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CLINICAL MONITORING OF LOCAL IMMUNE RESPONSE IN LACRIMAL FLUID AFTER EXCIMER LASER SURGERY

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Annotation. **Relevance.** The data available in the scientific literature on the role of cytokines as a special biological system, the function of which is the local regulation of regeneration processes, substantiate the relevance of the research task in this direction. **Purpose of the study.** Clinical monitoring of the level of cytokines in the lacrimal fluid in patients after LASIK and Femto-LASIK operations. **Materials and methods.** The prospective study included 40 patients (80 eyes) with mild to moderate myopia and complex myopic astigmatism operated on in 2022. During the study, lacrimal fluid was taken and its further biochemical study was performed to determine the level of cytokines IL-1β, IL-4, TNF-α. **Results.** In the main group, the frequency of detection of the cytokine IL-1β, which is the main pro-inflammatory agent, was 80%, while in the comparative group it was detected in 90% of tear fluid samples. Average IL-1β values were highest in the LASIK comparison group. Average TNF-α values were also the highest in the comparison group. At the same time, the differences in the average values between the main and comparative groups were statistically significant ($p<0.05$). Average IL-4 values were the highest in the main group, where the Femto-LASIK operation was performed. **Conclusions.** The course of the regenerative process in patients after excimer laser vision correction depends on the concentration of pro-inflammatory cytokines IL-1β and TNF-α and anti-inflammatory cytokine IL-4. Based on this, with a higher level of pro-inflammatory cytokines in the lacrimal fluid, the lengthening of the terms of pain relief and epithelialization after surgery was determined.

Key words: myopia, cytokines, Lasik, Femtolasik

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КЛИНИЧЕСКИЙ МОНИТОРИНГ ЛОКАЛЬНОГО ИММУННОГО ОТВЕТА В СЛЕЗНОЙ ЖИДКОСТИ ПОСЛЕ ЭКСИМЕРЛАЗЕРНЫХ ОПЕРАЦИЙ

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Аннотация. **Актуальность.** Существующие в научной литературе данные о роли цитокинов в качестве специальной биологической системы, функция которой состоит в местной регуляции процессов регенерации, обосновывают актуальность задачи по исследованиям в этом направлении. **Цель исследования.** Клинический мониторинг уровня цитокинов в слезной жидкости у пациентов после операций LASIK и Femto-LASIK. **Материалы и методы.** Проспективное исследование включало 40 больных (80 глаз) с миопией слабой и средней степени и сложным миопическим астигматизмом, прооперированных в 2022 г. В ходе исследования проводили забор слезной жидкости и ее дальнейшее биохимическое исследование с целью определения уровня цитокинов ИЛ-1β, ИЛ-4, ФНО-α. **Результаты.** В основной группе частота выявления цитокина ИЛ-1β, являющегося основным провоспалительным агентом, составила 80%, в то время как в сравнительной группе он был выявлен в 90% образцов слезной жидкости. Средние показатели ИЛ-1β были наиболее высокими в сравнительной группе, в которой выполняли операцию LASIK. Средние показатели ФНО-α также были наиболее высокими в сравнительной группе. При этом различия

в средних показателях между основной и сравнительной группами были статистически достоверными (p<0,05). Средние показатели ИЛ-4 были наиболее высокими в основной группе, где выполняли операцию Femto-LASIK. **Выводы.** Течение регенераторного процесса у пациентов после эксимерлазерной коррекции зрения находится в зависимости от концентрации провоспалительных цитокинов ИЛ-1β и ФНО-α и противовоспалительного цитокина ИЛ-4. Исходя из этого, при более высоком уровне провоспалительных цитокинов в слезной жидкости определено удлинение сроков купирования болевого синдрома и эпителизации после операции.

