Effect of combination treatment with vascular therapy and hyperbaric oxygenation on ocular hemodynamics in patients with recurrent herpetic stromal keratitis

Maksymova I. R. [1], Khramenko N. I. [2]

[1] Dnipropetrovsk Regional Clinical Ophthalmological Hospital, Dnipro (Ukraine)

[2] SI «The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine» Odesa (Ukraine)

Вплив комбінованого лікування із застосуванням судинної терапії та гіпербаричної оксигенації на гемодинаміку ока у хворих на рецидивуючий стромальний герпетичний кератит

Максимова І. Р. [1], Храменко Н. І. [2]

[1] КНТ «Дніпропетровська обласна клінічна офтальмологічна лікарня», Дніпро (Україна)

[2] ДУ «Інститут очних хвороб та тканинної терапії ім. В.П.Філатова НАМН України», Одеса (Україна)

Abstract

Purpose. *To use Doppler ultrasound for evaluating the effect of vascular therapy and hyperbaric oxygenation (HBO) on ocular hemodynamics in patients with recurrent herpetic stromal keratitis (HSK).*

Material and Methods. *Totally, 60 patients with unilateral HSK (mean age, 39.4 ± 9.5 years) were included in the study. They were divided into groups of 20 based on the treatment scheme. Group 1 was treated conventionally with anti-inflammatory and etiopathogenetic therapy only, group 2 received conventional treatment plus vascular therapy (vinpocetine) only, and group 3, conventional treatment plus vascular therapy and HBO (ten 45-minute sessions at 1.5 atmospheres). A Doppler ultrasound machine (Toshiba Nemio-20) was used to determine peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI) in the ophthalmic artery (OA) and central retinal artery (CRA), and PSV in the central retinal vein (CRV). Fellow eyes were used as controls. An integral vascular response index (IVRI) was calculated based on relative post-treatment changes (Δ%) in major Doppler parameters and was employed for evaluating hemodynamic response to treatment. Cohen's d was used for evaluating effect sizes.*

Results. *Vascular therapy, when used as an adjunct to conventional treatment, resulted in a significant improvement in OA hemodynamics, with increases in Δ% PSV (25.3–34.1%; $p<0.0001$) and Δ% EDV (40.4–41.0%; $p<0.0001$) compared to anti-inflammatory therapy only. Improvements in PSV and RI were most pronounced when vascular therapy was combined with HBO. Vascular therapy, when combined with HBO, resulted in a significant improvement in CRA hemodynamics, with sequential reductions in Δ%PSV (to –29.6%) and Δ%EDV (to –24.6%), reflecting the normalization of retinal blood flow. Among the three treatment groups, group 3 showed the PSV and EDV values closest to those in the fellow eyes, which reflected the most pronounced hemodynamic effect. The increase in IVRI reflected an additive response to reduced inflammation, normalized vascular tone, improved microcirculation and corrected tissue hypoxia in group 3.*

Conclusion. *Anti-inflammatory treatment combined with vascular therapy and HBO allowed for the best effect on and OA and CRA hemodynamics. IVRI values indicated that, HBO, when used as an adjunct to combination treatment for recurrent HSK, was associated with an additional improvement in ocular hemodynamics (most notable, OA hemodynamics).*

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Corresponding Author: Khramenko N.I., Ophthalmologist, Cand Sc (Med) and Senior Researcher; Ocular Diagnostics Department, SI «The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine», Odesa, Ukraine. Email: Khramenkon@gmail.com

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Резюме

Мета. *Вивчити вплив гіпербаричної оксигенаційної терапії (ГБОТ) та судинної терапії на показники очної гемодинаміки у хворих на рецидивуючий стромальний герпетичний кератит (СГК) за даними ультразвукової доплерографії.*

Матеріал та методи. *Обстежено 60 пацієнтів (середній вік – 39,4±9,5 року) з рецидивуючим монолатеральним СГК, яких залежно від схеми лікування розподілили на три групи (по 20 пацієнтів, 20 очей): 1-ша – стандартна протизапальна та етіопатогенетична терапія; 2-га – стандартна терапія, доповнена судинною терапією (вінпоцетин); 3-тя – стандартна та судинна терапія в поєднанні з курсом гіпербаричної оксигенаційної терапії (ГБОТ) (10 сеансів по 45 хв. при тиску 1,5 ата). Очну гемодинаміку досліджували методом ультразвукової доплерографії («Toshiba Nemio-20») з визначенням показників PSV, EDV та RI в a. ophthalmica і a. centralis retinae, а також PSV у v. centralis retinae. Парне інтактне око використовували як референсний контроль. Для оцінки гемодинамічної відповіді запропоновано інтегральний судинний індекс (IVRI), розрахований на основі відносних змін (Δ%) основних доплерографічних показників до та після лікування. Розмір ефекту лікування оцінювали за допомогою показника Cohen's d.*

Результати. *Додавання судинної терапії до стандартного лікування забезпечувало достовірне покращення гемодинаміки в басейні a. ophthalmica, що проявлялося збільшенням Δ% PSV (25,3–34,1% p<0,0001) та Δ% EDV (40,4–41,0% p<0,0001) порівняно з ізольованою протизапальною терапією. Найбільш виражений приріст PSV і RI спостерігався при поєднанні судинної терапії з гіпербаричною оксигенацією. У басейні a. centralis retinae застосування судинної терапії та гіпербаричної оксигенації супроводжувалося послідовним зменшенням Δ% PSV (до –29,6%) і Δ% EDV (до –24,6%), що відображало нормалізацію ретинального кровотоку. Найбільш виражений гемодинамічний ефект спостерігався в 3-й групі, де показники PSV та EDV були найближчими до значень парного ока. Зростання інтегрального судинного індексу (IVRI) відображає адитивний вплив на усунення запалення, нормалізацію судинного тонусу, покращення мікроциркуляції та корекції тканинної гіпоксії в 3-й групі хворих.*

