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# DOPPLER MONITORING OF PREVENTIVE MIGRAINE TREATMENT

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## Abstract

The article presents an analysis of literature data and the results of our own clinical and Doppler examination of 116 young patients with migraine. (18-45 years old), a clinical and neurological examination was performed, an assessment of the intensity of the degree of decrease in the patient's functional activity, a study of the state of cerebral arteries and cerebrovascular reactivity using ultrasound Doppler. Cerebral hemodynamics during a migraine attack is characterized by a pattern vasospasm in migraine without aura and a pattern of impaired perfusion in migraine with aura in the middle cerebral arteries, as well as increased perfusion in the cerebral arteries. Hyperreactivity to hypercapnic load and photoreactivity test is a characteristic Doppler pattern in patients with migraine without aura. Hyperreactivity to hyperventilatory load, reflecting a hyperconstrictive vascular response, predominates in migraine with aura. The use of Topiramate for the preventive treatment of migraine in both clinical groups significantly reduces the frequency, duration and intensity of migraine attacks. Under the influence of the drug, a decrease in the frequency, duration and intensity of attacks was observed. The vascular effect of the drug was manifested in a

decrease in the initially increased blood flow velocity in the MCA. The drug contributed to the normalization of cerebrovascular hyperreactivity, mainly to the CO2 test in patients with migraine with aura and to the photoreactivity test in patients with migraine without aura.

**Key words: migraine; transcranial duplex scanning; cerebral hemodynamics; cerebrovascular reactivity; Topiromax**

Migraine is one of the most common neurological pathologies in world [1] The high prevalence, steady increase in incidence in young, working-age individuals, as well as the difficulties of diagnosis and therapy determine the great interest in this problem [2-5]. This is due to the high frequency of this disease in the population and the significant impact on disability and loss of working capacity of the population.

Migraine is directly related to gender, since the male/female ratio with this pathology is 1:3-4 [6]. Approximately 18.2 and 6.5% of women and men suffer from migraine, respectively, of which the majority (62%) have at least one episode of severe headache per month [7].

The pathogenetic factor of the attack is changes in metabolism and cortical function [8, 9]. Cortical depression causes activation of sensory neurons of the trigeminal complex, increasing their sensitivity to nociceptive irritation of the vessels of the dura mater [10-12]. Migraine attacks can be triggered by stress, nervous or physical overexertion, sleep disturbances, consumption of certain foods or alcohol, weather factors, use of hormonal contraceptives. [13-15].

Migraine is a primary neurogenic cerebral dysfunction with the presence of genetically determined brainstem insufficiency, pronounced cortical hyperactivity with periodically occurring hypothalamic dysfunction [16-18].

Migraine is manifested by periodically recurring attacks of intense headache of a pulsating nature, which is localized mainly in one half of the head and in most cases is accompanied by nausea, vomiting, photo- and phonophobia , drowsiness. The duration of the attack is from several hours to 2-3 days, the frequency can vary from 1 time per year to 1 time per week. There are two main forms of migraine: without aura - characterized by attacks of headache with specific accompanying symptoms; with aura - characterized by local neurological symptoms that usually precede or accompany the headache [19].

Preventive treatment is performed only for relatively frequent and severe migraine attacks and excludes the use of specific drugs for the treatment of an acute attack [20].

The goals of treatment of patients with migraine are rapid and consistent resolution of the attack without the possibility of relapse, restoration of the ability to function normally, minimizing the use of drugs that alleviate symptoms, optimizing self-care, cost-effectiveness, and the absence/minimum number of side effects [21].

It was showed that successful preventive treatment of migraine reduces the frequency and severity of cephalgic attacks, helps reduce the amount of analgesics consumed, prevents the transformation of episodic headache into chronic, prevents the development of structural changes in the central nervous system, and improves the quality of life of patients [22].

The main indications for preventive treatment of migraine are the frequency of attacks (more than two per month), their duration (up to 5 or more days with pronounced patient maladaptation), the presence of contraindications to abortive therapy or its ineffectiveness. As a tool for implementing the aforementioned strategy, β-blockers, calcium channel blockers, serotonin antagonists, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants are used [23-25].