Ключевые слова: миопия, цитокины, Ласик, Фемтоласик

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EKSIMERLAZER JARROXLIGIDAN KEYIN KO'Z YOSHI SUYUQLIGIDA MAHALLIY IMMUNIY JAVOBNI KLINIK MONITORINGI

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Annotatsiya. Dolzarbligi. Regeneratsiya jarayonlarini mahalliy tartibga solish bo'lgan maxsus biologik tizim sifatidagi sitokinlarning roli haqidagi ilmiy adabiyotlarda mavjud bo'lgan ma'lumotlar ushbu yo'nalishdagi tadqiqot vazifasining dolzarbligini asoslaydi. **Тадқиқот мақсади.** LASIK va Femto-LASIK operatsiyalaridan keyin bemorlarda ko'z yoshi suyuqlikdagi sitokinlar darajasining klinik monitoringi. **Materiallar va usullar.** Istiqbolli tadqiqotga 2022 yilda operatsiya qilingan engil va o'rtacha darajadagi miyopiya va murakkab miyopik astigmatizm bilan og'rigan 40 nafar bemor (80 ko'z) ishtirok etdi. Tadqiqot davomida ko'z yoshi suyuqligi olindi va IL-1b, IL-4, TNF-a. sitokinlari darajasini aniqlash uchun uning keyingi biokimyoviy tadqiqoti o'tkazildi. **Natijalar.** Asosiy guruhda yallig'lanishga qarshi asosiy vosita bo'lgan IL-1b sitokinini aniqlash chastotasi 80% ni tashkil etgan bo'lsa, qiyosiy guruhda ko'z yoshi suyuqligi namunalarining 90% da aniqlangan. O'rtacha IL-1b ko'rsatkichlari LASIK taqqoslash guruhida eng yuqori bo'ldi. Taqqoslash guruhida o'rtacha TNF-a qiymatlari ham eng yuqori edi. Shu bilan birga, asosiy va qiyosiy guruhlar o'rtasidagi o'rtacha qiymatlardagi farqlar statistik ahamiyatga ega edi (p<0,05). O'rtacha IL-4 ko'rsatkichlari Femto-LASIK operatsiyasi o'tkazilgan asosiy guruhda eng yuqori bo'ldi. **Xulosa.** Eksimer lazerli ko'rishni tuzatishdan so'ng bemorlarda regenerativ jarayonning borishi yallig'lanishga qarshi IL-1b va TNF-a sitokinlari va yallig'lanishga qarshi IL-4 sitokinlarining kontsentratsiyasiga bog'liq. Shunga asoslanib, ko'z yoshi suyuqlikda yallig'lanishga qarshi sitokinlarning yuqori darajasi bilan operatsiyadan keyin og'riqni yo'qotish va epitelizatsiya muddatini uzaytirish aniqlandi.

Kalit so'zlar: miyopiya, sitokinlar, Lasik, Femtolasik

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Annotation. The study of the role of cytokines in the local regulation of regenerative processes indicates that this area is of extreme interest for further research. Recent advances in molecular immunology make it possible to understand the need for a deep study of the essence of restorative and regenerative processes in corneal tissues after keratorefractive operations. The starting mechanism for the beginning of regenerative processes in the cornea is the "evaporation" of the tissue elements of the cornea and the further development of apoptosis. In this case, these factors can significantly change the course of the regenerative reaction [1–4]. Literature data indicate that some cytokines have the ability to stimulate protective reactions in tissues, which involve various types of endothelial, epithelial and connective tissue cells with the development of a local specific inflammatory reaction in the lesion [5,6]. It has been proven that for a "favorable" course of the processes of physiological tissue regeneration, it is necessary to have a balance in the level of pro- and anti-inflammatory cytokines. However, with the development of their imbalance, pathophysiological shifts in regenerative processes begin, leading to stimulation of cell apoptosis, impaired epithelialization and restoration of nerve fibers [7–9].

In connection with the foregoing, it is advisable to study the level of cytokines in the lacrimal fluid in order to deeply understand the changes occurring in the foci of corneal tissue damage after excimer laser interventions.

Purpose of the study. Clinical monitoring of the level of cytokines in the lacrimal fluid at patients after LASIK and Femto-LASIK surgeries.