Висновки. *Поєднання протизапальної, судинної та гіпербаричної оксигенаційної терапії забезпечує найефективніший вплив на показники гемодинаміки в басейнах a. ophthalmica та a. centralis retinae. Запропонований інтегральний індекс судинної реактивності (IVRI) свідчить, що включення ГБОТ до комплексного лікування хворих на рецидивуючий СГК асоціюється з додатковим позитивним впливом на показники очної гемодинаміки, найбільш вираженим у басейні a. ophthalmica.*

Ключові слова: *кератит, вірус простого герпесу, регіонарна гемодинаміка, сльозопродукція, морфометрія рогівки, рогівка, ультразвукова діагностика, гіпербарична оксигенаційна терапія (ГБОТ)/*

Introduction

Herpetic keratitis (HK) is a leading cause of corneal blindness and visual impairment worldwide [1]. It is characterized by its clinical polymorphism, ranging from superficial epitheliopathy to stromal keratitis, keratouveitis and neurotrophic keratitis [2]. Herpetic stromal keratitis (HSK) develops in 25 to 50% of patients and is a major cause of persistent reduction in visual acuity. Patients with prolonged or recurrent HSK develop corneal scarring and neovascularization [3].

The changes in central and regional hemodynamics for adequate perfusion and metabolism to support tissue homeostasis are a manifestation of typical inflammatory response.

A 2011 work by Gaydamaka [4] demonstrated that the ocular circulation in HK depends on the stage and course of the disease. In acute HK, there is hyperemia as a manifestation of vascular inflammatory response, whereas in quiescent HK, especially in the course of the disease with frequent relapses, it decreases compared to the healthy fellow eye. Gaydamaka [4] found that corneal dystrophic changes are associated with insufficient ocular blood supply.

The main function of ocular blood flow is to supply sufficient oxygen and nutrients to the eye. Impaired ocular perfusion causes limited oxygen supply to the eye and the development of local tissue hypoxia and metabolic abnormalities which may contribute to the progression of dystrophic changes [5].

Hypoxia is a critical pathogenetic factor in many retinal diseases, including glaucoma, hypertensive and diabetic retinopathy, retinal arterial occlusion and retinal vein occlusion. The primary driver of hypoxia-induced changes in the retina is the activation of hypoxia-inducible factor 1-α (HIF-1α), leading to downstream activation of vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS) [6, 7].

Just as hypoxia can induce inflammation, inflamed lesions often become severely hypoxic. Contributors to tissue hypoxia during inflammation include an increase in the metabolic demands of cells, abnormal perfusion, compression (interstitial hypertension), trauma, and increased oxygen consumption by infected cells during intracellular pathogen replication. In the case of inflamed tissue, hypoxia is not a bystander, but an important regulator of immune

response, and activates oxygen-dependent mechanisms of transcriptional regulation, and, above all, the host's HIF pathway, which results in a change in the expression of numerous genes involved in angiogenesis, cell metabolism and tissue remodeling [8].

Chronic inflammation is associated with the development of tissue hypoxia, mitochondrial dysfunction and metabolic tissue remodeling. Under conditions of oxygen deficiency, cells shift to a state of metabolic activation, and synthesize biologically active metabolites which perform signaling functions and support immune response. Consequently, hypoxia, oxidative stress, mitochondrial dysfunction and metabolic cellular changes are considered interrelated mechanisms which determine the course of chronic inflammation [9].

The use of therapeutic hyperbaric oxygenation (HBO) as an adjunct to multicomponent therapy for HK promoted clinical recovery by accelerating corneal re-epithelialization, resorption of infiltrates, and resolution of pericorneal injection and reduction of hospital stay length [10].

To the best of our knowledge, no study has reported on the effect of HBO on regional and local ocular hemodynamics in recurrent HK. Therefore, it is important to investigate the role of HBO in the restoration of blood supply to tissues, improvement in ocular hemodynamics and modification of immune response in this disease.

The purpose of the study was to use Doppler ultrasound for evaluating the effect of vascular therapy and HBO on ocular hemodynamics in patients with recurrent HSK.

Material and Methods

Totally, 60 patients (29 men and 31 women; mean age, 39.4 ± 9.5 years) with active unilateral chronic recurrent HSK were examined at the Dnipropetrovsk Regional Clinical Ophthalmological Hospital. The clinical forms of the disease were determined based on the classifications by Liesegang [11] and Holland and Schwartz [12]. Immune (non-necrotizing) was diagnosed in 42 patients (42 eyes), and group 2 (necrotizing HSK), in 18 patients (18 eyes).

This prospective clinical comparison study was approved by the Bioethics committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (Meeting Minutes No. 2 of April 18, 2025) and followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association, ICH guideline for good clinical practice and relevant laws of Ukraine. Informed consent was obtained from all subjects.

Patients were divided into three treatment groups. At baseline, there was no significant between group difference in age, sex, disease duration or major clinical characteristics.

The treatment scheme for patients in group 1 (20 patients; 20 eyes) included conventional anti-inflammatory and etiopathogenetic therapy. Topical treatment included miramistin, levofloxacin and ganciclovir ophthalmic gel. In the presence of corneal epithelial defects, this treatment was continued until corneal re-epithelialization was complete; otherwise, it was administered for five days and then tapered over the next three weeks. In the absence of epithelial defects or corneal ulceration, topical corticosteroids were administered after the initiation of anti-viral therapy; otherwise, they were administered after corneal re-epithelialization was complete. Tear substitutes were also used and topical dexpanthenol was administered nightly. Systemic therapy included valacyclovir 1000 mg 3 times daily for 3 days, followed 2 times daily for up to 14 days, and then 500 mg 2 times daily as supportive therapy. Additionally, the B vitamins and essential phospholipids were administered throughout the period of treatment. Systemic corticosteroids were administered based on individual clinical indications. The duration of topical therapy was up to three weeks, and the duration of systemic or supportive therapy, up to one month.

