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Pharmacological characteristics of intranasal dosage forms containing Ginkgo biloba extracts

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Abstract

Background: This article reviews the pharmacological characteristics of developed dosage forms for intranasal administration. The influence of the type of dosage form on the efficacy of the drug is significant. Gel-like structures are interesting objects for research. Interest in understanding the nature and properties of such structures is due to the variety of effects observed when gels are used. The active ingredient in the studied forms is ginkgo biloba extract obtained by ultrasonic extraction followed by thickening. The object of comparison is standardized dried ginkgo biloba extract (EGB 76). The study of cerebrotropic activity of the developed gels was conducted on the model of bilateral occlusion of the common carotid arteries. The studied objects and the reference preparation were administered therapeutically after modeling cerebral ischemia once a day for 3 weeks. **Aim of the study:** To evaluate specific pharmacological activity of the developed dosage forms of ginkgo biloba. **Materials and Methods:** Studies were performed in an appropriate design by simulating cerebral ischaemia in rabbits using simultaneous bilateral occlusion of the common carotid arteries. Changes in cerebral blood flow velocity were performed by Doppler using an appropriate transducer and software package. The data obtained were statistically processed using an application software package. **Results:** Conducted investigations revealed that under conditions of experimental cerebral ischemia simulated by simultaneous occlusion of the common carotid arteries in large laboratory animals (rabbits), the use of the developed dosage forms promoted the reduction of the severity of neurological deficit, the restoration of cerebral hemodynamics and pro/antioxidant balance in the hippocampus. **Conclusions:** Developed nasal gels based on chitosan and sodium alginate are promising agents for chronic cerebrovascular accident with antioxidant mechanism of action and therapeutic potential similar to oral administration of standardized ginkgo biloba extract – EGB 761.

Key words: intranasal dosage forms; ginkgo biloba extract; cerebrotropic activity

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Introduction. The impact of dosage forms as one of the basic building blocks of biopharmacy is now increasingly seen in relation to efficacy and safety of medicines. The range of dosage forms today is very broad. It ranges from the traditional group, led by the classic tablet, to more recent generations of dosage forms and innovative dosage forms that include delivery agents. However, even within this considerable list, there are areas of priority. These include the intranasal route of administration and, accordingly, intranasal dosage forms. At present, the choice for this group is still limited, primarily in terms of research subjects, of which there are many and their pharmacological areas are quite large, but the effectiveness of research is low, and the transfer of relevant developments into production is extremely rare. This is due to the complexity of creating rational nasal dosage forms, developing appropriate adjuvant compositions and, of course, solving questions about research models, due to the peculiarities of the application surface. As a model we chose one of the well-known and sought-after medicines – Ginkgo biloba, which has undoubted cerebrotropic activity. It is known that the Ginkgo biloba phytocomplex reduces capillary permeability, activates blood circulation, first of all, at the level of arterioles and capillaries, increases venous tone. However, the range of dosage forms of this object is represented rather narrowly; for the most part these are solid dosage forms and, what is important, mostly by preparations of foreign origin. In this regard, it was decided to use the drops and gel as the studied dosage forms, presented in 2 variants, as different gel formers were considered. Thus, studies regarding the pharmacological activity of developed specific models of intranasal forms – drops and gel based on Ginkgo biloba are quite relevant and appropriate [1, 2, 3].

Materials and methods. Experimental animals.

The assessment of the specific pharmacological activity of the developed dosage forms of Ginkgo biloba was performed on 24 male Californian rabbits weighing 2.5-3.0 kg, obtained from the laboratory animal nursery "Rappolovo" (Leningrad Region). The standardized extract of Ginkgo biloba (EGB 761), obtained from Hunan Warrant Pharmaceuticals (PRC), was used as a comparison drug. The analyzed dosage forms were drops, sodium alginate-based gel, and chitosan-based gel with the Ginkgo biloba phytocomplex obtained by ultrasonic extraction. [4]. Before the study, the animals were kept in quarantine conditions for 14 days. During the direct conduct of the experiment, the rabbits were kept in a vivarium under controlled climatic conditions: at an air temperature of 20 ± 2 °C, a relative humidity of $60 \pm 5\%$ and a 12-hour change of the daily cycle in mesh metal cages equipped with a drip drinker and a feed supply tank. The number of species in one cell was four. The animals' access to food and water was not restricted. The experimental procedures and the keeping of animals corresponded to the generally accepted principles of the international ethical principles of working with laboratory animals, set out in ARRIVE 2.0 [4].