Materials and methods. The study included 40 patients (80 eyes) with mild to moderate myopia. The distribution of patients by gender was as follows: male — 17 (39.5%), female — 23 (60.4%). The age of the patients ranged from 19 to 28 years, the mean age was 23.9±1.8 years. Patients underwent excimer laser vision correction at the Department of Ophthalmology of the Innovative Clinic of Dr. Maksudova (DMC) in June-August 2022. A prospective study was conducted. The patients were divided into 2 groups. The comparison group (n=20, 40 eyes) underwent LASIK surgery, while the main group (n=20, 40 eyes) underwent Femto-LASIK surgery. During the study, lacrimal fluid was taken and its further biochemical study was carried out in order to determine the level of cytokines. The collection and study of tear fluid was performed on the 3rd day after surgery in the morning without stimulation of tear production. The operation was performed under local anesthesia with a 0.5% solution of alkaine. All patients underwent laser vision correction using a Wavelight EX 500 excimer laser unit (Alconlab., USA) under the "Wavefront optimized" program. In the comparative group, the flap was formed using an Evolution 3E microkeratome with a 130 μm head (MORIA SA, France). In the main group, the flap was formed using a femtosecond laser using a Wavelight FS 200 device (Alcon lab., USA) with a programmed flap thickness of 110 μm.

Results and discussion. IL-1β is the main pro-inflammatory cytokine, the increase in the level of which is associated with the activation of the immune response by the type 1 T-helper mechanism, and associated with the development of inflammatory and destructive processes. This cytokine is responsible for providing tissue repair processes by stimulating the processes of migration in the epithelium, the synthesis of collagen fibers and the regeneration of nerve endings. An increase in the level of this cytokine in biological fluids is accompanied by the development of a local inflammatory reaction and serves as a signal for the activation of other cytokines [3,9,10]. According to our data, the study of the concentration of IL-1β in the lacrimal fluid of patients showed that in the main group, the frequency of detection of this cytokine, which is the main pro-inflammatory agent, was 80%, while in the comparative group it was detected in 90% of lacrimal fluid samples. Average IL-1β scores were highest in the comparative LASIK group. At the same time, the differences in the average values between the main and comparative groups were statistically insignificant ($p<0.05$). However, it should be noted that the average indicators of both the main and comparative groups in relation to the indicators of the control group, in which the cytokine was detected only in 25% of samples, were statistically significant ($p<0.05$) (Fig. 1).

