Питання клінічної офтальмології

Impact of preservative-free vs preserved latanoprost 0.005% on the bulbar conjunctiva in patients with primary open-angle glaucoma

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Вплив латанопросту 0,005% без консервантів та з консервантами на бульбарну кон'юнктиву у пацієнтів з первинною відкритокутовою глаукомою

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Abstract

Purpose: *This study aimed to assess the state of the bulbar conjunctiva in patients with primary open-angle glaucoma (POAG) when using latanoprost 0.005% eye drops with and without preservatives.*

Methods. *Thirty-six patients with POAG were divided into two study groups. Study group 1 included 21 patients (21 eyes) who used benzalkonium chloride (BAK)-preserved latanoprost 0.005% eye drops, and study group 2, 15 patients (15 eyes) who used preservative-free latanoprost 0.005% in the Protriaxin matrix. Twenty-one healthy participants comprised the control group.*

Results. *We found that use of anti-glaucoma medication without or with a preservative does not affect the cytological landscape of the bulbar conjunctiva. However, we observed the presence of inflammatory cells in 42.8% of patients taking BAK-preserved latanoprost and in 6.6% of patients taking the preservative-free medication (p=0.0279). Patients in study group 1 had 10.5 times the odds of presence of inflammatory cells than those in study group 2 (OR= 10.5; 95% CI [1.15 -95.25], P=0.0366).*

Conclusion. *These findings support the preferential use of preservative-free antiglaucoma eye drops, particularly in patients with pre-existing or suspected ocular surface damage, to minimize cytological changes and subclinical inflammation during long-term therapy.*

Keywords: *ocular surface damage, dry eye disease, impression cytology, latanoprost, glaucoma.*

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Резюме

Мета. *Оцінити стан бульбарної кон'юнктиви у пацієнтів з первинною відкритокутовою глаукомою при використанні очних крапель латанопросту 0,005% з консервантами та без них.*

Матеріал та методию *Тридцять шість пацієнтів з відкритокутовою глаукомою були додатково розділені на дві досліджувані групи: досліджувана група 1 – 21 пацієнт (21 око) використовував латанопрост 0,005% з консервантами у формі очних крапель, досліджувана група 2 – 15 пацієнтів (15 очей) – інстиляції латанопросту 0,005% (у матриці Протріаксин) без консерванту; двадцять один здоровий учасник становив контрольну групу.*

Результати. *Ми виявили, що використання протиглаукомних препаратів без консерванту або з ним не впливає на цитологічний ландшафт бульбарної кон'юнктиви. Однак, ми спостерігали наявність запальних клітин у 42,8% пацієнтів, які отримували латанопрост з бензалконію хлоридом (БХХ), та у 6,6% пацієнтів, які приймали препарат без консервантів (p=0,0279). Пацієнти у дослідницькій групі 1 мали в 10,5 раза вищу ймовірність наявності запальних клітин, ніж пацієнти у дослідницькій групі 2 (ВШ=10,5; 95% ДІ [1,15-95,25], P=0,0366).*

Висновок. *Ці результати підтверджують перевагу використання очних крапель проти глаукоми без консервантів, особливо у пацієнтів з попереднім або підозрюваним пошкодженням поверхні ока, для мінімізації цитологічних змін та субклінічного запалення під час тривалої терапії..*

Ключові слова: *пошкодження поверхні ока, синдром сухого ока, імпресійна цитологія, латанопрост, глаукома.*

Introduction

Glaucoma, a global multifactorial disease characterized by progressive optic nerve degeneration with or without elevated intraocular pressure (IOP), is the most common cause of irreversible blindness, with an estimated global prevalence in adults aged 40 to 80 years of 3.54% [1].

Topical medical therapy has been the most commonly used for many years. In a study by Prajwal and colleagues [2], the average number of medications prescribed was 3.09, with eye drops making up the bulk of therapy [2]. Prolonged instillation of the medication, in particular prostaglandin analogues, especially those with preservatives, combined with other factors such as age and systemic comorbidities and their treatment, significantly contributes to the development of ocular surface diseases (OSD).

The active ingredients in antiglaucoma medications can directly irritate and disrupt the ocular surface through several mechanisms, such as toxicity to the corneal epithelium, leading to cytokine activation, inflammation, immune system dysfunction, epithelial cell stress, tear evaporation, and hyperosmolarity, contributing to the symptoms of dry eye disease (DED).

Benzalkonium chloride (BAK) is the most common preservative in ophthalmic pharmaceuticals. It is a nonspecific antiseptic detergent that acts by disrupting lipid bilayers. BAK is used to prevent colonization by gram-positive and gram-negative bacteria and fungi [3]. However, this same property can also damage cells on the surface of the eye. When exposed to BAK in vitro, epithelial cells swell, exfoliate, and lose stability of tight junctions [4]. Although the in vitro effects of BAK are well documented, the in vivo effects are less well defined. After long-term treatment with BAK, keratocyte activation, loss of microvilli, and decreased corneal surface epithelial density were observed compared with controls that did not receive BAK or did not receive preservatives [5, 6].