The treatment scheme for patients in group 2 (20 patients; 20 eyes) included the above mentioned conventional anti-inflammatory and etiopathogenetic therapy. Additionally, these patients received vascular therapy (vinpocetine 5 mg three times daily for two months), which was administered once inflammation has subsided and the patient's clinical status has stabilized. Depending on the clinical course of the diseases, this corresponded to two to three weeks after the initiation of the anti-inflammatory and etiopathogenetic therapy.

Patients in group 3 (20 patients; 20 eyes) received not only the above mentioned conventional therapy and vascular therapy, but also a course of HBO (ten daily 45-minute sessions of hyperbaric 95-percent medical oxygen at 1.5 atmospheres in a BLKS 301M monoplace chamber) in the presence of vascular therapy. Pneumothorax was an absolute contraindication to HBO. Other contraindications included a severe lung disease with an increased risk of barotrauma, acute upper respiratory and ear infections, uncontrolled seizures, decompensated heart failure, pregnancy, a history of vitreoretinal surgery and history of intraocular gas (SF6, C2F6, etc) use.

Doppler ultrasound evidence of post-treatment functional changes in regional hemodynamics was the main subject of analysis.

A Doppler ultrasound machine (Toshiba Nemio-20, Toshiba Medical Systems, Tokyo, Japan) with a 8-MHz linear transducer, 3-MHz convex transducer, and 3.75-MHz microconvex transducer was used to assess hemodynamics in the ophthalmic artery (OA), central retinal artery (CRA) and central retinal vein (CRV). Peak systolic velocity (PSV; cm/s), end diastolic velocity (EDV; cm/s), and resistance index (Ri) were determined bilaterally in the OA and CRA, and PSV only was determined in the CRV. Fellow eyes were used as controls.

The Shapiro-Wilk test was used for statistical analysis if the data were normally distributed. Normally distributed data are presented as mean ± standard deviation (SD) or mean [95% confidence interval (CI)]. The independent t-test was used for group comparison of normally distrib-

uted data. The following formulas were used to determine percentage changes in maximum PSV, EDV, and RI (post and pre indices correspond to baseline and post-treatment):

$\Delta\%PSV = ((PSVpost - PSVpre) / PSVpre) \times 100\%$

$\Delta\%EDV = ((EDVpost - EDVpre) / EDVpre) \times 100\%$

$\Delta\%RI = ((RIpost - RIpre) / RIpre) \times 100\%$.

An integrated vascular response index (IVRI) reflects total post-treatment changes in major Doppler parameters and was proposed for a comprehensive evaluation of hemodynamic response in every local vascular bed. Since the above parameters differ in their contribution to the hemodynamic profile, each component was standardized for subsequent unification of directions of changes:

$ZPSV = (\Delta PSV - M\Delta PSV) / SD\Delta PSV$

$ZEDV = (\Delta EDV - M\Delta EDV) / SD\Delta EDV$

$ZRI = (\Delta RI - M\Delta RI) / SD\Delta RI$

As a result, the standardized index IVRIstd was obtained:

$IVRIstd = (ZPSV + ZEDV + ZRI)/3$,

where Z is a standardized value (dimensionless quantity); Δ, a change with treatment in the characteristic in a patient; M, a mean value of Δ for the entire sample or group; SD, standard deviation of Δ for the group.

Additionally, we proposed to use a ratio of the IVRI for the eye affected by keratitis to the IVRI for the fellow eye (Keratitis/Fellow Ratio or KFR) for the quantitative evaluation of interocular asymmetry in vascular response. Cohen's d was used for evaluating effect sizes and characterizes a standardized value of the difference in IVRI between two groups and reflects the clinical significance of changes found regardless of the units of measurement of characteristics. Cohen's d is defined as a difference between two means divided by the pooled SD for those two means.

Cohen's d was used for evaluating treatment effect sizes and enables evaluating practical (clinical) significance of the differences found in IVRI. Cohen's D effect sizes were interpreted as follows: below 0.2 = no effect; 0.2 to 0.5 = small; 0.5 to 0.8 = medium; and above 0.8 = large.

Results

The percentage change in PSV (Δ%PSV) in the OA of the eye with HSK was higher in groups 2 and 3 (25.3% and 34.1%, respectively) than in group 1 (1.2%), and the difference was significant (Table1). The highest Δ% PSV in the OA of the eye with HSK was observed in group 3 (34.1% versus 25.3% for group 2; p = 0.008) (Table 1). These results indicate that vascular therapy as an adjunct to the conventional therapy promoted the recovery of OA inflow, whereas adjunctive HBO allowed additional activation of systolic perfusion, which was manifested by increased Δ% PSV. The normalization of PSV in the OA of the eye with HSK was observed only in group 3, where the mean value (37.8 ± 1.5 cm/s) was close to that for the fellow eye (38.8 ± 2.2 cm/s; p = 0.03) (Table 1).

