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MORPHOLOGICAL CHANGES IN THE STRUCTURAL ELEMENTS OF THE EYEBALL IN CONTUSION INJURY IN RABBITS

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The purpose of the study was to investigate pathomorphological, morphometric, and densitometric changes in the structural elements of the eyeball (choroid and retinal neurons) in rabbits during modeled contusion syndrome, and to evaluate the comparative efficacy of l-lysine-(s)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate 1 % and citicoline 2 % eye drops with hyaluronic acid. The study was performed on 20 California rabbits with modeled ocular contusion injury. Animals were treated with either l-lysine-(s)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate 1 % or citicoline 2 % eye drops with hyaluronic acid 3 times a day. After 10 days, retinal sections were analyzed morphometrically and densitometrically using the VIDAS-386 system to evaluate nuclear area, RNA concentration, cell density, percentage of apoptotic neurons. Untreated ocular contusion injury led to pronounced retinal neurodegeneration, manifested by a significant decrease in neuronal density, nuclear area, RNA concentration, and thickness of all retinal layers, alongside a sharp increase in apoptosis. Both investigated drugs exerted a distinct neuroretinoprotective effect, stimulating transcriptional processes and decreasing apoptotic cell death. Notably, l-lysine-(s)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate demonstrated superior therapeutic efficacy over citicoline 2 % eye drops with hyaluronic acid, showing a statistically significant advantage in increasing retinal layers thickness, density of ganglion cells, bipolar cells. Course administration of l-lysine-(s)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate 1 % eye drops shows high neuroretinoprotective potential, exceeding the reference drug citicoline 2 % eye drops with hyaluronic acid under conditions of experimental ocular trauma.

Key words: contusion syndrome, retina, choroid, experimental ocular contusion, neuroprotection, apoptosis.

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МОРФОЛОГІЧНІ ЗМІНИ В СТРУКТУРНИХ ЕЛЕМЕНТАХ ОЧНОГО ЯБЛУКА ПРИ КОНТУЗІЙНІЙ ТРАВМІ У КРОЛІВ

Метою дослідження було вивчити особливості патоморфологічних, морфометричних та денситометричних змін структурних елементів очного яблука (судинної оболонки та нейронів сітківки) кролів при моделюванні контузійного синдрому та провести порівняльну оцінку терапевтичної ефективності очних крапель l-лізину-(s)-2,6-діаміногексанової кислоти 3-метил-1,2,4-тріазоліл-5-тіоацетату 1 % та очних крапель 2 % цитиколіну з гіалуроновою кислотою. Дослідження виконано на 20 кроликах породи Каліфорнійська зі змодельованою контузійною травмою ока. Тварини отримували інстиляції 1 % крапель l-лізину- (s)-2,6-діаміногексанової кислоти 3-метил-1,2,4-тріазоліл-5-тіоацетату або референс-препарату 2 % цитиколіну з гіалуроновою кислотою 3 рази на добу. Через 10 діб зрізи сітківки оцінювали морфометрично та денситометрично в системі VIDAS-386 (визначали площу ядер, вміст РНК, щільність клітин, % апоптозу). Нелікована контузійна травма ока викликала глибокі дегенеративні зміни нейронів, що підтверджувалося зниженням їхньої щільності, площі ядер, концентрації РНК. Обидва препарати продемонстрували виражений нейроретинопротективний ефект, активуючи транскрипційні процеси та знижуючи рівень клітинної загибелі. l-лізин-(s)-2,6-діаміногексанової кислоти 3-метил-1,2,4-тріазоліл-5-тіоацетат достовірно перевершив 2 % цитиколін з гіалуроновою кислотою за здатністю відновлювати щільність гангліонарних, біполярних клітин. Курсове застосування очних крапель l-лізину-(s)-2,6-діаміногексанової кислоти 3-метил-1,2,4-тріазоліл-5-тіоацетату 1 % має потужний нейроретинопротективний потенціал, що перевищує ефект референс-препарату 2 % цитиколіну з гіалуроновою кислотою в умовах експериментальної травми ока.

Ключові слова: контузійний синдром, сітківка ока, хоріоідея, експериментальна контузія ока, нейропротекція, апоптоз.