Among anticonvulsants in the treatment of migraine, valproate, gabapentin and topiramate have found wide application. According to the literature, topiramate deserves special consideration among these drugs. The evidence base allows us to consider topiramate as the drug of choice in pharmacoprophylaxis of antimigraine therapy. This is possible to explain multimodal effects of topiramate on the CNS, as well as its impact on the leading mechanisms of migraine pathogenesis [26, 27].

The multiplicity of mechanisms of action of topiramate is reduced to the following factors: blockade of potential-dependent $Na^+$ channels of the neuronal membrane, which limits the current of sodium ions into the cell; activation of GABA receptors due to the extension of the opening time of $Cl^-$ channels; inhibition of excitatory glutamatergic neurotransmission by selective blockade of AMPA-/kainate receptors; blockade of “fast” potential-dependent L-type $Ca^{2+}$ channels, and inhibition of the activity of the carbonicanhydrase enzyme [28-30].

Topiramate (50-200 mg per day) significantly reduces the frequency of migraine attacks in adults, and the effect may persist even after discontinuation of the drug. In 46.3% of patients taking topiramate, the number of migraine attacks decreased by 50%, in 6% the attacks stopped completely. A progressive decrease in the frequency of attacks was found in the period 6 months after the start of topiramate intake [31].

Topiramate effectiveness was shown in the form of a reduction in the frequency of attacks per month compared to placebo, as well as a reduction in the number of days with

migraine attacks compared to baseline. The number of patients who responded to therapy was significantly higher in the topiramate group than in the placebo group. Also, as a result of the studies, it was found that a 3-month course of taking topiramate significantly reduces the frequency of migraine attacks (in general in the group by 2,1 times), and also reduces the duration of the attack and the intensity of the pain syndrome [32].

Topiramate has also been reported to be effective in various pain syndromes other than migraine: cluster headache, SUNCT syndrome, and phantom pain [33]. Thus, the neurochemical mechanisms of action of topiramate are directed at blocking the main factors of migraine pathogenesis.

The method of transcranial Dopplerography (TCD) of the main vessels of the head has long been successfully used for the diagnosis of lesions of the extracranial and intracranial departments of the main arteries [34, 35]. Recently, a fairly large number of works have been published devoted to the study of cerebral hemodynamic disorders in patients with migraine with and without aura, in the period between attacks and during the attack.

Their results are very contradictory. Blood flow indicators in the ophthalmic artery and external carotid artery were found to be increased in the ultrasound assessment. In patients with migraine without aura, an increase in blood flow velocity indicators and a decrease in the pulsation index in the arteries of the base of the brain were noted, and in the group of people with migraine with aura, a decrease in velocity indicators and an increase in peripheral resistance indices [36, 37].

There are no data in the available publications on the results of a combined study of cerebral hemodynamics and cerebrovascular reactivity using the TCD method in patients with different types of migraine. paroxysms . In this regard, the issue of using modern diagnostic methods becomes of paramount importance for the study of this pathology.

**The aim of the work** is to investigate the efficacy of clinical and Doppler study of young patients with migraine on the background of preventive treatment.

**Material and methods**

We conducted a clinical and Doppler examination of 116 young patients (18-45 years old), including 49 men and 67 women. All patients wrote informed consent before the beginning of the study which allowed to use their test results for scientific purposes.

The inclusion criteria for patients in the study were: migraine without aura (group 1 - 61 patients), migraine with aura (group 2 - 65 patients) according to the criteria of the international classification of headache (ICH-3, 2018). The exclusion criteria were the presence of occlusions

and hemodynamically significant stenosis of the MAH. The control group consisted of 25 patients of the corresponding sex and age.

All patients underwent a clinical and neurological examination. The intensity of the cephalgic syndrome was assessed using a visual analog scale and a headache diary filled in by the patient himself.

