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Noninvasive Neural Stimulation in Migraine

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Migraine is the commonest chronic neurological disease. Migraine is one of the five main causes of inability to work and impairments to quality of life. Various noninvasive neuromodulation methods have been found to be effective in different types of migraine in recent years. This articles presents an analysis of clinal studies and analyzes clinical cases demonstrating the efficacy and safety of noninvasive stimulation of the first branch of the trigeminal nerve in migraine.

Keywords: migraine, treatment, neuromodulation, Cefaly.

Migraine is one of the commonest neurological disorders, though its importance remains underestimated mainly because of the transient nature of the impairments. Contemporary epidemiological studies have convincingly demonstrated that it is an error to underevaluate migraine. The prevalence of migraine in the population is about 15% [1]. Migraine, along with backpain, reduced hearing, iron deficiency anemia, and major depressive disorder, is one of the five major causes of work incapacity and decreased quality of life [2]. Despite the large number of medicinal substances approved for the acute and preventive therapy of migraine, the treatment of this disease when attacks are frequent and severe presents significant difficulties. On the one hand, triptans are effective in curing attacks in no more than two out of three episodes. On the other, the efficacy of prophylactic treatment before onset with monoclonal antibodies to CGRP is no more than 60–70% [3]. At one year from treatment initiation, about 20% of patients continue therapy, while most decide to withdraw treatment because of adverse events (AE) or lack of efficacy [4]. In recent years, neuromodulation methods have been used effectively in a variety of neurological diseases. Several versions of both invasive and noninvasive neuromodulation have been used in primary headaches (see Table 1) [5]. Due to its high safety, simplicity, and efficacy, noninvasive stimulation is the most widely used method in the treatment of migraine. International practice makes use of noninvasive neurostimulation of the area of the first branch of the trigeminal nerve and the vagus nerve, transcranial magnetic stimulation, and transcutaneous remote electrical stimulation (at the level of the shoulder) [6]. The advantages of these methods are that they can be used both independently and in combination with pharmacotherapy to treat attacks and for the prophylaxis of migraine, and they can also be used in patients with intolerance or contraindications to drug treatment, in pregnancy and breastfeeding, and in childhood and adolescence.

Electrical stimulation of peripheral nerves has been used for many years in the treatment of pain. In the first century, the Roman physician Scribonius Largus described use of the electrical discharge of the skate for treating headache [7].

The analgesic effect obtained by stimulation of peripheral nerves can be explained in terms of a number of processes: activation of afferent Aβ fibers and gate control at the spinal level, activation of structures of the endogenous opioid system, and increases in top-down antinociceptive supraspinal influences [8]. Electrical stimulation of peripheral nerves was initially widely used in chronic pain syndromes such as neuropathic pain, complex regional pain syndrome, and failed back surgery syndrome [9]. Peripheral neuromodulation has been actively used in primary headache (migraine, cluster headache) in recent years [10, 11].

Studies of the pathogenetic mechanisms of the analgesic effect of neuromodulation in headache were initially car-

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TABLE 1. Neuromodulation Methods in Migraine

Neuromodulation	Noninvasive	Invasive
Peripheral	Stimulation of peripheral nerves	Occipital nerve
	trigeminal	Pterygopalatine ganglion
	vagus	
	remote stimulation	
Central	Transcranial direct-current magnetic stimulation	Deep brain/spinal cord stimulation

ried out using invasive stimulation (electrode implantation) of the greater occipital nerves (migraine, cluster headache, and neuralgia of the pterygopalatine ganglion). Considering the difficulty of neurosurgical manipulation and the efficacy/safety ratio, the following indications have now been approved for invasive neuromodulation in headache [10]:

1. Refractory chronic migraine, including migraine combined with drug-induced headache;

2. Refractory chronic cluster headache.

Thus, for invasive neurostimulation, the indications and selection of patients are limited and require patients to consult specialist pain centers for detailed assessment of the indications and contraindications.

Over the last decade, techniques for peripheral noninvasive neurostimulation for primary headaches have been under active development. Data from clinical studies and analysis of results from practical use have demonstrated the efficacy and high level of safety of methods for noninvasive neurostimulation in migraine (monotherapy, combined treatment with pharmacotherapy) to cure acute pain during attacks and for prophylactic treatment [6, 12].

