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Glycine influence on cerebral blood flow parameters in practically healthy individuals evaluated with transcranial Doppler sonography

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An insufficient perfusion of the brain tissue can cause a decrease in cognitive functions, and long-term ischemia also leads to emotional and motor disorders. At the same time, check-up of the state of the cerebral blood flow is an important aspect of monitoring the progression of many pathological conditions. The amino acid glycine has been widely used in neurological practice for over 30 years, which helps improve hemodynamic characteristics and metabolic processes in the brain tissue.

The aim of the work was to analyze the effect of a sublingual administration of glycine on the cerebral blood flow velocity in practically healthy subjects using transcranial Doppler (TCD) sonography.

Material and methods. The pilot randomized controlled study included 20 healthy subjects aged 25 to 65 years, equally divided into 2 groups, one of which took glycine sublingually at a dose of 300 mg/day for 30 days, and the second group was a control group and did not receive the drug. In the first group, a load testing was carried out with 1000 mg of glycine, and in the control group – with 1000 mg of placebo. All the subjects underwent an assessment of the blood flow in the extracranial and intracranial vessels using standard protocols of TCD.

Results. In Group I, after a month of glycine intake, the peak systolic (by 11.9 cm/s) and average maximum (by 6.3 cm/s) velocities in the left middle cerebral artery (MCA) increased significantly (p <0.01), while in the right MCA there was an increase in the peak systolic (by 9.3 cm/s), and diastolic (by 2.8 cm/s) and average maximum (by 5.8 cm/s) velocities. In turn, in the control group, there was no significant increase in velocity. During the load testing with glycine / placebo, the relative increase in the peak systolic velocity in the MCA in the main group was 7.6% [1.2; 10.9], in control group was 1.5% [-3.6; 5.5] (p=0.03).

Conclusion. Glycine intake for 30 days contributes to a reliable improvement in cerebral hemodynamics in healthy individuals, such as an increase in the linear blood flow velocity in the MCA. At the same time, a single dose of 1000 mg of glycine leads to an increase in the peak systolic and average maximum intracranial blood flow velocities up to 10%.

Keywords: transcranial Doppler sonography; blood flow velocity; middle cerebral artery; glycine

Abbreviations: TCD sonography – transcranial Doppler sonography; PS – peak systolic blood flow rate; ED – end diastolic blood flow rate; TAMAX – Time Averaged Maximum Velocity; PI – pulsatility index; RI – peripheral resistance index; CCA – common carotid artery; ECA – external carotid artery; ICA – internal carotid artery; VA – vertebral artery; MCA – middle cerebral artery; ACA – anterior cerebral artery; PCA – posterior cerebral artery.

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Оценка влияния приёма глицина практически здоровыми лицами на параметры мозгового кровотока по данным транскраниальной допплерографии

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Недостаточность перфузии мозговой ткани может вызывать снижение когнитивных функций, а длительно сохраняющаяся ишемия приводит также к эмоциональным и двигательным нарушениям. При этом контроль состояния церебрального кровотока является важным аспектом мониторинга прогрессирования многих патологических состояний. В неврологической практике уже более 30 лет широко применяется такая аминокислота, как глицин, которая способствует улучшению гемодинамических характеристик и метаболических процессов в тканях мозга.

Цель. Анализ влияния сублингвального приёма глицина на скоростные показатели мозгового кровотока у практически здоровых испытуемых с помощью транскраниальной допплерографии (ТКДГ).

Материал и методы. В пилотное рандомизированное контролируемое исследование было включено 20 здоровых испытуемых в возрасте от 25 до 65 лет, разделённых на 2 группы (n=10 для каждой группы). Группа I в течение 30 дней принимала препарат глицин сублингвально в дозе 300 мг/сутки, а группа II была контрольной (препарат не получала). Также в первой группе нагрузочная проба проводилась с 1000 мг глицина, а в контрольной группе – с 1000 мг плацебо. Всем испытуемым проводили оценку показателей кровотока в экстракраниальных и интракраниальных сосудах по данным ТКДГ с использованием стандартных протоколов.

Результаты. В группе I через месяц приёма глицина в левой средней мозговой артерии (СМА) значимо (p <0,01) увеличились пиковая систолическая (на 11,9 см/с) и средняя максимальная (на 6,3 см/с) скорость, а в правой СМА наблюдалось увеличение пиковой систолической (на 9,3 см/с), конечной диастолической (на 2,8 см/с) и средней максимальной (на 5,8 см/с) скоростей. В свою очередь, в контрольной группе значимого прироста скорости не произошло. При нагрузочной пробе с глицином / плацебо относительный прирост пиковой систолической скорости в СМА в основной группе составил 7,6% [1,2; 10,9], в контрольной группе – 1,5% [-3,6; 5,5] (p=0,03).