The percentage change in EDV (Δ%EDV) in the OA of the eye with HSK was higher in groups 2 and 3 (40.4% and 41.0%, respectively) than in group 1 (1.9%), and the

Table 1. Peak systolic velocity (PSV) in the ophthalmic artery in patients before and after treatment for herpetic stromal keratitis (HSK)

Parameter	1		2		3		p
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
PSV (cm/s) in the OA in the eye with HSK; mean ± SD; n = 20	29.7±3.3	30.2±2.9	28.9±3.3	35.8±2.9	28.4±2.7	37.8±1.5	$P_{1post\text{-}treatment} = 0.6$ $P_{2post\text{-}treatment} < 0.0001$ $P_{3post\text{-}treatment} < 0.0001$
Δ %PSV in the OA in the eye with HSK; mean (95% CI); n=20	1.2 (0.12-3.4)		25.3 (16.9-33.7)		34.1 (27.0-40.2)		$P_{1\text{-}2} < 0.0001$ $P_{1\text{-}3} < 0.0001$ $p_{2\text{-}3} = 0.008$
PSV (cm/s) in the OA in the fellow eye of a patient with HSK; mean ± SD; n=20	39.7 ±2.1	38.1±8.3	38.3±2.3	40.3±2.0	38.3±2.1	40.2±1.7	$P_{1post\text{-}treatment} = 0.2$ $P_{2post\text{-}treatment} = 0.003$ $P_{3post\text{-}treatment} = 0.001$
Δ%PSV in the OA in the fellow eye of a patient with HSK; mean (95% CI); n=20	0 (-14.0-4.7)		5.3.(2.9-7.8)		4.8 (3.2-6.4)		$P_{1\text{-}2} < 0.0001$ $P_{1\text{-}3} < 0.0001$ $P_{2\text{-}3} = 0.8$

Note: 1, anti-inflammatory therapy only; 2, anti-inflammatory therapy with adjunctive vascular therapy; 3, anti-inflammatory therapy with adjunctive vascular therapy and hyperbaric oxygenation; Δ% PSV, a pre-to-post-treatment percentage change in peak systolic velocity after treatment; CI, confidence interval; n, number of eyes; HSK, herpetic stromal keratitis; OA, ophthalmic artery; PSV, peak systolic velocity; SD, standard deviation

Table 2. End diastolic velocity (EDV) in the ophthalmic artery in patients before and after treatment for herpetic stromal keratitis (HSK)

Parameter	1		2		3		p
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
EDV (cm/s) in the OA in the eye with HSK; mean ± SD; n = 20	7.0±0.8	7.1±0.8	6.9±0.7	9.6±0.9	7.1±0.7	10.0±0.8	$P_{1post-treatment}$ = 0.3 $P_{2post-treatment}$ < 0.0001 $P_{3post-treatment}$ < 0.0001
Δ %EDV in the OA in the eye with HSK; mean (95% CI); n = 20	1.9 (0.48-3.4)		40.4 (31.2-49.58)		41.0 (34.2-47.8)		P_{1-2}<0.0001 P_{1-3}<0.0001 P_{2-3}=0.8
EDV (cm/s) in the OA in the fellow eye of a patient with HSK; mean ± SD; n = 20	9.7±0.9	9.7±0.8	9.6±0.9	10.3±0.9	9.9±0.9	10.7±0.6	$P_{1post-treatment}$ = 0.9 $P_{2post-treatment}$ = 0.01 $P_{3post-treatment}$ = 0.0006
Δ% EDV in the OA in the fellow eye of a patient with HSK; mean (95% CI); n=20	0.14 (0.48-3.4)		6.3 (2.6-10.8)		6.7 (4.6-12.1)		P_{1-2} < 0.0001 P_{1-3} < 0.0001 P_{2-3} = 0.5

Note: 1, anti-inflammatory therapy only; 2, anti-inflammatory therapy with adjunctive vascular therapy; 3, anti-inflammatory therapy with adjunctive vascular therapy and hyperbaric oxygenation; Δ%EDV, a pre-to-post-treatment percentage change in end diastolic velocity; CI, confidence interval; n, number of eyes; EDV, end diastolic velocity; HSK, herpetic stromal keratitis; OA, ophthalmic artery; SD, standard deviation

difference was significant (Table 2). There was, however, no significant difference between groups 2 and 3. The results indicate that vascular therapy as an adjunct to the conventional therapy promoted the recovery of diastolic OA blood flow. The fact that adjunctive HBO did not result in additional improvement in Δ% EDV indicated the achievement of the maximum OA hemodynamic response. The mean EDV for the fellow eye was 9.7 ± 0.9 cm/s. EDV in the affected eye normalized with treatment only in patients in group 3, with a mean value of 10.0 ± 0.8 cm/s.

The increase in RI in the affected eye to a level close to that found for the fellow eye reflects the recovery of the mechanisms involved in regional vascular autoregulation. The percentage change in RI (Δ%RI) in groups 2 and 3 was 1.4% (p = 0.03) and 3.4% (p < 0.0001), respectively, which was statistically significantly higher, that in group 1, with the largest Δ% RI found for group 3 (Table 3). The mean RI for the fellow eye was 0.75 ± 0.009. RI in the affected eye normalized with treatment only in patients in group 3, with a mean value of 0.74 ± 0.01 (Table 3).

The IVRI that we had proposed reflected the total magnitude of the OA vascular response, demonstrating clear gradient dynamics with an increase in value from group 1 to group 3 both for the effected eye and the fellow eye. Among the three groups, group 3 had the highest IVRI values for the affected eye and the fellow eye (26.58 ± 9.41 та 4.96 ± 2.81, respectively), followed by group 2 (22.74 ± 13.89 and 4.97 ± 3.72, respectively), and group 1 with a wide range of variation (0.28–1.26). This indicates an increase in OA vascular response, which was most marked in group 3 and predominantly in the eye with HSK. KFR showed a downward trend in IVRI asymmetry, from 7.2 for group 1 to 6.2 for group 3, with no significant between group differences, likely due to a high between individual variability.

