Chapter 11
Neuromodulation in Migraine

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Like other primary headaches, migraine can be treated by neuromodulation techniques based on electrical stimulation of the nervous system. These neuromodulation techniques can be invasive and noninvasive and have different targets.

11.1 Invasive Neuromodulation in Migraine

11.1.1 Occipital Nerve Stimulation (ONS)

Initially proposed to treat occipital neuralgia, ONS was also used to treat primary headaches including migraine with the same devices as those used to treat neuropathic pain by spinal cord stimulation.

Evidence Migraine preventative treatment using ONS has been the topic of several randomized controlled trials (RCT), and the results are disappointing. PRISM study was a multicenter, prospective, double-blind, sham-controlled trial promoted by Boston Scientific. It involved 140 subjects with episodic migraine (EM) or chronic migraine (CM) who previously failed of at least two acute treatments and two preventative treatments and regardless presence of medication overuse. There was no significant difference in the primary endpoint that was the reduction in monthly migraine days (−5.5 for the active and −3.9 for the sham, $p = 0.29$) from baseline to 3 months after implantation, and only the abstract was reported [1]. ONS-STIM trial

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was a multicenter, prospective, randomized, single-blind, feasibility study promoted by Medtronic. It involved 61 subjects who suffered from CM with a previous failure of at least two preventative treatments, an associated medication overuse being an exclusion criterion. An innovative study design was utilized to compare medical management, preset (sham) stimulation, and adjustable (active) stimulation. This methodology allowed a randomized comparison between groups with a 2:1 active to sham ratio among implanted individuals who had been randomized, and the study was conducted in single blind. Ultimately, 28 were implanted in the adjustable stimulation group, 16 in the preset group, and 17 in the medically managed group. No primary endpoint was specified, but the feasibility of multiple outcome measures for future studies was assessed. After 12 weeks of stimulation, a responder was defined as a subject who achieved at least 50% reduction in the number of headache days per month or a three-point or greater reduction in overall pain intensity compared to baseline. Using this definition, 39% of patients were responders in the adjusted stimulation group compared with 6% in the preset stimulation group ($p = 0.032$) and 0% in the medically managed group ($p = 0.003$) [2]. A third trial, promoted by Saint Jude Medical, concerned 157 subjects suffering from CM with previous failure of at least two acute treatments and two preventative treatments and regardless presence of medication overuse. In this multicenter, prospective, double-blind trial, subjects were randomized into two arms according whether they were treated with ONS (105 subjects) or sham stimulation (52 subjects). On the primary endpoint, that was a 50% reduction in mean daily visual analog scale (VAS) scores, this study did not find any significant difference between the ONS arm (17.1%) and stimulation sham arm (13.5%). Nevertheless, this RCT showed significant superiority of ONS regarding a 30% reduction in VAS scores and other secondary endpoints such as the number of headache days per month (−7.3 in active stimulation vs. −4.2 in sham stimulation, $p = 0.015$) [3]. In addition to these three industrial RCTs, ONS was evaluated in two smaller, academic, monocenter RCTs whose results were in favor of it [4, 5]. Using these five RCTs and seven open series that included at least ten patients, a meta-analysis suggested that the ONS could be effective in the preventative treatment of CM but insisted on the modest effect size with pooled results from the three industrial RCTS showing a mean reduction of 2.59 headache days per month at 3 months compared to sham (95% CI 0.91 to 4.27, I2 = 0%) and probably exaggerated by the bias related to the difficult double-blind respect due to paresthesia induced by ONS in the great occipital nerve territory that is essential to achieve the therapeutic effect [6]. This meta-analysis also insisted on the absence of efficacy data after 3 months, but the long-term results of the study promoted by Saint Jude Medical were subsequently published showing persistent efficacy after 1 year of stimulation [7]. Such an ONS persistent efficacy in CM was also recently reported in an open series involving 53 patients with a mean follow-up of 4 years [8] and another open series involving 37 patients with a mean follow-up of 7 years [9].

Limits The European Headache Federation stated that in CM, the use of ONS seems "acceptable" although based on limited evidence [10]. In this context, a CE mark to ONS in CM was obtained by Saint Jude Medical for its devices. However,

the use of ONS in CM is now limited by the withdrawal of this CE mark. This withdrawal has been justified by a large number of adverse events reducing benefit/risk of ONS in this indication. The mean incidence of total complications of ONS in CM treatment was estimated to 66% [11]. Like any implantable neuromodulation technique, NSO is limited by a risk of immediate or delayed infection. ONS also exposes a risk of early battery depletion due to high-stimulation intensities and the fact that stimulation is most often used continuously during the day and night. Finally, ONS can be complicated by a lead migration secondary to the neck mobility and which, when it occurs, imposes a surgical revision.

