Non-Invasive Neurostimulation for Migraine Treatment

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One of the recent innovations in migraine treatment was the detection of several types of neurostimulation for acute and preventive treatment. The basic idea behind this is the stimulation of peripheral and cranial nerve structures or of the cortex to reduce migraine pain or to decrease migraine frequency. This follows a general development in pain therapy showing that specific stimulations of specific nervous structures can lead to a decrease in pain. The most commonly studied and used non-invasive methods are vagal nerve stimulation, electric peripheral nerve stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation. Other stimulation techniques, including mechanical stimulation, play only a minor role.

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1. Transcutaneous Vagal Nerve Stimulation

Non-invasive transcutaneous vagal nerve stimulation (tVNS) is a device applying electrical stimulation to the part of the neck in which the area can be found where the vagal nerve descends. The vagal nerve contains the majority of parasympathetic nerve fibers for the rest of the body. Stimulation of the vagal nerve can modulate neuronal activity probably involved in the pathophysiology of migraine (and other disorders such as epilepsy and depression), including the locus coeruleus, nucleus tractus solitarious, and trigeminal spinal tract [1].

In an open pilot study, this method was efficacious in the treatment of acute migraine attacks [2]. However, controlled studies replicating this finding are missing. The non-invasive Vagus Nerve Stimulation as Acute Therapy for Migraine (PRESTO) trial [3] examined patients with migraine using tVNS versus sham treatment as an acute therapy of migraine attacks (using the gammaCore™ device). The primary endpoint (pain freedom at 2 h) was not met, but some secondary endpoints were statistically significant in favor of tVNS, including pain freedom at 0.5 and 1 h. A post hoc analysis of this study showed that tVNS also led to decreased intake of rescue medication and that those participants with a mild headache at onset reached statistically significant pain freedom at 2 h.

Many more trials were performed on the prophylactic treatment of migraine with tVNS. The first observation on four patients with severe chronic migraine responding to tVNS, with a decrease in headache days, was published in 2009 [4].

The EVENT study with 59 patients with chronic migraine randomized with regard to using tVNS versus sham treatment did not show relevant significant differences between the intervention and control groups with respect to

migraine prophylaxis [5]. Additionally, another trial on the prophylaxis of migraine, the PREMIUM trial, did not show a statistically significant reduction in migraine days (primary endpoint) when comparing tVNS to sham in patients with episodic migraine. Significant benefits were only seen in a post hoc analysis of participants who were particularly compliant with the treatment [6]. The most recent study published on the efficacy of tVNS in migraine prophylaxis [7] also showed no significant efficacy of tVNS. A pooled analysis of these three randomized trials [5][6][7] showed an absence of heterogeneity but did not demonstrate a significant efficacy of tVNS in migraine day reduction (0.187, 95% CI: 0.379 to 0.004) [8].

The tVNS as applied by the gammaCore™ device in the prophylaxis of migraine consists of two stimulations (each 2 min long) thrice a day. For acute attacks, treatment consists of two stimulations applied at headache onset, followed by two more after 20 min and after 2 h if needed. Side effects include stiff neck, frequent urination, lip/facial droop, mild confusion, and dizziness. Contraindications include active devices near the site of stimulation (such as pacemakers, defibrillators), as well as carotid atherosclerosis, history of cervical vagotomy, significant hypertension, hypotension, bradycardia, or tachycardia.

A small study investigated the efficacy, safety, and tolerability of the stimulation of an auricular branch of the vagal nerve [9]. The stimulation was applied for 4 h per day. Those patients stimulated with a frequency of 1 Hz showed a significantly higher reduction in headache days per month than those patients stimulated with 25 Hz (−7.0 ± 4.6 versus −3.3 ± 5.4 days, $p = 0.035$). However, there was no sham control and there is no replication study on this type of vagal nerve stimulation.

Although the evidence for the acute treatment of migraine attacks by tVNS is poor and the evidence for prophylactic treatment is negative, the device received FDA approval for both acute and prophylactic treatment in the USA.