Study design (Fig. 1): The study of the cerebrotropic activity of the developed dosage forms of Ginkgo biloba was carried out on a model of bilateral occlusion of the common carotid arteries. The standardized extract of Ginkgo biloba (EGB 761), obtained from Hunan Warrant Pharmaceuticals (PRC), was used as a comparison drug. The studied dosage forms and the reference drug were administered in a therapeutic mode after modeling brain ischemia once a day for 3 weeks. The comparison drug was administered orally at a dose of 35 mg/kg [5], the analyzed dosage forms (drops, a gel based on sodium alginate and a gel based on chitosan) were administered

intranasally at a dose equivalent to the reference drug, calculated in such a way that one drop and one dose of the gel contained 35 mg/kg of the extract obtained by us. The comparison drug was administered orally at a dose of 35 mg/kg [5, 6], the analyzed dosage forms (drops, sodium alginate-based gel and chitosan-based gel) were administered intranasally at a dose equivalent to that of the compar-

ison drug. During the study, changes in neurological deficits were determined according to the McGraw scale (the initial indicator, as well as that on the 3rd, 7th, 14th and 21st days of the experiment), the average systolic velocity of cerebral blood flow (on the 3rd, 7th, 14th and 21st days of the experiment) and the pro/antioxidant balance in the hippocampus (on the 21st day of the study).

