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Clinical and Experimental Substantiation Of Application Of A Non-Enzym Vitreolysis To Induce Posterior Detachment Of The Vitreous At The Vitreoretinal Pathology.

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INTRODUCTION

The main group of vitreoretinal pathology requiring surgical intervention are: tractional retinal detachment, rhegmatogenous retinal detachment, proliferative vitreoretinopathy, intraocular hemorrhages, diabetic macular edema with traction component, idiopathic macular laceration, vitreomacular traction syndrome, age-related macular degeneration, myopic maculopathy [1]. The development of intraocular hemorrhage, as well as fibrin and thrombogenesis play an important role in the pathogenesis of many diseases of the eye and are complicating factors in performing vitrealsurgery[2].

The posterior hyaloid membrane of the vitreous body is the initial matrix for the growth of proliferative tissue, which plays a major role in the pathogenesis of the development of many vitreoretinal pathologies. Induction of the posterior vitreous layers plays an important role in the prevention, treatment and stabilization of the proliferative process in vitreoretinal pathology [3].

Clinical observations show that after complete removal of the posterior hyaloid membrane of the vitreous in the course of vitrectomy, the newly formed vessels are reduced, and the growth of the fibrovascular tissue completely ceases [4,5].

Existing techniques of induction of the posterior hyaloid of the vitreous are mechanical and biochemical. Thus, the mechanical method of inducing posterior hyaloid from the internal boundary membrane with the help of endovitreous instruments has a number of disadvantages: it does not provide complete removal of the posterior hyaloid layers of the vitreous and, as a consequence, there is a high risk of development of iatrogenic complications. At present, the biochemical method is of great interest to surgeons, as less traumatic in comparison with the mechanical one. However, the introduction in the vitreous of various enzymatic agents lysing vitreous components has a number of disadvantages: toxicity, the occurrence of various autoimmune reactions. In addition, enzymatic preparations in an acceptable, non-toxic concentration do not cause detachment of the posterior hyaloid, which hampers their wide clinical use (6,7). Induction of detachment of the posterior layers of the vitreous with the help of pharmacological non-enzymatic vitreolysis is a promising direction in conservative and surgical treatment of the patients with vitreoretinal pathology. The literature survey showed sufficient number of reports about the mechanical methods of induction of the posterior hyaloid [8-13].

The idea of intravitreal injection (IVI) of various substances for the purpose of inducing posterior hyaloid for a number of researchers is the most attractive by allowing to avoid the manipulation with sharp instruments in the immediate vicinity of the retina, as well as complications associated with the use of laser or thermal energy [14-16].

Keywords: urea, non-enzymatic vitreolysis, proliferative vitreopathy

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The search for non-invasive methods of treating vitreoretinal diseases aimed at eliminating the adverse effects of the vitreous on the retina led to the appearance of the term "pharmacological vitreolysis" [17-20]. According to the authors, data with pharmacological vitreolysis, the vitreous separates from the retina and its collapse, first, due to the liquefaction of the gel-like structure of the vitreous humor, and secondly, due to the weakening of the adhesion of the posterior hyaloid to the inner border plate [21-24]. As in the case of spontaneous posterior hyaloid detachment [25-28], the success of pharmacological vitreolysis depends on the simultaneous presence of both processes. Their separation, especially the induction of dilution and collapse of the vitreous without weakening vitreoretinal connections, can significantly aggravate the course of the disease.

One of the promising methods of pharmacological vitreolysis is non-enzymatic vitreolysis, through urea derivatives and other compounds capable of inducing non-enzymatic dissolution of the vitreous membrane. Such compounds include: non-enzymatic proteins, nucleosides, nucleotides and their derivatives (eg, adenine, adenosine, cytosine, citadine, guanine, guanidine, guanidine, thymidine, tititānidine, uradine, uracil, cystine); Uric acid, calcium acetylsalicylate and ammonium sulfate. There are separate reports on the ability of these compounds to cause dissolution of the vitreous membrane. In the literature, there are isolated reports on the use of Vitreosolve (Urea), a drug based on urea for inducing posterior hyaloid detachment in patients with nonproliferative diabetic retinopathy. There is limited information in the literature on the structure or mechanism of action of this drug. The early stages of experimental studies of this drug have not been published. Preliminary results indicate that induction of the posterior hyaloid is observed in 45% of patients after a single injection of 12 mg of Vitreosolve, and after a re-injection after 30 days, induction of the posterior hyaloid is observed in 75% of patients [29].

Pharmacological non-enzymatic vitreolysis is a promising direction in conservative and surgical treatment of patients with vitreoretinal pathology. Taking into account the above, the issue of developing new drugs for the induction of the posterior hyaloid is still relevant and of great scientific and practical interest.

