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EFFICACY OF NIGELLA SATIVA COMBINED WITH OZONE THERAPY IN THE COMPREHENSIVE TREATMENT OF HERPETIC STROMAL KERATITIS COMPLICATED BY UVEITIS AND OCULAR HYPERTENSION

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Herpetic stromal keratitis complicated by uveitis and ocular hypertension is characterized by a severe and prolonged course and requires comprehensive treatment. The aim of this study was to evaluate the efficacy of *Nigella sativa*-based preparation combined with ozone therapy as an adjunct to conventional treatment. The study included 20 patients (20 eyes), aged 23–69 years, divided into a study group and a control group of 10 patients each. The study group additionally received *Nigella sativa*-based preparation and intravenous ozone therapy. The mean time to resorption of corneal infiltration, edema, and precipitates was 15.4±0.9 days in the study group versus 19.6±0.6 days in controls ($p<0.05$). Treatment duration was significantly shorter (16.8±0.7 vs 21.4±0.62 days; $p<0.05$). Recovery was achieved in 80 % and 60 % of patients, respectively. The combined treatment demonstrated good tolerability without toxic or allergic reactions and improved clinical treatment outcomes.

Key words: herpetic stromal keratitis, uveitis, ocular hypertension, *Nigella sativa*, ozone therapy.

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ЕФЕКТИВНІСТЬ ЗАСТОСУВАННЯ NIGELLA SATIVA У ПОЄДНАННІ З ОЗОНОТЕРАПІЄЮ У КОМПЛЕКСНОМУ ЛІКУВАННІ СТРОМАЛЬНОГО ГЕРПЕТИЧНОГО КЕРАТИТУ, УСКЛАДНЕНОГО УВЕЇТОМ З ОФТАЛЬМОГІПЕРТЕНЗІЄЮ

Стромальний герпетичний кератит, ускладнений увеїтом з офтальмогіпертензією, характеризується важким і тривалим перебігом та потребує комплексного лікування. Метою дослідження була оцінка ефективності застосування *Nigella sativa* у поєднанні з озонотерапією як доповнення до традиційного лікування. До дослідження було включено 20 пацієнтів (20 очей) віком 23–69 років, розділених на основну та контрольну групи по 10 пацієнтів. Пацієнти основної групи додатково отримували *Nigella sativa* та внутрішньовенну озонотерапію. Середній термін розсмоктування інфільтрації, набряку рогівки та преципітатів становив 15,4±0,9 дня в основній групі та 19,6±0,6 дня в контрольній групі ($p<0,05$). Тривалість лікування була достовірно коротшою: 16,8±0,7 проти 21,4±0,62 дня ($p<0,05$). Одуження відзначено у 80 % та 60 % пацієнтів відповідно. Комбіноване лікування характеризувалося хорошою переносимістю, відсутністю токсико-алергічних реакцій та поліпшенням клінічних результатів лікування.

Ключові слова: стромальний герпетичний кератит, увеїт, офтальмогіпертензія, *Nigella sativa*, озонотерапія.

Herpes virus is considered one of the oldest representatives of all pathogenic microorganisms. Among all viruses of this family, herpes simplex virus type 1 (HSV-1), for a number of reasons, is considered a model virus as a neurotropic pathogen

causing severe forms of ocular herpes [5, 10].

The main biological and pathogenetic features of herpesviruses are long-term persistence in the body of an infected person, polytropism to various tissues, and the ability to reactivate. These properties of

herpesviruses determine the polymorphism of clinical manifestations, multiorgan involvement in generalized forms, and a high probability of transition of the infection to a chronic recurrent course [10].

Innate and adaptive immune responses are key to combating HSV, and the virus has developed mechanisms that allow it to evade them. The immune response may also contribute to pathogenesis, as observed in stromal keratitis and encephalitis. The fact that some people are more susceptible to severe disease when infected with HSV than others may be partly explained by the existence of genetic polymorphisms in humans. Like all herpesviruses, HSV has two replication cycles: lytic and latent. During lytic replication, HSV produces infectious viral particles that infect other cells and organisms, whereas during the latent period there is limited gene expression and an absence of infectious viral particles. HSV establishes a latent state in neurons and may cause disease both during primary infection and during reactivation. The mechanisms leading to latency and reactivation, and the virus-host interaction factors controlling these processes, have not been fully studied; therefore, the use of natural immune-regulating agents without adverse side effects may be considered an extremely important direction in the therapy of ocular herpes [5].

