journal of clinical practice 2024 Vol 15 №3

PATENT FORAMEN OVALE AND MIGRAINE IN ISCHEMIC STROKE PATIENTS: INCIDENCE, PATHOGENETIC INTERRELATION AND THE EFFECTS OF ENDOVASCULAR CLOSURE

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ABSTRACT

BACKGROUND: *Migraine is a chronic neurovascular disease with high incidence rate and medical-social significance. Despite more than half a century of studying the disease, the pathogenesis of migraine is not yet completely clear. The results of separate research works demonstrate the inter-relation of migraine with the presence of patent foramen ovale and circulation shunting from the right side to the left one.* ***AIM:*** *Detailing the incidence rates and the clinical characteristics of migraine, as well as the effects of endovascular installation of the occluding device into the patent foramen ovale in terms of migraine course in a cohort of patients that had an ischemic stroke episode according to the mechanism of paradoxical embolism due to having a functionally significant patent foramen ovale.* ***METHODS:*** *The examined population included 97 patients aged from 18 to 50 years old (mean age 32.29±2.19 years; 70.8% females), undergoing examination procedures at the Research Center of Neurology from January 2018 until October 2023. All the patients previously had an ischemic stroke that had involved the mechanism of paradoxical embolism, associated with the presence of patent foramen ovale and high functional significance shunting. All the patients underwent an assessment of their conditions associated with the presence of a patent foramen ovale — migraine with or without aura, other procedures included the detailing of headache characteristics and of the effects of migraine on social adaptation. The endovascular intervention was performed in 61 patients. Dynamic follow-up data were obtained for 36 patients, of which 24 migraine patients had an assessment of headache characteristics before and after the foramen ovale closure.* ***RESULTS:*** *Within the cohort of patients with patent foramen ovale accompanied with functionally significant shunting and with a previous episode of ischemic stroke, the incidence of migraine was 39.2% (no aura — 21 patients or 55%; with aura — 17, or 45%), while the proportions of women and men being 1.9:1. The rate of headache attacks was 4 [1; 7] days per month. In 6 months after the installation of the foramen ovale occluder, migraine patients were showing a significant decrease in the rate of headache onsets from 4 [2; 24] to 2 [1; 5] days a month (p=0.009); a decrease was reported for pain intensity from 7 [7; 9] to 3 [3; 7] points of the visual analogue scale for pain (p=0.0001) along with a decrease in the degree of migraine affecting the patients' everyday activity from 20 [6; 89] to 17 [2; 26] points (p=0.019) of the MIDAS questionnaire.* ***CONCLUSION:*** *The present research has confirmed the high incidence found in a cohort of patients with patent foramen ovale. Installation of the occluder resulted in a decrease in the rate and intensity of headache along with a decrease of migraine affecting the social adaptation. The research limitations were a small number of patients and the absence of data on the residual shunting circulation.*

Keywords: *patent foramen ovale; migraine; migraine with aura; ischemic stroke; paradoxical embolism; right-left shunt; patent foramen ovale closure.*

For citation:

Belopasova AV, Chechetkin AO, Merezhko VD. Patent foramen ovale and migraine in ischemic stroke patients: incidence, pathogenetic interrelation and the effects of endovascular closure. *Journal of Clinical Practice*. 2024;15(3):49–59. doi: https://doi.org/10.17816/clinpract634497

Submitted 21.07.2024 Revised 07.08.2024 Published online 07.08.2024

ОТКРЫТОЕ ОВАЛЬНОЕ ОКНО И МИГРЕНЬ У ПАЦИЕНТОВ, ПЕРЕНЁСШИХ ИШЕМИЧЕСКИЙ ИНСУЛЬТ: РАСПРОСТРАНЁННОСТЬ, ПАТОГЕНЕТИЧЕСКАЯ ВЗАИМОСВЯЗЬ, ВЛИЯНИЕ ЭНДОВАСКУЛЯРНОГО ЗАКРЫТИЯ

