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THE EFFECT OF THE ENZYME «GEMAZA» ON THE EFFECTINESS OF HEMOPHTHALMUS TREATMENT IN DIABETIC RETINOPATHY

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ABSTRACT

To study the comparative effectiveness of various routes of administration of Hemase and Emoxipin in the treatment of patients with hemophthalmia and diabetic retinopathy, in clinical studies, we analyzed the results of treatment of 46 patients with a proliferative stage of diabetic retinopathy complicated by hemophthalmus (49 eyes): in group I (n = 20), "Emoxipine" was administered parabulbarly; in II (n = 16) - in subconjunctives «Gemaza»; in III (n = 13) – intravitreal «Gemaza» . Within 30 days, the dynamics of visual acuity and hemophthalmus index, which were the same before treatment, as well as the frequency of hemorrhagic and allergic complications, were evaluated in patients. Intravitreal administration causes accelerated resorption of hemophthalmus and restoration of visual acuity in comparison with subconjunctival and parabulbar administration of Emoxipin, which allows retinal laser coagulation to begin earlier.

Relevance

Diabetes mellitus (DM) ranks third in the world after cardiovascular diseases and oncological pathology among the most dangerous nosologies of our time. Currently, there is an increase in the number of patients with type 1 diabetes mellitus (DM 1). According to the WHO Expert Committee on Diabetes Mellitus (2006), the life expectancy of patients with the development of pathology in childhood is about 30 years (50% of the norm).The high prevalence and growing incidence of insulin-dependent diabetes mellitus among children both in our country and abroad, the early development of late vascular complications determine the relevance of the problem of prevention, early diagnosis and treatment of complications of diabetes mellitus (Amstov AC 2002, Balabolkin M.I. 2000. , Dedov I.I. 2006, Kondratyev Ya.Yu. 2007) According to the International Diabetes Federation, as of January 1, 2016, about 415 million people aged 20 to 79 in the world suffer from diabetes.The difficulties that ophthalmologists have to face in the treatment of hemorrhagic complications in patients with diabetes mellitus are associated with the anatomophysiological features of the vitreous body (ST). The vitreous body practically does not have fibrinolytic activity, and blood resorption, in the case of

hemophthalmia, proceeds slowly [8, 9], therefore, the use of enzymes is pathogenetically justified in the treatment of vitreous hemorrhages [2, 9, 13].

Even with the use of modern enzyme preparations, the resorption of hemorrhages occurs extremely slowly [8], which is associated with the insufficient efficiency of existing methods of drug administration and the impossibility of creating a sufficiently high concentration of the drug with extraocular routes of administration due to the high selectivity of the blood-ophthalmic barrier.

The aim of the study was to study the comparative effectiveness of different methods of administration of "Gemaza" and "Emoxipin" in the treatment of patients with hemophthalmia and diabetic retinopathy.

Material and methods

We observed 46 patients with a proliferative stage of diabetic retinopathy complicated by hemophthalmos (49 eyes), patients of group I (n = 20) received "Emoxipin" parabulbarly, II (n = 16) - in the subtenon space " Gemaza ", III (n = 13) - intravitreal" Gemaza "(Table 1.) All patients were under the supervision of an endocrinologist for type I diabetes mellitus for 10–35 years (on average, about 20). Enzyme therapy was used to restore the transparency of the vitreous body for subsequent prophylactic laser coagulation. The basic therapy in all groups was the same.

Table 1

Distribution of patients by sex and age

Groups	I	II	III
Sex, m / f	8/12	8/8	7/6
Average age, years	59,9 ± 12,7	57,9 ± 9,1	58,88 ± 15,9

Timing from the moment of hemorrhage

Table 2

Groups	I	II	III
Up to 3 days	7 (35%)	5 (31.25 %)	5 (38.5 %)
4 to 7 days	8 (40 %)	7 (43.75 %)	5 (38.5 %)
8 to 14 days	5 (25 %)	4 (25 %)	3 (23 %)

In group I, patients received daily injections of "Emoxipin", which was injected parabulbarically once a day at a dose of 1% - 0.5 ml for 7 to 10 days (on average, 9 days).