The US Food Drugs Administration (FDA) and the European Medicines Agency (EMA) have now approved four devices for individual noninvasive neurostimulation: a device for stimulation of the first branch of the trigeminal nerve (Cefaly) and the vagus nerve, transcutaneous remote electrical stimulation (at the level of the shoulder), and independent transcranial magnetic stimulation.

The Cefaly device is approved in the Russian Federation for electrical stimulation of the supraorbital zone using currents of 1–16 mA and frequency 60–100 Hz. Stimulation parameters are selected individually depending on sensitivity and tolerance. Two operating regimes are available:

1. Program for analgesia during migraine attacks (60-min session, 100 Hz);

2. Program for preventing migraine (daily, once a day, 20 min, frequency 60 Hz).

The efficacy of the Cefaly for curing attacks and preventing migraine bas been demonstrated in double-blind, placebo-controlled studies with comparison with a simulated stimulation procedure [6, 12].

Comparative efficacy analysis showed that use of the Cefaly significantly decreased pain intensity as compared with sham stimulation: -3.46 ± 2.32 vs. -1.78 ± 1.89 points (VAS, $p < 0.0001$) and –59% vs. –30% (proportions of patients with regression of headache, $p < 0.0001$). Complete regression of pain at 2 h was obtained in about one third of patients (32%), while decreases in pain intensity were noted in 85% using noninvasive supraorbital neurostimulation in the acute attack treatment mode [13].

Another study included stratification of patients by attack severity and analyzed the efficacy of the Cefaly in pain and concomitant symptoms (photophobia, phonophobia, nausea, vomiting) during moderate and severe attacks. Neurostimulation was performed for 120 min in the first 4 h from onset of the attack. Pain was absent at 2 h in 35.4% of cases and significant reductions were noted in 70.8%; at 2 h from the start of stimulation, concomitant symptoms were completely absent in 45.8% of patients and significant reductions in severity were noted in 60.4%. Thus, use of neurostimulation of the first branch of the trigeminal nerve in migraine attacks effectively decreases not only the intensity of pain, but also that of concomitant symptoms. It is interesting that regression of photophobia and phonophobia at 2 h occurred in 63% and 70.8%, respectively. These values were greater than those obtained using non-steroidal anti-inflammatory drugs (NSAID) or triptans as monotherapy [14].

The efficacy and safety of the Cefaly in preventive mode has also been evaluated in double-blind controlled studies using a reference group given sham procedures. Significant decreases in days with migraine were obtained from the number in the placebo stimulation group (–25%, from 6.9 to 4.8 per month, $p < 0.05$), along with a decrease in the number of migraine attacks (–19%) an a decrease in the number of analgesics used per month (–37%) [15]. Daily stimulation for 20 min/day was applied for three months. A separate clinical study assessed the efficacy of noninvasive stimulation of the first branch of the trigeminal nerve (Cefaly) in patients with chronic migraine (15 days or more with headache per month). In chronic disease, one third of patients showed significant responses to supraorbital neurostimulation, with an average decrease in the number of days with migraine from 18.1 to 7.6 per month, i.e., chronic migraine was converted to the episodic form. Decreases in the number of analgesics consumed per months were obtained in 49.6% of patients [16].

All studies showed high levels of safety for noninvasive stimulation of the first branch of the trigeminal nerve

(Cefaly). The mean frequency of developing AE was 4.3% and all reactions were mild and reversible. The most frequent AE were intolerance of stimulation (1.25%), feelings of tiredness during and after sessions (0.65%), background headache after use (0.52%), and irritation of the skin by the electrodes (0.22%) [13–16].