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АННОТАЦИЯ

Обоснование. *Мигрень — хроническое нейрососудистое заболевание с высокой распространённостью и медико-социальной значимостью. Несмотря на более чем полувековую историю изучения заболевания, патогенез мигрени до конца не раскрыт. Результаты отдельных исследований демонстрируют взаимосвязь мигрени с наличием открытого овального окна и шунтирующего кровотока справа налево.* ***Цель исследования*** *— уточнение распространённости и клинических характеристик мигрени, а также влияния эндоваскулярной установки окклюдера открытого овального окна на течение мигрени в когорте пациентов, перенёсших ишемический инсульт по механизму парадоксальной эмболии вследствие функционально значимого открытого овального окна.* ***Методы.*** *Обследовано 97 пациентов в возрасте от 18 до 50 лет (средний возраст 32,29±2,19 года; 70,8% женщин), проходивших обследование в Научном центре неврологии с января 2018 по октябрь 2023 года. Все пациенты перенесли ишемический инсульт по механизму парадоксальной эмболии, ассоциированный с наличием открытого овального окна и шунтом высокой функциональной значимости. Всем пациентам проводилась оценка состояний, ассоциированных с наличием открытого овального окна — мигрени с аурой и без ауры, уточнялись характеристики головной боли и влияние мигрени на социальную адаптацию. Эндоваскулярное вмешательство проведено 61 пациенту. Получены данные динамического обследования 36 пациентов, из них у 24 пациентов с мигренью были оценены характеристики головной боли до и после закрытия овального окна.* ***Результаты.*** *Среди когорты пациентов с открытым овальным окном с функционально значимым шунтом, перенёсших ишемический инсульт, распространённость мигрени составила 39,2% (без ауры — у 21 человека, или 55%; с аурой — у 17, или 45%), соотношение женщин и мужчин 1,9:1. Частота приступов головной боли составила 4 [1; 7] дня в месяц. Через 6 месяцев после установки окклюдера овального окна у пациентов с мигренью выявлено достоверное снижение частоты приступов головной боли с 4 [2; 24] до 2 [1; 5] дней в месяц (p=0,009); сокращение интенсивности боли с 7 [7; 9] до 3 [3; 7] баллов по визуальной аналоговой шкале оценки боли (p=0,0001); уменьшение степени влияния мигрени на повседневную активность пациентов с 20 [6; 89] до 17 [2; 26] баллов (p=0,019) согласно опроснику MIDAS.* ***Заключение.*** *Настоящее исследование подтвердило высокую распространённость мигрени в когорте пациентов с открытым овальным окном. Установка окклюдера привела к уменьшению частоты и интенсивности головной боли, уменьшению влияния мигрени на социальную адаптацию. Ограничением исследования стали небольшое число пациентов и отсутствие данных по остаточному шунтирующему кровотоку.*

Ключевые слова: *открытое овальное окно; мигрень; мигрень с аурой; ишемический инсульт; парадоксальная эмболия; право-левый шунт; установка окклюдера овального окна.*

Для цитирования:

Белопасова А.В., Чечеткин А.О., Мережко В.Д. Открытое овальное окно и мигрень у пациентов, перенёсших ишемический инсульт: распространённость, патогенетическая взаимосвязь, влияние эндоваскулярного закрытия. *Клиническая практика.* 2024;15(3):49–59. doi: https://doi.org/10.17816/clinpract634497

Поступила 21.07.2024 Принята 07.08.2024 Опубликована online 07.08.2024

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BACKGROUND

Migraine is a widespread neurological disease (found in 12–15% of the population), the pathogenesis of which is not completely clear [1, 2]. During the last decades, the factors are being studied that predispose the development of cephalgia, one of which is the presence of a patent foramen ovale.

Patent foramen ovale is the form of intracardial communication, anatomically representing an opening, located in the central part of the interatrial septum. Patent foramen ovale is a rudiment form of normal embryonic circulation, which normally should close during the first year of life in a child, however, it remains unclosed in 1/4 of the population [3]. The morphological variability is found both in the dimensions and in the shape of the oval foramen — from a simple opening covered by a valve to a long corrugated passage. The structure of the patent foramen ovale defines the degree of shunting circulation passing through the opening, which may vary from small to significant. The diagnostics of the patent foramen ovale is being carried out using the transthoracic and transesophageal echocardiography. For the purpose of verifying the degree of shunting circulation, a micro-bubble test with intravenous administration of the contrasting agent is used (most frequently — an aerated physiological saline), allowing for quantitative assessment of the shunting degree by means of calculating the number of signals from the micro-bubbles. The most widespread and informative method used to perform the micro-bubble test is the transcranial Doppler sonography with the registration of embolic air signals in the middle cerebral arteries [4, 5].

The relation between the patent foramen ovale and migraine was first described by S.M. Del et al. [6] in 1998. The authors have found that the rate of patent foramen ovale presence in migraine patients was significantly higher comparing to healthy individuals. Later on, a number of research works have confirmed that the occurrence rate of migraine among the individuals with patent foramen ovale is 2–3 times higher than in the general population [7–10], correlating with the degree of shunting circulation [11]. Besides the possible interrelation with the onset of migraine attacks, patent foramen ovale plays a role in the development of stroke by employing the paradoxical embolism mechanism. In younger patients with cryptogenic ischemic stroke and migraine with aura, the occurrence rate of having a patent foramen ovale reaches up to 93% [12, 13].