Pairwise comparison found marked between group differences with large effect sizes (Cohen's d), reflecting clinically significant differentiation in the hemodynamic profile depending on the type of therapy. For the OA bed in the eye with HSK, effect sizes were d_{1-2} = 1.42; d1-3 = 2.58; and d_{2-3} = 1.11, which corresponds to large effects and reflects marked dynamic changes in the vascular reactivity in the presence of therapy. The most substantial effects sizes were observed for the groups with a vascular component of treatment (groups 2 and 3). For the OA bed in the fellow eye of patients with HSK, effect sizes were lower (d_{1-2} = 1.18; d_{1-3} = 1.95; d_{2-3} = 0.88) than those in the affected eye, which corresponds to large effects of a lower magnitude, indicating a contralateral secondary systemic vascular response with a limited range of functional remodeling. This may be explained by the absence of marked tissue hypoxia in, and preserved perfusion of, the fellow eye, which resulted in HBO failing to provide additional effects on hemodynamics.

Therefore, patients in group 3 (who received anti-inflammatory therapy with adjunctive vascular therapy and HBO) showed most marked hemodynamic response of the OA vascular bed, which was manifested by maximum

Table 3. Resistivity index (RI) in the ophthalmic artery in patients before and after treatment for herpetic stromal keratitis (HSK)

Parameter	1		2		3	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
RI in the OA in the eye with HSK; (mean ± SD); n = 20	0.68±0.05	0.68±0.05	0.71±0.03	0.72±0.03	0.70±0.03	0.74±0.01
Δ%RI in the OA in the eye with HSK; mean (95% CI); n = 20	0		1.4 (0.6-2.1)		3.4 (2.1-6.3)	
	P_{1-2}=0.03; P_{1-3}<0.0001; P_{2-3}=0.03					
RI in the OA in the fellow eye of a patient with HSK; (mean ± SD); n = 20	0.75±0.007	0.75±0.006	0.75±0.009	0.75±0.009	0.75±0.009	0.75±0.009
Δ%RI in the OA in the fellow eye of a patient with HSK; mean (95% CI); n = 20	0		0		0	

Note: 1, anti-inflammatory therapy only; 2, anti-inflammatory therapy with adjunctive vascular therapy; 3, anti-inflammatory therapy with adjunctive vascular therapy and hyperbaric oxygenation; Δ%RI, a pre-to-post-treatment percentage change in resistivity index; CI, confidence interval; HSK, herpetic stromal keratitis; n, number of eyes; OA, ophthalmic artery; RI, resistivity index; SD, standard deviation

IVRI values and most profound changes in vascular characteristics. Pairwise comparison found marked between group differences with large effect sizes (Cohen's d), with the most marked effects observed in group 3.

The percentage change in PSV (Δ%PSV) in the CRA of the eye with HSK was higher in groups 2 and 3 (22.3% and 29.6%, respectively) than in group 1 (0.3%), and the difference was significant. After treatment, the mean PSV in the CRA of the affected eye in group 3 was 12.7 ± 0.9 cm/s, which was closer than those in groups 1 and 2 to the mean value for fellow eye (11.4 ± 1.3 cm/s) (Table 4). Additionally, we noted sequential reductions in Δ%EDV, from –1.3% in group 1 to –8.8% and –24.6% in groups 2 and 3, respectively, which reflected remodeling of diastolic retinal blood flow. After treatment, the mean EDV in the CRA of the affected eye in group 3 was 4.5 ± 0.7 cm/s, which was closer than those in groups 1 and 2 to the mean value for fellow eye (3.8 ± 0.7 cm/s) (Table 5).

The IVRI for the CRA demonstrated clear gradient dynamics with an increase in value from group 1 to group 3 both for the effected eye and the fellow eye. Among the three groups, group 3 had the highest IVRI values for the CRA for the affected eye and the fellow eye (38.72 ± 12.56 and 9.18 ± 6.11, respectively), followed by group 2 (28.94 ± 18.21 and 6.31 ± 6.24, respectively), and group 1 with a wide range of variation (1.32 ± 3.87 and 0.18 ± 0.66, respectively). Moreover, among the three groups, group 3 showed the greatest changes in PSV, EDV and RI for the CRA, with reductions compared to other groups, which reflected the most marked vascular response and remodeling of the arterial blood flow (Tables 4, 5). With these changes, the parameters mentioned approached the values found for the fellow eye (i.e., reference values). The ratio of the IVRI for the affected eye to that for the fellow eye (KFR) gradually reduced from 7.33 for group 1 to 4.59 for group 2 and 4.22 for group 3, reflecting a reduction in asymmetric response to treatment and an increase in systemic vascular response in the presence of adjunct therapy.

Pairwise comparison found marked between group differences in the IVRI for the CRA with large effect sizes (Cohen's d), reflecting clinically significant between group differences in the intensity of vascular response to treatment. Particularly, for the CRA bed in the eye with HSK, effect sizes between groups 1 and 2 and between groups 1 and 3 were large (d_{1-2} = 1.34; d_{1-3} = 2.21), while that between groups 2 and 3 was also marked but smaller (d_{2-3} = 0.78). Additionally, for the CRA bed in the fellow eye, effect sizes between groups 1 and 2 and between groups 1 and 3 were also large (d_{1-2} = 1.18; d_{1-3} = 1.56), while that between groups 2 and 3 was moderate (d_{2-3} = 0.62), which reflected a clinically significant increase in hemodynamic response, which was most marked in group 3. Therefore, Cohen's d analysis demonstrated that the most clinically significant hemodynamic changes were noted in the groups treated with adjunctive vascular therapy.