Practical Features in the Application of Noninvasive Supraorbital Neurostimulation (Cefaly). *Clinical case 1*. Patient V, female, age 33 years, presented to the clinic complaining of episodic headache mainly in the frontal and parietal-temporal areas, headaches being pressure and pulsatile in nature and reaching 8–9 points on the VAS. Headache attacks were accompanied by nausea, nonsystemic vertigo, and phonophobia, often combined with neck pain. On primary attendance, headache frequency was 6–12 days per month. Neurological examination revealed no abnormalities. Neuroorthopedic status noted a myofascial trapezius muscle syndrome on both sides, with no movement restriction. Investigations: brain MRI: small retrocerebellar cyst, occasional foci in the white matter of the brain of size up to 3 mm; cervical spine x-ray: degenerative-dystrophic changes to the C4/5, C5/6, and C6/7 intervertebral disks and uncovertebral arthrosis at C5/6. Cervical spine MRI scan: degenerative-dystrophic changes to the cervical spine. Extrusion of the C5/6 intervertebral disk to 3 mm without neural compression. Bulging of C4/5, C6/7, and T1/2. Before the clinic consultation, the patient had been diagnosed with vertebrogenic cervicalgia and cervicocranialgia and had received repeat courses of massage, various types of manual therapy, and physiotherapy. Physical treatments produced temporary moderate improvements (decreased headache frequency to 5–7 per month for 1–2 months) with subsequent recovery of attack frequency. The diagnosis was reconsidered in the clinic. Migraine without aura with frequent attacks was diagnosed in terms of the criteria of the International Classification of Headache (3rd edition). Triptans were recommended to cure migraine attacks, starting at the beginning of attacks (possible variants: sumatriptan 100 mg, zolmitriptan 2.5 mg, eletriptan 40 mg), while metoprolol with gradual dose escalation to 100 mg/day was advised for prevention. It was noted at subsequent visits that triptans were effective in seven cases out of 10, though they did not completely eliminate headache or concomitant symptoms in the 2 h from the beginning of attacks. Addition of NSAID to triptans did not increase analgesic efficacy during attacks. Preventive treatment (metoprolol) decreased attack frequency in the first month of use, though bradycardia and orthostatic hypotension was noted when the dose was increased to 50 mg/day, and metoprolol was withdrawn because of this AE. Topiramate also produced AE (depressed mood, marked reduction in body weight). At follow-up visits, the patient reported that she was planning pregnancy and was discontinuing further selection of drug therapy. Also, throughout the observation period the people noted a high level of anxiety (the patient refused psychotherapist consultation and treatment).

At this stage, considering migraine without aura with frequent attacks, the planned pregnancy, the high level of anxiety, the incomplete effectiveness of triptans and NSAID for curing attacks, a treatment and management plan for the patient was designed: 1) a course of cognitive behavioral therapy (psychotherapist); 2) use of noninvasive neurostimulation of the first branch of the trigeminal nerve (Cefaly) in two modes:

– for analgesia during migraine attacks in combination with triptans (stimulation for 60 min);

– preventive treatment for migraine (daily sessions in the afternoon, 20 min, four-month course).

During the first month, treatment was noted to be effective in terms of decreasing the number of attacks to four per month, decreasing the level of anxiety, normalizing sleep, and improving the effectiveness of treating attacks (attacks regressed within 4 h of using a triptan and Cefaly). The course was continued to four months. Then, considering the stable reduction in the number of attacks (2–3 per month) and the onset of pregnancy, the patient was advised to use the neurostimulator for treating acute attacks.

Following the international clinical guidelines for the treatment of migraine, both modes of noninvasive supraorbital neurostimulation (Cefaly) were used in this case. Treatment produced improvements in efficacy of curing attacks and concomitant symptoms, along with a decrease in the number of attacks.

Clinical case 2. Patient M, female, aged 29 years, presented to a neurologist with an increase in headache frequency and aching neck pain to twice a week over a period of 4–6 weeks. The patient had experienced headaches since adolescence, bilaterally, sometimes more severe on the left, accompanied by nausea, photophobia and phonophobia, and sometimes nausea at the peak of pain. Occasionally (1–3 times a year), headache could be preceded by transient impairments of vision in the form of gradually developing (over 10 min) flashing scotoma. Attack intensity was 6–9 points on the VAS. Migraine with aura had previously been diagnosed. The patient was 14–15 weeks pregnant at the consultation. Examination revealed myofascial trigger points in the trapezius muscles and suboccipital muscles, greater on the left. Considering that pain-killers approved for use during pregnancy include paracetamol (first to third trimesters) and ibuprofen (first and second trimesters) and that these had maximal efficacy in our patient, and also considering the increase in attack frequency and the additional myofascial trigger points, the following therapy plan was designed in collaboration with the treating obstetrician/gynecologist:

1. Use of noninvasive neurostimulation of the first branch of the trigeminal nerve (Cefaly) in two modes:

– for analgesia during migraine attacks in combination with triptans (stimulation for 60 min);

– preventive treatment for migraine (daily sessions in the afternoon, 20 min, in this case for a 2.5-month course).