The mechanism of the effects of right-to-left shunting circulation on the onset of migraine attack is not yet completely clear. According to one of the hypotheses, 5-hydroxytryptamine (5-HT, or serotonin) contained in platelets, has one of the leading roles in the development of migraine. Normally, practically all the serotonin present in venous blood is being removed by decomposition in lungs. In case of the presence of a patent foramen ovale, it is supposed that the passage of platelets through the narrow opening of the foramen ovale promotes hyperaggregation of platelets with the secretion of serotonin and other vasoactive mediators into peripheral blood. High 5-HT concentrations induce vasoconstriction of meningeal arteries with developing aura symptoms, while lesser 5-HT concentration promotes vasodilation due to synergetic effects with nitrogen oxide (NO) and prostaglandins, stimulating the pain receptors of pial arteries, which leads to the development of the headache phase [14]. Alternative hypothesis considers the migraine attack predictor being the decrease in blood oxygen saturation due to right-to-left shunting. A research by T. Takano et al. [15] has shown that cortical spreading depression is associated with severe hypoxia, while the elevation of partial oxygen pressure (pO_2) shortens its duration. According to the third hypothesis, the development of spreading depolarization is related to microembolism of the cortical arteries. Animal studies conducted by M.A. Moskowitz et al. [16] at the laboratory of Harvard University, have demonstrated that air and platelet aggregates, injected to 28 mice directly into the carotid arteries, initiate cortical spreading depression. Upon the injection of air microemboli (with the diameter of <10 μm), polystyrene microspheres (10 μm) and cholesterol particles (<70 μm), the microembolism has induced the development of cortical spreading depression in 16 (57%) animals. Some mice had ischemic changes detected in the cortical neurons with no focal changes upon neurovisualization. Smaller emboli (with the diameter of <10 μm) have induced rapid and transient episodes of cortical spreading depression, related to significant decreases of cortical perfusion. Larger emboli (<70 μm) had higher probability of inducing microinfarctions, however, the latter were not detected upon cerebral visualization, though being verified upon histological examination. The authors draw up a conclusion that the majority of emboli are too small and they rapidly undergo spontaneous lysis, by this causing the onset of depolarization events with no developing clinically significant ischemia. In contrast, larger emboli, resistant to lysis, can become the culprit of cortical microinfarctions [17].

Endovascular closure of the patent foramen ovale using the special devices (occluders) is the main treatment method for functionally significant cases of foramen ovale. In 1992, the first transcutaneous closure of the patent foramen ovale was performed in a patient with ischemic stroke occurring via the mechanism of paradoxical embolism [18]. In 2000, P.T. Wilmshurst et al. [19] have first reported the benefits of patent foramen ovale closure in migraine patients. To the present moment, a significant number of observation research works were carried out in real clinical practice [20–24] along with several large randomized controlled research works, in particular, MIST (Migraine Intervention With STARFlex Technology), PRIMA (PRIMA PFO Migraine Trial) and PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) [20–22], which have demonstrated controversial results with regard to the effects of foramen ovale closure in the course of migraine.

In Russia, endovascular installation of occluders for closing the foramen ovale for the purpose of secondary prevention of paradoxical embolism-related ischemic stroke has been performed since 2018, however, there was no evaluation performed on the incidence of migraine among the patent foramen ovale patients and on the effects of foramen ovale occluder installation on the course of cephalgia until the present moment.

Research aim — detailing the incidence rates and clinical characteristics of migraine, as well as the effects of endovascular installation of the patent foramen ovale occluder on the migraine course in a cohort of patients that had an episode of ischemic stroke caused by the mechanism of paradoxical embolism due to functionally significant patent foramen ovale.

METHODS

Research design

A prospective non-randomized open-label research was carried out to assess the effects of patent foramen ovale occluder installation on migraine course within the Russian cohort of patients.

Conformity criteria

Inclusion criteria: group I — patients after an episode of ischemic stroke caused by the mechanism of paradoxical embolism; group II — patients with a past episode of ischemic stroke resulted by paradoxical embolism and after the procedure of patent foramen ovale closure with a past history of migraine.

Non-inclusion criteria: patients having a concurrent cause of developing a stroke; other neurological or mental disease; concomitant severe somatic disturbances; past history of hemiplegic migraine or cluster headache; preventive treatment of migraine (tablets or injectables) within 3 months prior to the inclusion into the research program.