Mechanisms of Action The mechanisms of action of ONS for the prevention of migraine are unknown. The background to propose the ONS in the treatment of migraine (and other primary headaches) was the convergent input from trigeminal and cervical afferents in the trigeminocervical complex (TCC) [12, 13]. Nevertheless, the effect latency observed in many patients suggests a more complex mechanism of action that are also suggested by functional imaging studies. A study using PET showed an activation of the rostro-dorsal pons (where migrainous generators are supposed to be located) associated with an activation of structures involved in the pain matrix, including the anterior cingulate cortex [14]

11.1.2 Others Invasive Neuromodulation Treatments

Sphenopalatine Ganglion Stimulation (SPGS) A chronically implantable neuromodulation device ("Pulsante"), specifically designed for acute SPGS, has been developed by the company Autonomic Technologies in order to be used on demand. The neurostimulator device is implanted in the pterygopalatine fossae, along the posterior wall of the maxillary bone, and fixed to the zygomatic process with a screwed plate, with the lead being placed in contact with the SPG. The neurostimulator does not contain a battery but is activated and powered by a remote controller using radiofrequency energy. Clinical development of this device mainly concerned the acute treatment of cluster headache [15], but a RCT in acute treatment of migraine has just ended and the results are pending (PATHWAY-M1/NCT01540799 clinicaltrials.gov).

Cervical Spinal Cord Stimulation (CSCS) The background for CSCS use in primary headaches is the assumption that the application of electrical pulses directly onto the dorsal columns at the C2–C3 vertebral level will provide a neuromodulatory effect on the TCC greater than stimulation of the greater occipital nerve. In a retrospective cohort, a Swiss team reported 12 patients experiencing a 50% response among 17 patients with refractory CM treated by CSCS [16]. A proof of concept trial investigating the safety and efficacy of CSCS in the treatment of refractory CM was carried out few years ago (NCT01653340 clinicaltrials.gov), but results are still pending. Until proper evidence is provided, CSCS is strictly avoided in patients with migraine as stated by EHF [10].

11.2 Noninvasive Neuromodulation in Migraine

11.2.1 Supraorbital Nerve Stimulation (SONS)

The stimulation of the supraorbital nerve is possible by Cefaly©, a noninvasive device which corresponds to a transcutaneous external stimulator specifically developed to stimulate this terminal branch of the trigeminal nerve and which is applied on the forehead.

Evidence Available evidence supports the Cefaly© use only in the prevention of EM. Data were obtained in the PREMICE study which is an RCT promoted by the manufacturer of this device with a partnership of the Belgian Headache Society [17]. The PREMICE study involved 67 subjects with EM who, after an evaluation period of 1 month, were randomized to use the Cefaly© or a stimulation sham for 3 months. The primary endpoint was the difference of monthly migraine days between the month prior to randomization and the third month of the randomized period. Intention-to-treat analysis showed a significant reduction (from 6.94 to 4.88/29;7% $p = 0.023$) in the Cefaly© arm and a nonsignificant one (from 6.54 to 6.22/4% $p = 0.608$) in the sham arm, but the comparison of this reduction between the Cefaly© arm and the sham arm did not reach significance level ($p = 0.054$). In a covariance analysis, using the number of migraine days before the randomization as a covariate, the significance level was reached, supporting the Cefaly© use in the EM prevention. No evidence is currently available to support the efficacy of Cefaly© in CM prophylaxis, and results of an RCT focused on the acute migraine treatment (NCT03465904 / clinicaltrials.gov) were pending.

Limits According to evidence, Cefaly© can be used in the preventative treatment of EM with a daily stimulation session lasting 20 min and performed using the second program proposed by this device. SONS induces frontal paresthesia which should not be unpleasant, stimulation intensity remaining under the control of the subject using the Cefaly©. The main advantage of SONS is its safety. An adverse event was reported by only 4.3% of more than 2000 subjects included in a post-marketing study, the most common adverse events being pain at the site of stimulation, paresthesia intolerance, poststimulation headache, or central side effects such as sleep disturbances [18]. Only two patients presented a local allergic reaction, and the manufacturer offers now hypoallergenic electrodes for acrylate allergic subjects. There is no contraindication to the use of Cefaly©, and this device can be used by pregnant women. This device has a CE mark and can be ordered from the manufacturer's website (www.cephaly.com). However, it is not supported by all health systems, and its price (40-day trial for 49€ and purchase for 295€) can be a limit to its use.