Urea is a product of the metabolism of proteins in the human body, it is excreted in human urine with an average amount of 30 g/day. Urea solutions for injection for more than 40 years are included in the US National Pharmacopoeia. As a medical product, urea for injection (intravenous) is allowed in the United States for more than 20 years. In medicine, urea is widely used as a diuretic and dehydrating remedy. Urea prevents and reduces cerebral edema, toxic pulmonary edema, lowers intraocular pressure.

The study of the possibility of using urea in ophthalmology was carried out by many researchers. So Tomambe R.E. and co-authors (1989) used the IVI method of urea solution in the treatment of retinal ruptures. In the opinion of the authors, IVI of the urea accelerates the reattachment of retinal ruptures, induces the induction of the posterior hyaloid membrane of the vitreous, which prevents the appearance of new retinal ruptures and retinal detachment associated with them [30].

In the literature described a clinical case of treatment of idiopathic macular rupture after IVI of urea [47]. Irvine, CA and co-authors (2012) used the IVI method for urea as an adjuvant before carrying out pneumoretinopexia in patients with retinal detachment. The literature also describes the method of IVI of urea in patients with hemophthalm on the background of diabetes mellitus. The rate of resolution of hemophthalm was significantly higher than that observed in clinical practice with standard methods of treatment [31].

Taking into account the above, we considered it promising to study the possibility of using urea for vitreolysis in the treatment of patients with vitreoretinal pathology.

Purpose. To develop and justify a new method of non-enzyme vitreolysis for induction of the posterior detachment of the vitreous humor.

Methods. In the first year of the study, the work was based on an analysis of instrumental research methods and morphological features of 30 experimental animals (rabbits of the Chinchilla breed weighing from 2.0 to 3.5 kg at the age of 4-6 months). The experimental substantiation of the possibility of intravitreal administration of the urea preparation (toxicity study, reaction of surrounding tissues) is performed on 60 eyes of 30 rabbits.

A solution for IVI is prepared immediately before the injection. All animals, 30 minutes before IVI, achieved medial mydriasis. Anesthesia was performed by intramuscular injection of a solution of "Xylanite" (1-3 mg / kg) and a 3-fold instillation into the conjunctival cavity of a 1% solution of "Alkain". After the application of the eyelid under the control of the binocular ophthalmoscope in the projection of the flat part of the ciliary body 3 mm from the limbus with a thin insulin needle on the syringe, a through puncture of the eye membranes was performed without opening the conjunctiva, and 0.1 ml of a solution containing various concentration of urea. In the control group 0.1 ml of 0.9% isotonic NaCl solution was injected into the vitreous cavity (Table 1). The preparation was administered under visual control of the tip of the needle, which was located in the central sections of the vitreal cavity. The puncture site was not hermetically sealed. At the end of the injection, 0.5% of levomycetin solution and 0.1% of dexamethasone solution were instilled into the conjunctival cavity.

Table 1: Distribution of material by study groups

Groups	Doses of the urea and Isotonic solution	Number of animals (eyes)	Terms of excluding from the study
1	OD – NaCl0,9% - 0.1ml	6(12)	1,7,14,30 days, 3 and 6 months
	OS – NaCl0,9% -0.1ml		
2	OD– Urea 1 % -0.1ml	6(12)	1,7,14,30 days, 3 and 6 months
	OS– Urea 12% -0.1ml		
3	OD –Urea 1,5% -0.1ml	6(12)	1,7,14,30 days, 3 and 6 months
	OS – Urea 24% mgr -0.1ml		
4	OD – Urea3 % -0.1ml	6(12)	1,7,14,30 days, 3 and 6 months
	OS – Urea 48% -0.1ml		
5	OD –Urea 6 % -0.1ml	6(12)	1,7,14,30 days, 3 and 6 months

To assess the irritating effect of various concentrations of the urea on the eye tissue, the following ophthalmic methods were used: biomicroscopy with a portable hand-held slit lamp, indirect binocular ophthalmoscopy and measurement of the irritating impact by the Setnikar scale [48].

To assess the external signs of irritation, the following scale was used:

- There are no visible changes (-);
- Hyperemia of the conjunctiva and the edges of the eyelids, the blinking membrane for 30 minutes, the closing of the eyelids no more than 5-10 minutes after the administration of the substance (+);
- Hyperemia of the conjunctiva and the edges of the eyelids, the blinking membrane, sclera, infiltration (compaction) of the eyelid tissue within 30-300 min (++);
- Hyperemia of the conjunctiva and the edges of the eyelids, a blinking membrane, sclera, infiltration lasting more than 300 min (+++);
- Hyperemia of the conjunctiva and the edges of the eyelids, a blinking membrane, sclera, opacity of the cornea, lasting more than 300 min (++++).