In group II, the patient was injected into the hospital with 5000 IU "Gemaza" in the sub-

Tenon space once a day at a dose of 5000 IU for 2 to 7 days (on average, 4 days).

In group III, "Gemaza" was administered intravitreally on the day of admission at a dose of 500-1000 IU once, then continued - subconjunctivally daily at a dose of 5000 IU for 2 to 5 days (average 3.5 days).

"Gemaza" is a lyophilized enzyme preparation containing recombinant prourokinase (RPU) placed on an inert carrier containing dextran and sodium chloride. RPU catalyzes the conversion of plasminogen into plasmin, a serine protease capable of lyzing fibrin clots, and has a high specificity of action, as it activates plasminogen mainly in the area of the clot, which reduces the risk of possible bleeding and hemorrhages. In accordance with the production technology of the Gemaza preparation, a sterile solution of rheopolyglucin is used to create an inert matrix, into which a purified recombinant prourokinase enzyme is introduced before the stage of sterilization and lyophilization of the preparation. The drug "Gemaza" created on the basis of RPU is intended for use as a fibrinolytic agent in ophthalmology. The specific activity of Ge ¬ maza is at least 85,000 IU per 1 mg of protein. The drug "Gemaza" is readily soluble in water and isotonic sodium chloride solution, sterile and pyrogen-free. Release form: 5000 IU lyophilized powder is packaged in 1 ml ampoules. "Gemaza" is stored at a temperature not exceeding +25 ° C in a dry, dark place for 1 year. The dosage form "Gemaza" is approved for use by the Pharmacological Committee of the Republic of Uzbekistan. Department of State Control of Quality, Efficiency, Safety of Medicines and Medical Equipment of the Ministry of Health of the Republic of Uzbekistan. Emoxipin injection solution 1%, active ingredient: Methylethylpiridinol. Pharmacological action - angioprotective, antihypoxic, antiaggregatory. Reduces vascular permeability and blood viscosity, normalizes tissue metabolism, incl. with stroke and heart attack.

Examination of patients with hemophthalmos included: visometry, refractometry and perimetry, biomicroscopy, ophthalmoscopy, tonometry, echobiometry, electrophysiological studies, optical coherence tomography, photo-registration of the fundus state, the dynamics of visual acuity was assessed, and visualized ocular fundus. Allied specialists were involved: endocrinologist, therapist. The observation period was 30 days.

The prevalence of hemorrhage in the CT was assessed on the basis of the “hemophthalmos index” [6, 14], calculated from the data of indirect binocular ophthalmoscopy with a +30 D lens. In this case, the retina was divided into 4 quadrants and the visibility of the details of the retina was assessed in points from 0 to 3:

0 - blood and its residues are not detected, all details of the retina are visible;

1 - minor hemorrhage or its remains, details of the retina are visible in the fog;

2 - moderate hemorrhage, a weak pink reflex is determined, but details are difficult to see;

3 - massive hemorrhage, pink reflex is absent, details of the retina are indistinguis

Table 3

Dynamics of the "hemophthalmos index", in points (M ± m)

Groups	Before treatment	Observation time, days				
		1	3	7	14	30
I	10,9 ± 0,18	9,8 ± 0,17	8,4 ± 0,18	5,9 ± 0,19	4,2 ± 0,18	3,1 ± 0,14
II	11,1 ± 0,17	9,6 ± 0,19	8,2 ± 0,19	4,9 ± 0,23	3,8 ± 0,18	2,6 ± 0,21
III	11,0 ± 0,21	9,1 ± 0,19	7,4 ± 0,2	4,3 ± 0,26	3,1 ± 0,21	2,2 ± 0,2

