

The sphenopalatine ganglion (SPG) has been a target for various lesional or local anesthetic techniques to treat cluster patients for over a century. The SPG is an extracranial structure lying in the pterygopalatine fossa, containing parasympathetic and sympathetic components. Because of its direct and indirect connections to somatic and visceral nerve structures of the face and to the trigeminovascular system, the superior salivary nucleus (SSN), and the hypothalamus, the SPG participates in cluster headache pathophysiological outflow and was chosen as a therapeutic target with some successful results. High-frequency SPG stimulation may primarily activate parasympathetic neurons or pre-/postganglionic parasympathetic nerve fibers and may physiologically block parasympathetic outflow, resulting in an acute effect on head pain and autonomic symptoms. In 2010, Ansarinia et al. placed temporary SPGs to treat six drCCH patients. They triggered CH attacks with alcohol, nitroglycerin, and other provoking techniques. They reported 18 attacks of CH in 5 patients. SPGs induced a complete resolution of pain in 11 acute events and partial resolution (>50% relief) in 4 events. Side effects were a transient mild facial pain, epistaxis, and a severe cluster attack in one patient [17].

A multicenter, randomized, controlled study (pathway CH-1) was performed in Europe, using an implantable microstimulator surgically positioned on the SPG in 32 patients for the acute treatment of chronic cluster headache. 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 ($P < 0.0001$). Although the study was designed for acute treatment, a preventive response was observed in some patients. Nineteen of 28 (68%) patients experienced a clinically significant improvement: 7 (25%) achieved pain relief in 50% of treated attacks and 10 (36%) a 50% reduction in attack frequency, and 2 (7%) had both acute and preventive effect. Five serious adverse events occurred (three lead revisions and two explants). Most patients (81%) experienced transient, mild/moderate loss of sensation within maxillary nerve regions, consistent with dental or oral procedures [18]. A responder rate of 61% was maintained in a population of 33 medically refractory chronic cluster headache patients followed for 24 months while receiving on-demand, acute SPG stimulation. Forty-five percent of patients were acute responders, 33% were frequency (preventive) responders, and six of these patients experienced both types of response [19].

In the long-term follow-up studies, the efficacy of the stimulation remains after 2 years SPG stimulation appears as a promising innovative, efficient, and safe therapeutic solution for patients suffering from severe CH. SPG stimulation has showed its efficacy to abort CH attacks versus placebo stimulation, suggesting that it is particularly adapted for CH patients who are not sufficiently improved by currently available abortive treatments such as sumatriptan and oxygen. Additionally, the pilot study suggested that repeated SPG stimulation might have a preventive action on CH attack frequency. A new study in patients with chronic cluster, performed in the United States with bigger number of patients, has confirmed the results of the European study (American Headache Society, San Francisco, 2018).

14.4 Vagus Nerve Stimulation

There are numerous connections between the nucleus tractus solitarius and spinal trigeminal nucleus. Early studies suggest that inhibition of pain by vagus nerve stimulation (VNS) occurs by direct inhibition of vagal afferents to the caudal trigeminal nucleus, as an acute effect [20]. More recent evidence suggests that VNS may also inhibit pain by reducing glutamate levels in the trigeminal nucleus caudalis, which is in line with the longer-lasting preventive effects of VNS [21]. Vagus nerve stimulation (VNS), a well-established neuromodulation treatment for epilepsy and medication-resistant depression, has been successfully used open label in CH, chronic migraine (CM), and high-frequency episodic migraine (HFEM).

Historically, approved VNS devices were surgically implanted, while more recently, noninvasive VNS methods have been designed to avoid the risks of invasive approaches. *gammaCore*® was developed as a noninvasive vagus nerve stimulation (nVNS) portable device for transcutaneous stimulation of the cervical branch of the vagus nerve. ACT1 was a randomized, double-blind, sham-controlled study conducted in the United States. It demonstrated that nVNS as acute treatment produced a therapeutic response within 15 minutes and pain relief that was sustained through 60 minutes in patients with episodic CH [22]. ACT2 study also compared nVNS and a sham device with respect to efficacy and safety in the acute treatment of episodic CH (eCH) and chronic (cCH). In this study, nVNS was superior to sham therapy for acute treatment of attacks in patients with eCH but not those with cCH or in the total population. nVNS was safe and well tolerated in all patients. These results confirm and extend findings from the previous ACT1 study and demonstrate that nVNS is an effective acute attack treatment option for patients with eCH, with a favorable risk/benefit profile [23]. On the other hand, Barbanti et al. studied the efficacy of nVNS (*gammaCore*®) in patients with HFEM and CM. In this open-label, single-arm, multicenter study, patients with HFEM or CM self-treated up to three consecutive mild or moderate migraine attacks that occurred during a 2-week period by delivering two 120-s doses of nVNS at 3-min intervals to the right cervical branch of the vagus nerve. Of the 50 migraineurs enrolled (CM/HFEM: 36/14), 48 treated 131 attacks. The proportion of patients reporting pain relief, defined as $a \geq 50\%$ reduction in visual analog scale (VAS) score, was 56.3% at 1 h and 64.6% at 2 h. Of these patients, 35.4% and 39.6% achieved pain-free status (VAS = 0) at 1 and 2 h, respectively. When all attacks ($N = 131$) were considered, the pain relief rate was 38.2% at 1 h and 51.1% at 2 h, whereas the pain-free rate was 17.6% at 1 h and 22.9% at 2 h [24].