Biomicroscopy and ophthalmoscopy were performed during the first 6 hours (every hour) after IVI of urea, and also during the whole observation period. During biomicroscopy, attention was paid to the conjunctival condition of the eyelids, the transitional folds of the eyeball, the degree of conjunctival injection and the presence of an allergic reaction. While examining the cornea, the condition of the epithelium was assessed, the presence or absence of erosion or other changes.

The sensitivity of the cornea was determined using a thin metal wire in the form of a loop with a diameter of 2 mm. Tactile action was performed at 13 points of the cornea in all meridians. The response was thought to be the emergence of the eyelid closure reflex in response to stimulation [48]. Studies were performed 6 hours after urea administration and on the first day. Investigation of the effect of different

concentrations of urea on the level of intraocular pressure with intravitreal administration was performed before, 15 minutes and 1 to 3 days after the IVI of various concentrations of aqueous urea solution.

Exclusion from the study was carried out by euthanasia of animals after the study by intravenous administration of ketamine 5% 10.0 ml and arduan 1.0 mg. Enucleation of the eyes was performed on 1,7,14, 30, 90 and 180 days with the subsequent histological examination. The coloration of glass preparations of eyeballs was carried out by hematoxylin and eosin, picrofuxin according to Van Gison. For microscopic examination, light microscopy was used in transmitted light using a Nikon Eclipse E200 microscope, photographing microscopic preparations of eyeballs were performed on the Olympus System VS120 OLYMPUS CORPORATION: Olympus EVK-S5-056 microscope with Olympus U-TV0.5XC-3 digital camera with software VS-ASW Virtual Slide System.

RESULTS

After IVI of various concentrations of aqueous urea solution and also in the control group, after IVI of 0.1 ml of isotonic NaCl solution, a short-term blepharospasm was noted up to 2-5 minutes. At the injection site there was local congestion of the conjunctiva, which persisted for 24 hours. The cause of local hyperemia, in our opinion, is the traumatic effect of the injection needle at the site of injection with intravitreal administration of the drug. The degree of local irritation of urea, as well as the sensitivity of the cornea after intravitreal administration of various concentrations were estimated in Table 2.

Table 2: The degree of irritation of the eye and the sensitivity of the cornea after IVI of various concentrations of aqueous urea solution

Group	Eye / Dosage of the Urea or isotonic NaCl solution	Degree of irritation by the Setnikar scale	Sensitivity of the cornea
1	OD – NaCl 0,9% - 0.1 ml	-	Normal
	OS – NaCl 0,9% - 0.1 ml	-	Normal
2	OD– Urea 1 % -0.1 ml	-	Normal
	OS– Urea 12% -0.1 ml	++++	Normal
3	OD – Urea 1,5% % -0.1 ml	-	Normal
	OS – Urea 24% -0.1 ml	++++	Normal
4	OD – Urea 3 % -0.1 ml	-	Normal
	OS – Urea 48% -0.1 ml	++++	Normal
5	OD – Urea 6 % -0.1 ml	-	Normal
	OS – Urea 96% -0.1 ml	++++	Normal

As follows from Table 2, the maximum irritant effect was observed with IVI of 0.1 ml of 12%, 24%, 48% and 96%. Minimal - 1%, 1.5%, 3% and 6% of urea, as well as in the control group. After IVI of urea in all groups, the sensitivity of the cornea was maintained throughout the observation period.

With biomicroscopy and binocular reverse ophthalmoscopy immediately after IVI of urea, the clinical picture of the experimental and control eyes of the majority of animals was similar and was caused by the influence of IVI. After IVI of 1%, 1.5%, 3% and 6% urea solution, as well as in the control group, all eyes were biomicroscopically calm, without signs of photophobia, lacrimation, blepharospasm, with a slight mucous discharge in the corner of the eye. Injection of the vessels of the conjunctiva was not noted, there was focal edema of the conjunctiva in the area of injection. The cornea remained transparent without signs of its edema, the moisture of the anterior chamber was also transparent. Puffiness and hyperemia of the iris were not noted, the pupil was in the state of medial mydriasis. Ophthalmoscopic picture of the majority of eyes was similar: the cavity of the vitreous remained transparent without signs of exudation and hemorrhages, the reticular membrane adhered, there were no signs of its edema or detachment, changes in the retinal vessels and in the optic nerve disk were also not noted. A day after the injection, the biomicroscopic pattern of most eyes remained practically the same. All eyes were calm, without signs of photophobia, lacrimation, blepharospasm. Injection of conjunctival vessels was not noted, focal edema of the conjunctiva in the area of injection was not increased. The cornea remained transparent without signs of edema, the moisture of the

anterior chamber was also transparent. The pupil was in the state of medial mydriasis. Ophthalmoscopy of the posterior segment of the eye a day after IVI 1.0%, 1.5%, 3% and 6% urea solution, and also in the control group in most cases also did not reveal significant changes. The vitreal cavity was transparent with single opacities of the CT. During the rest of the observation period, the biomicroscopic and ophthalmoscopic pattern remained unchanged.