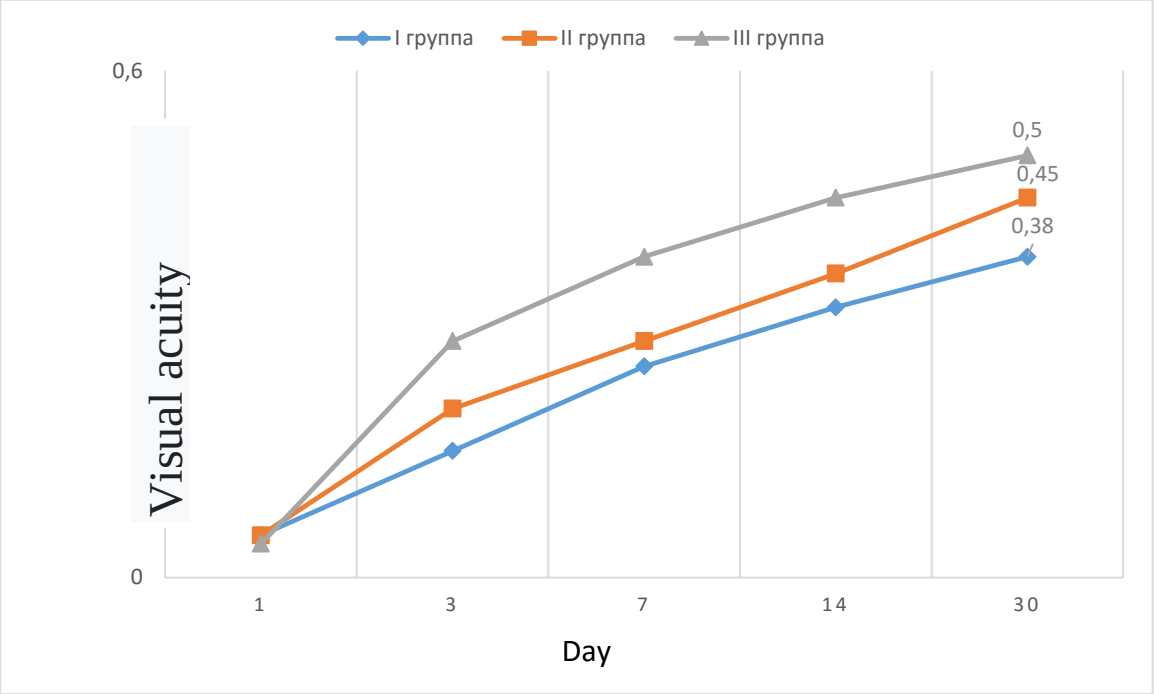

Fig. 1. Dynamics of visual acuity in patients with diabetic retinopathy complicated by hemophthalmos. (M ± m)

The examination results in points for each quadrant were added and the "hemophthalmic index" was obtained, which was assessed in three groups on days 1, 3, 7, 14, 30 of observation. The difference between the mean indices of the "hemophthalmos index" for individual groups was assessed using the Student's coefficient of reliability (t) (Table 3).

Additionally, as the transparency of the optical media was restored, the day on which the fundus was visualized was recorded in each patient. To assess the general status, indicators of general clinical and biochemical blood tests were analyzed, as well as indicators characterizing the state of the coagulation system: prothrombin index, fibrinogen, active recalcification time, clotting time and bleeding time. These data

were analyzed before starting treatment and again after 7 days.

Attention was drawn to the tolerance and development of local and systemic manifestations of allergic reactions when using drugs, as well as the frequency of repeated hemorrhages and the frequency and severity of detachment of the posterior hialoid membrane (PCM).