Заключение. Приём глицина в течение 30 дней способствовал достоверному улучшению церебральной гемодинамики у здоровых лиц, которое выражалось в увеличении линейной скорости кровотока по СМА. При этом однократный приём 1000 мг глицина приводил к росту пиковой систолической и средней максимальной скоростей интракраниального кровотока до 10%.

Ключевые слова: транскраниальная допплерография; скорость кровотока; средняя мозговая артерия; глицин

Список сокращений: ТКДГ – транскраниальная допплерография; PS – пиковая систолическая скорость кровотока; ED – конечная диастолическая скорость кровотока; TAMAX – средняя по времени максимальная скорость кровотока; ОСА – общая сонная артерия; НСА – наружная сонная артерия; ВСА – внутренняя сонная артерия; ПА – позвоночная артерия; СМА – средняя мозговая артерия; ПМА – передняя мозговая артерия; ЗМА – задняя мозговая артерия.

INTRODUCTION

The brain consumes large amounts of energy during its functioning. To maintain these high metabolic demands, a significant volume of blood is required. A cerebral blood flow, which provides oxygen and nutrients to the brain tissues, as well as a removal of metabolic products, accounts for up to 20% of the total cardiac output [1]. A blood supply to the brain is carried out by large arteries located on its surface, which form an extensive multiply branching network. Even a slight deterioration of the cerebral blood circulation leads to cognitive disorders, and a

significant impairment is one of the main causes of mortality [2].

A reduced cerebral perfusion can occur both due to microangiopathies and in case of lesions of larger caliber arteries, for example, when the elastic properties of the vascular wall deteriorate [3]. A significant factor is also an insufficiently flexible change of the blood supply to different brain regions in response to the changes in their energy requirements [4]. In addition, an impaired effective autoregulation, which ensures the constancy of the cerebral blood flow even with significant fluctuations in the systemic pressure, is often observed in patients with an arterial hypertension and atherosclerosis [5]. This fact dramatically increases the risk of a cognitive impairment progression [6].

Thus, monitoring a cerebral blood flow is an essential factor in the study of the progression dynamics of the cerebral tissue perfusion insufficiency, as well as an important component of screening in patients with risk factors without established diagnoses. PET-CT (positron emission tomography and computed tomography) is one of the ways of a direct assessment of a cerebral blood flow, as well as the “gold standard” in the study of a cerebral vascular reactivity. However, there are other methods such as near-infrared spectroscopy (NIR spectroscopy), single-photon emission computed tomography, functional magnetic resonance imaging (fMRI), and transcranial Doppler (TCD) sonography [7]. TCD sonography is a rather reliable, inexpensive, widespread noninvasive technique for assessing hemodynamic parameters of intracranial vessels, in particular, blood flow velocity indices [8, 9]. The indices calculated on the basis of the obtained values (a pulsation index and a peripheral resistance index) also provide an indirect assessment of a perfusion in the studied vascular basin [10].

In the neurological practice, neurometabolic drugs, such as ginkgo biloba, choline alphoscerate, glycine, vinpocetine, and citicoline, are widely used to reduce the activity of pathological processes in the nervous tissue arising during ischemia [4, 11]. An important aspect of therapy is to slow down the progression of a cognitive decline in various types of cerebral vascular lesions, since many drugs do not have such a vasodilating effect, but to a greater extent, affect the components of the vascular tone regulation, thus improving both hemodynamic characteristics and metabolic processes in the brain tissue [6].

Amino acid glycine has long been used to correct disorders of the autonomic nervous system, as well as in the cognitive decline. Its pharmacological properties are due to its participation in a variety of metabolic processes and a direct neurotransmitter action [12, 13]. The therapeutic effect of glycine on the clinical course of an acute ischemic stroke especially when administered early, has been shown [14]. The administration of 1000 mg of the drug in the first few days contributed to the regression of a neurologic deficit in 68.9% of cases, which significantly exceeded the similar indicator in the placebo group (31.5%) [15]. The addition of glycine to the basal therapy of newborn infants with perinatal hypoxic CNS lesions led to the normalization of neuropsychiatric development rates, as well as an improvement of the neurological status and behavioral characteristics [16]. In animal studies, the vasodilating effect of a glycine solution, expressed as a 50–80% increase in the diameter of arterioles when directly applied to the pial membranes, occurred within a few minutes [17]. It was also experimentally shown that a sublingual administration of 200 mg of glycine promotes a 1.5-fold increase in the concentration of glucose in the nervous tissue compared to the initial data, thus increasing the efficiency of its functioning [18]. In addition, the efficacy of a course glycine administration in dyscirculatory encephalopathy has been proved; both the improvement of microcirculatory processes, the improvement of the cognitive component, and a reduction of anxiety and emotional lability were observed [19].