It is believed that epithelial toxicity may lead to an inflammatory cascade, decreasing the density of the subepithelial nerve plexus and further reducing tear secretion [7]. The conjunctiva may also be damaged by BAK both structurally and functionally. Numerous studies have shown a decrease in goblet cell density, an increase in fibroblasts, and conjunctival keratinization in patients receiving BAK-preserved eye drops [8]. This may be the result of chronic changes in the conjunctiva, including upregulation of inflammatory factors, leading to metaplasia and subepithelial fibrosis. Clinical findings related to BAK and the ocular surface include decreased tear breakup time (TBUT), decreased Schirmer score, and conjunctival lissamine green staining [7, 8].These changes not only reduce patient comfort and adherence to therapy but may also compromise treatment outcomes [9].

Despite the extensive research on epithelial and stromal cells, there is paucity of published data on immune cells in the conjunctival immune microenvironment related to preservative-free versus preserved latanoprost. Therefore, studying the morphological effects of prolonged antiglaucoma therapy on the conjunctival cellular lanscapeis essential for optimizing long-term management and minimizing ocular surface complications.

Aim: to assess the state of the bulbar conjunctiva in patients with primary open-angle glaucoma (POAG) when using latanoprost 0.005% eye drops with and without preservatives.

Material and method

This study included 36 patients with POAG who were treated with prostaglandins. They were divided into two study groups based on the treatment: 21 patients (21 eyes) treated with BAK-preserved latanoprost 0.005% eye drops, and 15 patients (15 eyes) treated with preservative-free latanoprost 0.005% in the Protriaxin matrix. Twenty-one healthy participants comprised the control group.

Patients underwent clinical ophthalmological examination. Ocular Surface Disease Index (OSDI), TBUT, and

Shirmer's test scores were recorded, blinking rate was measured and bulbar conjunctival impression cytology (CIC) was performed.

Impression cytology specimens were obtained via application of 0.22 μm Millipore cellulose acetate filter paper over the nasal quadrant of the conjunctiva. It was gently pressed to the ocular surface and removed in a peeling fashion with blunt ophthalmologic forceps after 4-8 s of exposure. Then an impression from the conjunctiva was taken again in the same place.Then the strip was immediately transferred into a fixative solution (95% ethyl alcohol) followed by histological staining (Papanicolaou or haematoxylin and eosin stains) [10]. The mounted slides were examined by light microscopy (ECLIPSE-E 200; Nikon, Tokyo, Japan) at a magnification of 100x and 400x.

The presence of squamous metaplasia was assessed using Nelson's scale. This system is graded from 0 to 3, based on the morphology of the epithelial cells, their staining behavior and integrity, the nucleoplasmic ratio, as well as the density and the Periodic acid-Schiff (PAS) staining of the goblet cells [11, 12]:

Grade 0: Epithelial cells are round and small with eosinophilic cytoplasm. The nuclei are large and uniform, with a nuclear-cytoplasmic ratio of 1:2. The goblet cells are abundant, loose, and oval. Intercellular spaces are well preserved.

Grade I: Round epithelial cells are slightly larger, polygonal epithelial cells begin to appear among the former, and the cytoplasm is eosinophilic. The nuclei are smaller with a nuclear-cytoplasmic ratio of 1:3. Goblet cells are decreased in number but still retain their loose oval shape. Intercellular spaces are expanded in some areas.

Grade II: Epithelial cells are larger, polygonal, sometimes multinucleated, with eosinophilic cytoplasm, and a nuclear-cytoplasmic ratio of 1:4 to 1:5. Goblet cells are markedly decreased in number, with depleted cytoplasm. Intercellular spaces are expanded, with a loss of intercellular junctions seen in some areas.

Grade III: Epithelial cells are large and polygonal, with cytoplasmic basophilia and uniform pyknotic small nuclei. Loss of intercellular junctions and keratinization are seen. Goblet cells are absent.

Grades 0 and I reflect a normal state of, whereas grades II and III are characteristic of pathological changes in, the bulbar conjunctival epithelium.

Signs of squamous metaplasia of the conjunctival mucous membrane include changes in the cell shape, cytoplasm color, and nucleus size in epithelial cells; a decrease in number or absence of goblet cells; and the expansion of intercellular spaces.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Local Committee of Bioethics and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Patients consented to the publication of the images.

Statistical analysis was performed using Statistica 10.0 (StatSoft, USA).

Data are presented as percentages or mean ± standard deviation (SD).

A two-tailed t-test was used to evaluate between group differences for continuous variables with normal distribution (the Kolmogorov–Smirnov test). Correlations were evaluated using Spearman's rank correlation. Differences in qualitative variables were assessed with the exact Fisher's test. A two-tailed t-test for independent samples was performed to assess the differences between the first and second measurements. P-value < 0.05 was considered statistically significant.

