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COMPARATIVE ANALYSIS OF THE RESULTS OF USING PEPTIDES AND CITICOLINE AT DIFFERENT STAGES OF RETINITIS PIGMENTOSA

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Retinitis pigmentosa is a severe hereditary pathology in ophthalmology and represents a medical and social problem. The purpose of the study was to establish hemodynamic parameters in the vessels of the eye and electrophysiological parameters of the retina in patients with different stages of retinitis pigmentosa before and after the use of peptides and citicoline and to conduct a comparative analysis of the results. 56 patients (112 eyes) diagnosed with retinitis pigmentosa aged 25–44 were examined. Electroretinography and colour Doppler mapping of the central retinal artery and short posterior ciliary arteries were performed. The patients were treated with endonasal electrophoresis with Retinalamin and Omk1 instillation. All patients showed a statistically significant decrease in hemodynamic parameters and electroretinography parameters. After treatment, hemodynamic and electroretinography parameters increase, and the effect is longer in the subgroup with combined therapy.

Key words: retinitis pigmentosa, hemodynamics, electroretinography, peptides, citicoline.

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ПОРІВНЯЛЬНИЙ АНАЛІЗ РЕЗУЛЬТАТІВ ЗАСТОСУВАННЯ ПЕПТИДІВ І ЦИТИКОЛІНУ ПРИ РІЗНИХ СТАДІЯХ ПІГМЕНТНОГО РЕТИНІТУ

Пігментний ретиніт є важкою спадковою патологією в офтальмології і є медичною та соціальною проблемою. Метою дослідження було вивчити гемодинамічні параметри в судинах ока та електрофізіологічні показники сітківки у пацієнтів з різними стадіями пігментного ретиніту до та після застосування пептидів та цитиколіну та провести порівняльний аналіз результатів. Було обстежено 56 пацієнтів (112 очей) з діагнозом пігментний ретиніт у віці 25–44 років. Ми проводили електроретинографію та кольорове допплерівське картування центральної артерії сітківки, задніх коротких циліарних артерій. Пацієнтам проводили курс терапії ендоназального електрофорезу з Ретиналаміном та інстиляції Омк1. У всіх пацієнтів виявлено статистично достовірне зниження гемодинамічних параметрів та показників електроретинографії. Після лікування підвищуються гемодинамічні параметри та показники електроретинографії, причому у підгрупі з комбінованим лікуванням ефект більш тривалий.

Ключові слова: пігментний ретиніт, гемодинаміка, електроретинографія, пептиди, цитиколін.

As in all branches of medicine and ophthalmology, hereditary diseases are a severe pathology and are considered a medical and social problem. Retinitis pigmentosa (RP) is one such disease. It is a genetically determined progressive disease of the organ of vision with primary damage to the photoreceptor layer and pigment epithelium. RP is the most common form of hereditary retinal dystrophy. RP's clinical, genetic and morphological heterogeneity makes it an extremely complex ocular lesion. The prognosis of RP is considered unfavorable due to the constant development of the degenerative process, leading to complete blindness [2, 4].

In recent years, several scientific and clinical studies have demonstrated the role of oxidative stress, leading to ischemia of the posterior segment of the eyeball, in some common retinal diseases, including RP [5, 8]. There are works confirming the disturbance of blood flow during RP, observed throughout the progression of the dystrophic process [5, 13]. However, the specific mechanism of blood flow disturbances in RP is not entirely clear, and further research is required to clarify the role of vascular disorders.

Currently, there is no effective therapeutic strategy for RP. In recent years, many therapeutic approaches have become promising with the development of molecular biology techniques. New therapeutic agents can be tailored depending on the stage of the disease. In the early stages, the first approach will be to try to stop the degeneration using gene therapy or pharmacological treatment. The second approach aims to combat the death of photoreceptor cells using neurotrophic growth factors or anti-apoptotic factors [4, 12].

In recent years, works have been devoted to studying peptides' neuro- and retinoprotective properties. The positive effect of peptides on the functioning of the photoreceptor apparatus and neuronal tissue has been confirmed in several scientific studies [6, 9]. It has been established that using peptides improves the functional interaction of the retinal pigment epithelium and the outer segments of photoreceptors, regulates metabolic processes, activates antioxidant protection and restores the retina's light sensitivity [6, 9]. It justifies using such drugs to maintain and improve photoreceptor function, which is necessary for RP.