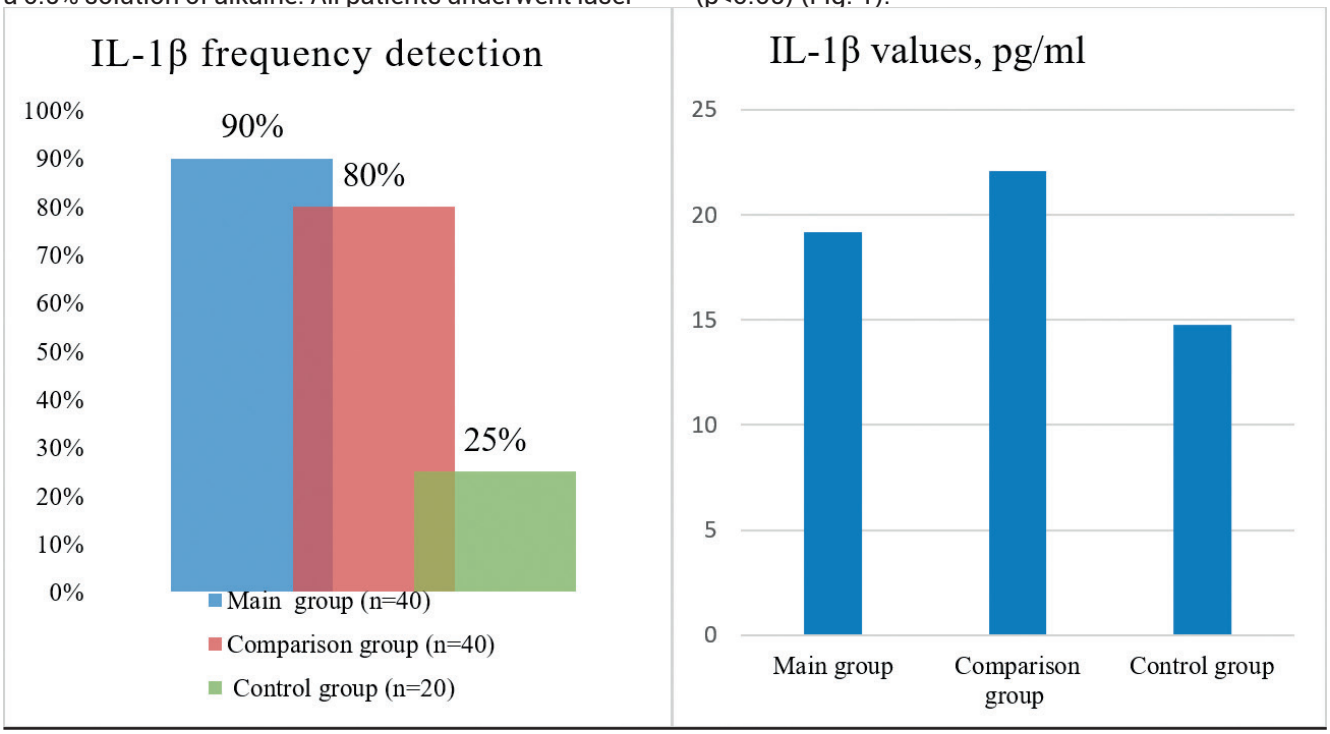

Fig. 1. Comparative characteristics of IL-1β concentration in patients in the study groups (pg/ml)

Tumor necrosis factor (TNF-α or cachectin) is one of the most important proteins involved in the activity of the cytokine system. It belongs to the group of pro-inflammatory cytokines, being a marker of inflammation and regeneration. The main cells synthesizing TNF-α are monocytes and tissue macrophages. At the same time, receptors for TNF-α can be found in all cells of the body, except for erythrocytes. The need to study the level of TNF-α

