



<https://doi.org/10.34883/PI.2023.13.2.015>



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The Effectiveness of the Ozone Therapy in Prevention of Relapses in Patients with Ophthalmic Herpes

Conflict of interest: nothing to declare.

Authors' contribution: concept, study design, literature analysis, data collection, processing and analysis – Guliyeva M.; preparation of the article, final editing – Gasimov E.

Submitted: 28.04.2023

Accepted: 10.05.2023

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Abstract

Introduction. Recurrent eye herpes is one of the major causes of blindness and low vision, and prevention of recurrences is one of the urgent problems of ophthalmology.

Purpose. Efficiency in evaluation of ozone therapy in combination with standard treatment, for preventing relapses of ophthalmic herpes.

Materials and methods. The study included 134 patients (134 pairs of eyes) with ophthalmic herpes. The age of patients ranged from 20 to 64 (42.7 ± 10.4) years (70 males, 64 females). A test group of 67 patients (67 pairs of eyes) underwent the course of treatment with the ozone-therapy in combination with conventional treatment. The control group of 67 patients (67 pairs of eyes) underwent the conventional treatment.

Results. The efficiency of an anti-recurrent therapy was higher in 74.6% of patients (50 individuals out of 67), no aggravation was noted in follow-up, compared to the control group treated with prophylactic doses of acyclovir in the inter-recurrent period as an anti-recurrent therapy – 43.3% (29 out of 67 patients) ($p < 0.05$). No effect, or an increase in frequency of recurrences after the treatment was observed in the basic group – 3.1% (2 individuals) compared to the control group – 32.8% (22 individual) ($p < 0.05$). All patients treated with ozone therapy, did not have any side effects and a good tolerance was noted.

Conclusion. In case of recurrent ophthalmic herpes, the ozone therapy in combination with traditional anti-herpetic treatment has a preventive effect, causing a significant reduction in the frequency of recurrences and, as a consequence, extending inter-recurrent period, in comparison with the control group of patients treated with anti-recurrent medicines of the abnormal nucleotides group in remission period ($p < 0.05$). For a prevention of ophthalmic herpes recurrences and for an achievement of optimal results of anti-recurrent therapy, in patients with recurrent ophthalmic herpes, it is indicated simultaneously with the start of standard anti-herpetic treatment to begin courses of ozone therapy.

Keywords: ophthalmic herpes, prevention of recurrences, ozone therapy

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Эффективность озонотерапии в профилактике рецидивов у пациентов с офтальмогерпесом

Конфликт интересов: не заявлен.

Вклад авторов: концепция, дизайн исследования, анализ литературы, сбор, обработка и анализ данных – Гулиева М.Г.; подготовка статьи, окончательное редактирование – Касимов Э.М.

Подана: 28.04.2023

Принята: 10.05.2023

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Резюме

Введение. Рецидивирующий герпес глаз является одной из основных причин слепоты и слабовидения, а профилактика рецидивов – одна из актуальных проблем офтальмологии.

Цель. Оценка эффективности озонотерапии в профилактике рецидивов офтальмогерпеса на фоне традиционного лечения.

Материалы и методы. Под наблюдением находились 134 пациента с рецидивирующими формами офтальмогерпеса переднего отдела глаза (герпетический кератит, кератоувеит, увеит). В исследовании принимали участие 70 мужчин и 64 женщины, возраст колебался от 20 до 64 лет ($42,7 \pm 10,4$). Число включенных в основную группу пациентов, проходивших курс противорецидивной терапии озонотерапией, – 67 (67 глаз), так же как и в группу сравнения, получивших курсы противорецидивного лечения препаратами группы ацикловира, – 67 (67 глаз).

Результаты. В основной группе из 67 человек выраженный терапевтический эффект (отсутствие обострений) зарегистрирован у 50 (74,6%) пациентов, частичный терапевтический эффект (снижение частоты рецидивов) наблюдался у 15 (22,3%), отсутствие эффекта – у 2 (3,1%). В контрольной группе из 67 пациентов выраженный терапевтический эффект наблюдался у 29 (43,3%) пациентов, частичный терапевтический эффект (снижение частоты рецидивов) – у 16 (23,9%), отсутствие эффекта – у 22 (32,8%).

Выводы. Для профилактики рецидивов офтальмогерпеса и достижения оптимального результата противорецидивной терапии у пациентов с рецидивирующим офтальмогерпесом показано одновременно с началом стандартного противогерпетического лечения начинать курсы озонотерапии.