However, until recently, no direct effect of the drug administration on cerebral vessels has been shown. In this regard, the dilating effect of glycine on human cerebral vessels has been investigated in this work. To study this phenomenon, the effect of the sublingual glycine administration on hemodynamic parameters of the cerebral blood flow in practically healthy people was analyzed using TCD sonography.

THE AIM of the work was to analyze the effect of a sublingual administration of glycine on the cerebral blood flow velocity in practically healthy subjects using TCD sonography.

MATERIALS AND METHODS

Study design

This pilot randomized controlled trial included 20 practically healthy subjects aged 25 to 65 years. The study was conducted between August and November 2022 at the Institute of Cytochemistry and Molecular

ОРИГИНАЛЬНАЯ СТАТЬЯ
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Pharmacology (Moscow) in accordance with the Declaration of Helsinki and was approved by the Local Ethical Committee (Protocol No. 3 dated 04 July 2022). All participants signed an informed consent for the participation prior to the inclusion in the study.

Eligibility criteria

The *inclusion criteria* were: men and women aged 25 to 65 years who had the possibility of the blood flow visualizing through the left and right middle cerebral artery (MCA) through the transtemporal window was confirmed at the entrance ultrasound. The inclusion *criteria* were as follows: presence of chronic diseases of cardiovascular system and any other diseases in the exacerbation stage; reduction of cerebral blood flow through the main vessels by more than 20% of the age norm established at the entrance examination; previously established hypersensitivity to glycine; taking glycine and other nootropic drugs within a month before the study; pregnancy, breastfeeding period; patient's refusal to participate in the study. *Exclusion criteria*: none of the patients was excluded from the study.

Description of medical intervention

Initially, all the patients included in the study underwent a clinical examination, which comprised an assessment of the anamnestic data: a general condition of the subject, heredity, past diseases, the presence of chronic diseases; and an entrance ultrasound of the main head vessels at extra- and intracranial levels on a Mindray DC-80 device using a linear transducer L12-3E (3.0–13.5 MHz), a convex transducer C5-1E (1.3–6.0 MHz), a sectorial transducer Sp5-1E (1.0–5.0 MHz): an assessment of blood flow parameters of the carotid and vertebrobasilar insufficiency: a common carotid artery (CCA), an external carotid artery (ECA), an internal carotid artery (ICA) and a vertebral artery (VA), a middle cerebral artery (MCA), an anterior cerebral artery (ACA) and a posterior cerebral artery (PCA).

Then the patients were randomized by random number generation into two groups of 10 people each. The first group (Group I, *n*=10) took glycine, 100 mg sublingual tablets, for 30 days, 1 tablet 3 times daily. In Group I, the loading testing was performed with 1000 mg of glycine (10 tablets of 100 mg). In the control group (Group II, *n*=10), the loading test was performed with 1000 mg placebo (10 tablets containing 100 mg lactose and 0.1 mg sucralose to mimic the sweet taste of glycine); the subjects had not taken the study drug until the blood flow was reassessed. The duration of the follow-up in both groups was 30 days.

Each subject underwent 4 transcranial blood flow measurements in the MCA, ACA, and PCA at 5-minute intervals to level out individual baseline variability. The study determined the linear peak systolic (PS), end-diastolic (ED), and time-averaged maximum blood flow velocity (Time Averaged Maximum Velocity — TAMAX), a pulsatility index (PI), a peripheral resistance index (RI), and a systolic / diastolic ratio (S/D) in the MCA, ACA, and PCA in each of the patients. The flow correction angle corresponded to the direction of the vessel and was maintained in subsequent measurements.

Then the patient sublingually took 1000 mg of glycine (Group I) or 1000 mg of placebo (Group II), after which the values in the indicated arteries were taken after 5, 10, and 15 min (Fig. 1). This dose is safe and recommended[1] for a single administration in acute cerebral circulatory disorders (including those suspected to occur). Thus, the possible dilative effect of glycine on cerebral vessels in practically healthy subjects was evaluated. Subsequently, the subjects took glycine (Group I) for 30 days 3 times a day in a dosage of 100 mg (a total daily dose was 300 mg), or took nothing (Group II). At the end of the drug course, a follow-up study including the blood flow measurement in the intracranial arteries at rest, was performed. For a quantitative comparison of hemodynamic effects, a transcranial assessment of the blood flow in the MCA was chosen, since this artery is a direct continuation of the ICA and supplies a significant part of the brain. In accordance with the study design, each patient underwent multiple measurements of flow values at rest, which makes it possible to compare the effects of a glycine administration course on the blood flow parameters with the control group, as well as to evaluate the response of the cerebral arteries to a high dose compared to placebo.