The drug Citicoline is also of interest for use in vascular disorders. It is a nootropic drug that exhibits neuroprotective and neuroreparative activity and protects the membranes of nerve fibre cells from damage. Citicoline has been shown to inhibit glutamate release, protecting nerve cells [3]. Various studies have shown that citicoline is effective and safe in the treatment of cerebrovascular disorders [1]. Despite the different pathogenetic mechanisms of such pathologies as age-related macular degeneration, diabetic retinopathy, glaucoma, retinopathy of prematurity, as well as birth defects, studies are confirming the harmful effects of oxidative stress in all these pathologies [5, 8]. The retinal ischemia caused by oxidative stress leads to neuronal and vascular dysfunction. Therefore, we considered it appropriate to use citicoline, which has neuroprotective and neuroreparative properties, also for RP.

The purpose of the study was to establish hemodynamic parameters in the vessels of the eye and electrophysiological parameters of the retina in patients with different stages of retinitis pigmentosa before and after the use of peptides and citicoline and to conduct a comparative analysis of the results.

Materials and methods. 56 patients (112 eyes) with RP aged 25–44 were examined. Among them, 32 patients were male and 24 were female. Patients with a severe form of cardiovascular or pulmonary disease, with chronic or recurrent eye diseases (uveitis, scleritis, etc.), with an infection, eye injury or surgery within the last 6 months, as well as with acute or progressive retinal diseases were not included in the examination. All patients underwent routine ophthalmological examinations and electrophysiological and Doppler studies.

Using the Nemio XG SSA-580A device from TOSHIBA (Japan), hemodynamic parameters in the eye vessels were studied using Colour Doppler flow mapping (CDFM) to determine the state of the hemodynamics of the eye. Using a linear probe with a frequency of 8 MHz, blood flow in the central retinal artery (CRA) and short posterior ciliary arteries (SPCA) was visualized. Quantitative blood flow parameters were studied: peak systolic velocity (Vmax), end-diastolic velocity (Vmin) and resistance index (RI). Electrophysiological studies included general electroretinography (GERG) and rhythmic electroretinography (RERG). The ERG indicators were recorded using the Super Color Ganzfeld Q450 SC device from Roland CONSULT (Germany).

Taking into account functional disorders, according to the severity of the dystrophic process, patients were divided into 2 groups according to stages. Group I included 31 patients (62 eyes) with the initial stage of RP. In these patients, during ophthalmoscopy, deposition of single characteristic “bone bodies” type was observed on the extreme and middle periphery of the fundus, the field of vision was concentrically narrowed to 40 degrees, and visual acuity averaged 0.95±0.03. Group II included 25 patients (50 eyes) with a moderate stage of RP. In these patients, during ophthalmoscopy, pronounced pigmentation of the “bone body” type was observed on the extreme and middle periphery of the fundus, the field of vision was concentrically narrowed from 40 to 20 degrees, and visual acuity averaged 0.50±0.26. The control group consisted of 10 healthy volunteers aged 25–44 years to determine normative ERG values and 50 practically healthy people aged 25–44 years to determine reference values of hemodynamic parameters.

Depending on the treatment performed, 2 subgroups of patients were identified in each group. Subgroup 1 (Sgr 1) included patients who underwent endonasal electrophoresis (ENE) with Retinalamin (Geropharm), which is a preparation of biogenic peptides. Subgroup 2 (Sgr 2) included patients who received combined treatment – ENE and instillation of OMK-1 (Farmigea S.p.A. Italy), containing citicoline. ENE was carried out using a BTL 4000 electrotherapy device (Great Britain). The current strength during the procedure was determined individually according to the patient’s feelings. The course of ENE-a consisted of 10 sessions over 2 weeks. Citicoline instillations were carried out over a course of 3 months. All patients were examined before therapy and overtime after 2 weeks, 1 month and 3 months.

Statistical data processing was carried out using the statistical package SPSS 26, which used the methods of variation analysis in dependent and independent groups to calculate the Mann-Whitney reliability index (pU), according to Wilcoxon (pW).

Results of the study and their discussion. The GERG and RERG indices were statistically significantly reduced before the start of therapy in all patients of groups I and II. After the treatment, positive dynamics were revealed.

A comparative analysis of ERG parameters after treatment between Sgr 1 and Sgr 2 patients revealed the following results. For the amplitude of the a-wave GERG, pU 2 weeks after therapy was equal to 0.549, after 1 month – 0.094, which is not statistically significant. After 3 months, the difference was statistically significant; pU was equal to 0.012*. For the latency of the a-wave GERG, pU after therapy after 2 weeks was equal to 0.174, after 1 month – 0.051. After 3 months, the pU was equal to 0.003*. For the b-wave amplitude of the GERG, pU after treatment after 2 weeks was equal to 0.811, after 1 month – 0.155, after 3 months pU was <0.001**. For the latency of the b-wave GERG, pU 2 weeks after therapy

was 0.517. After 1 month, it was 0.096. After 3 months, pU was 0.014*. For the N1-P1 indicator of GERG, pU after therapy after 2 weeks was equal to 0.972. After 1 month, it was <0.001**, and after 3 months – 0.003* (Table 1).