With IVI 0.1 ml of 12% and 24% mg of aqueous urea solution, a longer blepharospasm was observed - more than 300 minutes, conjunctival hyperemia was observed in 2 or more quadrants and disappeared on day 3-7. IVI 0.1 ml 48% and 96% aqueous urea solution caused pronounced flushing, conjunctival chemosis and corneal syndrome lasting up to 14 days. On day 3-6, a picture of endophthalmitis was revealed in two experimental animals in the eyes with doses of urea of 12% and 48%. These experimental animals were withdrawn from the experiment on day 7. On the 14th day, 4, 12%, 24% and 48% doses of urea were observed in the eyes with doses of urea, as well as in two with a 96% dose, the opacity of the lens varied in different degrees. These experimental animals were withdrawn from the experiment on day 14. A significant part of the experimental animals with dosages of 12%, 24% and 48% and 96% vitreal cavity was with turbidity of varying intensity. During the rest of the observation period, the biomicroscopic and ophthalmoscopic pattern remained unchanged.

Indicators of the state of the level of intraocular pressure (IOP) before and after IVI of various concentrations of urea are presented in Table 3.

Table 3 - IOP level (mmHg) before and after intravitreal administration of various concentrations of aqueous urea solution

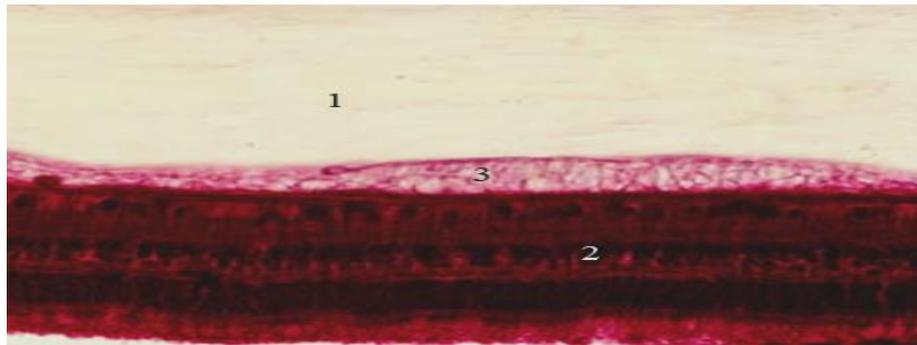
Group	Eye / Dosage of the Urea or isotonic NaCl solution	Mean Level of IOP (mm.Hg) (M±m)				
		Before	After 15 min	After 1 day	After 2 days	After 3 days
1	2	3	4	5	6	7
1	OD – NaCl 0,9% - 0.1 ml	18,3±0,4	18,5 ±0,3	18,5±0,3	18,6 ±0,2	17,6 ±0,3
	OS – NaCl 0,9% - 0.1 ml	17,6±0,4	18,2±0,2	18,2±0,2	18,3±0,2	17,6±0,4
2	OD– Urea 1 % - 0.1m ml	18,0±0,3	17,8±0,2	17,7±0,2	18,2±0,2	17,0 ±0,2
	OS– Urea 12% - 0.1 ml	17.7±0,1	17,8±0,3	18,3±0,3	18,6±0,1	17,1±0,2
3	OD–Urea 1,5 % - 0.1 ml	17,3±0,1	17,5±0,2	17,0±0,2	16,8±0,2	17,0±0,2
	OS – Urea 24 % - 0.1ml	17,0±0,2	17,0±0,3	17,5±0,3	17,6 ±0,3	17,6±0,4
4	OD – Urea 3 % - 0.1 ml	18,3±0,4	18,5 ±0,3	18,5±0,3	18,6 ±0,2	17,0 ±0,2
	OS – Urea 48% - 0.1 ml	18,2±0,3	18,2±0,2	18,2±0,2	18,3±0,2	16,8±0,3
5	OD – Urea 6 % - 0.1 ml	18,0±0,3	17,8±0,2	17,7±0,2	18,2±0,2	16,8±0,2
	OS – Urea 96 % - 0.1 ml	17.7±0,1	17,8±0,3	18,3±0,3	18,6±0,1	17,1±0,2

As can be seen from Table 3, before the injection of IOP, the drug was within the normal range. IOP at 15 minutes and 1-3 days after the introduction of urea remained within normal limits.

Macroscopically in all the examined eyeballs, the vitreous body was liquefied on the 1st and the 7th day, the transparency of the vitreous body was noted, and on the 14th and 30th days the turbidity of the vitreous with fibrinous inflammatory transudate was noted, as well as the turbidity of the lens of different intensity, which is characteristic of the uremic endophthalmitis associated With a direct toxic effect of urea. Such changes in the control group were not observed.