Statistical processing

Statistica 10 program (Statsoft, USA) was used for statistical data processing. The studied features could not be normally distributed, therefore the quantitative data are presented in the form of Me [Q25; Q75], where Me – median, Q25 – lower quartile, Q75 – upper quartile; nominal and categorical data – *n* (%), where *n* – absolute value, % – relative frequency of occurrence. To assess the statistical significance of differences between the quantitative data, the Mann-

[1] Registration certificate for glycine. Russian State Register of Medicines. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=c73870d4-a6c3-41d5-aa4e-393b4a099a62

Whitney *U*-test (for independent samples) and the Wilcoxon test (for dependent samples) were used. The Fisher's exact test and the Pearson's χ^2 test were used to compare the fractions (frequencies). The nonparametric Spearman's correlation coefficient was used to assess the relationship between the signs. The results were considered statistically significant at the p <0.05.

RESULTS

Study participants

Twenty practically healthy subjects aged 27 to 46 years were included in the study. The clinical and demographic data of the volunteers are presented in Table 1. The gender and age characteristics and the number of patients with a reported history of vascular diseases did not differ significantly between the study groups.

Main study results

The evaluation of the blood flow through the main head and neck vessels revealed no significant differences between the groups (Table 2). However, in group II, the systolic velocity was slightly higher than in group I. In general, the values of indices corresponded to the age norms [10] with insignificant differences in linear velocities on the left and right.

The initial transcranial assessment of the blood flow parameters in the MCA revealed significant differences between the left and right flows, but their values were within the physiologic range. In eight subjects, the linear peak systolic, end-diastolic, and mean maximum velocities were significantly greater on the left, in four subjects on the right, and in eight subjects, the differences were nonsignificant. In the overall statistical evaluation, the values of the indices on the right were significantly smaller (p <0.05), and this trend was maintained at the second measurement (Table 3). The asymmetry of the cerebral bolod flow up to 20% is considered physiologically acceptable and can be explained by both a functional asymmetry of the cerebral hemispheres and morphological features of the paired vessels [20].

Despite the similar characteristics of the two groups, baseline blood flow values in the MCA differed significantly between the groups, and they were lower in group I (PS on the left and right, p <0.01; TAMAX on the left and right, p <0.01; ED on the right, p <0.05). Due to the asymmetry detected, the left and right flow values were further analyzed independently. After one month of the glycine administration (in group I), there was a significant increase in velocities on the left and right (medians of both velocity values and increases in each measurement were evaluated) (Fig. 2). It was shown that peak systolic (by 11.9 cm/s) and mean maximum (by 6.3 cm/s) velocities increased on the left, while peak systolic (by 9.3 cm/s), end-diastolic (by 2.8 cm/s), and mean maximum (by 5.8 cm/s) velocities increased on the right (Table 3). In group II, there were no significant changes on the right side, with significant decreases in end-diastolic (by -2.8 cm/s, p <0.05) and mean maximum (by -2.7 cm/s, p <0.05) velocities on the left. The average increase in the peak systolic velocity was 10% after 30 days of the glycine administration and -2% in group I, the relative increase in one subject could be as high as 40%. It is important that in both groups, the blood flow indices after the change were within the physiologic range [10].

To assess the baseline blood flow in the 1000 mg glycine / placebo sample, the mean value on the left and right of 4 measurements during 15 min of lying at rest was calculated for each subject. The mean change in the flow relative to this value was then calculated 5, 10, and 15 min after the drug administration. In the glycine / placebo trial, the relative increase in the peak systolic velocity was 7.6% [1.2; 10.8] in group I and 1.5% [-3.6; 5.5] in group II (the significance level of differences between groups p=0.03). The mean peak velocity increased by 9.6% [0.6; 15.7] in group I and by 3.0% [-2.5; 8.0] in group II (the significance level of differences between groups p=0.08). The relative changes of the peak systolic blood flow velocity in the left and right middle cerebral artery are presented in Fig. 3.