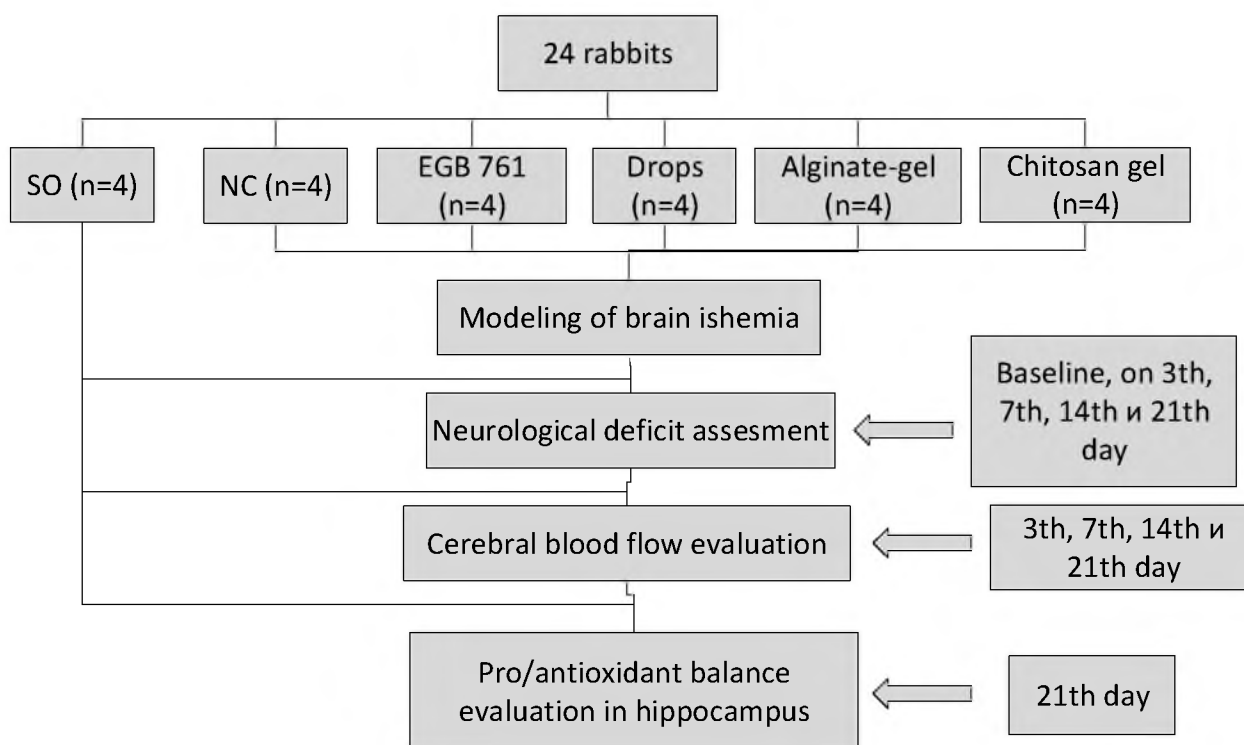


Fig. 1. Study design. SO – sham-operate animals, NC – negative control animals

Experimental modeling of brain ischemia

Cerebral ischemia was modeled in rabbits by simultaneous bilateral occlusion of the common carotid arteries. The animals were anesthetized by chloral hydrate 350 mg/kg, intraperitoneally. Their skin area on the neck near the trachea was depilated. Then, an incision of the skin was made and soft tissues were dissected, exposing the carotid arteries. A silk thread was placed under the arteries and tied at the same time. The topography of soft tissues was restored, the wound was sutured and

treated with an antiseptic solution (povidone-iodine 10%) [7].

Methods for assessing neurological deficits.

The McGraw psychometric scale was used to assess the degree of development of neurological deficits. The estimated indicators are presented in Table 1. According to this scale, the sum of points 0.5-2.0 corresponds to a mild degree of neurological deficit; 2.5-5.0 – to moderate severity; 5.5-10 – to severe neurological deficit. The neurological deficit was defined by the sum of the corresponding points [8].

Table 1

McGraw neurological deficit assessment scale

Parameter	Score
Lethargy	0.5
Tremor	1
Unilateral semitosis	1
Bilateral semitosis	1.5
Inability to pull back a limb while holding it	1.5
Unilateral ptosis	1.5
Bilateral ptosis	1.5
Short movements	2.0
Paresis of 1-4 limbs	2-5
Paralysis of 1-4 limbs	3-6
Coma	7.0
Mortality rate	10.0

Methods for assessing changes in the speed of local cerebral blood flow

The speed of cerebral blood flow was measured by the Doppler method using the ultrasound Doppler system sensor UZOP-010-01 with an operating frequency of 25 MHz and the MM-D-K-Minimax Doppler v. 2. 1 software package (“Minimax”, St. Petersburg, Russia). The registration of changes in cerebral hemodynamics was carried out in the middle cerebral artery circulation. For this, a burr hole was made in this area with a boron, the dura mater was removed and a sensor was installed. The contact gel “UNIAGEL” was used as a sound-conducting medium. After recording the blood flow level, the integrity of the cranial box was restored with a polycarboxylate polymer [7].

Preparation of biological material for the assessment of changes in the pro/antioxidant balance

Changes in the pro / antioxidant balance were evaluated in the hippocampus of experimental animals, for which the rabbits were decapitated under chloral hydrate anesthesia and the brain was extracted. Then, the hippocampus was separated and was homogenized in a Tris-HCl buffer with pH= 7.4. The obtained homogenate was centrifuged at 1000g for 10 min. The supernatant was removed for analysis.

Methods for assessing changes in the pro/antioxidant balance

Determination of the activity of superoxide dismutase (SOD). The activity of SOD was

evaluated in the post-nuclear fraction by inhibiting the formation of nitrotetrazolium chloride (NTH) formazane. NTH was used as an indicator of the formation of a superoxide anion. For the production of O₂ a system containing a solution of riboflavin (2.8*10⁻⁵ M), TMED – Tetramethylethylenediamine (0.01 M in a 0.05 M phosphate buffer pH 7.8) was used when irradiated with a daylight lamp for 5 minutes. The reaction was terminated by adding a 20% solution of TCA (trichloroacetic acid) and acetone. The optical density was recorded on CPK-3 at 440 nm. The activity of SOD was expressed in units/ mg of protein [8]. The protein content was determined in the reaction with the dye Coomassie Brilliant Blue G-250 [9].