During the entire follow-up period, the morphological study of the control group showed the normal structure of the CT. The main structure of CT was collagen fibers, consisting of type II collagen. The retroental space corresponding to the front boundary layer of the CT remained unchanged. In the posterior part of the eye above the retina and the optic nerve, a posterior border layer of the CT was observed, which in all cases was adjacent to the retina and DZN all along. In the area of orraserata, the preserved base (base CT) densely adhered to the retina, also had a fibrous structure with close-packed, parallel structures (Figure 1).

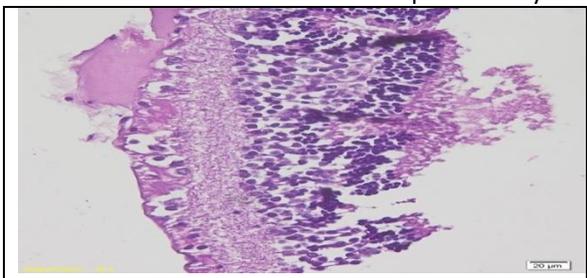
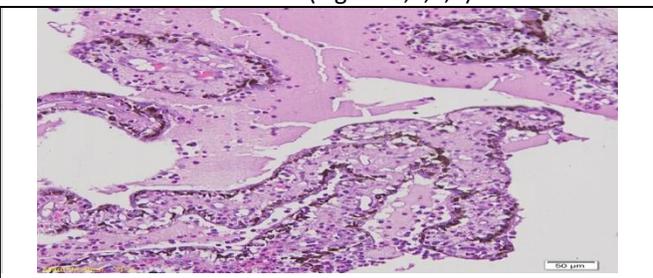
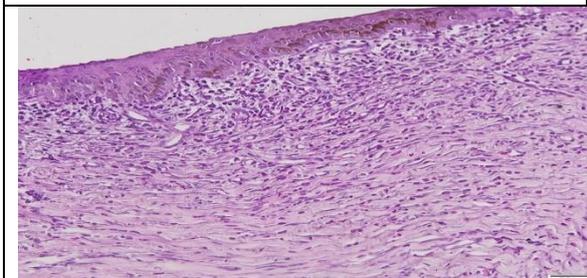
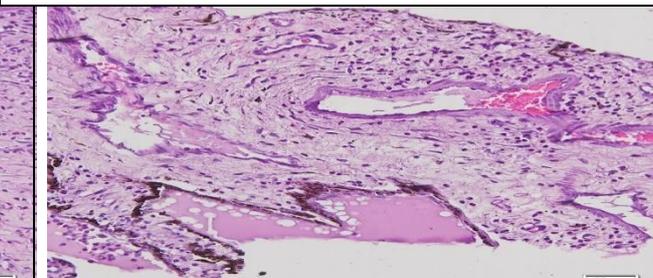
**Figure 1–Microphoto of the rabbit eye from the control group.
No changes in the posterior pole are identified**



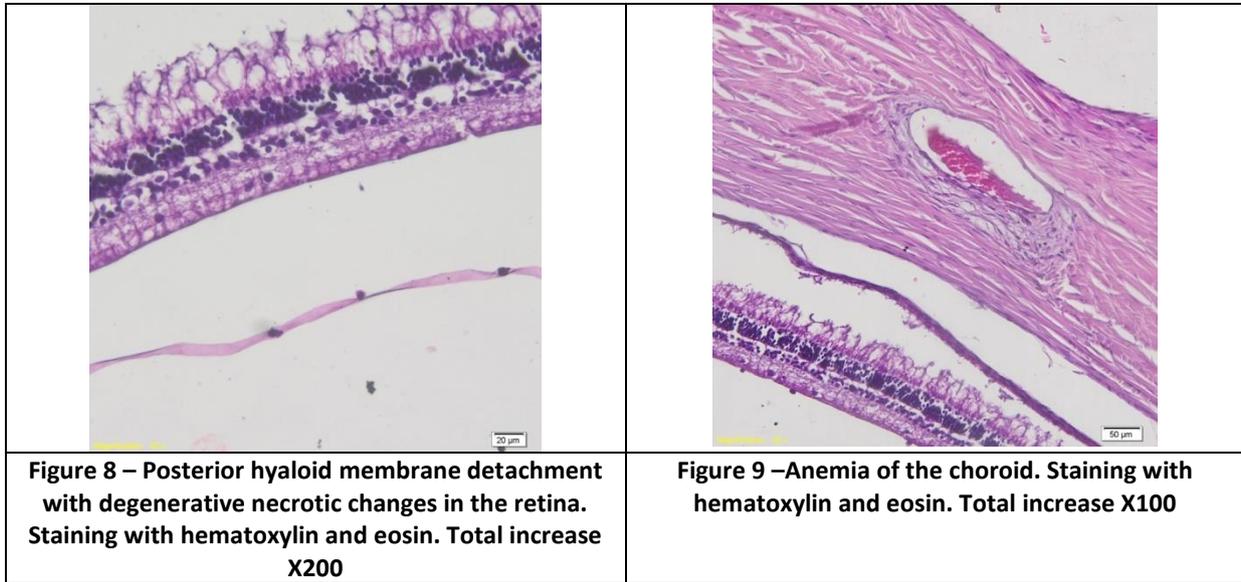
1 – vitreous body; 2 – retina; 3 – posterior hyaloid membrane VanGizonmagnification x40

