

Editorial

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Neuromodulation and Non-Pharmacological Treatment of Migraine

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Migraine is a chronic brain disorder that is believed to be due to dysfunction of the brain and brainstem that result in dysmodulation of sensory processing of the head and vascular tone. The exact pathomechanism of migraine is not known but some genes including mutations in the sodium and calcium channels and Na⁺/K⁺ pump have been implicated in migraine with aura.¹⁻⁸

Several drugs are currently used in the acute and preventive treatment of migraine. These include the non-steroidal anti-inflammatory drugs, the triptan family, anti-epileptic drugs, beta-blockers, calcium channel blockers, steroids, and recently antibodies against calcitonin gene-related peptide (CGRP) or its receptor among other drugs.^{5,9} Some other drugs are under investigation and the CGRP receptor antagonists (the gepant family drugs), were discontinued although other drugs in this category are still under investigation.¹⁰⁻¹⁶ However, there are some medically intractable headaches or unsatisfactory patient management or medications are poorly tolerated, therefore, additional treatment options might be helpful.

A number of nonpharmacological methods such as education, reassurance, avoiding the triggers of migraine, and physical and/or complementary medicine when appropriate, have also been recommended in the treatment of migraine and other headaches.^{17,18} Dietary modifications and lifestyle changes have also been suggested.¹⁹ Other methods such as physical therapy with relaxation and thermal biofeedback have also been used in the treatment of migraine.^{20,21}

A recent meta-analysis of biofeedback in treatment of pediatric migraine shows some effectiveness but more research is needed.²²

A recent pilot randomized controlled trial shows that frontal electromyography biofeedback added to traditional pharmacological therapy is promising in the prophylactic treatment of medication overuse headache by reducing the frequency of headache and analgesic intake.²³

Other nonpharmacological approaches such as behavioral, and body/mind treatment of headache were reported to be effective²⁴ and an 8-week mindfulness-based stress reduction method by meditation in adult migraine patients shows some beneficial effects²⁵ although more studies are needed.

Other methods such as massage therapy of the neck and upper thoracic region²⁶⁻²⁸ or acupuncture studies have shown some efficacy in the treatment of chronic headache²⁹⁻³¹ but more research is necessary.³²

The nonpharmacological treatment options of migraine warrants a review paper by itself to understand current opinion in this area. However, our focus in this issue will be on neuromodulation by electrical stimulation of peripheral and central nerves/neurons that are currently being used in clinical studies for the acute and preventive treatment of migraine.³³

Currently, electrical stimulation of various nerves is being used through a number of

invasive and non-invasive methods in clinical studies for the acute and preventive treatment of chronic migraine particularly on those patients with medically intractable headaches, non-responders to medication, or when medication is poorly tolerated.

For the invasive procedures the stimulating devices are implanted subcutaneously by surgery. They are powered by implantable batteries or controlled wirelessly. The noninvasive devices are applied on the skin close to the nerve and are also self-administered by the patient.³⁴

Some of the neurostimulation methods used in clinical studies include the invasive electrical stimulation of greater occipital nerve and the sphenopalatine ganglion, and non-invasive electrical stimulation of supraorbital nerve or vagus nerve, and single-pulse transcranial magnetic stimulation.

Electrical stimulation of greater occipital nerve is an invasive method that has been used by some investigators in clinical studies in recent years to treat chronic migraine. Among these, two studies were prominent: the ONSTIM feasibility study was one of the first multicenter, randomized, blinded studies aimed for the preventive treatment of chronic migraine.³⁵ They used Occipital Nerve Stimulation (ONS) by means of a pulse generator device implanted subcutaneously superficial to the fascia and muscle layer at the level of C1.³⁵ The study had 110 participants and they found 39% 3-month responders with 50% or more reduction in the number of headache days per month in the adjustable stimulation group compared to 6% 3-month responders rate in the preset stimulation group and 0% in medical management group.³⁵

Similarly, another large-scale, multicenter, investigation with ONS performed on 105 chronic migraine patients and 52 with sham stimulation showed only a significant difference in the percentage of patients who had 30% pain reduction (decrease in mean daily visual analog scale scores by 12 weeks) following the procedure, since the difference between the active stimulated and the sham stimulated group was not significant at their primary end point designated for $\geq 50\%$ pain reduction.³⁶

Other ONS studies are not mentioned here. In spite of some success reports in ONS, results are diverse and more clinical studies are needed to fully recommend it for the preventive treatment of migraine.³⁷

Electrical stimulation of the Sphenopalatine Ganglion (SPG) is also an invasive method. It has been used in one clinical study for ≤ 60 minutes in 10 patients with refractory migraine and relieved the pain in 50% of the patients. The ganglion was accessed by a needle through infrazygomatic trans coronoid approach under fluoroscopy and then stimulated by means of a Medtronic 3057 test stimulation lead after induction of migraine.³⁸ Clinical trials (NCT01540799, and NCT02510742, <https://clinicaltrials.gov>) might shed light into the effect of the electrical stimulation of the SPG in migraine patients. Although currently, the procedure is not yet recommended for migraine treatment,³⁷ SPG innervation and function may correspond to some autonomic symptoms seen in migraine and cluster headaches. Therefore, this area of clinical research is very interesting and may add more insight in our understanding of the pathomechanism and treatment of headache.

Another invasive study using high cervical spinal cord stimulation with an implanted device in 17 chronic migraine patients for 15 months (with a range of 2-48 months following implantation) shows some positive outcomes.³⁹ In that study, the mean pain intensity decreased by 60%, where 71% of patients had 50% or more reduction of pain but more studies are warranted.³⁹

Another similar invasive study delivering 10 kHz spinal cord stimulation in 14 successfully implanted patients with chronic refractory migraine who had the implant for 6 months shows that seven (50%) of the 14 subjects had $>30\%$ reduction in headache days and that the procedure did not cause paresthesia, one of the problems often encountered in nerve stimulation.⁴⁰

There are a number of non-invasive electrical stimulation procedures such as transcutaneous vagal nerve stimulation,⁴¹⁻⁴⁶ the transcutaneous electrical stimulation of supraorbital nerve⁴⁷⁻⁴⁹ and single-pulse transcranial magnetic stimulation⁵⁰⁻⁵² that have shown some efficacy in the acute and preventive treatment of migraine but more studies are necessary. Among these, vagal nerve stimulation is promising and more studies are necessary to understand the mechanism of pain relief which might be due to modulatory effect of vagal afferent terminating in the brain stem trigeminal nucleus and brain centers.^{53,54}

The mechanism of pain relief by electrical stimulation of the nerves might be the modulation of neurotransmitters and neuropeptides release in the central nervous system and closing the gate of pain and brain centers involved in pain modulation.^{55,56}

In conclusion, neuromodulation studies show some efficacy in the acute and preventive treatment of migraine. The results of vagal nerve stimulation are promising and sphenopalatine ganglion stimulation studies might be very interesting and may shed light into our understanding of pathomechanism of headache. More clinical studies using neurostimulation are needed to see their

efficacy, long-term effects and side effect, tolerability and convenience in patients.

Currently, the European Headache Federation consensus statement on clinical use of neuromodulation in headache recommends the use of neurostimulation devices in patients with medically intractable syndromes taking part in valid investigations or those procedures that have proven effective in controlled studies with side effects that are acceptable.⁵⁷

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CONFLICTS OF INTEREST

There is no conflicts of interest.

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