Results and its discussion

Comparison of the dynamics of the average visual acuity showed no statistically significant difference in the groups before treatment. As follows from Figure 1, visual acuity in patients of groups I and II increased significantly ($p < 0.05$) starting from 3 days of observation compared to the initial one, and in patients of group III after the first day. In patients in whose treatment Gemaza was used intravitreally, visual acuity indices from day 3 to the end of the observation period exceeded ($p < 0.05$) the indices of the group with Parabulbar Emoxipin and Subtenon administration Gemaza. At the end of the observation period, the average visual acuity in group III was 0.50 ± 0.02, in group II - 0.45 ± 0.02, and in group I - 0.38 ± 0.03. The parameters of the "hemophthalmos index" in patients of all groups before the start of treatment were approximately the same (Table 3). However, one day after the start of treatment and until the end of the observation period in group III, the "hemophthalmos index" was lower ($p < 0.05$) than in groups I and II.

When examining the general condition, we compared the average indicators of the general clinical blood test before and 7 days after the start of treatment in each group, as well as a comparison of the indicators of the biochemical blood test between the groups. No statistically significant differences were found in the study groups. However, in all observation groups, an increase in the average blood glucose level was noted, since there were patients with diabetes mellitus in the study groups.

According to the results of the analysis of the data of ultrasound scanning in group III, in 3 cases, the development of complete detachment of the BM on the 14th day of observation was noted, in groups I and II by the 30 days of observation, one case of complete detachment of the BM was noted. Repeated hemorrhages were noted: in group I in 3 cases, in group II in 2 cases, and in group III in 2 cases. The studied groups are close in composition, average age and include cases of hemophthalmos in patients with proliferative diabetic retinopathy with hemorrhage up to 14 days old. Preliminary studies have shown almost the same average visual acuity and the degree of transparency of optical media in all groups before treatment. This testifies to equal initial conditions in each group. Further, as the course of therapy is carried out, the dynamics of average indicators differ depending on the observation gro "Gemazu" is used [1, 4, 10, 11] to increase the effectiveness of treatment of hemophthalmos of various genesis, the drug is most effective in the resorption of partial hemophthalmos. With recurrent hemophthalmia (including proliferative diabetic retinopathy), the effectiveness of the course of treatment is maximal with the first hemorrhage and decreases with subsequent relapses. There is a decrease in the effectiveness of the drug with the development of mooring processes in the vitreous body. In severe proliferative

changes in the retina with recurrent hemorrhagic complications, the use of Gemaza may be associated with an increased risk of recurrent hemorrhage. In an experimental study of the pharmacokinetics of "Gemaza" [1, 5, 7, 12], it was proved that 90% of the administered dose enters the vitreous body after intravitreal administration. With extraocular methods of introducing "Gemaza": subconjunctivally, parabulbarly, into the subtenon space with a needle or with the help of subtenon implantation of a collagen infusion system (SICIS) in the vitreous, its content is much less - from 0.05 to 5% of the administered d

Extraocular application of "Emoxipin" is widely used in the treatment of intraocular traumatic hemorrhages [4], however, one must take into account the fact that with a closed and, even more so, with an open injury of the eye, the permeability of the blood-ophthalmic barrier for injected drugs sharply increases. In clinical practice, intravitreal administration of various fibrinolytics (urokinase, TAP) has shown their high efficiency in the treatment of patients with hemophthalmos [9]. When analyzing the dynamics of the average indicators of visual acuity and the "hemophthalmic index" in the groups, it was noted that within a day the highest visual acuity and the largest decrease in the "hemophthalmic index" occurred in group III, where "Hemase" was injected intravitreally. The half-life of the drug from the vitreous body is about 8 hours [1, 5, 7], this allows you to start the reaction of fibrinolysis in the vitreous body immediately after the administration of the drug. In groups I and II, the accumulation of the drug in an amount sufficient for effective fibrinolysis occurs at a later date, therefore clot lysis begins later, therefore the average visual acuity in these groups has a statistically significant difference from the initial on the 3rd day observation