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Traumatic injuries to the organ of vision remain one of the most acute and socially significant problems in modern ophthalmology and combat medicine. Within the structure of general ocular trauma, ocular contusion (blunt trauma) accounts for 30 % to 45 % of all clinical cases, demonstrating a steady upward trend due to the increasing incidence of domestic, traffic, and industrial injuries, as well as specific combat-related acoustico-barotraumas and blast-induced ocular injuries [1, 9].

Eye trauma is one of the leading causes of blindness worldwide and remains a major cause of unilateral vision loss. Approximately 38–52 % of all visits to ophthalmic emergency departments are related to ocular injuries, and 0.9–1.8 % of cases require hospitalization due to the severity of the condition [8, 10]. It is estimated that around 55 million eye injuries occur annually, of which 19 million result in visual impairment or complete loss of vision [15].

The pathomorphological consequences of mechanical impact on the eyeball are not limited to localized changes in the anterior segment of the eye; rather, they bear a systemic destructive nature that affects the choroid and internal neurosensory structures. Contusion syndrome initiates a cascade of pathophysiological reactions that lead to delayed, progressive disability in patients due to the irreversible loss of visual functions caused by retinal degeneration.

The retina, being a highly specialized part of the central nervous system extended to the periphery, is exceptionally sensitive to the hydrodynamic shock and acoustic waves generated during blunt trauma. Primary mechanical compression and tissue deformation trigger secondary injury cascades. A pivotal role in this process is attributed to acute local microcirculatory impairment, hemodynamic disorders in the choriocapillaris, ischemia, and pronounced edema of the inner layers of the eye [12, 14]. The development of endothelial dysfunction, plasmorrhagia, as well as mucoid and fibrinoid swelling of the connective tissue elements within the vascular wall, induces retinal hypoxia. The ischemic-hypoxic state, in turn, activates an excessive release of excitatory amino acids (excitotoxicity), induces mitochondrial dysfunction, and stimulates an avalanche-like generation of reactive oxygen species (ROS), thereby initiating oxidative stress processes.

The primary targets of these pathological processes are the retinal neurocytes: retinal ganglion cells (RGCs), bipolar neurons. Contemporary studies indicate that the death of retinal neurons following contusion occurs predominantly via programmed cell death—apoptosis, which is accompanied by the suppression of intracellular nucleic acid synthesis, chromatinolysis, karyopyknosis, and the destruction of cytoplasmic organelles [2]. Given that retinal neurocytes possess an extremely limited regenerative potential, each phase of the apoptotic cascade irreversibly reduces the thickness of the functional retinal layers, clinically manifesting as a progressive narrowing of visual fields, decreased visual acuity, and the development of traumatic optic neuropathy.

The use of corticosteroids (usually in high doses) is aimed at reducing inflammation and edema, which may improve blood flow in the optic nerve region. However, the effectiveness of this approach remains controversial, as some studies have demonstrated a limited impact on long-term outcomes. In a prospective observational study involving 50 patients with traumatic optic neuropathy who received high-dose corticosteroid therapy, S. Ashwani Siddardha concluded that after 3 months, 46 % of patients showed visual improvement, whereas no improvement was observed in 54 % of patients [13]. The Corticosteroid Randomisation After Significant Head Injury (CRASH) trial evaluated the efficacy and safety of corticosteroids in patients with acute traumatic brain injury. After 6 months of follow-up, the risk of death was higher in the corticosteroid group compared with the placebo group. The CRASH trial demonstrated that corticosteroid therapy in patients with significant head injury was associated with an increased mortality risk and did not provide clinical benefit compared with placebo [11].

Consequently, conventional therapeutic strategies aimed solely at symptom relief (anti-edematous, anti-inflammatory, and hemostatic therapies) are insufficient to prevent long-term neurodegenerative processes in the posterior segment of the eye. The current paradigm of pharmacotherapy in ophthalmology is shifting toward preventive neuroretinoprotection. An urgent task is the search for and implementation of medicinal agents capable of directly blocking apoptotic triggers, enhancing local metabolism, stimulating transcription and translation processes (RNA and protein synthesis) within damaged neurons, and stabilizing the vascular wall of the choroid.