Determination of the concentration of TBA (2-thiobarbituric acid)-active products. The concentration of TBA-active products (TBA-AP) was determined by the thiobarbituric method. The method is based on the formation of a colored complex with an absorption maximum at 532 nm. The protein was precipitated by adding a 17% solution of TCA. The measurement of extinction of the colored complex of malondialdehyde with thiobarbituric acid (0.8% solution) was made by using a PE-8000 spectrophotometer at a wavelength of 532 nm and expressed in micromol/ mg of protein [10].

Determination of the reduced glutathione (GHS) concentration. The concentration of reduced glutathione was determined by a spectrophotometric method based on the oxidation reaction of glutathione with a sulfhydryl

reagent of 5.5' – dithio-bis-2-nitrobenzoic acid with formation of 5'-thio-2-nitrobenzoic acid, colored yellow. The optical density was recorded at 412 nm [11].

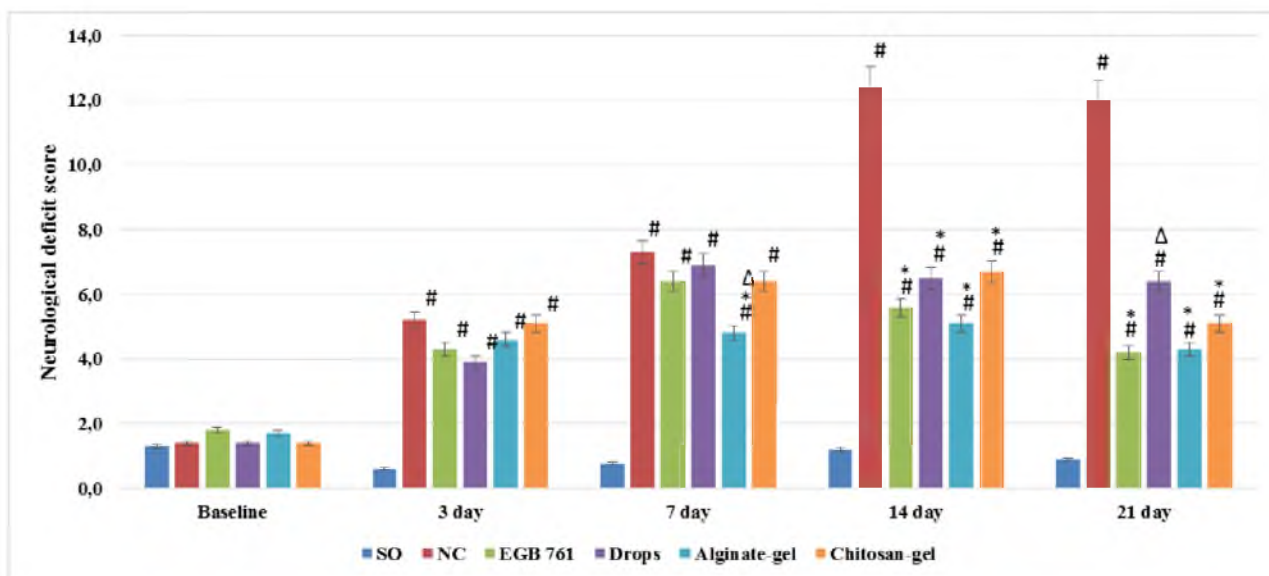
Statistical methods. The data obtained during the study were subjected to statistical processing by using the STATISTICA 6.0 application software package (StatSoft, USA) and MS Excel 10 for the Windows operating system. The average value (median value) and the standard error of the average were calculated, the data were presented in the form of $M \pm m$. The obtained results were subjected to a test for the normality of the distribution (the Shapiro-Wilk criterion). If the data obeyed the law of normal distribution, ANOVA with the Tukey post-test was used to compare the averages. Otherwise the statistic processing of the experimental results was carried out by using the Kruskal-Wallis criterion.