The percentage change in PSV (Δ%PSV) in the CRV of the eye with HSK was higher in group 3 than in groups 1 and 2 (Table 7). The mean PSV in the CRV of the eye with HSK in group 3 was 5.5 ± 0.6 cm/s, which was similar to the fellow eye (5.2 ± 0.3 cm/s).

Therefore, the multicomponent therapy in group 3 provided the most marked recovery of hemodynamics in all vascular beds examined, with the mean values of PSV,

Table 4. Peak systolic velocity (PSV, cm/s) in the central retinal artery (CRA) in patients before and after treatment for herpetic stromal keratitis (HSK)

Parameter	1		2		3		p
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
PSV (cm/s) in the CRA in the eye with HSK; mean ± SD; n=20	18.7±3.4	18.7±3.1	17.9±2.8	13.8±2.9	18.2±1.8	12.7±0.9	$P_{1post\text{-}treatment} = 0.9$ $P_{2post\text{-}treatment} < 0.0001$ $P_{3post\text{-}treatment} < 0.0001$
Δ%PSV in the CRA in the eye with HSK; mean (95% CI); n=20	-0.3 ((-0.8)-0.21)		-22.3 ((-27.0)- (-17.4)		-29.6 ((-32.8)-(-25.7)		$P_{1-2} < 0.0001$ $P_{1-3} < 0.0001$ $p_{2-3} = 0.03$
PSV (cm/s) in the CRA in the fellow eye in patients with HSK; mean ± SD; n=20	11.4±1.2	11.3±1.2	11.8±1.3	11.7±1.1	11.1±1.3	10.9±1.1	$P_{1post\text{-}treatment} = 0.9$ $P_{2post\text{-}treatment} = 0.7$ $P_{3post\text{-}treatment} = 0.6$
Δ%PSV in the CRA in the fellow eye in patients with HSK; mean (95% CI); n=20	-0.17((-0.99)-0.65)		-1.0((-3.6)- 1.4)		-1.7((-3.8)-0.38)		$P_{1-2} = 0.1$ $P_{1-3} = 0.01$ $p_{2-3} = 0.8$

Note: 1, anti-inflammatory therapy only; 2, anti-inflammatory therapy with adjunctive vascular therapy; 3, anti-inflammatory therapy with adjunctive vascular therapy and hyperbaric oxygenation; Δ%PSV, a pre-to-post-treatment percentage change in peak systolic velocity after treatment; CI, confidence interval; CRA, central retinal artery; HSK, herpetic stromal keratitis; n, number of eyes; PSV, peak systolic velocity; SD, standard deviation

Table 5. End diastolic velocity (EDV) in the central retinal artery in patients before and after treatment for herpetic stromal keratitis (HSK)

Parameter	1		2		3		p
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
EDV (cm/s) in the CRA in the eye with HSK; mean ± SD; n = 20	5.8±1.6	5.6±1.3	5.5±1.1	4.9±0.8	6.1±1.2	4.5±0.7	$P_{1post\text{-}treatment} = 0.8$ $P_{2post\text{-}treatment} = 0.09$ $P_{3post\text{-}treatment} < 0.0001$
Δ%EDV in the CRA in the eye with HSK; mean (95% CI); n=20	-1.3((-2.9)-0.34)		-8.8((-12.4)-(-5.9))		-24.6((-29.1)-(-20.5)		$P_{1-2} < 0.0001$ $P_{1-3} < 0.0001$ $P_{2-3} < 0.0001$
EDV (cm/s) in the CRA in the fellow eye of patients with HSK; mean ± SD; n = 20	3.7±0.9	3.7±0.9	3.7±1.0	3.7±1.0	3.5±0.8	4.0±0.5	$P_{1post\text{-}treatment} = 1.0$ $P_{2post\text{-}treatment} = 0.4$ $P_{3post\text{-}treatment} = 0.03$
Δ%EDV in the CRA in the fellow eye of patients with HSK; mean (95% CI); n=20	0		6.4(0.4-12.0)		18.5(8.4-28.7)		$P_{1-2} = 0.1$ $P_{1-3} = 0.003$ $P_{2-3} = 0.07$

Note: 1, anti-inflammatory therapy only; 2, anti-inflammatory therapy with adjunctive vascular therapy; 3, anti-inflammatory therapy with adjunctive vascular therapy and hyperbaric oxygenation; Δ% EDV, a pre-to-post-treatment percentage change in end diastolic velocity; CI, confidence interval; CRA, central retinal artery; EDV, end diastolic velocity; HSK, herpetic stromal keratitis; n, number of eyes; SD, standard deviation

Table 6. Resistivity index (RI) in the central retinal artery in patients before and after treatment for herpetic stromal keratitis (HSK)

Parameter	1		2		3	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
RI in the CRA in the eye with HSK; mean ± SD; n = 20	0.68±0.02	0.68±0.02	0.68±0.03	0.66±0.02	0.69±0.03	0.64±0.01
Δ % RI in the CRA in the eye with HSK; mean (95% CI); n = 20	0		1.4 (0.6-2.1)		3.4 (2.1-6.3)	
RI in the CRA in the fellow eye in patients with HSK; mean ± CD; n=20	0.63±0.008	0.64±0.007	0.63±0.01	0.63±0.01	0.63±0.01	0.63±0.01
Δ % RI in the CRA in the fellow eye in patients with HSK; mean (95% CI); n=20	0.08 ((-0.08)-0.24)		-0.07 ((-0.45)-0.30)		0.32 ((-0.14)-0.8)	

Note: 1, anti-inflammatory therapy only; 2, anti-inflammatory therapy with adjunctive vascular therapy; 3, anti-inflammatory therapy with adjunctive vascular therapy and hyperbaric oxygenation; Δ%RI, a pre-to-post-treatment percentage change in resistivity index; CI, confidence interval; CRA, central retinal artery; HSK, herpetic stromal keratitis; n, number of eyes; RI, resistivity index; SD, standard deviation