In this context, the development of topical formulations (eye drops) capable of penetrating the blood-ocular barrier to exert a targeted effect directly within eye tissues is of particular interest. One of the promising innovative domestic agents is L-lysine (S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate. Previous experimental and clinical studies of this molecule in acute cerebrovascular accidents and traumatic brain injuries demonstrated its potent endothelial-protective, antioxidant, metabolitotropic, and anti-ischemic properties, its ability to normalize energy metabolism by preserving the ATP pool and activating the GABA shunt, as well as to reduce systemic markers of neurodestruction (NSE, S100) [5]. However, the pathomorphological aspects of L-lysine (S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate 1 % eye drops regarding structural reorganization and nucleic acid dynamics specifically during ocular contusion syndrome remain poorly understood.

To objectively evaluate the efficacy of novel agents in global practice, it is customary to utilize reference drugs with proven neuroprotective action. In ophthalmology, citicoline formulations serve as such a benchmark, specifically citicoline 2 % eye drops with hyaluronic acid. Citicoline is a naturally occurring endogenous mononucleotide that acts as an intermediate metabolite in the biosynthesis of structural phospholipids in neuronal cell membranes, stimulates the dopaminergic system, improves the functional activity of RGCs, and decelerates the progression of neurodegeneration [6, 7]. Conducting a comparative morphometric and densitometric analysis of the efficacy of L-lysine (S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate and citicoline 2 % eye drops with hyaluronic acid will allow for the determination of the depth and

pathogenetic features of their retinoprotective action under conditions of experimental trauma.

The purpose of this study was to investigate the features of pathomorphological, morphometric, and densitometric changes in the structural elements of the eyeball (choroid and retinal neurons) in rabbits during modeled contusion syndrome, as well as to perform a comparative evaluation of the therapeutic efficacy and neuroretinoprotective potential of L-lysine (S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate 1 % eye drops versus the reference drug citicoline 2 % eye drops with hyaluronic acid.

Materials and methods. The experiments were performed on 20 California rabbits of both sexes weighing 3.0–3.5 kg, obtained from a farm in the Zaporizhzhia district. During the work with laboratory animals, the methodological recommendations of the "State Expert Center of the Ministry of Health of Ukraine" and bioethical requirements were strictly observed in accordance with the National "General Ethical Principles of Experiments on Animals" (2001) and the relevant provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes".

The study was conducted at Zaporizhzhia State Medical University from February 2025 to October 2025. Bioethics Committee Protocol No. 2 dated February 10, 2025.

Experimental ocular contusion in rabbits, induced by exposure to a pressurized carbon dioxide gas flow, was modeled according to our own methodology using a gas-cylinder pneumatic pistol "Baikal MP-654K" with a liquefied CO_2 mass of 12 g under pressure (Crosman, USA, serial number 456739).

Immediately after inducing the contusion injury, the affected eye was treated with the investigational drug – Angiolin® 1 % eye drops (manufactured extemporaneously at the Department of Pharmaceutical, Organic and Bioorganic Chemistry of ZSMU from a substance obtained from the Scientific and Technological Complex "Institute for Single Crystals" of the National Academy of Sciences of Ukraine), administered at a dose of 0.2 mL three times daily. The reference drug – OMK-1 eye drops (citicoline 2 %) (Omikron Italia S.r.l., Viale Bruno Buozzi, 5, 00197 Rome, Italy) – was also administered.

The eyeball was washed in an isotonic solution at +5°C. Subsequently, the eyeball was cleared of residual conjunctiva and muscles. Utilizing microsurgical instruments under a binocular loupe, the anterior segment of the eye, along with the lens, was removed, and the vitreous body was extracted. The cornea was excised along the limbus. Four incisions were made on the remaining part of the eyeball, and the posterior segment was flattened onto a sheet of filter paper placed in a Petri dish cooled to +4°C so that the fundus was accessible for inspection. Using an ophthalmic microsurgical scraper spatula, specific areas of the retina were marked and isolated, and then placed in Carnoy's fixative for 24 hours. Following the standard tissue dehydration procedure and infiltration with chloroform and paraffin, the retina was embedded in Paraplast (McCormick, USA). Serial histological sections with a thickness of 5 μm were prepared on a Microm-325 rotary microtome (Microm Corp., Germany), which were subsequently deparaffinized in xylene, rehydrated in descending concentrations of ethanol (100 %, 96 %, 70 %), and rinsed in physiological saline.