Ключевые слова: офтальмогерпес, профилактика рецидивов, озонотерапия

■ INTRODUCTION

The variety of clinical manifestations of herpes virus infection, the peculiarities of pathogens, the possibility of their spread, by almost all known ways of transmission allowed the European regional Office of the world Health Organization, to include herpetic infections into the group of diseases that determine the future of infectious pathology [1–3].



According to the first WHO global, the prevalence of herpes simplex virus type I (HSV-I), published in 2015, demonstrated that more than 3.7 billion people under the age of 50, or 67% of the world's population, are infected by the virus [3].

The increase in the percentage of the incidence of ophthalmic herpes (in the world the number of patients with ophthalmic herpes reaches up to 10 million per year) is associated with the widespread use of steroid drugs, antibiotics, with an increase of influenza epidemics that provoke outbreaks of viral eye lesions [4, 5]. In recent years, the range of proven risk factors for relapse of ophthalmic herpes, associated with the introduction of new technologies, has significantly expanded:

- refractive surgery,
- PRK,
- LASIK,
- laser iridotomy,
- cataract surgery,
- keratoplasty,
- keratoprosthetics,
- femtosecond laser keratotomy [6–8].

It is generally recognized that in recent years, there has been not only an increase, but also an aggravation of herpetic eye lesions. Recurrent ophthalmic herpes is the most common form of eye lesions in HSV, developing in conditions of antibodies circulating in the body. It is believed that 95% of herpetic keratitis are recurrences that occurred long after the initial infection [4, 5].

According to H.E. Kaufman, if the patient has first attack of herpetic keratitis, then there is 25% possibility that he will have a second attack within next 2 years, with a repeated attack 43% probability of having another relapse in the next 2 years. Each subsequent relapse is more difficult, the reaction to conservative therapy is worse, increases the duration of the disease and the number of complications, surgery is often requiring.

Reactivation of HSV occurs under adverse circumstances and with a decrease of the immunological reactivity of the body (any unfavorable conditions can make HSV become active:

- hypothermia or overheating,
- stress or infection,
- pregnancy, breastfeeding,
- a high dose of alcohol, and sometimes beyond computation purely individual factors for a person) [1–4].

According to various authors, despite the attempts to prevent relapses by various methods, none of the modern methods of prevention of ophthalmic herpes prevent and none of them have a significant effect on the frequency of relapses of herpetic eye lesions [9–11].

In recent years, there is an increasing interest of modern medicine to alternative non-drug treatments, which is associated with a number of factors:

- the frequency of allergic reactions to drugs;
- a large number of contraindications and side effects in the appointment of potent drugs;
- increasing the number of comorbidities and concomitant that;
- on the one hand, requires a comprehensive treatment;

- and on the other-increases the number of contraindications for the appointment of different types of treatment;
- increasing the number of resistant strains of microorganisms to existing antibiotics;
- high price of medicines.

Among these methods of treatment, ozone therapy received the greatest recognition, each year ozone therapy finds more supporters among practitioners in more than 50 countries. The Madrid Declaration of 2010, signed by representatives of 34 countries, contributes to the introduction and dissemination of ozone therapy.

The active use of ozone therapy is defined by its wide range of therapeutic effects:

- bactericidal;
- viricidal;
- antifungal;
- antiprotozoal;
- anti-inflammatory;
- immunomodulatory;
- antioxidant;
- antihypoxic;
- detoxication;
- analgesic;
- reparative etc.

Ozone therapy is widely used in various fields of medicine and surgery:

- gastroenterology;
- cardiology;
- rheumatology;
- pediatrics;
- dermatology;
- pulmonology,
- nephrology,
- neurology,
- traumatology, etc. [12–17].

Recently, ozone therapy has been actively used in various areas of ophthalmology for injuries:

- glaucoma;
- endophthalmitis;
- retinal diseases;
- uveitis;
- keratitis [18–29].

■ PURPOSE

To evaluate the anti-relapse efficacy of ozone therapy against the background of traditional treatment in patients with ophthalmic herpes.

■ MATERIALS AND METHODS

In total, 134 patients were under our supervision – all 134 (100%) patients had recurrent forms of ophthalmic herpes of the anterior eye (herpetic keratitis, keratouveitis, uveitis), which were observed during the study period (2010–2018).



The etiological diagnosis of ophthalmic herpes was carried out in Virology laboratory of NCO named after Acad. Z. Aliyeva by identifying the antigen of herpes virus in scrapings from the conjunctiva of fluorescent antibody method (FIA), determination of serum IgM and IgG antibodies to structural antigens of the virus of simple herpes of the first and second type (HSV-I and HSV-II).