Table 1

GERG and RERG parameters in Groups I and II

ERG parameters		Terms	Group I Sgr 1/Sgr 2	Group II Sgr 1/Sgr 2
GERG				
a-wave	amplitude (μV) Norm 155-356	before	91.8±2.8**/91.8±2.8**	47.8±1.3**/49.8±1.0**
		2 weeks	124.2±4.2**/127.5±3.9**	64.7±2.6**/64.6±1.8**
		1 month	113.8±3.6**/122.4±3.8**	58.5±2.5**/59.7±1.9**
		3 months	99.5±3.6*/111.5±3.7**	51.6±1.9*/57.6±2.0**
	latency (ms) Norm 14-22	before	20.8±1.4**/20.6±0.7**	22.5±0.1**/22.5±0.1**
		2 weeks	19.5±0.2**/18.9±0.3**	21.0±0.2**/20.9±0.2**
		1 month	20.1±0.2**/19.3±0.3**	21.7±0.1**/21.3±0.2**
		3 months	20.7±0.2/19.6±0.3**	22.1±0.1*/21.7±0.1**
b-wave	amplitude (μV) Norm 290-654	before	208.2±2.1**/203.9±1.8**	92.3±0.7**/92.0±0.7**
		2 weeks	252.8±5.5**/247.7±4.1**	133.5±3.7**/143.7±3.1**
		1 month	244.4±5.3**/252.9±5.5**	126.9±3.6**/112.4±3.2**
		3 months	222.1±3.2**/245.2±5.1**	112.3±2.7**/141.2±3.3**
	latency (ms) Norm 33-46	before	43.5±0.2**/43.4±0.2**	46.3±0.1**/46.2±0.1**
		2 weeks	41.5±0.3**/41.2±0.3**	45.0±0.2**/44.9±0.2**
		1 month	42.1±0.3**/41.3±0.3**	45.6±0.2**/44.9±0.2**
		3 months	43.2±0.3/42.3±0.3**	46.0±0.2*/45.3±0.2**
RERG – N1-P1 Norm 57-223		before	52.2±0.9**/53.4±0.7**	28.3±0.8**/29.0±0.6**
		2 weeks	63.9±0.9**/64.0±0.8**	49.8±1.6**/52.8±1.2**
		1 month	59.1±1.0**/63.9±0.8**	43.0±1.5**/50.1±1.3**
		3 months	56.5±0.9**/60.2±0.7**	35.7±1.6**/48.2±1.3**

* – $p < 0.05$; ** – $p < 0.001$ – statistically significant difference

These results indicate that using citicoline in Sgr 2 group I patients provides a longer-lasting positive effect.

The Mann-Whitney reliability index between Sgr 1 and Sgr 2 of patients of group II for the amplitude of the a-wave of the GERG after therapy after 2 weeks was equal to 0.756, after 1 month – 0.763. It is a statistically unreliable result. After 3 months, the difference was statistically significant; pU was equal to 0.049*. For the a-wave latency of the GERG, pU 2 weeks after therapy was 0.907, after 1 month – 0.161, and after 3 months, pU was 0.025*. For the GERG b-wave amplitude, pU 2 weeks after therapy was 0.123, after 1 month – 0.006*, after 3 months, it was <0.001**. For GERG b-wave latency, pU 2 weeks after therapy was 0.579; after 1 month, it was 0.028*. After 3 months – 0.010*. For the N1-P1 RERG index, pU 2 weeks after therapy was equal to 0.240. After 1 month and after 3 months, pU was <0.001**. The results in group II also confirm the maintenance of the positive effect of therapy through the use of citicoline.

Based on the CFM in the CRA and SPCA, significant disturbances in hemodynamic parameters were identified, which were statistically significant, in both groups of patients (Table 2, Figs. 1, 2).

According to a comparative analysis of hemodynamic parameters after therapy in patients of group I in the CRA between Sgr 1 and Sgr 2, pU for Vmax after 2 weeks was equal to 0.568, after 1 month – 0.375, which is not statistically significant. After 3 months, there was a statistically significant difference; pU was equal to 0.042*. For Vmin, 2 weeks after therapy, pU was equal to 0.408, after 1 month – 0.042*. After 3 months, pU was <0.001**. For IR, 2 weeks after treatment, pU was 0.323; after 1 month, pU was 0.002**; after 3 months, pU was also 0.002**.