It was found out that the baseline mean in group I was below the overall mean (for all subjects), -5.4% [-20.0; 7.0], and in group II, it was above 10.7% [-5.1; 18.0]; p <0.05. The changes were multidirectional in different patients, but the maximum deviations in group I were observed at 5 and 10 min, whereas in group II they were erratic. A significant correlation (p <0.05) was found out between the increase in velocity and the deviation of the individual baseline velocity value from the group mean (for PS r=0.68, p <0.05; for TAMAX r=0.73, p <0.05). In other words, the changes were aimed at correcting deviations from the physiological norm, and the magnitude of the changes was greater the more deviated the values were.

None of the study participants had adverse events (including allergic reactions and intolerance) associated with a sublingual administration of glycine 100 mg three times a day for 30 days, as well as a single intake of 1000 mg, which confirms a good tolerability of this drug in the indicated doses.

ОРИГИНАЛЬНАЯ СТАТЬЯ
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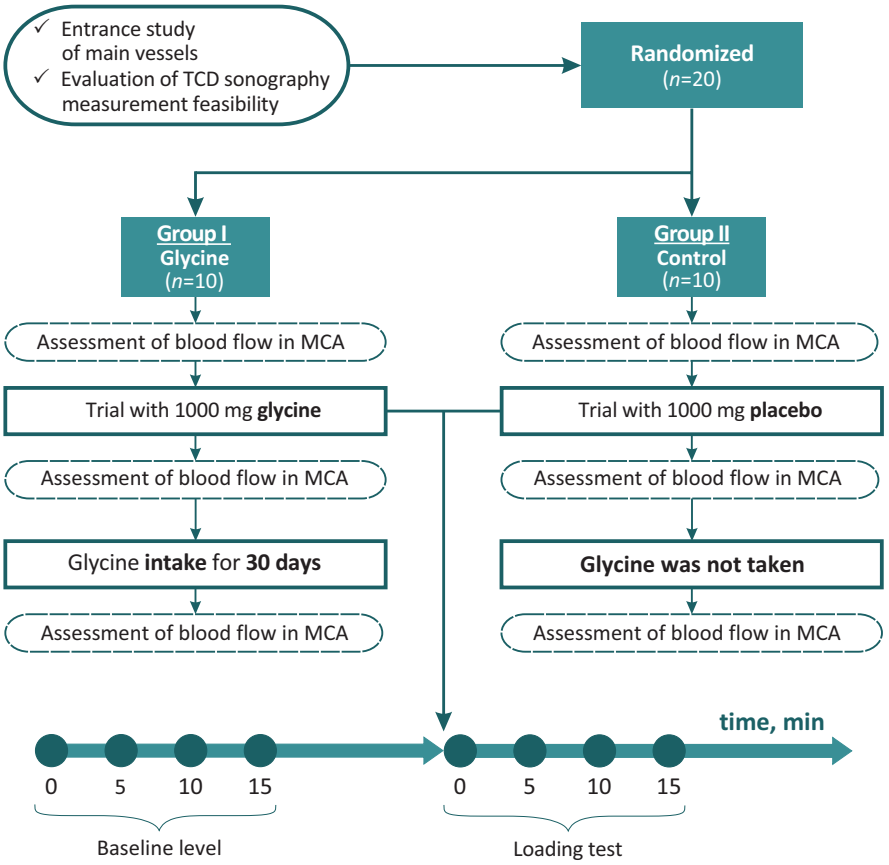

Figure 1 – Study design
Note: TCD sonography – transcranial Doppler sonography; MCA – middle cerebral artery.

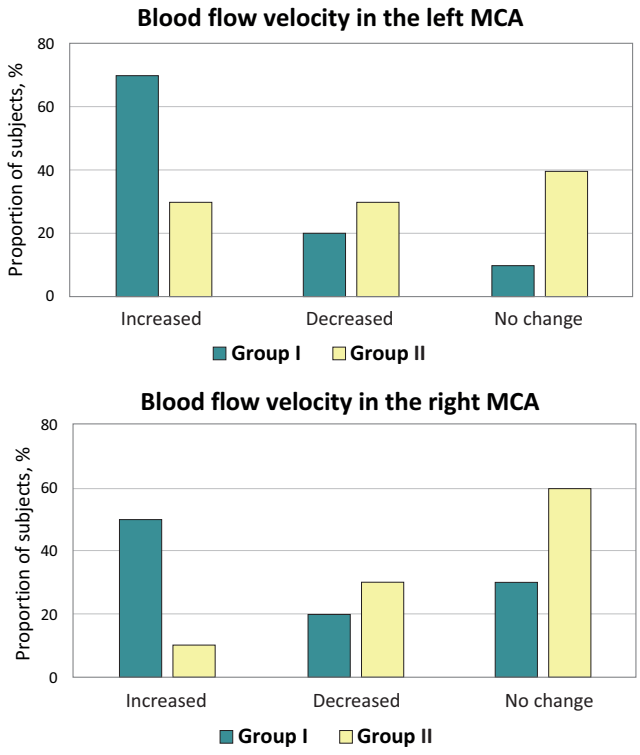

Figure 2 – Dynamics of peak systolic blood flow velocity in the left and right middle cerebral artery at transcranial examination 30 days after the start of the study in both groups
Note: MCA – middle cerebral artery. The observed differences between groups in the blood flow velocity changes on the left (p=0.02) and right (p <0.001) are statistically significant.