The condition of the main arteries of the head and neck, indicators of cerebrovascular reactivity (CVR) were studied using an ultrasound device “Ultima PA” (RADMIR, Ukraine). The time-averaged maximum blood flow velocity (TAMX) in the middle cerebral (MCA), anterior cerebral (ACA), posterior cerebral (PCA), internal carotid artery siphons ( ICA), vertebral arteries (VA), as well as the reactivity coefficients to hypercapnic (CrCO2), hyperventilation (CrO2) loads, and coefficient of photoreactivity (CPhR) were studied.

Statistical analysis and processing of the material was carried out using the software package “Statistica 6.0”. Differences with CG indicators were considered statistically significant at p value <0.05.

**Results**

Pain syndrome during the attack period in patients with migraine was characterized by the following criteria: frontal -ocular-temporal localization of pain was predominant in both clinical groups (85.2% in group 1, 96.3% in group 2). By the nature of pain during the attack, the pulsating type was detected (72.1% of patients in group 1 and 81.8% of patients in group 2), bursting - 8.2% and 5.4%, respectively, a combination of these types - in 16.4% and 12.7%. In 47.5% of patients in group 1 and in 36.3% of patients in group 2, the localization of the pain attack was mainly left-sided, in 34.4% of patients in group 1 and in 39.9% of patients in group 2 - mainly right-sided, in 18.1% of patients in group 1 and in 23.8% of patients in group 2 - alternating sides.

Attacks upon awakening were characteristic of 49.1% of patients in group 1 and in 38.1% of patients in group 2, daytime attacks - in 42.6% and 50.9% of cases, respectively, night attacks - in 8.3%. and 11.0%. The characteristic accompanying symptoms of migraine attacks were photophobia (73.7% and 88.3%), phonophobia (72.1% and 78.2%), a feeling of pulsation in the head (42.6% and 39.9%), nausea and vomiting (39.3% and 60.0%), dizziness (32.8% and 30.9%). The attacks were stopped after taking combinations of analgesics and antimigraine drugs of the triptan series (spontaneous elimination of the attack during sleep was less common).

The leading subjective symptoms in the inter-attack period in patients with migraine were: general weakness and decreased performance (42.6% in group 1 and 50.9% in group 2),

signs of emotional instability combined with irritability and tearfulness in 39.3% and 36.3% of patients, dizziness, mainly of a non-systemic nature - 32.8% and 38.1% of patients, noise in the head - 26.2% and 23.8% of patients, sleep disturbances - 14.7% and 16.3% of patients, memory loss - 11.4% and 14.5% of patients.

In the neurological status of patients with migraine, the following symptoms were noted: increased tendon reflexes - in 62.3% and 65.4% of patients, vegetative stigmata - in 42.6% and 52.7%, respectively, swaying in the Romberg position - in 22.9% and 18.1% of patients, mild oculomotor disorders - in 14.7% and 16.3% of patients, mild asymmetry of facial muscles - in 9.8% and 9.0% of patients.

Hemodynamic patterns in the intracranial arteries were characterized by the presence of vasospastic reactions in the MCA in patients of group 1 (86.2 ± 10.4 cm/s ($p<0.05$). Blood flow in the MCA in patients of group 2 is characterized by a pattern of impaired perfusion.

The indicators of cerebrovascular reactivity in patients with migraine were studied. Patients in group 1 showed hyperreactivity to CO2, O2 and photoreactivity loading, while patients in group 2 showed pronounced hyperreactivity to O2 and photoreactivity loading.

The next task of the study was to study the preventive effect of topiramate on the quantitative indicators of migraine paroxysms and hemodynamic patterns in patients with migraine. The drug Topiromax (“Acino”) was chosen as a preventive agent. Topiromax was taken as monotherapy , in the 1st week of taking the dosage was 25 mg per day, then the dosage was 50 mg per day, the course of treatment was up to 6 months.

Against the background of Topiromax therapy, a decrease in the frequency of attacks was noted from 5.8±3.1 to 3.2±2.6 in the 1st group, from 5.2±2.7 to 3.1±1.9 in the 2nd group. The average duration of attacks also decreased - from 43.8±11.7 to 28.4±10.2 in the 1st group, from 57.6±12.2 to 32.8±13.3 in the 2nd group. The most significant was the decrease in pain intensity according to VAS: from 6.9±1.6 to 3.4±1.8 ($p<0.05$) in the 1st group, from 8.2±1.4 to 4.6±1.7 ($p<0.05$) in the 2nd group (Fig.1).