2. Consultation with physical therapy physician followed by exercises (postisometric relaxation).

Treatment produced improvement by one week, with regression of neck pain and decreased intensity of headache attacks to once a week from the second week, a significant reduction in attacks (pain and associated symptoms) by 2 h from the beginning of using Cefaly in the attack treatment mode. Starting from week 22 of pregnancy, migraine attacks regressed completely, which was probably linked with the natural course of the disease during pregnancy.

There are few data on the safely of using noninvasive neurostimulation of the trigeminal nerve. Most experts and experience accumulated to date indicate high levels of safety and the suitability of the Cefaly for use during pregnancy and breastfeeding. In addition, studies in 2017 and 2019 analyzed the safety of noninvasive stimulation of peripheral nerves (the vagus nerve) in epilepsy [17, 18]. No effects on the status of pregnant women or children were found. A wider analysis and studies are undoubtedly required in relation to the safety of neurostimulation during pregnancy.

Clinical case 3. The parents presented a girl aged 14 years who for six months had experienced headache attacks accompanied by nausea, nonsystemic vertigo, phonophobia, and osmophobia. At age 5–8 years the patient had had frequent episodes of abdominal pain without identifiable organic origin, which by the time of presentation had virtually settled. From early age, to nine years, the patient had suffered from severe kinetosis. At consultation she had headaches of varying intensity (5–9 points on the VAS) occurring 3–6 times a week (more than 15 headache days per month, with an increase in frequency over 4–5 months on the background of severe workload in general and music schools, sleep impairment, and elevated anxiety. Neurological status showed no deviations from normal. Neuroorthopedic status showed myofascial syndrome of the trapezius muscles and suboccipital muscles on both sides, with no movement restriction. Data from previous instrumented investigations (brain MRI scan, ultrasound scan of the brachiocephalic vessels, cervical spine x-ray) revealed no clinically significant abnormalities. Previous treatment with group B vitamins, magnesium, and nootropic drugs was ineffective. The child's mother and grandmother had migraine with aura. According to the ICH-3 (2018) classification, a diagnosis of chronic migraine, episodic syndromes in children, migraine-associated (abdominal migraine) was made. Considering the chronic form of migraine, the following treatment plan was designed:

1. Behavioral therapy (cognitive behavioral therapy, normalization of scholastic workload, observation of sleep regime and diet, regular aerobic therapeutic exercise), detection and elimination of possible dietary triggers of migraine.

2. Use of a headache diary.

3. Consultation with a physical therapy physician followed by course of exercises (postisometric relaxation).

4. Medication – propranolol 20 mg b.i.d., course of at least six months. Monitoring of arterial blood pressure and heart rate.

5. Use of noninvasive neurostimulation of the first branch of the trigeminal nerve (Cefaly) in two modes:

– for analgesia during migraine attacks in combination with ibuprofen 400 mg (stimulation for 60 min);

– preventive treatment of migraine (daily 20-min sessions in the evening, six-month course).

Combined use of the Cefaly and ibuprofen improved outcome quality for acute attacks, and in most cases attacks regressed over 60 min. It is important to use a complex approach to the treatment of patients of any age with chronic migraine, using behavioral therapy, medication, and correction of comorbid states. Use of a multidisciplinary approach combined with neurostimulation methods in children has been shown to be effective in observational studies [19]. Use of the above therapeutic program produced notable regression of attack frequency within the first month, along with decreases in anxiety and normalization of sleep; improvements persisted with continuing treatment. At the time of writing, one year after withdrawal of treatment, migraine attack frequency varies from zero to four attacks per month and attacks are effectively cured with ibuprofen or a combination of ibuprofen and the Cefaly.

Thus, data from randomized, placebo-controlled studies and analysis of the experience of practical application leads to the conclusion that noninvasive supraorbital neurostimulation is an effective and safe approach to the treatment of migraine. Summarizing current data allows us to identify the main directions of practical application of noninvasive neurostimulation of the first branch of the trigeminal nerve (Cefaly): 1) separate or combined treatment of migraine attacks; 2) separate or combined preventive treatment for migraine; 3) effective in migraine without aura and migraine with aura; 4) demonstrated efficacy in episodic and chronic migraine; 5) can be used in pregnancy; 6) can be used in adolescence.

It is important to note that the treatment of migraine, especially the chronic forms, in frequent, severe attacks is difficult, requiring a combination of nondrug and medication-based methods and work with comorbid states.

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