In patients of group II in the CRA between Sgr 1 and Sgr 2, pU for Vmax was equal to 0.540 after 2 weeks, 0.053 after 1 month, and 0.039* 3 months after therapy. For Vmin, pU was 0.036* at 2 weeks, 0.01* at 1 month, and 0.001* at 3 months after treatment. For IR, pU was equal to 0.474 2 weeks after therapy and was <0.001** at 1 and 3 months after treatment.

A comparative analysis of hemodynamic parameters after therapy in the SPCA between Sgr 1 and Sgr 2 patients revealed the following results. For Vmax, 2 weeks after therapy, pU was equal to 0.29, after 1 month – 0.843, which is not statistically significant. After 3 months, the difference was statistically significant; pU was equal to 0.047*.

For Vmin, 2 weeks after therapy, pU was equal to 0.802, and after 1 month – 0.019*. After 3 months, the pU was <0.001**. For IR, 2 weeks after treatment, pU was 0.813, after 1 month – 0.003*, and after 3 months, pU was <0.001**.

Table 2

Hemodynamic parameters in the CRA in Groups I and II

Parameters	Terms of observation	Group I Sgr 1/pU (pW) Sgr 2/pU (pW)	Group II Sgr 1/pU (pW) Sgr 2/pU (pW)
Vmax (cm/sec) Norm 13.6±0.1	before	8.9±0.2/<0.001** 8.6±0.2/<0.001**	7.5±0.2/<0.001** 7.5±0.2/<0.001**
	after 2 weeks	10.1±0.2/<0.001** 10.3±0.2/<0.001**	8.3±0.3/<0.001** 8.6±0.2/<0.001**
	after 1 month	9.8±0.2/<0.001** 10.1±0.2/<0.001**	7.8±0.4/<0.085 8.7±0.3/<0.001**
	after 3 months	9.1±0.3/<0.055 9.9±0.2/<0.001**	7.4±0.3/<0.547 8.4±0.3/<0.001**
Vmin(cm/sec) Norm 3.99±0.04	before	3.4±0.0/<0.001** 3.3±0.0/<0.001**	3.2±0.0/<0.001** 3.1±0.0/<0.001**
	after 2 weeks	3.6±0.0/<0.001** 3.6±0.0/<0.001**	3.5±0.0/<0.001** 3.3±0.0/<0.001**
	after 1 month	3.5±0.0/<0.022* 3.6±0.0/<0.001**	3.3±0.0/<0.005* 3.5±0.0/<0.001**
	after 3 months	3.4±0.0/<0.622 3.6±0.0/<0.001**	3.2±0.0/<0.876 3.4±0.0/<0.001**
IR Norm 0.70±0.002	before	0.63±0.004/<0.001** 0.62±0.004/<0.001**	0.61±0.004/<0.001** 0.60±0.003/<0.001**
	after 2 weeks	0.65±0.003/<0.001** 0.66±0.003/<0.001**	0.65±0.002/<0.001** 0.65±0.002/<0.001**
	after 1 month	0.65±0.003/<0.001** 0.66±0.003/<0.001**	0.64±0.002/<0.001** 0.66±0.002/<0.001**
	after 3 months	0.64±0.003/<0.004* 0.66±0.003/<0.001**	0.63±0.003/<0.001** 0.65±0.002/<0.001**

* – p < 0.05; ** – p < 0.001 – statistically significant difference

In patients of group II, according to the results of a comparative analysis between Sgr 1 and Sgr 2 in SPCA, pU for Vmax, 2 weeks after therapy was equal to 0.612, after 1 month – 0.117, after 3 months, the difference turned out to be statistically significant, pU was equal to 0.004*. For Vmin, 2 weeks after therapy, pU was equal to 0.961, after 1 month – 0.063, and after 3 months –0.001*. For IR, 2 weeks after treatment, pU was 0.504, after 1 month – 0.018*, after 3 months – 0.001**.

The results of a comparative analysis of data in the CRA and SPCA indicate that using citicoline in Sgr 2 in patients of both groups ensures the maintenance of a long-term positive effect on hemodynamics.