Recently, there has been increasing interest in modern medicine in alternative non-pharmacological methods of treatment, which is associated with the high frequency of adverse side effects of chemotherapeutic drugs, contraindications, and many other aggravating factors [2, 3, 12, 16].

Ozone therapy, as a natural method of treatment, has long attracted the interest of physicians of various specialties. The active use of ozone therapy is determined by its broad spectrum of therapeutic effects: bactericidal, virucidal, fungicidal, antiprotozoal, anti-inflammatory, immunomodulatory, antioxidant, antihypoxic, detoxifying, analgesic, reparative, and many others. Medical ozone is widely used in various fields of medicine, including dentistry, dermatology, neurology, oncology, and many others, and in ophthalmology for dry eye and age-related macular degeneration [17, 19, 20].

Among various medicinal plants, *Nigella sativa* (black cumin) stands out as a miraculous plant with a rich history, since numerous studies have revealed its broad pharmacological potential and therapeutic effects - anti-inflammatory, antimicrobial, antioxidant, immunomodulatory, antitumor, antidiabetic, and others [11, 13-15, 18]. Literature data indicate the high therapeutic efficacy of *Nigella sativa* in the treatment of patients with various pathologies [1, 4, 6-9].

Both Ozone Therapy and *Nigella sativa*-based preparation are multifactorial, polysystemic natural methods of treatment that do not disturb the natural balance of the body; therefore, the time has come for the full-scale introduction of Ozone Therapy and *Nigella sativa* into the pharmaceutical sphere, meeting all requirements of quality, efficacy, and safety, rather than regarding them as an alternative or esoteric approach.

The purpose of the study was to evaluate the efficacy of *Nigella sativa*-based preparation in combination with Ozone Therapy in the comprehensive treatment of herpesvirus stromal keratitis complicated by uveitis with ocular hypertension.

Materials and methods. The study was conducted at the basis of National Ophthalmology Center named after Academician Z. Aliyeva during the period of March 2024–February 2025.

Our study included 20 patients (20 eyes) with stromal herpetic keratitis and uveitis with ocular hypertension, including 12 men and 8 women; age ranged from 23 to 69 years, and the mean age was 42.9 ± 12.5 years. The patients were divided into two groups equivalent in terms of the severity of clinical symptoms.

The patients presented at different times (from several weeks to several months) after the development of the disease. Objectively, pericorneal injection, pronounced corneal edema, thickening and infiltration of the stromal layer of the cornea, isolated areas of de-epithelialization, and multiple pigmented precipitates of various sizes were observed; all patients had increased intraocular pressure and a pronounced decrease in vision of varying degrees. Before presenting to us, the patients had been given various diagnoses (two patients with very low vision had been diagnosed with terminal glaucoma) and had received corresponding treatment, which aggravated the condition of the eye.

Etiological diagnosis of herpetic keratitis was performed in the virology laboratory of the National Ophthalmology Center named after Academician Z. Aliyeva by detecting herpesvirus antigen in conjunctival scrapings (immunofluorescence assay), determining serum IgM and IgG against structural antigens of HSV-1 and HSV-2, as well as determining serum IgG antibodies against early regulatory nonstructural antigens of HSV-1 and HSV-2 (ELISA). The diagnosis was also established on the basis of clinical and anamnestic data.

During the examination and follow-up of patients, methods generally accepted in ophthalmological clinical practice were used: determination of visual acuity using a test-object projector; examination under diffuse daylight and focal electric illumination; biomicroscopy; fluorescein test; esthesiometry; anterior-segment OCT; ophthalmoscopy; pneumotometry; Goldmann or Maklakov tonometry; refractometry; and A-B scanning.