Also was carried out the determination of serum IgG antibodies to the early non-structural regulatory antigens of HSV-I and HSV-II by enzyme-linked immunosorbent assay (ELISA). As a marker of herpes virus reactivation, were selected IgG antibodies to non-structural "early" regulatory viral antigens, during the recurrence of infection these antibodies are detected significantly more frequently than IgM-antiviral antibodies ($p < 0.05$). The level of antibodies was determined in blood serum in solid-phase enzyme immunoassay with bioservice (RF) in the initial treatment of the patient and in a month after treatment. For comparison, in parallel in blood serum were determined the levels of the classically used in the diagnosis highly liquid IgG to structural antigens HSV-I and HSV-II.

The diagnosis was also established according to clinical and anamnestic data.

During the examination and observation of patients, were used the methods, generally accepted in clinical practice of ophthalmologists:

- the determination of visual acuity on the projector of test objects;
- examination in diffuse day and focal electric light;
- biomicroscopy;
- fluorescein test;
- esthesiometry;
- OCT of the anterior segment;
- ophthalmoscopy;
- tonometry;
- refractometry;
- and in A-B scanning.

The study involved 70 men and 64 women; age ranged from 20 to 64 years (42.7 ± 10.4).

In our study took part patients with a rare (1 to 2 relapses per year) – 64 patients, medium (3 to 5 relapses per year) – 50 patients and often recurrent (6 times a year to monthly) – 20 patients with relapsing forms of ophthalmic herpes.

Table 1

Results of comparative evaluation of the frequency of detection of elevated levels of IgG to HSV1 and HSV2 antigens in primary treatment

Type of antibodies	Frequency detections antibodies to HSV1, n, %	Frequency detections antibodies to HSV2, n, %
IgG antibodies to "early" antigens	51 (79.7%)	21 (32.8%)
IgG to structural antigens	35 (54.7%)	13 (20.3%)

Table 2

Comparative assessment of the frequency of detection of elevated levels of IgG to HSV1 and HSV2 antigens a month after treatment

Type of antibodies	Frequency detections antibodies to HSV1, n, %	Frequency detections antibodies to HSV2, n, %
IgG antibodies to "early" antigens	14 (21.9%)	5 (7.8%)
IgG to structural antigens	17 (26.6%)	7 (10.9%)

The patients were divided into two groups of the same frequency of relapses and severity of clinical symptoms. The differences between the groups of patients (sex, age, disease duration, number of patients, etc.) were statistically unreliable.

The number of patients included in the main group was 67 (67 eyes), in the comparison group was 67 patients (67 eyes). Patients of both groups received identical traditional drug treatment, which included both selective antiherpetic and pathogenetic symptomatic treatment. As an antiherpetic treatment, patients of both groups received 3% zovirax eye ointment or 1.5% virgan gel 5 times a day, valtrex tablets (500 mg 2 times a day) or zovirax tablets (200 mg 5 times a day), eye drops of ophthalmoferon (5–6 times to 3–4 times a day) and poludan (100 UNITS) for subconjunctival or parabular introduction.

In our research, patients of the main group received ozone therapy as an anti-relapse treatment during the traditional treatment. Patients received ozone therapy in the form of intravenous infusions of ozonated physiological solution (OPP) – 200 ml of physiological saline for 10–15 minutes was saturated with ozone on the device "Medozone BM" of Russian production (ozone dose in each case was selected individually according the weight, severity of the disease and the general condition of the patient) and during 15–20 minutes was administered intravenously (the average ozone dose was 5–9 mg/l, for a course of 5–12 procedures during the month).

As an anti-relapse treatment, patients of the control group, after traditional treatment in the inter-relapse period during influenza, colds and other adverse factors that provoke a relapse of ophthalmoherpes, took prophylactic doses of acyclovir group – zovirax tablet or acyclovir tablet 400 mg 2 times a day in the morning and evening.

The evaluation of clinical efficacy of preventive therapy was carried out on the base of changes in the frequency of relapses, lengthening of the inter-relapse period in the evaluated period, and also as the improvement of clinical indicators during relapse.