Exclusion criteria: less than 80% of headache diary keeping compliance; refusal from repeated visiting the neurologist after the installation of patent foramen ovale occluder.

Research facilities

The research included 97 patients aged from 18 to 50 years old (39 females and 56 males, mean age: 32.29±2.19 years old), undergoing examination procedures at the Federal State Budgetary Scientific Institution "Research Center of Neurology" from January 2018 until October 2023. All the patients had an episode of ischemic stroke caused by paradoxical embolism, associated with the presence of patent foramen ovale with moderate and severe interatrial shunting circulation.

Medical procedure description

The degree of shunting circulation from the right side to the left one was evaluated using transcranial Doppler sonography with the administration of the contrasting agent — agitated mixture of 9 mm 0.9% physiological saline and 1 ml of air. The shunting degree was calculated using the number of registered microembolic signals: no shunting — 0 microembolic signals; insignificant — from 1 to 20 microembolic signals; moderate — more 20 microembolic signals with no "curtain effect"; severe — a "curtain" of microembolic signals, where a single signal cannot be recognized within the circulation spectrum [7].

The evaluation of the interrelation of the stroke episode in the past with the detected patent foramen ovale was carried out using the paradoxical embolism risk score (Risk of Paradoxal Embolizm, RoPE). The mean RoPE scale value in the group was 8.3±1.09 points, which confirms the high (84%) probability of an interrelation between the ischemic stroke and the presence of patent foramen ovale [23].

All the patients have underwent an assessment of their conditions, associated with the presence of the patent foramen ovale, in the settings of having migraines with aura (MA) and without aura (MnA). The migraine diagnosis was set in accordance with the International headache classification, beta-version (3rd edition,

https://doi.org/10.17816/clinpract634497

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2018, IHC 3 beta) [24]. In case of having migraine, the patients were included into research group 1: ischemic stroke + patent foramen ovale + migraine (group I, IS+PFO+Migraine). The algorithm used for selecting the patients is provided in Fig. 1.

After the confirmation of paradoxical embolism, all the patients had been given the recommendations of installing the patent foramen ovale occluder for the purpose of secondary prevention of strokes. Endovascular interventions were performed in 61 patients. After the occluder installation, the patients had a 6 months period of taking double antiplatelet therapy (Acetylsalicylic acid + Clopidogrel), then, according to the European recommendations from the Endovascular surgery society on managing the patent foramen ovale patients (2019) — only acetylsalicylic acid at a dosage of 75–100 mg/day [25]. Six months after the foramen ovale closure, repeated patient's visit was scheduled for evaluating the somatic and neurological status.

As of the moment of drafting the article, the data were obtained from dynamic follow-up of 36 ischemic stroke patients with patent foramen ovale occluder installed, of which 24 patient had migraine, which were included in to the second research group: ischemic stroke + patent foramen ovale + occluder + migraine (group II, IS+PFO+Occluder+Migraine), where the cephalgia characteristics were assessed before and after the endovascular closure of the foramen ovale.

Methods for registration of outcomes

The patients in the main research groups were filling in a standard questionnaire including the demographic data, the clinical features of migraine course (duration of disease, attack rate during the last month, attack intensity according to visual analogue scale), the information on the presence of vascular risk factors (arterial hypertension, diabetes mellitus, smoking and intake of oral contraceptive pills) and the presence of past or chronic diseases.

The rates and clinical characteristics of migraine attacks were assessed using the paper or digital version of headache diary, which the patient had to fill in for 3 months before the installation of the patent foramen ovale occluder and for 3 months after the