Results

The influence of the studied dosage forms and the referent on the change of

neurological deficit in animals under conditions of cerebral ischemia.

When analyzing the changes in neurological deficit in rabbits under conditions of brain ischemia, it was found that after occlusion of the common carotid arteries in animals of the NC group, the neurological deficit on the 3rd day of the study was 8.5 times ($p < 0.05$) higher compared to the SO group of rabbits. Subsequently, on the 7th, 14th and 21st days of the experiment, the neurological deficit in the NC group of animals was higher than that in the SO group of rabbits by 9.4 ($p < 0.05$); 10.3 ($p < 0.05$) and 13.3 ($p < 0.05$) times respectively (Fig. 2). The use of EGB 761 contributed to a decrease in the degree of neurological deficit compared to the NC group of animals on the 14th and 21st days of the study by 54.8% ($p < 0.05$) and 65.0% ($p < 0.05$) respectively, while the indicators of the 3rd and 7th days in rabbits treated with EGB 761 did not significantly differ from those in the NC group of animals.



Note: SO - sham-operate animals, NC – negative control animals. The figure shows the median value; # - is statistically significant relative to SO animals (Kruskall-Wallis criterion, $p < 0.05$); * - is statistically significant relative to the NC group of animals (Kruskall-Wallis criterion, $p < 0.05$); Δ - is statistically significant relative to animals treated with EGB 761 (Kruskall-Wallis criterion, $p < 0.05$).

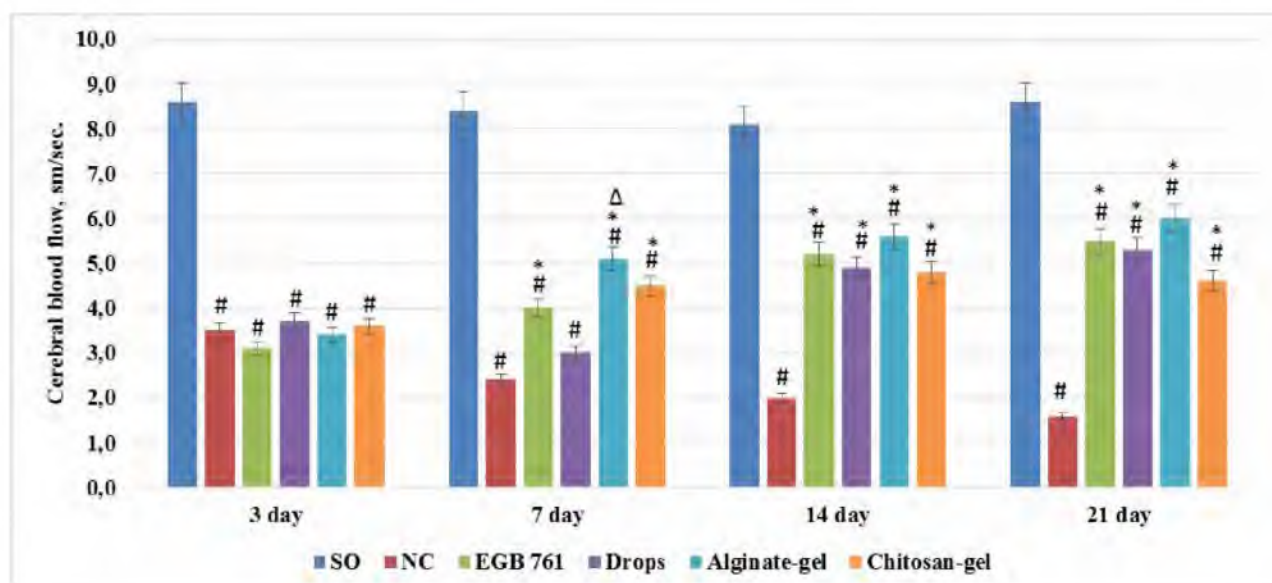
Fig. 2. The effect of the developed dosage forms and the comparison drug on the change of neurological deficit in rabbits under conditions of brain ischemia