2. Transcutaneous Nerve Stimulation

Different types of transcutaneous nerve stimulation (tNS) were tested in migraine treatment. The principle is always the same: applying an electrode over a peripheral (cranial) nerve and daily stimulation with different intensity and frequency. The bilateral transcutaneous stimulation of the supraorbital nerve (which in reality often includes in part also of the supratrochlear nerve) has been studied most often [10]. In a sham-controlled study, 67 patients were included [11]. After 3 months, the number of migraine attacks was significantly reduced by the verum stimulation (6.94 versus 4.88; $p = 0.023$) in contrast to sham stimulation (6.54 versus 6.22; $p = 0.608$). The 50% response rate was significantly higher after verum stimulation (38.1%) than after sham stimulation (12.1%). In two open trials on patients with episodic migraine and on patients with chronic migraine, 75% and 50%, respectively, of the patients reached a significant reduction in days with acute analgesic/triptan intake or with headache [12][13].

Another study examined the simultaneous use of three tNS devices to stimulate the face, the cervico-occipital region, and the hand. The stimulation was used 5 days/week for three consecutive weeks and was compared to laser therapy and to acupuncture [14]. Only qualitative analysis was performed. After one month, tNS and laser

therapy where more efficacious than acupuncture. Two trials examined the use of occipital tNS as a prophylactic therapy for migraine. One of them used 40 Hz stimulation and was negative [15]. Various stimulation parameters were used for the other one, and 100 Hz was positive as compared to sham but less effective than topiramate [16]. Recently, one study combined the oral migraine prophylactic drug flunarizine with supraorbital nerve stimulation, and a significant additional effect of the stimulation was shown as compared to sham stimulation [17]. In another study on patients not tolerating or refractory to topiramate for the prophylaxis of chronic migraine, tNS of the supraorbital nerve resulted in a decline in headache days over 3 months [18].

The results of the trials on migraine prophylaxis were also reflected in a survey on 2313 patients having used the Cefaly™ device [19]. After a testing period of about 60 days, 46.6% of the patients were not satisfied and returned the device, and the compliance check showed that they used it for 48.6% of the recommended time. Overall, 54.4% of the patients were satisfied with the device. Meanwhile, 4.3% reported one or more adverse event (particularly paresthesia and local pain).

The Acute Treatment of Migraine with External Trigeminal Nerve Stimulation (ACME) trial examined the acute use of the Cefaly™ device in episodic migraine patients [20]. This was a randomized, double-blind, sham-controlled trial with 106 patients showing improvement in the primary outcome (change in pain score at 1 h compared to baseline) with a significant result in both the treatment and the sham group, although the findings were more significant for the verum group (59% versus 30%, $p < 0.0001$). Pain measurements using the visual analog scale (VAS) also showed statistically significant differences between the treatment and the sham group at 1, 2, and 24 h. A recent study replicated this finding in the emergency room, with a significant effect of supraorbital nerve stimulation in acute migraine attacks [21].

Applying the Cefaly™ device consists typically of a 60 min session for acute therapy and 20 min daily for prophylactic use. This method is typically well-tolerated. Side effects include forehead paresthesia (in particular when used outside an acute migraine attack), sleepiness, fatigue, insomnia, and headache. Contraindications for its use include recent facial trauma, metallic head implants, or intracardiac lines or pacemaker devices. Cefaly™ received FDA approval for both acute and prophylactic treatment.

Even a combination of two different eNT (Relivion™) has been studied. Patients received the combination of external occipital nerve and supraorbital nerve stimulation for the treatment of migraine [22]. However, only review data on the efficacy of this device have been published so far, and no primary trial results could be found in the literature, although this device received FDA approval.

A single double-blind study showed mild efficacy by stimulating the mastoid region percutaneously [23]. Eighty patients with episodic migraine were included. In the verum group, 82.5% were 50%-responders, whereas, in the sham group, only 17.5% responded. The same group recently compared supraorbital tNS versus tNS of the mastoid region and observed a statistically significant reduction in migraine days in the third month in both groups [24]. The difference between the two groups was not significant (77.8% responders in the mastoid group and 62.2% in the supraorbital nerve group).

3. Magnetic Stimulation

3.1. Acute Attack Treatment

Probably the first scientific study on the impact of magnet fields on headache was published in 1985 [25]. Forty patients with different types of headache were treated with alternating pulsed magnetic field stimulation or with a sham stimulation, both around the whole head. An improvement of headache was reported by the majority of patients after verum stimulation but not after sham stimulation. Interestingly, the results were better for tension-type headache than for migraine. However, this study did not apply a regional magnetic impulse but a global magnetic field. Another study on different headache types observed similar results when a global magnetic field was used [26]. Since this time, different methods have been tested to treat migraine and headache by magnetic stimulation. These include single pulse transcranial magnetic stimulation (sTMS) and the repetitive transcranial magnetic stimulation (rTMS), in addition to peripheral nerve magnetic stimulation.