■ RESULTS AND DISCUSSION

It was established that in the early stages of the disease, the level of increased IgG to the "early" HSV-I and HSV-II antigens was detected more frequently than the level of IgG to structural antigens. A month after treatment, the level of both types of antibodies was decreased, accordingly was reduction in the frequency of detection of antibodies of high titer. During this period of the research was revealed an increased level of high-avidity IgG to the structural antigens HSV-I and HSV-II more often. A high level of IgG antibodies to non-structural HSV-I and HSV-II antigens in a month after treatment may predict the risk of herpes virus activation and repeated relapse of ocular herpes. 10 patients from 19 patients with elevated levels of IgG antibodies to the "early" HSV-I and HSV-II antigens, had a relapse in the month after treatment. The results of these studies gave the reason for the courses of ozone therapy for the purpose to prevent relapses of ophthalmic herpes in this group of patients.

As a result of the research, it was established that in the main group, treated as an anti-relapse treatment ozone therapy, the effectiveness of anti-relapse therapy is higher – in 74.6% (50 people out of 67) patients during the period of observation were not any exacerbations, in compare with the control group, receiving an anti-relapse treatment preventive doses of acyclovir tablet – 43.3% (29 people out of 67 patients) ($p < 0.05$) during the inter-relapse period.



Table 3
Comparative evaluation of methods of anti-relapse therapy

Recurrence rate	Research group	Quantity of patients	Results after treatment		
			Without recurrence	Reducing of the frequency of relapses	Without effects
1–2 times in a year	basic	32 (47.8%)	25 (37.3%)	6 (8.9%)	1 (1.5%)
	tested	32 (47.8%)	17 (25.4%)	3 (4.5%)	11 (16.4%)
3–5 times in a year	basic	24 (35.8%)	18 (26.9%)	5 (7.5%)	1 (1.5%)
	tested	24 (35.8%)	9 (13.4%)	8 (11.9%)	7 (10.4%)
6 and more in a year	basic	11 (16.4%)	7 (10.4%)	4 (5.9%)	–
	tested	11 (16.4%)	3 (4.5%)	5 (7.5%)	4 (5.9%)
Total	basic	67 (100%)	50 (74.6%)	15 (22.3%)	2 (3.1%)
	tested	67 (100%)	29 (43.3%)	16 (23.9%)	22 (32.8%)

Absence of effect after treatment was lower in the main group – 3.1% (2 people), in compare with the control – 32.8% (22 people) ($p < 0.05$). The results are presented in table 3.

It was established that at patients in the main group, receiving ozone therapy simultaneously with traditional treatment, some clinical indicators-terms of resorption of corneal infiltration in keratitis (19.3 ± 0.62 and 22.9 ± 0.72 , $p < 0.05$), the terms of resorption of corneal and vascular infiltration in keratouveitis (21.4 ± 0.2 and 24.8 ± 0.1 , $p < 0.05$), the terms of resorption of infiltration of the vascular membrane in uveitis (19.28 ± 0.5 and 22.4 ± 0.6 , $p < 0.05$) and duration of treatment, respectively, (20.5 ± 0.2 and 23.7 ± 0.4 , $p < 0.05$), (22.1 ± 0.1 and 25.9 ± 0.5 , $p < 0.05$) and (20.3 ± 0.4 and 23.6 ± 0.3 , $p < 0.05$) were significantly shorter. The results are presented in tables 4–6, in figure 1, 2.

Thus, after the conducted researches it was established that in recurrent ophthalmoherpes, the use of ozone therapy in parallel with traditional treatment has a preventive effect, causing a significant reduction in the frequency of relapses and accordingly extension of the inter-relapse period, in compare with the control group of patients undergoing courses of anti-relapse treatment with preventive doses of drugs

Table 4
The comparative clinical parameters of the patients with herpetic keratitis

Research group	Index severity	The beginning of epithelialisation of cornea	The full of epithelialisation of cornea	Resorption of infiltration of cornea	Duration of treatment	Visual acuity before after	
Basic	21.58 ± 0.54	3.28 ± 0.49	17.9 ± 0.16	19.3 ± 0.62	20.5 ± 0.2	0.1 ± 0.08	0.61 ± 0.09
Tested	21.25 ± 0.7	3.87 ± 0.46	19.2 ± 0.84	22.9 ± 0.72	23.7 ± 0.4	0.18 ± 0.07	0.63 ± 0.08
Reliability of criteria	$p > 0.05$	> 0.05	> 0.05	< 0.05	< 0.05	> 0.05	> 0.05

Table 5
The comparative clinical parameters of the patients with herpetic keratouveitis