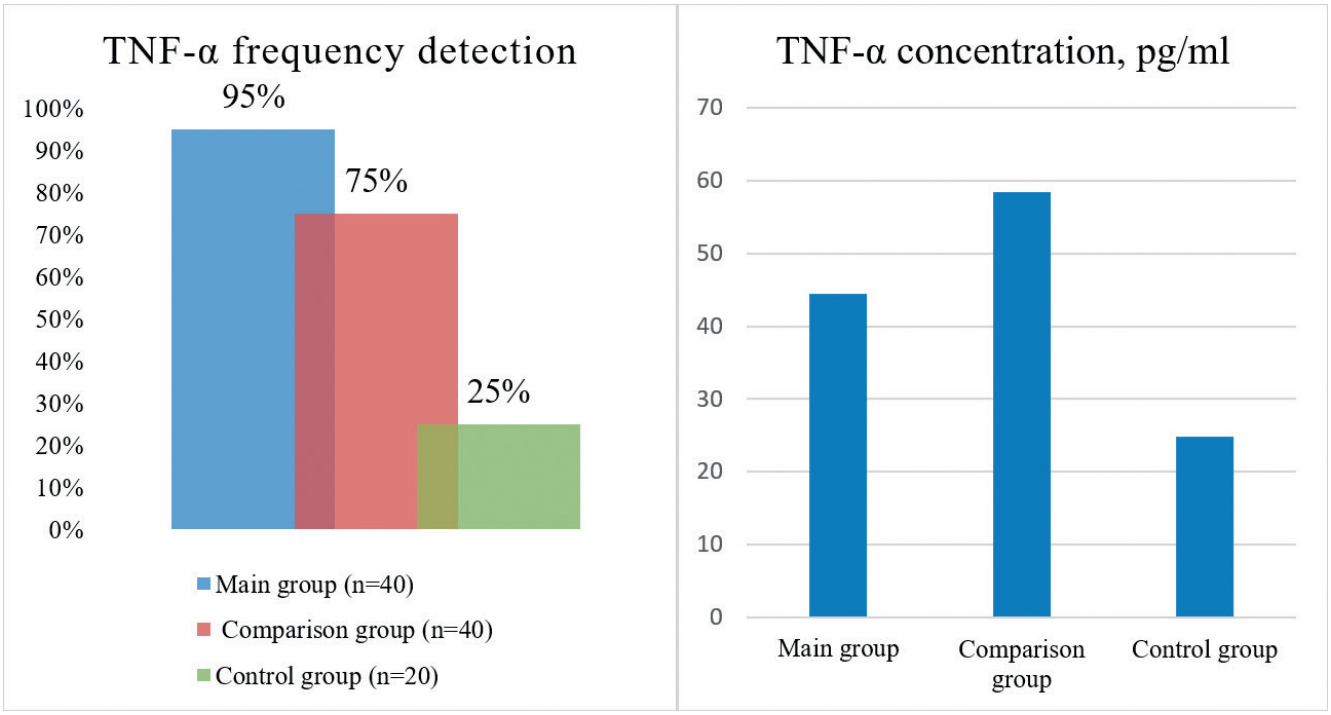

Fig. 2. Comparative characteristics of TNF-α concentration in patients in the study groups, pg/ml

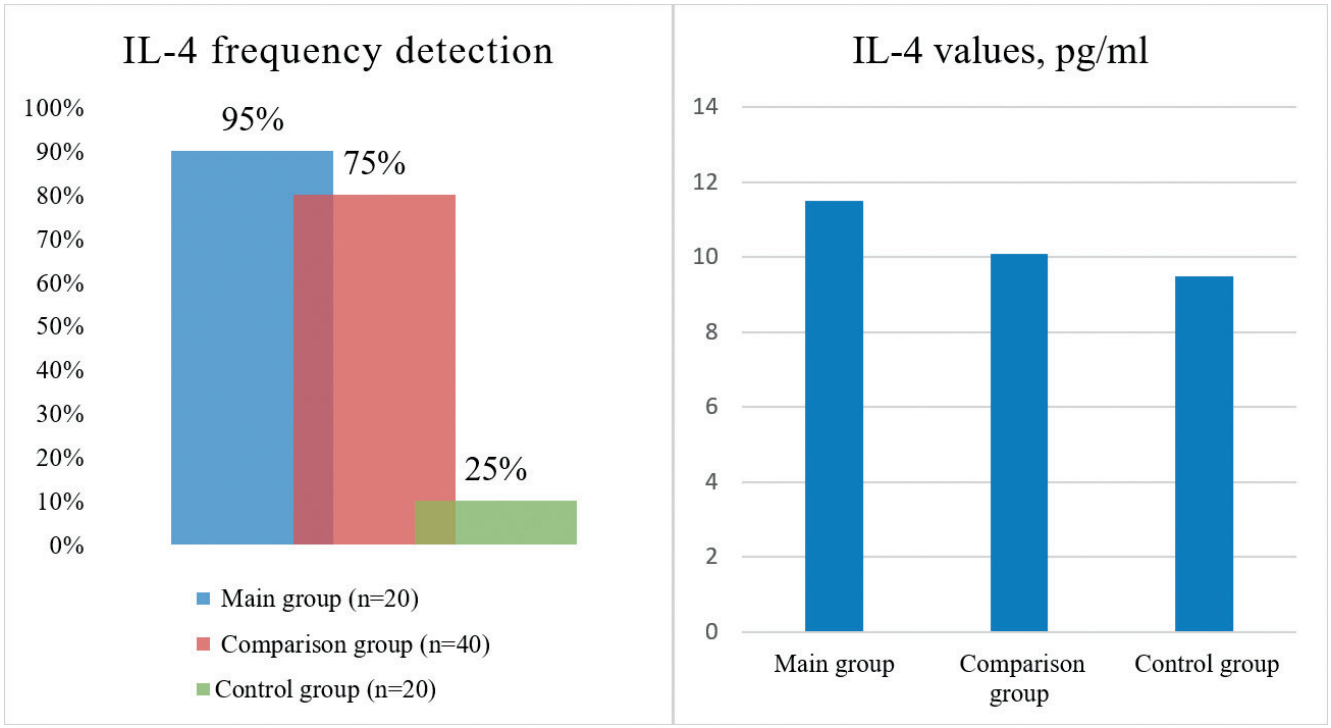

Fig 3. Comparative characteristics of IL-4 concentration in patients in the study groups, pg/ml