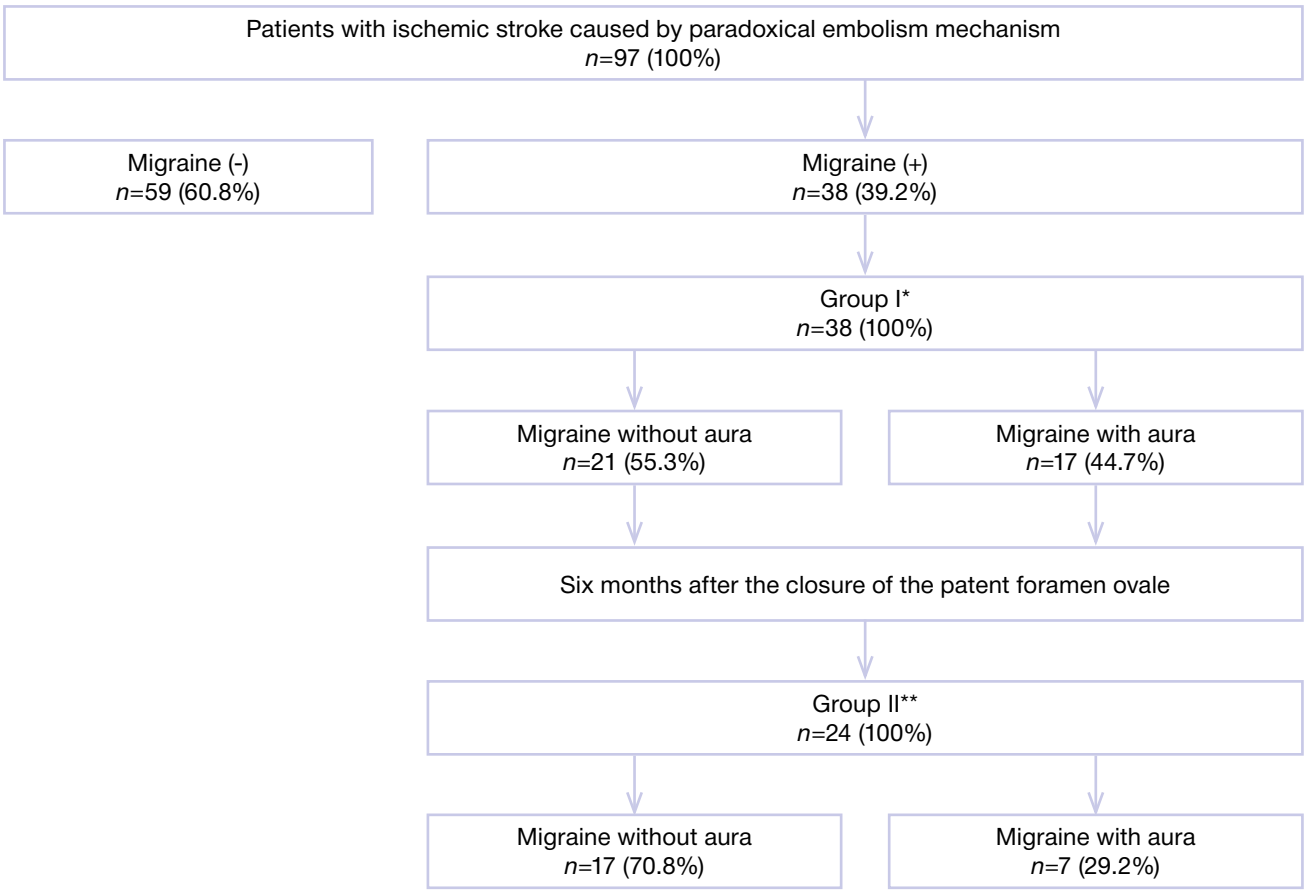

Fig. 1. Flowchart of the algorithm used for distributing patients into research groups.
Note. * Group I — ischemic stroke + patent foramen ovale + migraine. ** Group II — ischemic stroke + patent foramen ovale + occluder + migraine.

foramen ovale closure. The dairy had to be filled in on a daily basis and had to show at least 80% of dairy filling compliance.

For the purpose of assessing the quality of life and the effects of migraine on everyday activity and working capacity, all the patients had to fill in (twice — before and in 6 months after the occluder installation) the MIDAS questionnaire (Migraine Disability Assessment). According to the questionnaire, the total number of points ranging from 0 to 5 corresponded to low pain intensity, absence or minimal decrease of everyday activity; 6–10 points — moderate/severe pain, insignificant limitation of everyday activity; 11–20 points — severe pain, significant restriction of everyday activity; from 20 points and higher — severe pain, significant restriction of everyday activity [26].

Research outcomes

The research endpoint included changes in headache intensity, in the number of headache days and in the level of social de-adaptation in a patient in 6 months after the installation of patent foramen ovale occluder.

Ethical review

The research was approved by the local ethics committee of the Federal State Budgetary Scientific Institution "Research Center of Neurology" (minutes of the meeting No. 1-4/22 dd. 19.01.2022). Each patient had signed a voluntary informed consent for participating in the research activities.

Statistical analysis

The procedures of statistical analysis were carried out using the IBM SPSS Statistics 23.0 application software package. The main descriptive statistics for categorical and ordinal variables included the rate and the percentage (*n*, %), while for normal distribution of quantitative variables — the mean values and standard deviation (M±SD), as for the data, the distribution of which did not meet normality criteria — the median and quartiles 1–3 (Me [Q25%; Q75%]). The comparative analysis of two independent groups by quantitative variable was carried out using the Mann-Whitney test. The null hypothesis was rejected in case of $p < 0.05$.