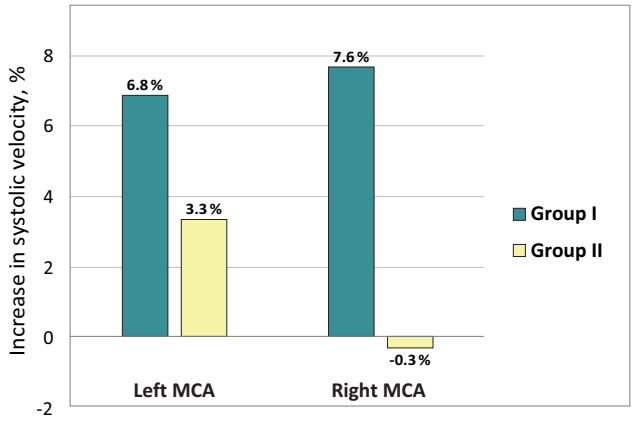

Figure 3 – Relative changes in peak systolic blood flow velocity in the left (*p*=0.24) and right (*p*=0.09) middle cerebral artery at transcranial examination after 1000 mg glycine or placebo administration

Note: MCA – middle cerebral artery.

Table 1 – Clinical and demographic characteristics of participants

Group		Group I (*n*=10)	Group II (*n*=10)	*p*
Age, years, Me [Q25; Q75]		35.5 [32; 43]	38.5 [33; 42]	0.496[1]
Gender, *n* (%):				
	Male	4 (40%)	4 (40%)	1,000[2]
	Female	6 (60%)	6 (60%)	
Atherosclerosis, *n* (%):				
	no	8 (80%)	6 (60%)	0,629[2]
	yes	2 (20%)	4 (40%)	
Migraine, *n* (%):				
	no	8 (80%)	9 (90%)	1,000[2]
	yes	2 (20%)	1 (10%)	
Arterial hypertension, *n* (%):				
	no	7 (70%)	9 (90%)	0,582[2]
	yes	3 (30%)	1 (10%)	

Note: To assess the statistical significance of differences in quantitative data, the authors used: [1] – Mann-Whitney *U*-criterion, [2] – Fisher's exact test. The differences between the groups by the presented characteristics are statistically insignificant (*p* >0.05).

Table 2 – Baseline peak systolic (PS) blood flow velocities through the main head and neck vessels in both groups

Artery		Peak systolic blood flow velocity (PS), cm/s		p
		Group I, Me [Q25; Q75]	Group II, Me [Q25; Q75]	
CCA, (norm is 50-169 cm/s)	Left	92.6 [83.7; 116.1]	103.7 [96.7; 117.8]	0.39
	Right	90.2 [73.7; 118.3]	95.6 [72.5; 103.8]	0.92
ECA, (norm is 45–136 cm/s)	Left	84.1 [78.6; 94.0]	106.2 [85.1; 118.5]	0.10
	Right	101.9 [73.4; 114.1]	109.8 [95.4; 119.3]	0.92
ICA, (norm is 36–115 cm/s)	Left	79.9 [64.5; 103.3]	88.5 [80.8; 117.0]	0.25
	Right	84.1 [67.2; 103.6]	91.4 [83.1; 115.5]	0.28
VA, (norm is 28–71 cm/s)	Left	47.2 [36.9; 53.8]	47.4 [42.3; 58.7]	0.76
	Right	38.5 [34.6; 50.1]	48.1 [43.7; 51.4]	0.13

Note: CCA – common carotid artery; ECA – external carotid artery; ICA – internal carotid artery; VA – vertebral artery. The Mann-Whitney *U*-criterion was used to assess the statistical significance of differences between the groups. Physiologic norms of velocities are given for persons of a corresponding average age (35±12 years) [10]. The values of velocities in each of the arteries in two groups were not statistically different (*p* >0.05).