was due to the fact that this cytokine is able to induce the activation of apoptosis, which is a morphological feature of the regenerative reaction of the cornea to excimer laser exposure [4,5]. The study of the concentration of TNF-α in the tear fluid of patients in our studies showed that in the main group the frequency of detection of this cytokine was 75%, while in the comparative group it was detected in 95% of the tear fluid samples, and in the control group — in 25% (Fig. 2). Average TNF-α values were highest in the comparative LASIK group. At the same time, the differences in the average values between the main and comparative groups were statistically significant ($p<0.05$). The average indicators of both the main and comparative groups in relation to the indicators of the control group were also statistically significant ($p<0.05$).

IL-4 is an anti-inflammatory cytokine capable of activating cell migration and adhesion. It has a significant impact on the development of destructive-inflammatory processes of various etiologies in the area of tissue damage [6,11]. The

Table 1.
Recovery rate of structural and functional parameters of the regenerative process in the cornea in the study groups, M±m

Parameters	Main group	Comparison group
Relief time of pain syndrome, hours	2,4±0,4*	3,6±0,5
Completion time of corneal epithelialization, hours	3,5±0,3*	4,3±0,4
Terms of recovery of the RTSP indicator, days	10,2±1,2*	14,4±1,3

Note: * - differences in comparison with the indicators of the comparative group are statistically significant (p<0.05)

study of the concentration of IL-4 in the lacrimal fluid of patients showed that in the main group the frequency of detection of this cytokine, which is an anti-inflammatory agent, was 95%, while in the comparative group it was detected in 75% of the lacrimal fluid samples. Average IL-4 values were the highest in the main group, in which the Femto-LASIK operation was performed (Fig. 3). At the same time, the differences in the average values between the main and comparative groups were not statistically significant (p<0.05). The average values of both the main and comparative groups, in comparison with the indicators of the control group, in which the cytokine was detected only in 10% of the samples, were statistically significant (p<0.05).

Thus, the results of laboratory studies of the concentrations of cytokines IL-1β, TNF-α and IL-4 in the lacrimal fluid of patients after excimer laser correction using LASIK and Femto-LASIK methods showed that the use of a femtosecond laser during flap formation is associated with a lower activity of pro-inflammatory cytokines and a more pronounced activity of anti-inflammatory cytokines. Table 1 summarizes the timing of the completion of recovery processes in the cornea after photorefractive surgery in 2 study groups. The results obtained indicate that the course of the postoperative period after Femto-LASIK is characterized by the minimum recovery time for the structural and functional elements of the cornea. It should be noted that in the main group, no processes of poor-quality regeneration were observed, the clinical expression of which is such complications as epithelial hyperplasia, the development of subepithelial fibroplasia, epitheliopathy, diffuse lamellar keratitis, epitheliopathy, and edema of the corneal flap.

Conclusion. Thus, the results of the study show that the course of the regenerative process in patients after excimer laser vision correction depends on the concentration of pro-inflammatory cytokines IL-1β and TNF-α and anti-inflammatory cytokine IL-4, since at a higher level of pro-inflammatory cytokines in the lacrimal fluid, prolongation of the terms of relief of pain syndrome and epithelization after surgery. It was found that during Femto-LASIK surgery, lower levels of pro-inflammatory cytokines in the lacrimal fluid are observed in the early postoperative period with a higher activity of the anti-inflammatory cytokine IL-4. This indicates that the use of a femtosecond laser for flap formation is less traumatic and ensures a favorable course of the regenerative process in the cornea after laser correction.

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