Mechanisms of Action The mechanisms of action of SONS are unknown. It could enhance segmental painful controls by the stimulation of Aα and Aβ fibers like any transcutaneous electrical stimulation. This segmental painful controls involvement

would induce an inhibition of nociceptive C afferents in the TCC. Nevertheless, experimental data suggest action on central nervous system since a study carried out in healthy volunteers found that SONS induces a reduction of vigilance [19]. Such a central action is also supported by neurophysiological studies showing that SNOS induces enhanced thalamocortical activity [20] and by neuroimaging studies showing that SNOS acts through a modulation of orbitofrontal and rostral anterior cingulate cortices [21].

11.2.2 Vagus Nerve Stimulation (VNS)

VNS was considered as a possible treatment for primary headache following the description of migraine improvement by epileptic patients with migraine comorbidity while their epilepsy was treated by implanted VNS [22]. The recent development of devices for noninvasive VNS has increased interest in this target, the gammaCore© device having been specifically developed for the treatment of primary headaches by noninvasive stimulation of the cervical branch of the vagus nerve.

Evidence The PRESTO study recently suggested the efficacy of VNS by gammaCore© in the acute migraine treatment [23]. This prospective, multicenter, double-blind, randomized, sham-controlled trial involved 248 subjects with EM who were randomized to receive VNS or sham within 20 min from pain onset with the possibility to repeat treatment if pain had not improved in 15 min. VNS (n = 120) was superior to sham (n = 123) for pain freedom at 30 min (12.7% vs. 4.2%; p = 0.012) and 60 min (21% vs. 10%; p = 0.023) but not for pain freedom at 120 min (30.4% vs. 19.7%; p = 0.067) that was the primary endpoint of this RCT. However, a post hoc repeated measures test provided further insight into the therapeutic benefit of VNS through 30, 60, and 120 min (OR 2.3; 95% CI 1.2–4.4; p = 0.012), and VNS demonstrated benefits across other endpoints including pain relief at 120 min. The EVENT study, a prospective, multicenter, double-blind, randomized, sham-controlled trial, failed to demonstrate therapeutic benefit of VNS in the CM prophylaxis [24]. In this pilot trial, 59 subjects with CM were enrolled and were subsequently randomized to receive VSN or sham for 2 months. Mean changes in the monthly headache days were −1.4 for the VNS and −0.2 for sham, and the difference between the two arms (Δ = 1.2) was not significant p = 0.56). However, at the end of the 6-month open phase following the 2-month randomized phase, the mean change from baseline in monthly headache days was −7.9 (95% CI −11.9 to −3.8; $p < 0.01$) suggesting the effectiveness of long-term preventative use of VNS. There is no evidence on the use of VNS in the EM prophylaxis, but one RCT is outstanding with results pending (PREMIUM study/NCT02378844 clinicaltrials.gov).

Limits GammaCore© device have proven to be safe in most trials that are available to date. Side effects of treatment included transient hoarseness, voice change, skin irritation, muscle ache, and uncomfortable paresthesia but were generally well

tolerated by patients. GammaCore© is also useful; the activated device delivers a single program cycle of 2 min with 1 or 2 cycles three times a day for preventative treatment and 2 cycles at the attack onset for acute treatment. However, there is no strong evidence as yet for using gammaCore in migraine. Otherwise, the price of this device is a limiting factor for its use. GammaCore© is available charged with either 150 or 300 treatment cycles, after which a new device must be purchased. If used for prevention only, the 300-treatment device lasts around 50 days; thus, a patient needs two devices to have the efficacy assessed at 3 months. If purchased direct from the manufacturer (https://gammacore.com), the 300-treatment device costs around 600€ without reimbursement by most of health systems.

Mechanisms of Action The mechanism of action of gammaCore© in migraine is not precisely known. Vagus nerve stimulation by gammaCore© was confirmed by a neurophysiological study [25] and a neuroimaging study [26]. The therapeutic effect of gammaCore© is probably related to stimulation of large-diameter myelinated afferences as suggested by a high-resolution multiscale computational model of the properties of the electric field induced by gammaCore© [27]. It has also been demonstrated on a mouse model that noninvasive stimulation of the vagus nerve induces a significant reduction in threshold, frequency, and speed of cortical spreading depression [28]. Further experimental work has shown a reduction in allodynia induced by dural inflammation, this change in skin sensitivity being associated with a reduction in the extracellular glutamate concentration in the pars caudalis of the spinal trigeminal nucleus [29].