During microscopic examination of eyeballs, it has been established that the duration of action of urea on internal media and the structure of the eye is a direct correlation of the time of action and the dose of urea administered.

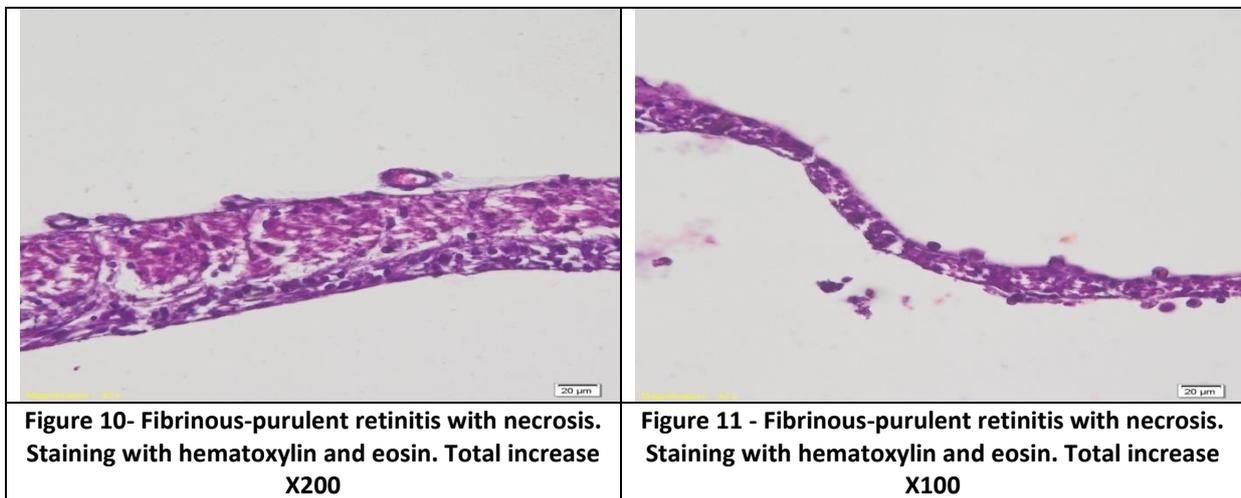
After IVI of 12% of the aqueous urea solution on the 1st and 7th days were observed changes in the inner shells with the detachment of posterior hyaloid membrane of the vitreous (Figure 2,3,4,5).

	
<p>Figure 2 - Acute purulent retinitis. Staining with hematoxylin and eosin. Total increase X200</p>	<p>Figure 3–Acute purulent uveitis. Staining with hematoxylin and eosin. Total increase X100</p>
	
<p>Figure 4–Acute purulent keratitis. Staining with hematoxylin and eosin. Total increase X100</p>	<p>Figure 5 – Acute purulent iridocyclitis. Staining with hematoxylin and eosin. Total increase X100</p>

After IVI of 24% aqueous solution of urea on the 1st and 7th day, more pronounced alterations with a total detachment of posterior hyaloid membrane with necrosis of the retina were revealed, and on the 14th and 30th days similar repair-plastic changes were noted. A partial detachment of posterior hyaloid membrane and retina with a subretinal accumulation of serous-hemorrhagic transudate was observed; In the retina degenerative-necrotic changes (Figure 8); The vascular envelope is anemic and thin (Figure 9), in the sclera, uneven plethora with a sludge-phenomenon.



After IVI 48% and 96% of the aqueous solution of urea on the 1st, 7th, 14th and 30th days in all the examined eyeballs, pronounced toxic changes in the internal structures of the eye with response processes of adaptation with retinal atrophy and in some cases with signs of compensatory repair of retinal structures and vascular Shells (Figure 10, 11).



On the 90th and 180th days after the IVI 0.1ml of an aqueous solution of urea in dosages of 12%, 24%, 48% and 96%, posterior hyaloid detachment was observed, as well as similar pronounced reparative plastic changes as a response to the prolonged toxic effect of urea.

Morphological study in groups with intravitreal administration of small doses of aqueous solutions of urea (1% and 1.5%, 3% and 6%) on day 1-7 revealed a segmental detachment of posterior hyaloid membrane with preservation of retinal morphological structures (Figure 12).