The idea behind magnetic stimulation to treat migraine attacks is influencing the cortical excitability by the magnetic impulse and thus stopping the migraine aura and the subsequent headache. In animal studies, it has been shown that a single magnetic impulse is able to stop the cortical spreading depression [27]. Two studies showed the good efficacy of sTMS in the acute treatment of migraine attacks with an aura [28][29].

In the first (uncontrolled) study, 42 patients were treated by two sTMS impulses over the painful skull (migraine without an aura) or over the occipital cortex (migraine with an aura) [28]. A reduction in headache intensity was observed both after low and after high stimulation intensity, and 32% of the patients reported complete headache abortion for 24 h. All patients with an aura reported a sudden effect on the headache. This observation led to the second study [29] which randomized 164 patients with migraine with aura. Migraine attacks were treated using a hand-held magnetic stimulation device with two impulses over the occipital cortex within one hour after onset of the aura. The study was sham-controlled. The responder rate for being pain-free after 2 h was significantly higher after verum treatment (39% for sTMS versus 22% for sham), as was being persistently pain free after 24 and 48 h. However, the global success of the treatment was rated better for the sham than for the verum stimulation. The device received FDA approval (sTMS mini™). A post-market pilot study performed in the United Kingdom in 2015 reported that 62% of patients experienced pain relief and a reduction in monthly headache days in both episodic and chronic migraine [30].

The methodological problems of these studies are the poor sham control, since the magnetic impulse led to an unpleasant feeling, whereas the sham impulse did not. This type of migraine attack treatment has only been proven in migraine with aura patients, which represent only up to 30% of all migraine patients; in addition, not all aura patients have an aura every time they have a migraine attack.

3.2. Prophylactic Treatment

The first anecdotal reports on the efficacy of rTMS in migraine was published in a study on rTMS in major depression. Two patients, blinded for the treatment with rTMS, reported a disappearance of their migraine during

the study phase [31].

In addition, controlled trials have been performed on the prophylaxis of migraine by rTMS. In one study, the left dorsolateral prefrontal cortex (DLPFC) was stimulated with 20 Hz rTMS. Attack frequency, headache index, and the number of acute medications were significantly reduced in six patients with chronic migraine as compared to five patients receiving sham stimulation [32]. Another study on 13 patients with chronic migraine applied 10 Hz rTMS and was unable to replicate the results of the first study, and rTMS was even less effective than sham stimulation [33]. In a further study, the cortical hyperexcitability in chronic migraine was lowered by 1 Hz rTMS over the vertex [34]. The frequency of migraine attacks was, however, not significantly reduced by the verum stimulation as compared to the sham stimulation.

Three studies (two conducted by the same group) used high frequency (10 Hz, 600 pulses) rTMS over the left primary motor cortex (M1) for the prophylaxis of chronic migraine. A single session reduced the number of headache days per month for chronic migraine sufferers by an absolute number of 3.2 days/month versus placebo [35]. In total, 98% of the patients had a more than 50% reduction in headache frequency after 2 weeks, and this improvement persisted until week 4 in 80.4% of the patients. Pain intensity, functional disability, and acute drug intake were reduced during the total study time; the best result, however, was obtained for the first 2 weeks. Later, the second study showed that three sessions did not provide better pain reduction than a single session of rTMS [36]. One study compared botulinum toxin A injection with high frequency rTMS (10 Hz, 2000 pulses per session) over the left M1 with a total follow-up of 12 weeks on patients with chronic migraine [37]. As compared to botulinum toxin A, rTMS showed no difference at weeks 4 and 8, but was less effective at week 12. The pooled analysis of these three studies focusing on high frequency rTMS over the left M1 suggested a positive effect, with a medium effect size of −0.533 (95% CI −0.940 to −0.126) [8].

The ESPOUSE study, a multicenter, open-label, observational study including 132 episodic and chronic migraine patients, found a mean reduction of −2.75 headache days from baseline versus placebo with −0.63 headache days ($p < 0.0001$) over a 3-month period of rTMS treatment [38].

Two other recent studies with stimulation of the left DLPFC were positive in the primary outcome, using a frequency of 5 Hz in one case [39] and intermittent theta-burst stimulation in the other [40]. However, the first study was negative for the reduction in headache days. The pooled analysis of these two studies focusing on high-frequency rTMS over the left DLPFC did not favor a positive effect and showed high heterogeneity between studies [8].

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