ОРИГИНАЛЬНАЯ СТАТЬЯ
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Table 3 – Linear peak systolic (PS) blood flow velocities in the left and right middle cerebral artery at transcranial examination in both groups

Arter	Group I, Me [Q25; Q75]				Group II, Me [Q25; Q75]				$p^0_{I–II}$
	Day 0	Day 30	$p^{0–30}$	Δ	Day 0	Day 30	$p^{0–30}$	Δ	
Peak systolic blood flow velocity (PS), cm/sec									
Left	104.6 [93.9; 117.1]	112.2 [105.3; 120.6]	<0.001[2]	11.9 [-5.9; 18.4]	117.7 [106.2; 124.7]	114.1 [99.5; 127.0]	0.44[2]	-4.8 [-11.6; 9.2]	0.001[1]
Right	99.8 [86.0; 110.4]	104.3 [97.0; 116.5]	<0.001[2]	9.3 [-3.7; 19.8]	108.8 [97.0; 119.7]	110.8 [94.0; 119.1]	0.54[2]	-3.9 [-9.8; 7.8]	0.002[1]
End diastolic blood flow velocity (ED) cm/sec									
Left	45.6 [41.5; 5.9]	48.5 [44.2; 53.1]	0.22[2]	1.1 [-4.2; 6.4]	49.6 [45.3; 54.9]	46.8 [43.2; 52.3]	0.02[2]	-2.8 [-7.2; 3.8]	0.09[1]
Right	43.4 [37.9; 48.3]	45.6 [41.1; 50.1]	0.01[2]	2.8 [-3.0; 6.3]	46.4 [42.2; 50.6]	46.3 [40.2; 51.1]	0.61[2]	-1.5 [-6.1; 4.0]	<0.05[1]
Time average maximum blood flow velocity (TAMAX), cm/sec									
Left	69.3 [63.1; 79.3]	75.6 [70.1; 82.5]	<0.001[2]	6.3 [-3.9; 13.6]	80.0 [68.6; 86.9]	74.2 [65.4; 86.2]	0.04[2]	-2.7 [-8.1; 4.3]	0.008[1]
Right	65.4 [59.8; 76.6]	73.3 [66.6; 79.0]	<0.001[2]	5.8 [-2.7; 12.9]	72.7 [64.1; 81.0]	73.7 [62.9; 80.1]	0.52[2]	-3.2 [-7.7; 5.4]	0.007[1]

Note: To assess the statistical significance of differences in quantitative data the authors used: [1] – Mann-Whitney *U*-criterion; [2] – Wilcoxon test. $p^{0–30}$ – significance level for the difference between the value of the indices on day 0 and day 30 in the group; $p^0_{I–II}$ – significance level for the difference between the value of the index on day 0 in both groups. The results were considered statistically significant at p <0.05.

DISCUSSION

One of the critical factors for an adequate brain function is to maintain an adequate blood supply to meet changing metabolic demands, but off the linear dependence on the systemic blood pressure [21]. Both acute and chronic kinds of cerebral ischemia are common causes of a reduced work capacity, disability and mortality of the population [22, 23].

In the brain tissue under a chronic hypoperfusion, as well as an ischemia-reperfusion, there is inevitably an imbalance of metabolic processes, antioxidant defense systems, and, as a consequence, neurotransmission disorders, a decreased neuroplasticity, the deterioration of the cognitive status and the one of the general functional status [4]. Asymptomatic or accompanied by mild cognitive decline cerebral vascular disorders are usually poorly diagnosed due to the absence of patient complaints. However, in such conditions as an arterial hypertension, atherosclerosis, diabetes mellitus, and in the presence of additional risk factors such as hypodynamia, obesity, and smoking, a cerebral circulation control is one of the most important aspects of a stroke and dementia prevention [6, 24].

Neuroprotective metabolic drugs are widely used in vascular cognitive disorders, because they have not only a nootropic effect, but also contribute to the normalization of the neuronal energy supply, exhibit antioxidant and antihypoxant properties, gently correct cerebral hemodynamic disorders [11]. One of such drugs is glycine, which has been used for more than 30 years both in severe neurological conditions and in practically healthy people for the correction of behavioral and vascular disorders, a reduction of anxiety and psychoemotional stress, an improvement of cognitive abilities [15, 19, 25, 26]. The wide range of pharmacological properties of the drug is due to the participation of this amino acid in a huge number of biochemical processes, as well as its unique neurotransmitter characteristics: an interaction with inhibitory glycine (GlyR), excitatory glutamate (NMDA-R) and metabotropic (mGlyR) receptors [13, 27].

In the present study, the effect of glycine on the state of cerebral vessels using the ultrasound was confirmed. TCD sonography is a sufficiently accurate, reproducible noninvasive method of assessing blood flow velocity parameters, as well as the reactivity of cerebral vessels [28, 29].