The current data confirm that nVNS is well tolerated and safe and is associated with treatment satisfaction and therapeutic adherence. From a risk-benefit perspective, nVNS therapy achieved pain relief without serious side effects, which may decrease patients' reliance on migraine medications and, in turn, lower the risk of medication overuse. *gammacore*® is approved by FDA for acute migraine in 2018. Besides, transcutaneous stimulation of the auricular branch of the vagal nerve (t-VNS) has been used in the treatment of chronic migraine. A monocentric randomized, controlled, double-blind study was conducted showing that the procedure

was safe and effective. The mean reduction of headache days after 12 weeks of treatment exceeded that reported for other nerve stimulating procedures [25].

14.5 Supraorbital Transcutaneous Stimulation (STS)

Transcutaneous stimulation of the supraorbital nerves using transcutaneous electric nerve stimulation technology by the *Cefaly*® device (STX-Med, Liège, Belgium) is another noninvasive peripheral neuromodulation method that has shown some positive results in migraine treatment. With reusable electrodes, a steady current at 16 mA is delivered to the end branches of the trigeminal nerve. A treatment session lasts 20 minutes and should be applied once daily for prophylactic treatment. An initial double-blind, randomized, sham-controlled trial (PREMICE study) investigated the efficacy of the *Cefaly*® device in 67 patients with migraine for the reduction of migraine days, migraine attacks, headache days, and intake of acute medication. In the treatment group, the 50% responder rate was 38% compared with 12% in the sham device group. Adverse events were not reported in the study. In a larger internet-based open-label study, the *Cefaly*® device was investigated in 2313 patients with headache who rented the device for a 40-day trial period. After a testing period of 58.2 days on average, 46% of the 2313 renters were not satisfied and returned the device, but the compliance check showed that they used it only for 48.6% of the recommended time. The remaining 54% of participants were satisfied with the treatment. Ninety-nine (4.3%) participants of the 2313 reported one or more adverse events, but none of them were serious [26].

In 2016, additional statistical analyses were performed on the outcome measures presented by Schoenen et al. to account for covariates. A rank analysis of covariance was performed, using the nonparametric Spearman's rank correlation coefficient. The results showed that age and disease duration do not influence study outcomes. However, the number of migraine days during the 1-month baseline period had an influence on the decrease in migraine days during the third month of treatment. In the original publication, the difference between verum and sham groups in the reduction of migraine days (respectively, 22.7% and 24.9%) just missed the significance threshold ($p = 0.054$). However, when baseline migraine days are considered as a covariate, this difference becomes significant ($p = 0.044$) [27].

This new analysis indicates that the beneficial effect of Cefaly for migraine prevention might be greater in patients with more frequent migraines, which is of interest for clinical practice. Cefaly was approved by FDA for acute migraine treatment in 2017.

14.6 Nonpainful Remote Electrical Stimulation (NRES)

Electrical stimulation has been extensively used, keeping the general rule of applying the stimulation adjacent to or within the same dermatome of the painful body location. It is considered an effective yet weak tool for pain reduction. The rationale