With normal baseline TAMX data on the background of taking Topiramax practically did not change. In the presence of vasospastic reactions in the background, their regression was noted in MCA in patients of group 1 (TAMX decreased from (84.2±7.4 cm/s to 80.4±4.7 cm/s). In patients of group 2, normalization of reduced MCA velocity indicators was observed (from 56.8±5.1 cm/s to 60.4±4.3 cm/s). No significant changes in blood circulation were observed in the VA (Fig. 2).

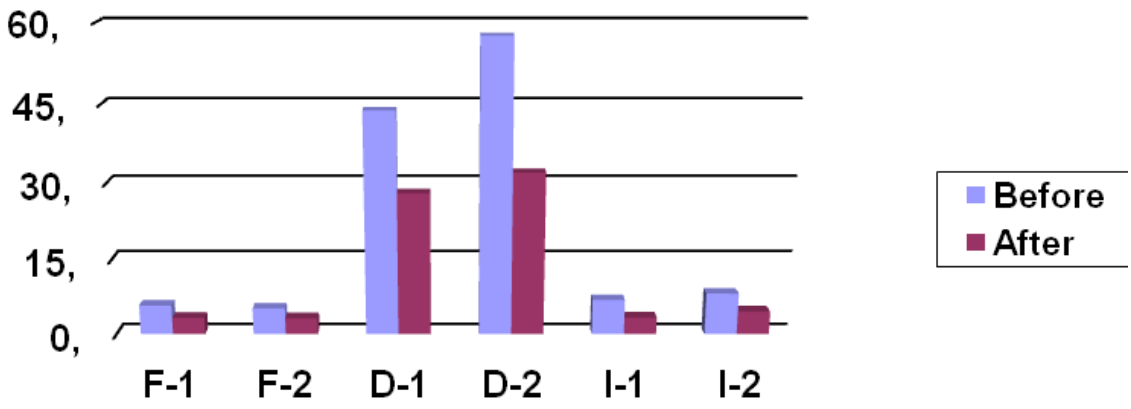


Fig.1. Dynamics of headache frequency (F), duration (D) and intensity (I) in patients with migraine on the background of Topiromax use.

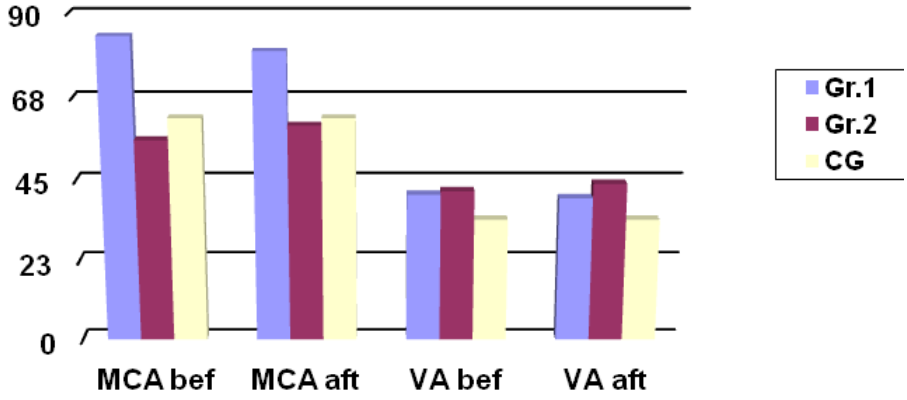


Fig. 2. Dynamics of TAMX indicators in patients with migraine against the background of Topiromax use.

Against the background of Topiromax course therapy, positive dynamics of changed CVR indicators were noted in all clinical groups. ($1^{st}$ group - 1.39±0.05 cm/s; $2^{nd}$ group - 1.37±0.04; CG - 1.28±0.04; $p<0.05$) and photoreactive test ($1^{st}$ group - 1.39±0.06; $2^{nd}$ group - 1.32±0.04; CG - 1.20±0.04; $p<0.05$).