The course sublingual glycine administration to relatively healthy volunteers for 30 days resulted in a significant increase in the linear blood flow parameters in the intracranial vessels. The change of velocity in some subjects reached 40%, and the maximum values of the increase were observed at initially lowered indices or an expressed interhemispheric asymmetry. In group II, the input velocity values were higher than in group I, despite the fact that the hemodynamic parameters for the cerebral main vessels obtained before the randomization, did not differ. A significant interhemispheric flow asymmetry was found in more than half of the subjects, and despite individual differences, the values on the right side were significantly lower for all participants. This phenomenon may be mediated by the left carotid artery branching directly from the aortic arch and has also been repeatedly shown in animals [1]. It

is interesting that the blood flow in the right half of the brain turned out to be more stable during the study both after the glycine administration and in the control group, where after 30 days small but significant decreases in velocities on the left side were recorded. The volumetric blood flow velocity characterizes the blood filling of an organ quite completely, it depends both on the linear velocity in the vessel and on its diameter. However, due to the difficulty in estimating intracranial vessel diameters and their low variability under physiological conditions, the linear velocities are usually chosen as hemodynamic parameters [3]. Herewith, patients with different vessel calibers may have different levels of the blood flow at the same values of linear velocities. In the future, a more detailed study of the relationship between a cerebral blood flow and a functional activity of the brain, including under the influence of drugs both in the norm and in various pathological conditions, may be of scientific and clinical interest.

Nevertheless, an increase in the blood flow velocities through cerebral arteries within the physiological norms definitely indicates an increase in the nervous tissue perfusion and can be regarded as a factor in expanding the range of the brain functional activity. Since the course of the glycine administration led to an increase in the MCA indices, it can be recommended both for a mild and moderate cognitive decline and during periods of a high mental stress to maintain an adequate brain functioning.

The administration of 1000 mg of glycine as a lump sum is recommended in the first day in the therapy of an ischemic stroke and other acute cerebral accidents, as well as in a suspected acute cerebral circulatory failure [15]. The study of the MCA velocity indices after an acute test with 1000 mg of glycine or placebo allowed us to evaluate the effect of a high dose of the drug on the cerebral blood flow in practically healthy subjects. It was shown that a single administration of 1000 mg of glycine caused a short-term significant increase in the MCA linear velocities up to 10%. At the same time, the change degree was proportional to the initial deviation from the mean age-related norm: the greatest effect was observed in the case of a significant deviation of the indices. However, it is obvious that such a dilatation can occur only with a preserved vascular reactivity, the assessment of which is also of interest in a further study of the described effects on a larger sample of patients. Thus, a prophylactic administration of 1000 mg of glycine to patients with a suspected stroke is safe and can be recommended because it does not lead to critical changes in the blood flow in case of preserved intracranial hemodynamics.

Study Limitations

According to the authors, the limitation of the study may be a relatively small sample size, so some of the results obtained could not be confirmed by statistical methods, and the analysis of the cerebral blood flow parameters was carried out in men and women in the aggregate. In addition, the effects of glycine described in this work were observed in conditionally healthy individuals, without taking into account the possible influence of possible cardiovascular diseases on the cerebral blood flow parameters. The study of the described effects on large groups of patients, including those with various vascular pathologies, will be of practical interest from the point of view of understanding the revealed regularities.

CONCLUSION

Thus, in this study, the effect of a sublingual glycine administration on the cerebral hemodynamic parameters was studied using TCDG. It is shown that a course administration of glycine leads to a reliable improvement of the intracranial blood flow in comparison with the control group. Thus, a sublingual administration of 100 mg of glycine 3 times a day for 30 days contributed to a significant change in cerebral hemodynamics. Although the trends were multidirectional, there were many more patients in group I in whom the MCA linear blood flow velocities increased compared with group II, where the values were unchanged or decreased. In addition, a short-term significant increase in the peak systolic and mean maximal intracranial blood flow velocities up to 10% was observed after a single 1000 mg dose of glycine, whereas no effect of this kind was observed after placebo.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ОРИГИНАЛЬНАЯ СТАТЬЯ
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AUTHORS' CONTRIBUTION

Elena V. Mashkovtseva – development of the study design and article concept, statistical processing of the results, writing the main text of the manuscript; Natalia A. Rudnikova – conducting ultrasound studies, editing the article; Veronika S. Kopylova – processing the ultrasound data, editing the article text; Yaroslav R. Nartsissov – participation in the development of the study design and article concept, approval of the final manuscript.

All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

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