For the specific detection of RNA, histological sections were stained for 24 hours with Einarson's gallocyanin-chrome alum and mounted in EUKITT polymer medium (O. Kindler GmbH, Germany) for subsequent microscopy. The retina was examined under an Axioskop microscope (Zeiss, Germany) using transmitted light. Utilizing an 8-bit CCD camera, COHU-4922 (COHU Inc., USA), images of the retinal regions were captured into the VIDAS-386 computer image analysis system (Kontron Elektronik, Germany) and digitized using a densitometric scale with 256 gradations of gray. In each experimental series, approximately 500 areas from different retinal layers were subjected to investigation.

The evaluation of morphometric and densitometric characteristics was performed on the VIDAS-386 computer system for digital image analysis (Kontron Elektronik, Germany). The image obtained from the AXIOSKOP microscope was transmitted into the digital image analysis system via the highly sensitive COHU-4922 video camera (COHU Inc., USA) and digitized according to a densitometric scale with 256 gradations of gray. Morphometric analysis of the cellular structure of the retinal layers was carried out in an automated mode using a macro program developed in the specialized programming environment VIDAS-2.5 (Kontron Elektronik, Germany). The following parameters were determined [14]: nuclear area (μm²); RNA concentration in neuronal nuclei in units of optical density (UOD), calculated as the logarithm of the ratio of the cell nucleus optical density to the optical density of the intercellular substance; density of neurons, as well as apoptotic and destructively altered neurons (number of cells per 1 mm² of the retinal section area); percentage of apoptotic cells (%) – the ratio of the number of surviving neurons to the total number of apoptotic and destructively altered neurons; thickness of the retinal layers.

Neurons exhibiting signs of karyopyknosis or cytolysis were considered degenerating. The software was used to measure neuronal density, the ratio of intact to dying neurons (neurodegeneration index), and the ratio of surviving neuron density under drug treatment to the density of intact neurons in the control group (survival improvement index).

The results of the study were calculated using standard statistical software packages: the licensed program "STATISTICA® for Windows 6.0" (StatSoft Inc., No. AXXR712D833214FAN5), as well as "SPSS 16.0" and "Microsoft Office Excel 2003." The normality of data distribution was assessed using the Shapiro-Wilk test. Data are presented as mean values. The significance of differences between the means was determined using Student's t-test for normally distributed data. In the case of a non-normal distribution, or during the analysis of ordinal variables, the Mann-Whitney U test was applied. For comparing independent variables across more than two groups, analysis of variance (ANOVA) was used for normally distributed data, or the Kruskal-Wallis test was employed for non-normal distributions. For all types of analysis, differences were considered statistically significant at $p < 0.05$ (95 %).

Results of the study. As seen from Tables 1–2, 10 days after the modeling of ocular contusion injury (OCI), degenerative changes are observed in the retinal neurons of rabbits, manifesting as a significant decrease in retinal neuronal density (bipolar cells, ganglion cells), nuclear area, and nuclear RNA concentration, alongside an increased proportion of apoptotically altered neurons.

Table 1

Retinal bipolar cell characteristics in experimental groups

Group	Nuclear area, μm²	RNA content, UOD	% of apoptotic cells	Cell density (cells/μm²)
Intact	19.94±0.72	1579.3±85.7	2.55±0.61	0.012±0.002
OCI (control)	12.63±0.36[1]	1136.9±40.4[1]	28.3±5.05[1]	0.0073±0.0006[1]
OCI + OMK-1 eye drops (cyticoline)	21.74±0.98[*]	1636.5±110.9[*]	2.74±0.24[*]	0.011±0.0018[*]
OCI + Angiolin eye drops	17.83±0.91[*]	1668.2±83.7[*]	2.83±0.32[*]	0.014±0.0015[*#]