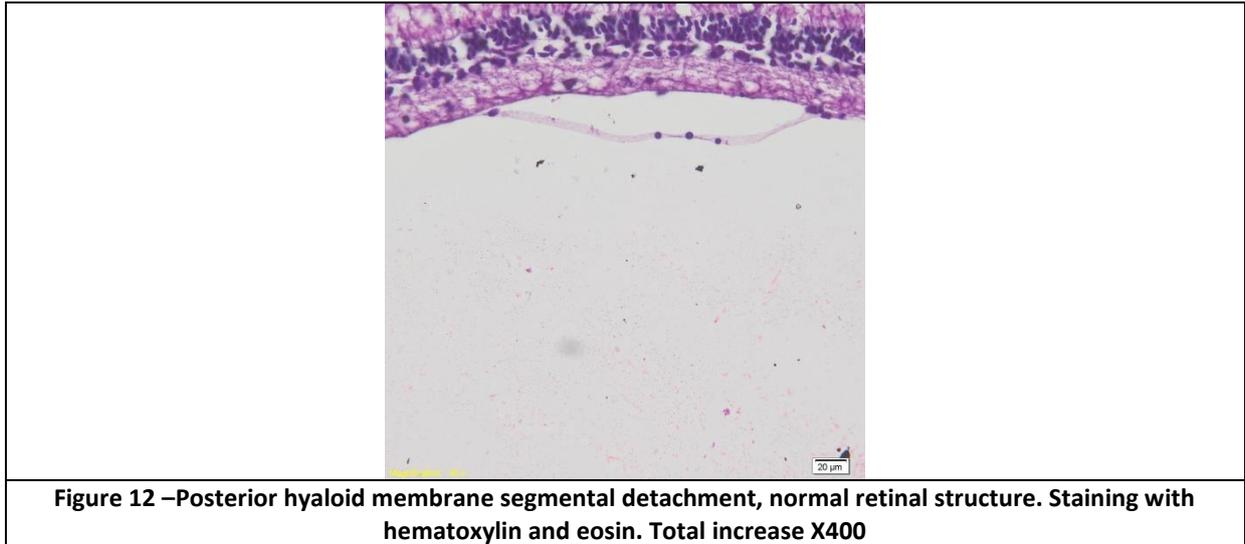
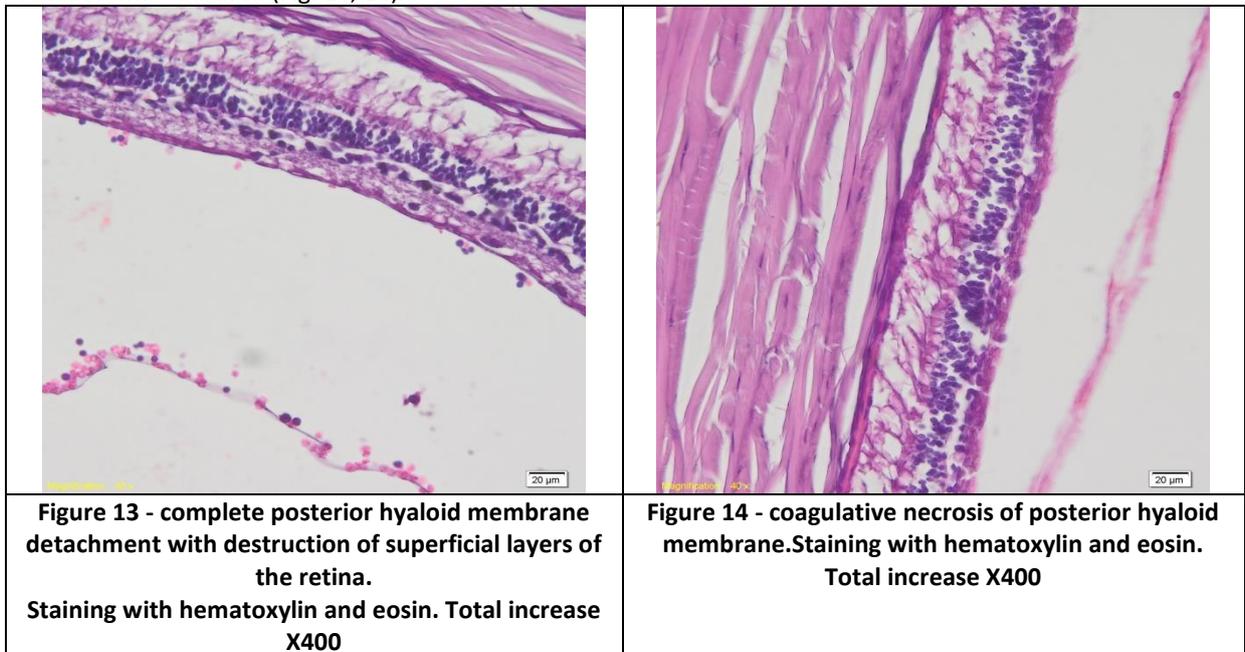


Figure 12 –Posterior hyaloid membrane segmental detachment, normal retinal structure. Staining with hematoxylin and eosin. Total increase X400

With the dosages of 1%, 1.5%, 3% and 6% on 14,30, 90 and 180 days, complete separation of posterior hyaloid membrane with reversible alterative and dystrophic changes in the retina without an inflammatory cell reaction was observed (Fig. 13, 14).