The study included 12 men and 8 women; age ranged from 23 to 69 years, and the mean age was 42.9 ± 12.5 years. The patients were divided into two groups equivalent in terms of the severity of clinical symptoms.

The number of patients included in both the main group and the comparison group was the same: 10 patients – 10 eyes in each group.

Symptomatic treatment included specific and nonspecific anti-inflammatory agents: Predac® eye drops (prednisolone acetate 1%; Orchidia Pharmaceutical Industries, Egypt) and Dicloftil® eye drops (diclofenac sodium 0.1%; Farmigea S.p.A., Italy),

as well as meloxicam tablets (meloxicam; manufacturer depending on the commercial preparation used). Mydriatic therapy included Tropicamide eye drops (tropicamide; manufacturer depending on the commercial preparation used) and Cycloplegisedol® eye drops (cyclopentolate hydrochloride; Portugal), administered three times daily. Intraocular pressure-lowering therapy included Oftan Timolol® eye drops (timolol maleate; Santen Oy, Finland) or Augenstock Combipress® eye drops (brimonidine tartrate 2 mg/mL + timolol maleate 5 mg/mL; Aristopharma Ltd., Bangladesh), administered twice daily. Antiallergic therapy consisted of Eslotin® tablets (desloratadine 5 mg; Laboratoria Bailly-Creat, France), one tablet at night. Cycloferon® (meglumine acridone acetate; POLYSAN) was administered subconjunctivally or parabolbarly at 50 units once daily for 7–10 days. As additional treatment, patients in the study group received Seydana capsules (*Nigella sativa* seed preparation, biologically active additive registered by the Ministry of Health of the Republic of Azerbaijan), one 400-mg capsule three times daily, in the morning, afternoon, and evening, during or after meals for one month.

Ethics Statement. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients were informed about the procedures and treatment provided, and informed consent was obtained from each participant prior to inclusion in the study. Patient confidentiality and anonymity were maintained throughout the study and during preparation of the manuscript.

Statistical analysis was performed using descriptive and comparative statistical methods. Quantitative variables are presented as mean $\pm$ standard deviation ($M \pm SD$), while categorical variables are expressed as absolute numbers and percentages. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. A p -value <0.05 was considered statistically significant.

Results of the study. Treatment efficacy in the study was evaluated according to the time of

resorption of corneal infiltration and edema and precipitates, normalization of intraocular pressure, dynamics of visual acuity, and duration of treatment.

Results of treatment in the main group of patients who, along with conventional treatment, additionally received *Nigella sativa*-based preparation Seydana capsules and intravenous Ozone Therapy were as follows. The time to complete resorption of infiltration, corneal edema, and precipitates ranged from 12 days (1 patient – 10 %) to 17 days (1 patient – 10 %); the mean period was 15.4 ± 0.9 days.

Visual acuity increased in all patients, on average from 0.05 ± 0.1 to 0.73 ± 0.2 . In 9 (90 %) patients, visual acuity above 0.1 was achieved, while in 3 (30 %) patients the maximum visual acuity of 1.0 was achieved.

The total duration of treatment was 16.8 ± 0.71 days. In 2 (20 %) patients, residual corneal infiltration and isolated precipitates were recorded by day 18 of treatment; these patients were classified as having improvement.

Treatment efficacy was assessed as follows: recovery – 8 patients (80 %); improvement – 2 patients (20 %). In the analysis of side effects, no signs of toxic-allergic irritation were observed in any case. The results of the general clinical examination (patients' subjective sensations, temperature response, urine and blood tests) indicated good tolerability of the combined use of *Nigella sativa*-based preparation Seydana and Ozone Therapy as part of conventional treatment.

Results of treatment in the control group of patients who received conventional treatment only demonstrated that the time to resorption of infiltration and corneal edema ranged from 17 days (1 patient – 10 %) to 25 days (1 patient – 10 %); the mean period was 19.6 ± 0.6 days.

Visual acuity increased in all patients, on average from 0.05 ± 0.2 to 0.69 ± 0.4 . In 7 (70 %) patients, visual acuity above 0.1 was achieved, while in 2 (20 %) patients the maximum visual acuity of 1.0 was achieved (Table 1).