is an activation of pain inhibitory centers, via the conditioned pain modulation (CPM) effect; remote noxious stimuli can exert a generalized analgesic effect. This is by the descending analgesia tracts originating at brainstem centers and terminating at spinal, including cervical trigeminal, nuclei. Since use of pain to inhibit another pain is not clinically appealing, we use nonpainful conditioning; we and others have shown that robust nonpainful conditioning stimuli are sufficient in many cases to induce pain inhibition. Presumably, the threshold for activation of the inhibitory pain control system is lower than that of pain perception. In a prospective, double-blinded, randomized, crossover, sham-controlled trial efficacy of remote nonpainful electrical upper arm skin stimulation in reducing migraine attack pain has been evaluated [28]. In 71 patients (299 treatments) with evaluable data, 50% pain reduction was obtained for 64% of participants based on best of 200-μs, 150-μs, and 100-μs pulse width stimuli per individual vs 26% for sham stimuli. Greater pain reduction was found for active stimulation vs placebo; for those starting at severe or moderate pain, reduction to mild or no pain occurred in 58% (25/43) of participants (66/134 treatments) for the 200-μs stimulation protocol and 24% (4/17; 8/29 treatments) for placebo ($p = 0.02$) and to no pain occurred in 30% (13/43) of participants (37/134 treatments) and 6% (1/17; 5/29 treatments), respectively ($p = 0.004$). Earlier application of the treatment, within 20 minutes of attack onset, yielded better results: 46.7% pain reduction as opposed to 24.9% reduction when started later ($p = 0.02$).

Nonpainful remote skin stimulation can significantly reduce migraine pain, especially when applied early in an attack. This treatment may be proposed as an attractive nonpharmacologic, easy to use, adverse event free, and inexpensive tool to reduce migraine pain.

14.7 Caloric Vestibular Stimulation (CVS)

CVS is a widespread clinical tool used both to diagnose balance disorders and to confirm the absence of brainstem function. Historically, water or air irrigators have been used to warm or cool the external auditory canal. Both warming and cooling temperature changes create convection currents in the endolymphatic fluid of the horizontal semicircular canal. These currents cause cupular deflection, which alters the tonic firing rate of the vestibular nerves and, in turn, elicits broad autonomic responses, including the vestibular-ocular reflex.

The potential for CVS to provide effective prophylaxis for episodic migraine is supported by several findings. First, while the precise pathology underlying migraine remains largely unknown and the neural circuits involved are widespread, results from several neuroimaging studies consistently suggest that migraine is a neurological disorder involving brainstem dysfunction. This hypothesis is relevant because the brainstem is among the many neural regions activated by CVS, a set of strong pathways corroborated by the well-established diagnostic sensitivity of CVS to brainstem dysfunction. Anatomical tracing studies have demonstrated dense and often reciprocal connections between the vestibular nuclei, located within the pons

and medulla, and other brainstem regions implicated in migraine—including the periaqueductal gray, the parabrachial nucleus, the locus coeruleus, the reticular formation, the dorsal spinal and mesencephalic trigeminal nuclei, and the dorsal raphe nuclei. Furthermore, recent transcranial Doppler sonography data demonstrate that CVS treatment with the device elicits changes in cerebrovascular dynamics that point to brainstem neuromodulation. A multicenter, parallel-arm, block-randomized, double-blinded, placebo-controlled clinical trial was conducted to determine the superiority of CVS therapy over placebo treatment [29].

After 3 months of treatment, active-arm subjects exhibited significantly fewer migraine days (−3.9 ± 0.6 from a baseline burden of 7.7 ± 0.5 migraine days). These improvements were significantly greater than those observed in control subjects (−1.1 ± 0.6 from a baseline burden = 6.9 ± 0.7 migraine days) and represented a therapeutic gain of −2.8 migraine days, CI = −0.9 to −4.7, $P = 0.012$. Active arm subjects also reported greater reductions in acute medication usage and monthly pain scores compared to controls. No adverse effects on mood, cognition, or balance were reported. Subjects completed the trial with an average rate of 90% treatment adherence. No serious or unexpected adverse events were recorded. The rate of expected adverse events was similar across the active and the placebo groups, and evaluation confirmed that subject blinding remained intact. CVS appears to provide a clinically efficacious and highly tolerable adjuvant therapy for the prevention of episodic migraine.

Conclusions

The variety of neuromodulatory approaches has enlarged our therapeutic options significantly, especially in drug-refractory patients with chronic cluster headache and chronic migraine. Implants require surgical expertise, are relatively costly, and are still restricted to a minority of patients. However, noninvasive transcutaneous stimulation techniques, like STS, VNS or e NRES, shown efficacy, tolerability, and less adverse effects. The main challenge will be the development of an effective stimulation paradigm and the determination of the most reasonable region to stimulate, both depending on the baseline pathophysiological hypothesis. It is important to develop new strategies that are less invasive and easier to use for the patient.

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