Table 2

Retinal ganglion cell characteristics in experimental groups

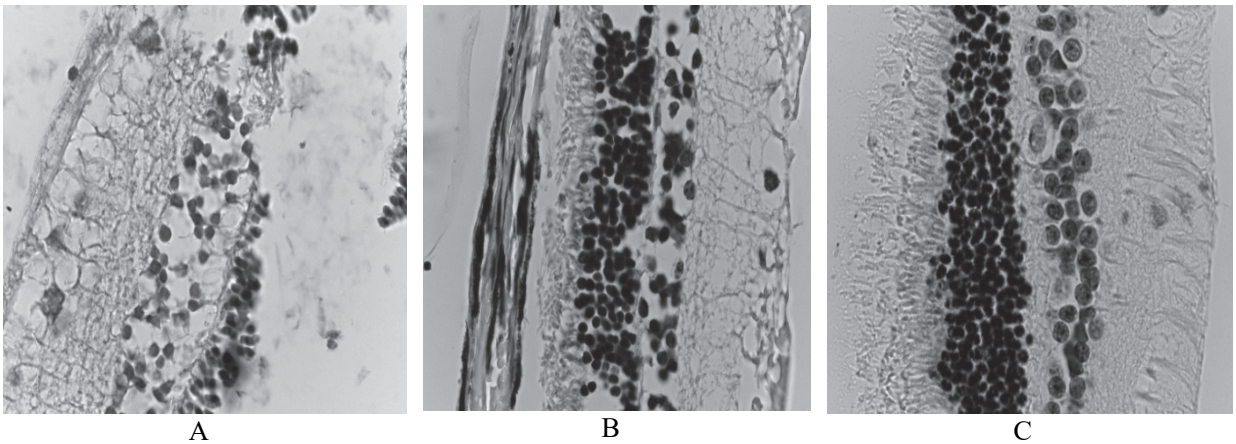
Group	Nuclear area, μm²	RNA content, UOD	% of apoptotic cells	Cell density (cells/μm²)
Intact	37.4±4.2	4418.7±584.5	0.34±0.03	0.0024±0.0006
OCI (control)	35.6±2.3	3397.6±288.2[1]	16.6±9.6[1]	0.0018±0.0008[1]
OCI + OMK-1 eye drops (cyticoline)	43.8±4.16	4848.4±18.1[*]	5.6±3.14[*]	0.0011±0.0006[*]
OCI + Angiolin eye drops	39.7±4.25	3935.7±506.2[*]	5.8±3.512[*]	0.0026±0.0009[*#]

Note: 1 – $p < 0.05$ compared to the intact group; * – $p < 0.05$ compared to the control group; # – $p < 0.05$ compared to the cyticoline group.

In the group of animals treated with OMK-1 (citicoline 2 %), restoration of the morphofunctional state of retinal neurons was observed; however, the administration of Angiolin 1 % provided a more pronounced neuroprotective effect.

In bipolar cells, treatment with Angiolin resulted in a significant increase in RNA content to 1668.2±83.7 UOD, which exceeded the value observed in the OMK-1 group (1636.5±110.9 UOD), as well as the most pronounced restoration of cell density – 0.014±0.0015 cells/μm² (Fig. 1.C) compared with 0.011±0.0018 cells/μm² after citicoline treatment (Fig. 1.B) The apoptosis level remained low and was comparable to that observed in the OMK-1 group.

In ganglion cells, Angiolin treatment contributed to a reduction in apoptosis levels to 5.8±3.51 % and restoration of cell density to 0.0026±0.0009 cells/μm², which was significantly higher compared with the citicoline group (0.0011±0.0006 cells/μm²). Moreover, the cell density after Angiolin treatment even exceeded the value of the intact group (Fig. 1.A).



A B C

Fig. 1. Treatment results. A – Intact, B – OCI+OMK-1, C – OCI+Angiolin eye drops.

Course administration of eye drops with cyticoline (OMK-1) and Angiolin eye drops to rabbits after ocular contusion injury led to a profound neuroretinoprotective effect. Both drugs significantly reduced the number of apoptotic neurons across all retinal layers, increased the nuclear area, and elevated nuclear RNA concentrations compared to the control group. This indicates the activation of transcriptional processes within neuronal cells and the initiation of adaptive mechanisms. Furthermore, Angiolin and OMK-1 significantly increased neuronal density in all retinal layers of rabbits with OCI compared to the untreated animals. Notably, Angiolin demonstrates superior efficacy over OMK-1 (cyticoline) regarding the density of ganglion, bipolar cell in the reduction in apoptotic signs. This comprehensive action of Angiolin is of paramount importance for the prevention and treatment of OCI.