Table 7. Peak systolic velocity (PSV) in the central retinal vein in patients before and after treatment for herpetic stromal keratitis (HSK)

Parameter	1		2		3		p
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
PSV (cm/s) in the CRV in the eye with HSK; mean ± SD; n = 20	7.3±0.8	6.6±0.4	7.0±0.4	6.2±0.2	7.5±0.6	5.5±0.6	$P_{1post\text{-}treatment}$ = 0.002 $P_{2post\text{-}treatment}$ < 0.0001 $P_{3post\text{-}treatment}$ < 0.0001
Δ %PSV in the CRV in the eye with HSK; mean (95% CI); n=20	-8.0((-10.7)-(-5.4)		-10.9((-13.0)-(-8.8))		-25.8((-29.1)-(-22.6)		$P_{1\text{-}2}$=0.6 $P_{1\text{-}3}$=0.005 $p_{2\text{-}3}$=0.009
PSV in the CRV in the fellow eye in patients with HSK; mean ± SD; n = 20	6.0±0.3	5.9±0.3	5.8±0.4	5.5±0.4	5.8±0.4	5.2±0.3	$P_{1post\text{-}treatment}$ =0.3 $P_{2post\text{-}treatment}$ =0.01 $P_{3post\text{-}treatment}$ <0.0001
Δ %PSV in the CRV in the fellow eye in patients with HSK; mean (95% CI); n = 20	-1.7((-2.6)-(-0.76)		-5.9((-7.6)- (-4.4))		-10.6((-12.4)-(-8.7)		$P_{1\text{-}2}$ = 0.08 $P_{1\text{-}3}$ = 0.005 $p_{2\text{-}3}$ = 0.07

Note: 1, anti-inflammatory therapy only; 2, anti-inflammatory therapy with adjunctive vascular therapy; 3, anti-inflammatory therapy with adjunctive vascular therapy and hyperbaric oxygenation; Δ%PSV, a pre-to-post-treatment percentage change in peak systolic velocity after treatment; CI, confidence interval; CRV, central retinal vein; HSK, herpetic stromal keratitis; n, number of eyes; PSV, peak systolic velocity; SD, standard deviation

EDV, RI and venous blood flow for the affected eye becoming most close to those for the fellow eye.

Discussion

Inflammatory process is known to be accompanied by remodeling of local hemodynamics, which is primarily manifested by the development of arterial hyperemia due to inflammation-induced vasodilation. Such a hemodynamic response is adaptive in nature and aimed at optimizing tissue perfusion to meet the increased metabolic demand of the inflammatory response. Normalization of hemodynamic parameters after the resolution of the inflammatory process indicates a reduction in inflammatory activity and functional recovery of the vascular bed [14].

Hypoxia influences immune cell functions by regulating metabolic pathways, and can be a pathogenic factor in some inflammatory diseases. Conversely, inflammation can lead to local hypoxia [15].

We have reported previously [16] that, in recurrent unilateral HSK, the nature of hemodynamic abnormalities did not depend on whether the HSK was necrotizing or non-necrotizing, but was significantly different from the fellow eye. In the OA bed of the affected eye, the PSV and EDV were 33.8% and 8.8%, respectively, lower, whereas the RI was 6.6% higher, compared to the fellow eye, which indicated lower OA inflow and higher peripheral vascular resistance. Additionally, in the affected eye, the PSV, EDV and RI in the CRA bed were 58.7%, 61.1% and 7.9 %, respectively, higher, and, the PSV in the CRV bed was 28.6% higher, compared to the fellow eye. Such a combination of changes reflects a compensatory redistribution of blood flow in inflammation: a reduction in blood flow velocities in the OA is accompanied by increased blood flow in the retinal vascular bed with the involvement of both arterial and venous microcirculation, indicating adaptive remodeling of intraocular hemodynamics in response to corneal inflammation.

In the current study, group 1 was treated conventionally with anti-inflammatory therapy only, group 2 received conventional treatment plus vascular therapy only, and group 3, conventional treatment plus vascular therapy and HBO.

Hyperoxia is a condition characterized by an excess of partial oxygen pressure (pO2) in blood and tissues, and can be achieved in patients receiving normobaric or hyperbaric oxygen support (oxygen therapy). Therapeutic HBO is a treatment in which the patient breathes almost 100% pure oxygen while inside a hermetic treatment chamber at a pressure higher than the normal atmospheric pressure [i.e., >1 atmosphere absolute (atm abs)]. The Undersea and Hyperbaric Medical Society (UHMS) considers a pO2 of 1.4 atm abs the minimum beneficial dosage for HBO therapy [13].

HBO increases the partial pressure of oxygen and the proportion of dissolved oxygen in plasma, resulting in the development of controlled therapeutic hypoxia. The increased bioavailability of oxygen enables effective oxygen diffusion into tissues and mitochondria, key organelles of aerobic metabolism. The oxygen entering the mitochondria can reverse tissue hypoxia, activating the electron transport chain to generate energy and increasing oxidative phosphorylation and adenosine triphosphate (ATP) synthesis. This is followed by stabilization of hypoxia-inducible factor (HIF)-1α and activation of a wide range of signaling cascades that regulate angiogenesis, cellular repair, metabolic adaptation, anti-inflammatory response and regenerative processes [17].