RESULTS

Research sample (participants)

Among 97 patients with ischemic stroke caused by paradoxical embolism, 38 (39.2%) were diagnosed with migraine, of which 21 (55.3%) had MnA and 17 (44.7%) had MA; the ratio of women and men was 1.9:1. The frequency of headache days per month was 4 [1; 7], which corresponds to criteria for infrequent episodic migraine. The main characteristics of headache corresponded to the average population values (table 1).

Group II (IS+PFO+Occluder+Migraine) consisted of 24 patients having migraine with or without aura. Further analysis did not include an assessment of dynamic changes in migraine characteristics after the installation of patent foramen ovale occluder within the MA and MnA groups due to insufficient statistical power of the research group (table 2).

Primary findings

Based on the results of analyzing the dependent samples (before and after the installation of occluder), a significant decrease was found in the frequency of migraine attacks — from 4 [2; 24] to 2 [1; 5] days

Table 1

Clinical characteristics of migraine in patients from group I (IS+PFO+Migraine)

Characteristics	Migraine patients *n*=38 (100%)	Migraine with no aura *n*=21 (55.3%)	Migraine with aura *n*=17 (44.7%)
Mean age, years (M±SD)	35.76±1.41	33.67±1.93	38.50±1.90
Age of headache onset, years (Me [Q25%; Q75%])	20.06±1.78	21.72±2.43	18.07±2.61
Headache history, years (Me [Q25%; Q75%])	16.12±1.85	13.17±2.38	19.67±2.70
Women, *n* (%)	25 (66)	13 (62)	12 (71)
Men, *n* (%)	13 (34)	8 (38)	5 (29)
Hereditary history, *n* (%)	22 (57)	13 (62)	9 (53)
Frequency — migraine days per month (Me [Q25%; Q75%])	4 [1; 7]	4 [1; 5]	4 [1; 12]
Headache intensity (VAS), points (Me [Q25%; Q75%])	6 [5; 7]	6 [6; 7]	6 [5; 6]
MIDAS, points (Me [Q25%; Q75%])	20 [5; 49]	25 [5; 49]	18 [6; 39]

https://doi.org/10.17816/clinpract634497

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Table 2

Demographical and Clinical characteristics in patients from Group II (IS+PFO+Occluder+Migraine) before the installation of patent foramen ovale occluder

Characteristics *n*=24		Parameter
Women, *n* (%)		17 (71)
Age, years (Me [Q25%; Q75%])		36 [30; 43]
Migraine with aura, *n* (%)		7 (29)
Number of headache days a month (Me [Q25%; Q75%])		4 [2; 24]
Pain intensity (VAS), points (Me [Q25%; Q75%])		7 [7; 9]
De-adaptation degree (MIDAS) (Me [Q25%; Q75%])		20 [6; 89]
Characteristics of the interatrial septum, *n* (%)	normal	14 (59)
	hypermobility	2 (8)
	aneurism	8 (33)
Shunting degree according to data from transcranial Doppler sonography, *n* (%)	insignificant	-
	moderate/severe	24 (100)

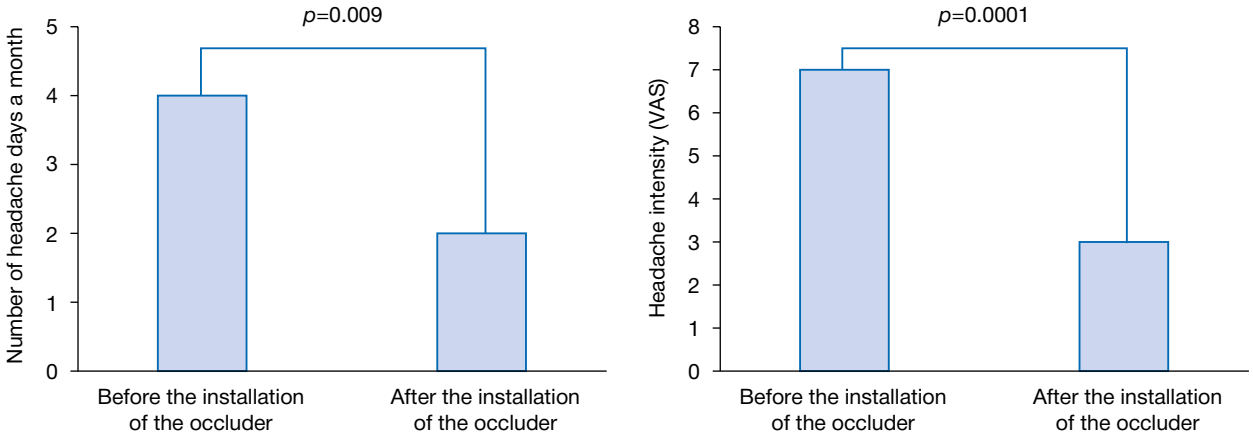

Fig. 2. Dynamic changes in the frequency and intensity of headache before and after the installation of PFO occluder.