Thus, with microscopic examination of eyeballs, it has been established that the duration of action of urea on the internal media and structures of the eye is a direct correlation of the time of action and the dose of urea administered. Thus, with the introduction of small doses of an aqueous urea solution of 1%, 1.5%, 3% and 6%, posterior hyaloid segmental detachment was achieved, without pathological changes from the retina and vascular membrane. At 14-180, a complete ablation of posterior hyaloid membrane with minimal alterations and changes in the retina was noted. Intravitreal administration of 12% aqueous urea solution on the 1st and 7th days marked changes in the inner membranes with posterior hyaloid membrane, on the 14th day there were reactive and alterative changes in the retina with signs of proliferation; on the 30th day there were reparative plastic changes, as a response to Long-term toxic effects of urea. Intravitreal administration of 24% aqueous urea solution on days 1 and 7 revealed more pronounced alterations with total posterior hyaloid membrane detachment with necrosis of the retina, and on the 14th and 30th days similar repair-plastic changes were noted. When intravitreal administration of 48% and 96% of urea on the 1st, 7th, 14th and 30th days in all investigated eyeballs, pronounced toxic changes in the internal structures of the eye with response processes of adaptation with retinal atrophy and in some cases with signs of compensatory repair of the retina and vascular structures . On the 90th and 180th days after the IVI 0.1ml of an aqueous solution of urea in

dosages of 12%, 24%, 48% and 96%, posterior hyaloid detachment was observed, as well as similar pronounced reparative plastic changes as a response to the prolonged toxic effect of urea.

Therefore, in order to achieve the maximum effect of detachment of posterior hyaloid without involvement in the pathological process of the retina and choroid, small doses (1.0%, 1.5%, 3% and 6%) should be used. Summarizing the results of the morphological studies on non-enzyme vitreolysis, it should be noted that when studying the toxic effect of an aqueous urea solution, we determined the minimum doses with their maximum clinical effect, and also the toxic doses causing irreversible changes in the internal structures of the eye, in particular the retina and the choroid.

CONCLUSIONS

The minimal irritant effect was observed only immediately after IVI 1%, 1.5%, 3% and 6% aqueous urea solution, as well as in the control group. This is due to the IVI procedure. After 24 hours, as well as during the entire follow-up period after the injection, the biomicroscopic and ophthalmoscopic patterns of most eyes remained virtually unchanged.

The maximum irritant effect was observed with IVI of 0.1 ml of 12%, 24%, 48% and 96% immediately after the administration of the drug and lasted up to 14 days. On the 14th day, 4, 12%, 24% and 48% doses of urea were observed in the eyes with doses of urea, as well as in two with a 96% dose, the opacity of the lens varied in different degrees. A significant part of the experimental animals with dosages of 12%, 24% and 48% and 96% vitreal cavity was with turbidity of varying intensity.

After IVI of urea in all groups, the sensitivity of the cornea was maintained throughout the observation period. The level of IOP before and after IVI of various concentrations of urea, as well as in the control group was within the normal range, during the entire follow-up period.

Morphological studies of eyeballs after intravitreal administration of urea solution for the purpose of inducing posterior vitreous detachment showed the possibility of practical use of this method. With the introduction of small doses of an aqueous urea solution of 1%, 1.5%, 3% and 6%, a segmental detachment of posterior hyaloid membrane was achieved, without pathological changes from the retina and vascular membrane. At 14-180, a complete ablation of posterior hyaloid membrane with minimal alterations and changes in the retina was noted. Intravitreal administration of high doses of aqueous urea solution (12%, 24%, 48% and 96%) revealed pronounced alterative and inflammatory processes in the internal structures of the eye, caused by direct toxic effects of urea. On the 30th, 90th and 180th days, repair-plastic changes were noted, caused by the adaptation and compensation processes in response to the prolonged toxic effect of urea.

Thus, the intravitreal administration of an aqueous urea solution at dosages of 12%, 24%, 48% and 96% has a pronounced local irritant and toxic effect on the eye tissue. Intravitreal administration of an aqueous urea solution at dosages of 1%, 1.5%, 3% and 6% does not have a local irritant and toxic effect on the eye tissue and can be used to induce the posterior hyaloid membrane of the vitreous.

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