Research group	Index severity	Resorption of infiltration	Visual acuity dynamics before after		Duration of treatment
Basic	23.15 ± 0.34	21.4 ± 0.2	0.04 ± 0.02	0.71 ± 0.09	22.1 ± 0.1
Tested	22.47 ± 0.4	24.8 ± 0.1	0.08 ± 0.03	0.66 ± 0.08	25.9 ± 0.5
Reliability of criteria	$p > 0.05$	< 0.05	> 0.05	> 0.05	< 0.05

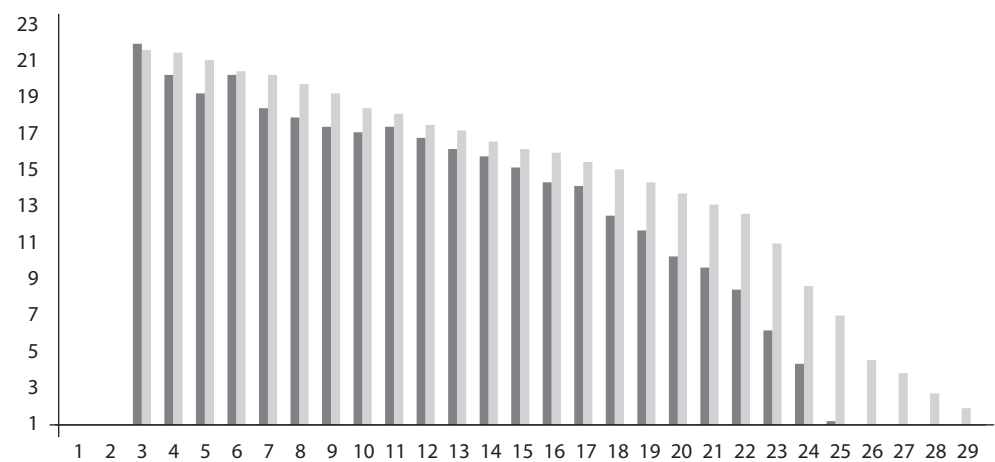


Fig. 1. Severity index dynamics

Table 6
The comparative clinical parameters of the patients with herpetic uveitis

Research group	Index severity	Resorption of infiltration	Duration of treatment	Visual acuity dynamics before after	
Basic	22.8±0.54	19.28±0.5	20.3±0.4	0.01±0.08	0.8±0.09
Tested	22.3±0.7	22.4±0.6	23.6±0.3	0.02±0.06	0.69±0.07
Reliability of criteria	p>0.05	<0.05	<0.05	>0.05	>0.05

of the acyclovir group ($p<0.05$). It was also found that the main group, which received the ozone therapy during relapse in parallel with traditional treatment, according some clinical indicators – the terms of resorption of corneal infiltration, choroid and duration of treatment – exceeds the control ($p<0.05$). It was also noted that in cases where after ozone therapy at one or another period relapse of ophthalmic herpes occurred, it proceeded in a lighter form with less expressed clinical signs, the duration of the disease was relatively shorter and less intensive treatment was required.

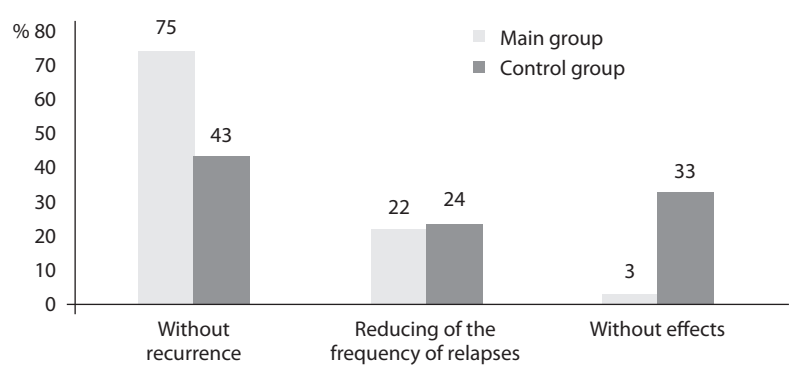


Fig. 2. The effectiveness anti-relaps therapy



At all patients, receiving ozone therapy, in no case were found side effects, toxic and allergic irritations and good tolerance was noted. In the control group, were observed side effects in the form of pain and discomfort in the stomach and kidneys, sleep disorders, headache, dizziness, etc. were observed at patients.

■ CONCLUSION

For the prevention of relapses of ocular herpes and achievement of the optimal result of anti-relapse therapy at patients with recurrent ocular herpes, it was noted to start ozone therapy courses with the beginning of standard antiherpetic treatment simultaneously.

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