a month (p=0.009) along with a decrease in the headache intensity from 7 [7; 9] to 3 [3; 7] points of VAS (p=0.0001) (Fig. 2). A statistically significant decrease was found in the degree of migraine affecting patient's everyday activity — from 20 [6; 89] to 17 [2; 26] points (p=0.019), according to MIDAS questionnaire (Fig. 3).

DISCUSSION

Despite the significant number of conducted researches studying the interrelation of migraine with the presence of patent foramen ovale and its endovascular closure, to the present moment, there is no univocal opinion regarding the commonness of the pathogenesis in the said conditions. Taking into consideration the wide spreading of both nosologies, there is a probability for both diseases (comorbidities) existing in a single person.

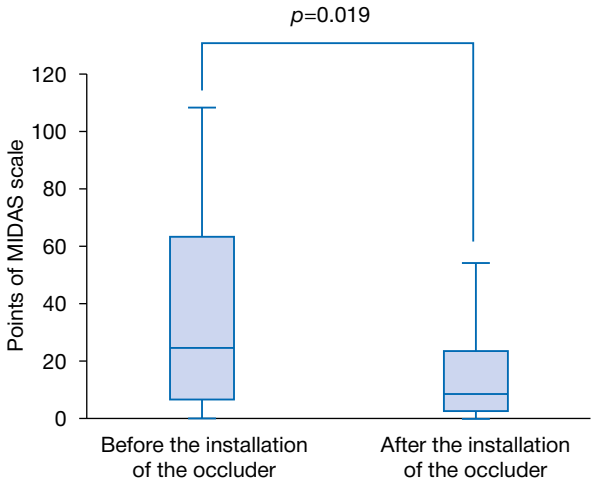

Fig. 3. Dynamic changes in the levels of social de-adaptation of migraine patients before and after the installation of PFO occluder.

Our research works has confirmed the thesis on the high incidence of migraine in patent foramen ovale patients: approximately 40% of research participants were suffering from cephalgia, which corresponds to the data from P.T. Wilmshurst [11], according to which, the incidence of migraine in cases of patent with patent foramen ovale with moderate shunting was 25%, while in cases of significant shunting — up to 53%.

The incidence for MA and MnA patients in our sample was 45% and 55%, respectively, while the patent foramen ovale, according to literature data, was associated predominantly with classic migraine (the occurrence rate for migraine with aura among the patients with patent foramen ovale is within the range of 46–88%) [27, 28].

The conducted research had a women to men ratio of 1.9/1, while the specific feature of migraine is the prevalence in female population with the ratio of women and men during the peak incidence period (30–45 years) being 3 – 4/1 [29].

When assessing the clinical characteristic of cephalgia, no specific features of the disease course were found, which complies with the results of SAM (Shunt-Associated Migraine) prospective multi-center observational research with the participation including 460 patients, the objective of which was to reveal the difference in the clinical signs of migraine depending on the presence of right-to-left shunting circulation. The differences in disease symptoms among the patients with patent foramen ovale (58%) and without one (42%) were also not detected. The authors came to the conclusion that the right-to-left shunt, apparently, plays a role in the initiation of migraine attacks, however, not affecting its clinical characteristics [30].

Data from real clinical practice indicate the presence of positive effects caused by foramen ovale occluder installation on the course of migraine, by this confirming the commonness of pathogenesis. From the beginning of 2000, more than ten observational research works were conducted, successfully demonstrating a decrease in the severity and in the duration of headache attacks along with the number of medicines used to alleviate migraine attacks, as well as an improvement in the quality of life according to data from HIT-6 and MIDAS scales in patients undergoing an installation of patent foramen ovale occluder [31–35]. So, the data from randomized controlled research are not so unambiguous. The objective of MIST [20], PRIMA [21] and PREMIUM [22] research works was an assessment of the effects caused by endovascular installation of the patent foramen ovale occluder on the course of migraine. Though none of the research activities had reached its primary endpoints (elimination of migraine in 6 months during the MIST research; decreasing the monthly rate of migraine attacks in 9–12 months during the PRIMA research; decreasing the migraine attacks >50% within 1 year during the PREMIUM research), upon achieving the secondary endpoints, a benefit was demonstrated for the patent foramen ovale closure, especially in patients having migraine with aura.