Table 1

Comparative clinical indicators of patients with stromal herpetic keratitis and uveitis with ocular hypertension

Indicator	Main group	Comparison group	Significance criterion
Severity index	16.3 ± 0.5	16.1 ± 0.7	$p > 0.05$
Resorption of infiltration	15.4 ± 0.9	19.6 ± 0.6	$p < 0.05$
Duration of treatment	16.8 ± 0.7	21.4 ± 0.62	$p < 0.05$
Visual acuity before treatment	0.05 ± 0.1	0.05 ± 0.2	$p > 0.05$
Visual acuity after treatment	0.73 ± 0.2	0.69 ± 0.4	$p > 0.05$

The total duration of treatment was 21.4 ± 0.62 days. In 4 (40 %) patients, residual corneal infiltration and precipitates were recorded by day 21 of treatment; these patients were classified as having improvement.

Thus, the duration of treatment was significantly shorter in the study group receiving *Nigella sativa*-based preparation Seydana in combination with ozone therapy as an adjunct to conventional treatment than in the control group receiving conventional

treatment alone (Fig.1).

Recovery was achieved in 80 % of patients in the study group and 60 % of patients in the control group, whereas improvement without complete recovery was observed in 20 % and 40 % of patients, respectively. Thus, the study group demonstrated a higher proportion of patients achieving recovery and a lower proportion classified as showing improvement compared with the control group (Fig.2).

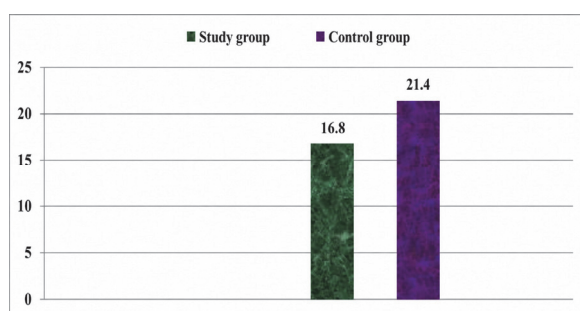


Fig. 1. Duration of treatment.

Discussion. Analysis of the study results in patients of the main group, who received Ozone Therapy in combination with *Nigella sativa*-based preparation (Seydana) as additional treatment, compared with the control group, which received conventional treatment only, showed that resorption of infiltration of the corneal stroma and vascular coat in patients of the main group was completed almost 4 days earlier than in the control group (15.4 ± 0.9 and 19.6 ± 0.6 , respectively; $p < 0.05$). The duration of treatment in patients of the main group was 4 days shorter than in the comparison group (16.8 ± 0.7 and 21.4 ± 0.62 , respectively; $p < 0.05$). Recovery was noted in 80 % and 60 % of cases, and improvement in 20% and 40% of cases, respectively; deterioration and absence of effect were not observed in any case. The effect of increased visual acuity was 0.73 ± 0.2 and 0.69 ± 0.4 , respectively ($p > 0.05$). Ocular hypertension normalized in both groups, but in the main group approximately 3 days earlier. In the main group, in which Ozone Therapy and *Nigella sativa*-based preparation (Seydana) were used as part of conventional treatment, a higher therapeutic effect was noted for some parameters (time to resorption of infiltration of the corneal stroma and vascular coat and duration of treatment) compared with the control group; the results were statistically significant.

The favorable clinical outcomes observed in the present study may be considered in the context of the biological properties of *Nigella sativa* reported in previous investigations. Ciesielska-Figlon et al. described its potential immunomodulatory activity, including modulation of inflammatory and immune responses [4]. Hannan et al. summarized a broad spectrum of pharmacological properties of *Nigella sativa*, including antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory effects [9].

Ardiana et al., (2020) in a meta-analysis of randomized controlled trials, found that *Nigella sativa* supplementation significantly increased superoxide dismutase activity, although significant changes in malondialdehyde and total antioxidant capacity were not demonstrated [1]. These findings provide a possible biological context for the shorter time to resolution of corneal infiltration, edema, and precipitates observed in our study group. Nevertheless, because the present study evaluated a combined treatment regimen rather than Seydana alone, the clinical improvement cannot be attributed exclusively to *Nigella sativa*.