Against the background of the injection of the developed nasal drops, there was a decrease (in comparison with the NC group of animals) in neurological symptoms in rabbits

on the 14th and 21st days of the experiment by 47.6% ($p < 0.05$) and 45.8% ($p < 0.05$), respectively. When using the studied nasal gel based on sodium alginate, the neurological deficit in

animals decreased compared to the NC group of rabbits on the 7th day of the study by 34.2% ($p < 0.05$); on the 14th day – by 58.9% ($p < 0.05$) and on the 21st day – by 54.2% ($p < 0.05$). It should be noted that in animals receiving the developed sodium alginate gel, the neurological deficit on the 7th day of the experiment was

lower than that in rabbits injected with EGB 761 by 25.2% ($p < 0.05$). The injection of a chitosan-based gel helped to reduce the severity of neurological deficit compared to the NC group of animals on the 14th and 21st days of the study by 46% ($p < 0.05$) and 57.5% ($p < 0.05$), respectively (Fig. 2).



Note: SO - sham-operate animals, NC – negative control animals # - is statistically significant relative to the SO group of animals (Tukey criterion, $p < 0.05$); * - is statistically significant relative to the NC group of animals (Tukey criterion, $p < 0.05$); Δ - is statistically significant relative to animals treated with EGB 761 (Tukey criterion, $p < 0.05$).

Fig. 3. The influence of the developed dosage forms and the comparison drug on the change in the speed of cerebral blood flow in rabbits under conditions of cerebral ischemia

The effect of the studied dosage forms and the referent on the change in the rate of cerebral blood flow in animals under conditions of cerebral ischemia.

After modeling brain ischemia on the 3rd day of the experiment, the NC group of animals, as well as rabbits that received the reference drug, the studied nasal drops, sodium alginate based gel and chitosan based gel, showed an almost equivalent decrease in the level of cerebral blood flow compared to SO animals by 59.3% ($p < 0.05$); 63.6% ($p < 0.05$); 59.6% ($p < 0.05$) 60.4% ($p < 0.05$) and 58.1% ($p < 0.05$), respectively. This allows an identical course of the ischemic process in all experimental groups. Then, a progressive deterioration of cerebral hemodynamics was noted in the animals of the NC group, which is evidenced by a decrease in the rate of cerebral blood flow in this group of rabbits compared to SO animals on the 7th, 14th and 21st days of the

experiment by 71.4% ($p < 0.05$), 75.3% and 81.4% ($p < 0.05$), respectively (Fig. 3). Against the background of injection of EGB761 to the rabbits, the rate of cerebral blood flow on the 7th, 14th and 21st days of the study were higher than the same in the NC group of animals by 66.7% ($p < 0.05$); 160.0% ($p < 0.05$) and 243.8% ($p < 0.05$), respectively. The use of the developed nasal drops helped to restore the level of cerebral blood flow, which was reflected in an increase in the average systolic blood flow rate on the 14th and 21st days of the experiment by 145.0% ($p < 0.05$) and 231.3% ($p < 0.05$), respectively. In animals treated with the studied sodium alginate-based gel, the rate of cerebral blood flow increased on the 7th, 14th and 21st days of the study, compared with the NC group of rabbits, by 112.5% ($p < 0.05$); 180.0% ($p < 0.05$) and 275.3% ($p < 0.05$), respectively. At the same time, on the 3rd day of the experi-

ment, the level of cerebral blood flow in animals receiving the developed sodium alginate-based gel was 27.5% higher than that in rabbits injected with EGB 761 ($p < 0.05$). When using a chitosan-based gel, an increase in the rate of cerebral blood flow was observed in relation to NC group rabbits on the 7th day of the experiment by 87.5% ($p < 0.05$); on the 14th day – by 140.0% ($p < 0.05$) and on the 21st day - by 187.5% ($p < 0.05$).

The effect of the studied dosage forms and the referent on the change in the pro / antioxidant balance in the hippocampus of animals under conditions of cerebral ischemia.