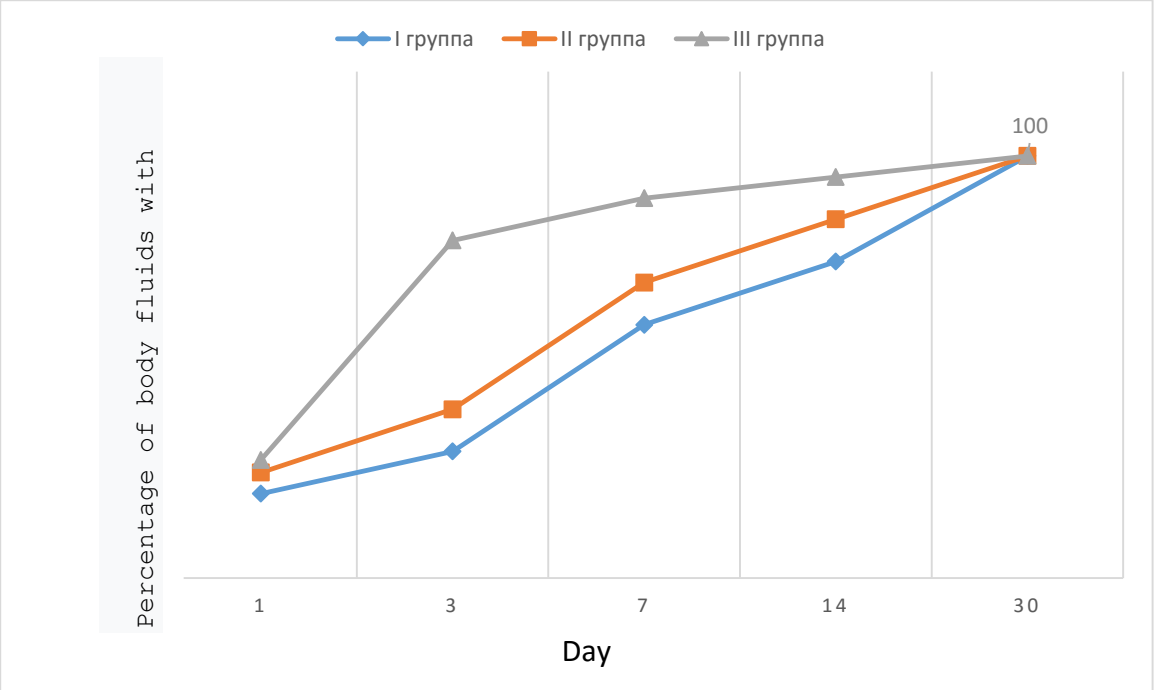

Fig. 2. Visualization of the fundus in dynamics

Since visual acuity can depend on the state of the retina, for an integral assessment of the restoration of the transparency of optical media, we analyzed the percentage of visualization of the fundus during ophthalmoscopy, depending on the timing of observation. When approximating the obtained data, graphs were built that show that in group III, the transparency of optical media is restored much faster, and by the 7th day in 90% of patients the fundus is visualized, in group II a little more than 50%, and in Group I only about 30% (Fig. 2). This allowed in group III to conduct a session of panretinal laser coagulation (PRLC) earlier, the average time from the start of treatment to the PRLC session was: in group I - 19 ± 3.5 days, in group II - 17 ± 3 days, and in group III - 10 ± 3.2 days.

When assessing the indicators of general clinical and biochemical blood analysis, general analysis of urine, statistically significant differences in the groups were not revealed, which confirms the absence of any systemic effect on the body with local administration of fibrinolytic drugs. Separately, the coagulogram indices were compared between the groups; no statistically significant differences were found in the mean indices of the active recalcification time, prothrombin index, fibrinogen level, platelet count, bleeding time, time of onset and end of coagulation. This confirms the absence of a systemic effect on hemostasis with local administration of Gemaza.

conclusions

Thus, the intravitreal administration of Gemaza prevails over other methods and opens up opportunities for earlier laser surgery in diabetic retinopathy.

At the same time, allergic complications from the use of "Gemaza" were not observed, and the frequency of repeated hemorrhages does not depend on the method of administration.

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