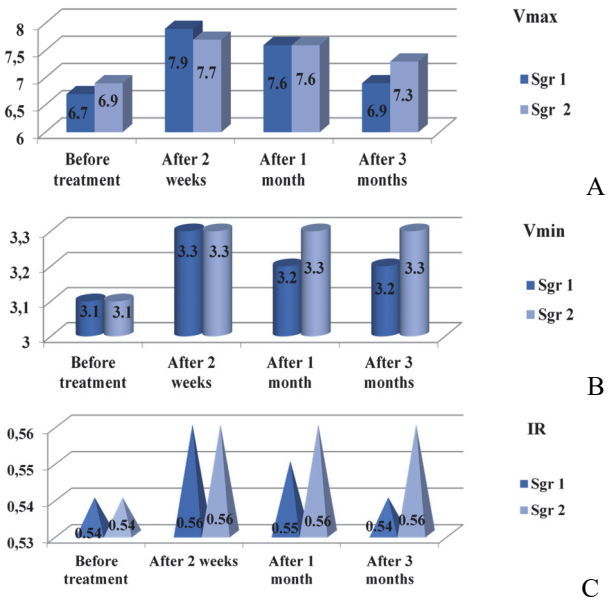

Fig. 1. Hemodynamic parameters in the SPCA in Group I. A – Vmax in Sgr 1 and Sgr 2 of Gr I, B – Vmin in Sgr 1 and Sgr 2 of Gr I, C – IR in Sgr 1 and Sgr 2 of Gr I.

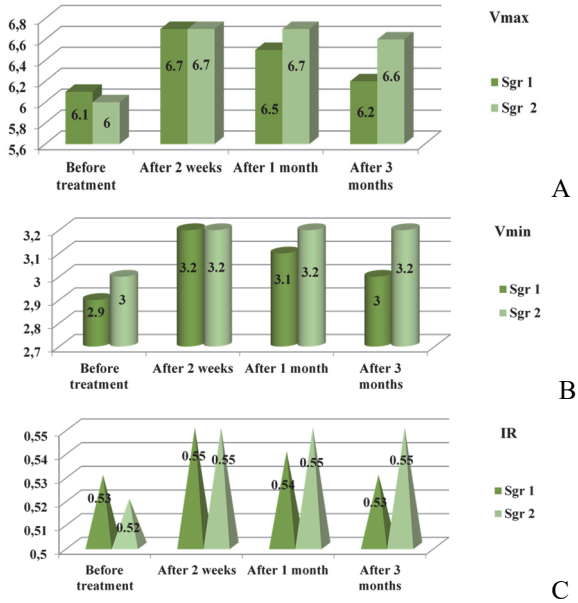

Fig. 2. Hemodynamic parameters in the SPCA in Group II. A – Vmax in Sgr 1 and Sgr 2 of Gr II. B – Vmin in Sgr 1 and Sgr 2 of Gr II. C – IR in Sgr 1 and Sgr 2 of Gr II.

Among the works devoted to the study of RP, there are studies by Jun Wang and Yi Jing et al., which discuss the role of ischemia and oxidative stress in some common retinal diseases, including retinitis pigmentosa [8, 13]. The authors confirm that improving reduced blood flow and enriching the retinal environment effectively reduce photoreceptor degeneration [13]. Also, of interest are works studying the stages of RP. In a study by Iftikhar M et al. similar to our work, a classification of disease severity in RP is presented for categorizing and comparing patients [7]. Nana I. et al., in their study, showed that the rate of progression of visual acuity and visual field tests differed depending on the stage of RP [11]. The authors believe that the work results can help predict the natural course of RP. There are also works studying the effects of peptides in RP. Kadymova F.E. et al. studied the use of Retinalamin and laser stimulation in patients with glaucoma [9]. The work results showed a positive effect of treatment on the optic nerve and retina, proving the drug's neuro- and retinoprotective properties. In the Gashimova N.F. et al. study, the effectiveness of Retinalamin as a retinoprotector has also been proven [6]. The authors administered Retinalamin injections in conjunction with magnetic stimulation and found an improvement in electrophysiological parameters and an increase in visual functions in children with RP. In the study of Savustyanenko A.V. et al., citicoline's effectiveness and safety in treating cerebrovascular disorders have been demonstrated [1]. The results of our study also confirm the neuroprotective effect of citicoline, given its positive impact on the function of photoreceptors, which are photosensitive neurons of the retina.

Conclusions

1. The use of peptides and citicoline is effective in the initial and moderate stages of RP, and the effectiveness is more pronounced in patients with the initial stage of RP.

2. The result of treatment proves the positive effect of peptides and citicoline on the hemodynamics of the eye and the electrophysiological properties of the retina.

3. Based on the results of a comparative analysis, it has been proven that using citicoline in combination with peptides provides a long-term positive effect.

Thus, the combination of peptides and citicoline can be recommended to treat RP. The classification of the severity of the dystrophic process we presented is appropriate for categorizing patients and comparing treatment results.

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