Taking into account the fact that cerebral hypoperfusion changes primarily affect the hippocampal zone, which leads to impaired cognitive functions and the development of neurological deficits, the influence of the developed dosage forms and the referent on the course of oxidative stress reactions in the hippocampus of animals as one of the main pathogenetic mechanisms of damage to brain structures in ischemia was evaluated in this work [12].

The results of the study are presented in Table 2.

Table 2

The effect of the studied dosage forms and the referent on the change in the pro/antioxidant balance in the hippocampus of animals under conditions of cerebral ischemia

Rate	SOD, unit/mg of protein	TBA-AP, μM / mg of protein	GSH nM/ mg of protein
SO	75.6 \pm 5	1.4 \pm 0.2	45.3 \pm 5.3
NC	23.4 \pm 5.3#	12.7 \pm 2.5#	21.1 \pm 4.7#
EGB 761	45.6 \pm 5.1*	5.6 \pm 0.9*	36.1 \pm 5*
Drops	34.1 \pm 4.3*	6.8 \pm 1.2*	27.9 \pm 6.5*
Alginate gel	56.9 \pm 4.6*	4.1 \pm 0.7*	39.1 \pm 6.2*
Chitosan-based gel	50.2 \pm 7.1*	6.4 \pm 1.1*	30.7 \pm 4.9*

Note: SO - sham-operate animals, NC – negative control animals. # - is statistically significant relative to the SO group of animals (Tukey criterion, $p < 0.05$); * - is statistically significant relative to the NC group of animals (Tukey criterion, $p < 0.05$).

During the course of the study, it was found that in the NC group of animals, compared with SO rabbits, there was a decrease in SOD activity by 69.0% ($p < 0.05$) and the concentration of reduced glutathione by 53.4% ($p < 0.05$) with an increase in the content of TBA-AP by 9.1 times ($p < 0.05$). The use of the comparison drug contributed to an increase in the activity of SOD and the concentration of GSH, as well as a decrease in the content of TBA-AP by 94.9% ($p < 0.05$); 71.1% ($p < 0.05$) and 55.9% ($p < 0.05$) relative to similar indicators of the NC group of animals. In rabbits receiving the studied nasal drops, the SOD activity was increased by 45.7% ($p < 0.05$); glutathione concentration – by 32.2% ($p < 0.05$), accompanied by a decrease in the content of TBA-AP by 46.5% ($p < 0.05$). Against the background of the injection of a sodium alginate based gel to animals, the activity of SOD and the GSH content were higher, and the concentration of TBA-AP, respectively, was lower

than those in the NC group of rabbits by 143.2% ($p < 0.05$); 85.3% ($p < 0.05$) and 67.7% ($p < 0.05$), while when using a chitosan based gel, these indicators changed by 114.5% ($p < 0.05$); 45.5% ($p < 0.05$) and 49.6% ($p < 0.05$), respectively (Table 2).

Conclusion. The conducted complex of studies allowed us to establish that in the conditions of experimental cerebral ischemia modeled by simultaneous occlusion of the common carotid arteries in large laboratory animals (rabbits), the use of the developed dosage forms contributed to reducing the severity of neurological deficit, restoring cerebral hemodynamics and pro/ antioxidant balance in the hippocampus. At the same time, the chitosan-based drops and gel demonstrated equivalent therapeutic efficacy to the EGB 761 comparison drug administered orally. The sodium alginate based gel in comparison with the referent, that is the studied nasal drops and the chitosan based gel, provided a faster development of the

pharmacological effect and its maintenance throughout the experiment, that is evidenced by the indicators of neurological deficit and the speed of cerebral blood flow analyzed on the 7th day of the study. Thus, based on the results obtained, it can be assumed that the developed nasal sodium alginate based gel may be a promising means of correcting chronic cerebral circulatory disorders with an antioxidant mechanism of action and therapeutic potential which is similar to the oral use of a standardized extract of Ginkgo biloba EGB 761.

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Conflict of interests

The authors have no conflict of interest to declare.

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