The greatest tendency towards normalization of initially elevated CVR values was observed during $CO_2$ loading in patients of group 2 (from 1.37±0.04 to 1.30±0.05), as well as in the photoreactive test in patients of group 1 (from 1.39±0.06 to 1.30±0.04) (Fig. 3).

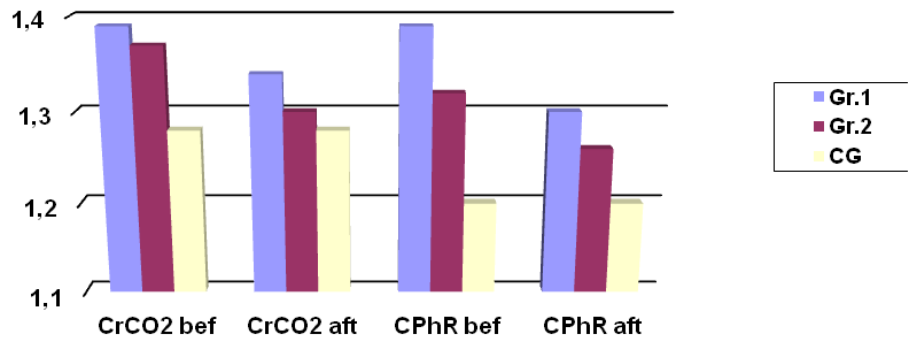


Fig.3. Dynamics of CrCO2 and CPhR in patients with migraine on the background of Topiromax use.

This effect indicates a reliable effect of Topiromax on the humoral-metabolic circuit of cerebral autoregulation . In this context, as in the situation with blood flow velocity indicators, Topiromax acts as a regulator of certain structural mechanisms of cerebral hemodynamics.

**Discussion**

Thus, the conducted studies have proven the presence of both a positive clinical and hemodynamic effect of Topiromax in patients with migraine. Under the influence of the drug, a decrease in the frequency, duration and intensity of attacks was observed. The vascular effect of the drug was manifested in a decrease in the initially increased blood flow velocity in the MCA. The drug contributed to the normalization of cerebrovascular hyperreactivity , mainly to the $CO_2$ test in patients with migraine with aura and to the photoreactive test in patients with migraine without aura.

In our opinion, both the normalization of the changed speed indicators and the normalization of vascular reactivity to functional loads are associated mainly with the influence on the humoral -metabolic circuit of vascular regulation through the implementation of mechanisms of activation of GABA receptors, inhibition of excitatory glutamatergic neurotransmission and blockade of voltage-gated L-type calcium channels.

**Conclusions**

1. Cerebral hemodynamics during a migraine attack is characterized by a pattern vasospasm in migraine without aura and a pattern of impaired perfusion in migraine with aura in the middle cerebral arteries, as well as increased perfusion in the cerebral arteries.

2. Hyperreactivity to hypercapnic load and photoreactivity test is a characteristic Doppler pattern in patients with migraine without aura. Hyperreactivity to hyperventilatory load, reflecting a hyperconstrictive vascular response, predominates in migraine with aura.

3. The use of Topiramate for the preventive treatment of migraine in both clinical groups allows significantly reducing the frequency, duration and intensity of migraine attacks as well as normalizing altered indicators of cerebral hemodynamics and cerebrovascular reactivity.

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**Author Contributions**

Conceptualization, (Kalashnikov V.Y.); methodology, (Stoyanov O.M.); formal analysis, (Kalashnikov V.Y.); data curation, (Stoyanov O.M.); writing - original draft preparation, (Vastyanov R.S.); writing - review and editing, (Vastyanov R.S., Stoyanov O.M.); supervision, (Kalashnikov V.Y.).

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**Informed Consent Statement**

The retrospective analysis of material was used. Written informed consent from the patients was not necessary to publish this paper.

**Data Availability Statement**

The data presented in this study are available on request from the author.

**Conflicts of Interest**

The authors declare no conflict of interest.