11.2.3 Cerebral Cortex Stimulation (CS)

The cerebral cortex has been considered as a potential neuromodulation target for the treatment of migraine due to the cortical spreading depression which is the support of the migraine aura and a possible trigger of migraine headache [30] as well as the lack of habituation which characterizes migraine susceptibility [31]. The possibility of considering a noninvasive cortical neuromodulation using magnetic stimulation or direct electrical stimulation has thus emerged. Such an approach has become all the more conceivable since transcranial magnetic stimulation has been possible via a portable and rechargeable medical device called SpringTMS©.

Evidence SpringTMS© was only evaluated in the acute treatment of migraine with aura during an RCT promoted by the manufacturer of this device and involving 267 adults suffering from migraine with aura and who, after an initial phase of learning to its use, were randomized to treat their attacks either by the SpringTMS© ($n = 102$) or by a similar device delivered a sham stimulation ($n = 99$) [32]. Patients were asked to treat attack as soon as possible, within 1 h after its onset, and the primary endpoint was the absence of headache 2 h after use of the device for the first treated attack. One hundred and sixty-four patients treated at least one attack with

SpringTMS© ($n = 82$) or sham device ($n = 82$) and this RCT demonstrated superiority of SpringTMS© (2 h pain-free for 32 of 82 subjects, 39%) on sham stimulation (18 of 82 subjects, 22%) with a significant therapeutic gain of 17% ($CI_{95\%}$ 3–31%; $p = 0.0179$). The sustained pain-free over 24 and 48 h was also significantly higher for SpringTMS©, and a non-inferiority of this device was demonstrated in terms of associated signs (nausea, photophobia, phonophobia) occurrence. No RCT were done to evaluate SpringTMS© in the acute treatment of migraine without aura or in the migraine prophylaxis. Nevertheless, an open study involving 426 subjects using SpringTMS©, of which 190 could be prospectively followed over 3 months, suggests an efficacy in both the acute treatment of migraine without aura and the migraine prophylaxis [33]. In addition to the industrial clinical development of SpringTMS©, noninvasive cortical neuromodulation applied to the treatment of primary headaches is the subject of several years of academic clinical research on transcranial magnetic stimulation and direct electrical stimulation. This academic clinical research mainly concerns migraine prophylaxis, and a meta-analysis that included eight RCTs did not show any superiority of noninvasive cortical stimulation [34]. However, a subgroup analysis done in this meta-analysis suggests the benefit of direct electrical stimulation that would merit evaluation in RCT with a rigorous methodology.

Limits Considering evidence available, SpringTMS© can be used in the acute treatment of migraine with aura. Its use is based on the device application on the occiput and the administration of two stimulations as early as possible at the attack onset. These two stimulations can be repeated every 15 min for 2 h or until pain ceases (later it is possible to increase the number of stimulations to 3 or 4). Safety and tolerability of SpringTMS© have been good in both the RCT [32] and the open study [33]. The adverse effects (dizziness, tinnitus, worsening of migraine) have been of mild to moderate intensity and transient. The use of SpringTMS© is contraindicated in case of epilepsy and implanted pacemaker. The risk in case of pregnancy is not known knowing that, in the open study, the SpringTMS© was used by three migraineurs pregnant without adverse event. SpringTMS© has a CE mark but is not supported by all health systems. With medical prescription, it is available on the website of the manufacturer (www.eneura.com) for rent (250US$ per month). Because of its simplicity and low cost, direct electrical stimulation could make noninvasive cortical stimulation much more accessible if its efficacy and safety were confirmed.

Mechanisms of Action SpringTMS© is a device developed with the hypothetical goal of modulating the cortical spreading depression at which the cortex is more vulnerable and which is the support of the migraine aura and a possible trigger of migraine headache [30]. Such a modulation was later confirmed by an elegant experimental work on a mouse model demonstrated in vivo that magnetic stimulation of the occipital cortex limited the cortical spreading depression mechanically and chemically induced in the occipital cortex. This work also highlighted the absence of effect on the trigeminocervical complex and an inhibition of thalamic

neurons activity with a possible opioidergic mediation [35]. Direct electrical stimulation and repetitive magnetic stimulation targeting other cortical regions could obviously use other mechanisms.

Neuromodulation for the treatment of migraine has been the object of increasing interest over the past 10 years. First considered with targets imposing an invasive approach that was reserved for refractory migraine, it gradually developed with noninvasive approaches allowing its first-line use either alone or in add-on treatment. However, despite several studies, use of neuromodulation in migraine treatment is not supported by a robust evidence. To date, considering the available data, only SONS by Cephaly© and CS by SpringTMS© can be recommended in the EM prophylaxis and the acute treatment of migraine with aura, respectively.

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