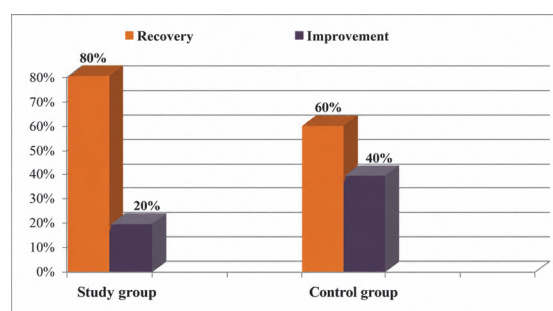


Fig. 2. Treatment efficacy.

The results may also be discussed in relation to the reported biological effects of ozone therapy. Zanardi et al. (2016) described controlled ozone administration as capable of inducing adaptive responses to oxidative stress and discussed its potential therapeutic use in combination with established treatments [20]. Other studies included in our reference list have investigated ozone therapy across different clinical settings, including wound treatment, dermatological disorders, dentistry, and degenerative disc disease [12,16,17,19]. Although these conditions differ substantially from herpetic stromal keratitis, the available literature supports continued investigation of ozone therapy as an adjunctive approach rather than as a replacement for established treatment. In our study, the addition of ozone therapy and *Nigella sativa*-based preparation (Seydana) to conventional antiherpetic treatment was associated with a significantly shorter duration of treatment (16.8 ± 0.7 vs 21.4 ± 0.62 days; $p < 0.05$) and earlier resolution of corneal infiltration (15.4 ± 0.9 vs 19.6 ± 0.6 days; $p < 0.05$). However, the small sample size and combined administration of both adjunctive interventions do not allow the independent contribution of Ozone Therapy and *Nigella sativa*-based preparation (Seydana) to be determined.

Thus, as a result of the conducted open comparative studies evaluating therapeutic efficacy and studying the tolerance of the combined use of Ozone Therapy and *Nigella sativa*-based preparation (Seydana), it was established that both natural agents exert a pronounced therapeutic effect. It was shown that the combined use of natural agents with different mechanisms of action – Ozone Therapy and Seydana – mutually enhances antiviral, anti-inflammatory, and immunomodulatory effects of an additive, synergistic nature and produces a more pronounced therapeutic effect, reducing the time to resorption of infiltration of the cornea and vascular coat and the duration of treatment.

The results of virological examination of scrapings from the conjunctiva of the eye were negative in all patients. In the analysis of side effects, no signs of toxic-allergic irritation were observed in any case. The results of the general clinical examination (patients' subjective sensations, temperature response, urine and blood tests) indicated good tolerability of the combined treatment. The results of immunological blood testing with determination of the level of specific

immunoglobulins revealed a more significant decrease in the level of HSV-I IgG and IgM after treatment in the main group compared with the control group.

Conclusion

Thus, the conducted open comparative clinical studies evaluating therapeutic efficacy and studying the tolerance of the combined use of Ozone Therapy and *Nigella sativa*-based preparation as part of conventional treatment showed that comprehensive use makes it possible to significantly increase the efficacy of treatment of herpetic stromal keratitis complicated by uveitis with ocular hypertension, improves clinical indicators, and does not cause toxic-allergic phenomena. It can be concluded that the combined use of two natural multifactorial and polysystemic therapeutic agents – Ozone Therapy and *Nigella sativa*-based preparation – together with conventional chemotherapeutic drugs increased treatment efficacy, demonstrated good tolerability, and did not cause toxic-allergic irritation or other undesirable adverse effects in patients with herpetic stromal keratitis complicated by uveitis with hypertension. Future studies with larger patient cohorts and longer follow-up periods are warranted to further evaluate the clinical efficacy, safety, and long-term outcomes of combined *Nigella sativa*-based preparation and ozone therapy in patients with herpetic stromal keratitis.

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