Our research has shown positive dynamic changes in cephalgia parameters in 6 months after the installation of patent foramen ovale occluder, namely: a statistically significant shortening of frequency (in days) and a decrease in the intensity of headache; a decrease in the degree of migraine affecting the patient's everyday activity. The obtained results confirm the method's efficiency, just like the previously conducted observational researches. Insufficient level of evidence found in the results of randomized controlled researches, may be related to specific features of selecting the patients with drug-resistant migraine, which often resists any correction, including also the drug-free modalities. Our cohort, like in other research works employing the settings of real clinical practice, had a prevalence of patients with initially low rate of headache days, corresponding to episodic migraine.

After an installation of the occluder, all the patients were receiving double antiplatelet therapy with acetylsalicylic acid and clopidogrel, thus, besides the elimination of shunting, the prescribed therapy was directed to decreasing the aggregation properties of platelets. Taking into consideration the hyper-aggregation theory of migraine pathogenesis [14], the literature contains a discussion on what is causing the efficiency of endovascular treatment for patent foramen ovale — the fact of eliminating the shunt itself, the drug-induced decrease in platelet aggregation during the post-surgery period or the synergy of both methods. That being said, the CANOA research (Clopidogrel for the prevention of new migraine after transcatheter closure of the interatrial septal defect) has shown that, among the patients with a past episode of transcatheter closure of interatrial septal defect using the Amplatzer apparatus, the combination of acetylsalicylic acid and clopidogrel taken for 3 months after the procedure, as compared to acetylsalicylic acid monotherapy, resulted in lesser number of migraine attacks within 3 months [36]. The retrospective research by R.J. Sommer et al. [37] has shown that successful inhibition of platelet thienopyridine P2Y12-receptors improves the course

https://doi.org/10.17816/clinpract634497

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of migraine in patients with patent foramen ovale and is considered a prognostic marker of the efficiency of endovascular patent foramen ovale closure for the prevention of migraine. Investigators propose using the sensitivity to thienopyridine antiaggregants when selecting migraine patients for further research works on the closure of patent foramen ovale.

In January 2021, the European recommendations were issued on managing the patients with patent foramen ovale and migraine [38], containing regulations on the endovascular treatment of functionally significant patent foramen ovale in case of diagnostic procedures being performed among the patient with transient ischemic attacks or ischemic stroke caused by paradoxical embolism and with concomitant migraine, as well as on the procedures of occluder installation as a "salvage therapy" in patients with refractory migraine and the significant decrease in the quality of life. Taking into consideration the literature data mentioned above, as well as the proprietary clinical experience within the framework of the conducted research, the conclusions drawn up by the colleagues appear justified and rational.

Research limitations

The limitations of the present research were a small patient sample and insufficient duration of migraine course dynamic assessment after the occluder installation.

When assessing the research results, the data on the presence of residual shunting circulation were not registered. The research by E. Ben-Assa et al. [8] has shown the significance of residual shunting for the dynamic course of migraine. The absence of shunting from the right side to the left was associated with a decrease in migraine burden by more than 50% (OR4.60; 95%CI 1.30–16.10; p=0.017). Besides, the main research population included patients after an ischemic stroke, which is why the obtained results cannot be projected to the general cohort of patients with migraine and patent foramen ovale.

CONCLUSION

Further research on the effects of endovascular closure of the patent foramen ovale on the course of migraine shall take into account the sensitivity to thienopyridine antiaggregants with evaluating the dynamic course of the disease during a time period of not less than 12 months after the installation of occluder with a background of initiating and canceling the double antiaggregant therapy. The important aspect is also an evaluation of the procedure safety and efficiency (complete closure of the right-to-left shunt or preserving residual shunting) for the treatment of such a patient cohort.

ADDITIONAL INFORMATION

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. *A.V. Belopasova* — concept development, literature analysis, patient selection and examination, data analysis and interpretation, manuscript writing, data collection; *A.O. Chechetkin* — examination of patients, data collection, analysis and interpretation of the data obtained, manuscript writing; *V.D. Merezhko* — literature analysis, data analysis and interpretation, manuscript writing. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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https://doi.org/10.17816/clinpract634497

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