Therapeutic hypoxia temporarily increases levels of reactive oxygen species (ROS) which act as signaling molecules, modulating intracellular signaling pathways and inhibiting NF-κB activation, which is accompanied by reduced production of pro-inflammatory mediators. As a result, the production of acute-phase proteins and pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6) and chemokines decreases. HBO modulates the functional activity of immune cells by moderately increasing the levels of ROS, which increases the bactericidal activity of neutrophils and macrophages and efficacy of phagocytosis, and contributes to the activation and proliferation of T-cells. Additionally, the production of growth factors and anti-angiogenic mediators (VEGF, FGF, TGF-β) increases, contributing to tissue repair, angiogenesis and the recovery of microcirculation [18, 19].

After treatment, in all study groups, there was sequential remodeling of ocular hemodynamics, as manifested by changes in arterial inflow, peripheral vascular resistance and venous outflow. The IVRI for the affected eye reflects an integrated local and regional hemodynamic response to treatment, while changes in IVRI in the fellow eye indicate the involvement of systemic mechanisms of vascular regulation. A transition from conventional anti-inflammatory therapy alone to that plus vascular therapy and to that plus both vascular therapy and HBO is accompanied by progressive remodeling of vascular response and IVRI. Finding of the largest effect size for the OA bed in group 3 indicated that anti-inflammatory therapy, when combined with both vascular therapy and HBO, allowed for the most complete recovery of regional hemodynamics in the eye with HSK. A similar trend was observed for the CRA bed, with a sequential increase in local hemodynamic response from group 1 to group 3, which was manifested by a progressive increase in the IVRI, and the best normalization of PSV, EDV and RI, with improvements in these parameters to levels close to those found for the fellow eye. This reflects an additive response to the relief of inflammation, normalization of vascular tone, improvement in microcirculation and correction of tissue hypoxia. Our results indicate that (1) tissue hypoxia is an important pathogenetic component of vascular abnormalities in HSK, and (2) the relief of tissue hypoxia provides an additional hemodynamic effect compared to anti-inflammatory therapy combined with only vascular therapy. Group 3 showed the most complete recovery of the integrated regulation of ocular circulation, which was manifested by concerted

normalization of arterial inflow, peripheral vascular resistance, microcirculation and venous outflow.

We found that the magnitude of the hemodynamic effect of HBO depended on the vascular bed. For the CRA bed in the eye with HSK, effect sizes between groups 1 and 2 and between groups 1 and 3 were large (d_{1-2} = 1.34; d_{1-3} = 2.21), while that between groups 2 and 3 was smaller (d_{2-3} = 0.78). Unlike in the OA, where the use of HBO as an adjunct resulted in a substantial increase in the hemodynamic effect (d_{2-3} = 1.11), the additional effect in the CRA was smaller. This indicates that correction of tissue hypoxia has the primary impact on the restoration of proximal regulation of ocular blood flow and perfusion in the OA, while the hemodynamic response of a local or regional vascular bed appears to be primarily determined by the normalization of inflammatory processes and microcirculatory mechanisms. It is reasonable that additional effects of HBO on hemodynamics were implemented to a greater extent in the OA bed, because the OA is a main large-caliber artery which characterizes the status of the total arterial inflow to the eye and is subject to systemic and autonomic mechanisms of vascular regulation, whereas the CRA reflects the hemodynamics of the retinal microcirculatory bed with a predominance of local autoregulation mechanisms.

In the current study, Doppler ultrasound evidence of post-treatment functional changes in regional hemodynamics was the main subject of analysis. A detailed analysis of the clinical efficacy of the HSK treatment schemes examined and their relationship with the characteristics of regional hemodynamics will be presented in a separate publication.

Conclusion

A combination of anti-inflammatory therapy with vascular therapy and HBO for HSK provides the most effective recovery of regional hemodynamics in the OA and CRA vascular beds, with the most pronounced normalization of PSV, EDV and RI and minimization of interocular asymmetry in hemodynamics. The IVRI proposed reflects a total hemodynamic response of vessels of the eye to treatment and demonstrates that HBO when used as an adjunct to a combination of anti-inflammatory therapy and vascular therapy provided an additional hemodynamic effect compared to that of the combination only. Group 3 had the most profound increase in the IVRI, reflecting the most complete recovery of the integrated regulation of ocular circulation, which was manifested by concerted normalization of arterial inflow, peripheral vascular resistance, microcirculation and venous outflow. The combination treatment provided a more profound effect of hemodynamic response (as assessed by Cohen's d) for the OA vascular bed than for the CRA vascular bed.

Author Contributions

MIR: Conceptualization, Methodology, Study Design, Data Curation, Data Analysis, Writing - original draft preparation; KNI, Conceptualization, Writing – Review and Editing. All authors have read and approved the final manuscript and agree to be responsible for all aspects of the work.

Disclaimers

The views expressed in this article are solely those of the authors and do not necessarily represent the official position of their affiliated institution or any funding source.

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Ethical Statement

This study involved 60 patients (29 men and 31 women) with recurrent HSK, followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association and was approved by the Bioethics committee of SI “The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine” (Meeting Minutes No. 2 of April 18, 2025).

Informed consent

Informed consent was obtained from all subjects.

Conflict of Interest

The authors state that they have no conflict of interest that could influence their view on the subject matter or materials described and discussed in this manuscript.

Data Availability Declaration

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Study Limitations

Single center design, small sample, non-randomized study, and no long-term follow-up.

Abbreviations

Cohen's d, Cohen's standardized effect size; EDV, end-diastolic velocity; FGF, fibroblast growth factor; HBO, hyperbaric oxygenation; HIF-1α, hypoxia-inducible factor 1-alpha; HSK, herpetic stromal keratitis; IL-1β, interleukin-1β; IL-6,interleukin-6; IVRI, integrated vascular reactivity index; NF-κB, nuclear factor kappa B; NOS, nitric oxide synthase; PSV, peak systolic velocity; pO_2, oxygen partial pressure; RI, resistive index; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

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