Discussion. Following ocular contusion combined with acoustic trauma, rod-cone retinal dystrophy frequently develops. In this condition, cones are primarily affected, leading to difficulties in reading or discerning fine details (due to the loss of central vision) or causing color vision impairments [4, 14]. Bipolar cells are the first to undergo neurodegeneration triggered by excitotoxicity, oxidative, and nitrosative stress following OCI [2, 16].

Military personnel who have sustained ocular contusion paired with blast-induced acoustic trauma may also complain of bright flashes of light in their eyes (phosphenes). According to US military medical reports, the loss of peripheral vision following blast-induced neurotrauma often takes an asymptomatic course; only a few patients notice this deficit initially, describing their vision as "tunnel vision" due to the concentric narrowing of peripheral visual fields. Consequently, service members encounter severe difficulties when performing combat missions at night, as well as complications when operating armored vehicles and aircraft at dusk or in foggy conditions (Hussain et al., 2021).

The mechanism underlying the neuroretinoprotective action of Angiolin reflects its neuroprotective effect established by earlier studies. Its neuroprotective properties are driven by the conversion of L-lysine into pipecolic acid, which enhances the affinity of the GABA-benzodiazepine receptor complex, thereby mitigating the manifestations of glutamate excitotoxicity. The drug substantially reduces neuronal death during ischemic and hemorrhagic strokes, normalizes the functioning of the compensatory GABA shunt, and increases ATP levels in brain tissues. Under conditions of acute cerebral ischemia, the drug preserves the functional activity of neuronal mitochondria and increases the concentration of HSP70 within them.

Moreover, the drug exhibits pronounced antioxidant properties, activates the glutathione arm of the thiol-disulfide system, increases the activity of glutathione peroxidase and glutathione transferase, suppresses the generation of reactive oxygen species, and diminishes the accumulation of oxidative and nitrosative stress markers. The endothelial-protective effect of the drug during cerebrovascular disorders and hypertensive disease is mediated by its capacity to regulate NO production, reduce the formation of peroxynitrite and homocysteine, enhance the activity of superoxide dismutase and NO synthase, and increase the preservation of reduced thiol groups and L-arginine. The drug elevates NO bioavailability and is capable of improving its transport to target cells when the endothelial function of cerebral vessels is compromised.

In cerebrovascular disorders and vascular surgeries, the drug preserves the morphofunctional parameters of endothelial cells in muscular-type vessels and cerebral capillaries, raises the RNA content in the nuclei and cytoplasm of endothelial cells, stimulates their proliferation, and activates the expression of vascular endothelial growth factor (VEGF). Finally, the drug exhibits anti-inflammatory properties, lowering the expression of the pro-inflammatory cytokine IL-1beta [2, 4].

Limitations. Although the mammalian eye structure shares many similarities with the human eye, the anatomical, physiological, and metabolic differences between the rabbit and human eye preclude direct extrapolation of the obtained dosages and therapeutic efficacy (of Angiolin and OMK-1) into clinical practice without additional trials. Furthermore, morphological and densitometric parameters were evaluated 10 days after the induction of contusion injury. This limits the ability to assess the long-term consequences of the trauma (such as the development of delayed rod-cone dystrophy or chronic neurodegeneration), as well as the sustainability of the drugs' protective effect in the long term

Conclusions

1. Modeling of experimental ocular contusion in rabbits leads to pronounced degenerative and dystrophic changes in the retina (bipolar, and ganglion cells) after 10 days. This is confirmed by a significant decrease in neuronal density, reduction of nuclear area, decline in RNA concentration, a sharp increase in the percentage of apoptotic cells, and a reduction in the thickness of all retinal layers.

2. Course instillation of Angiolin 1 % eye drops and the reference drug OMK-1 (cyticoline 2 %) after injury exerts a distinct neuroretinoprotective effect. Both agents significantly reduce the proportion of apoptotic cells, increase neuronal density and stimulate transcriptional processes by increasing nuclear area and RNA content in neurocytes.

3. The investigational drug Angiolin demonstrates superior therapeutic efficacy compared to the reference drug OMK-1. This is evidenced by a statistically higher density of ganglion cells and bipolar cells and a higher concentration of RNA within them.

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