Results

All participants enrolled in this study had mild DED based on the OSDI questionnaire. The mean age of the study groups and controls was not significantly different. Median duration of the disease was the same in all groups, ranging from one to six years (Table 1). Objective tear production and quality tests (Shirmer's test; TBUT) showed a significant difference between study group 1 and controls. Moreover, both tests showed a significant difference between study groups 1 and 2, which may be linked with abnormal tear production/quality among patients with glaucoma receiving Latanoprost with/without preservatives (Fig. 1).

Mean OSDI score did not differ between study groups but was significantly lower among controls (Table 1).

There was CIC evidence of defects and/or loss of intercellular junctions alongside widening of the extracellular matrix in 67% of patients in study group 1 (Fig. 2). In contrast, only 29% of study group 2 showed similar findings.

Grades 0 to 1 squamous metaplasia was seen in 23.8%, 40.0% and 85.7% of patients in study groups 1 and 2, and controls, respectively (Fig.3).

Epithelial round cells appear close to each other, and the cell shape changes from round to polygonal along the edge of the cell layer; these cells are evenly stained. Intercellular junctions are well preserved, and occasional widening of the intercellular space is observed along the

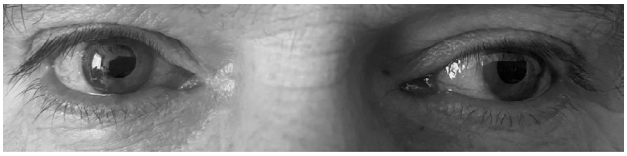

Fig. 1. Group 1: Patient P., 56 yo with bilateral POAG; (treatment regimen: latanoprost with preservatives, once daily; a disease duration of 1 year). On examination, the palpebral margins were thickened and hyperemic, the conjunctiva was red, and conjunctival vessels were moderately dilated. Additionally, the Schirmer's test score was 5 mm, and the TBUT test score, 9 s.

Table 1. Basic characteristics of groups

Characteristics		Study group 1 (n=21)	Study group 2 (n=15)	Control group (n=21)	p-value
Age, yo		60±4.30	57.9±3.9	58±6.1	p>0.05
Duration of disease		Median – 2 (min - 1, max - 6)	Median – 2 (min - 1, max - 4)	Median – 2 (min - 1, max - 6)	n/a
Shirmer's test		7.66±2.13	9.40±2.85	10.43±2.15	p_{1-c}=0.00015 p_{2-c}=0.2257 p_{1-2}=0.00439
TBUT test		6.95±2.22	9.13±1.68	11.19±1.66	p_{1-c}=0.00000 p_{2-c}=0.00089 p_{1-2}=0.00301
OSDI	1-12	3	5	11	p_{1-c}=0.0203 p_{2-c}=0.3204 p_{1-2}=0.2358
	13-22	11	9	10	p>0.05
	23-32	7	1	0	p_{1-c}=0.0086 p_{2-c}=0.4167 p_{1-2}=0.1038
	33-100	0	0	0	n/a
	M±SD	19.71±5.90	15.93±5.76	13.33±2.87	p_{1-c}=0.00006 p_{2-c}=0.08281 p_{1-2}=0.06409

Note. $p < 0.05$ has been considered statistically significant; p_{1-c} - difference between study group 1 and controls; p_{2-c} - difference between study group 2 and controls; p_{1-2} - difference between study groups 1 and 2; n – number of cases; M±SD – mean ± standard deviation; TBUT – tear break-up time; OSDI – Ocular Surface Disease Index

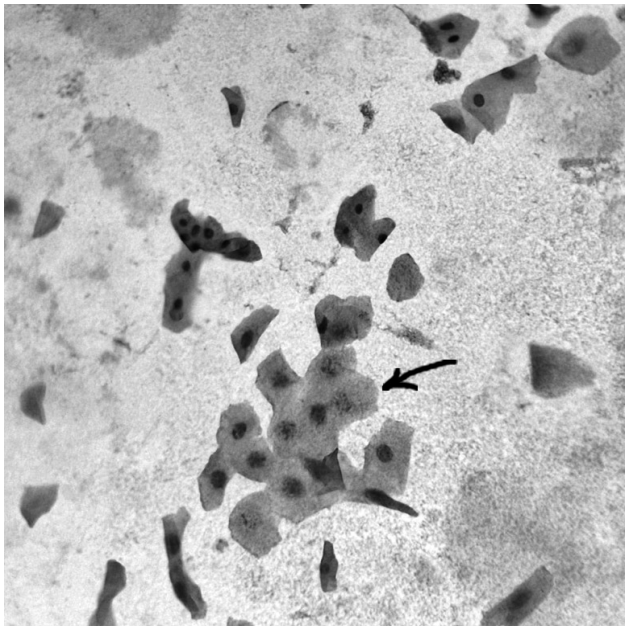

Fig. 2. Study group 1, Nelson's grade 3, widened and lost intercellular junctions, no goblet cells, karyopyknosis. Note epithelial cells (black arrow) (hematoxylin-eosin stain, original magnification 400×).

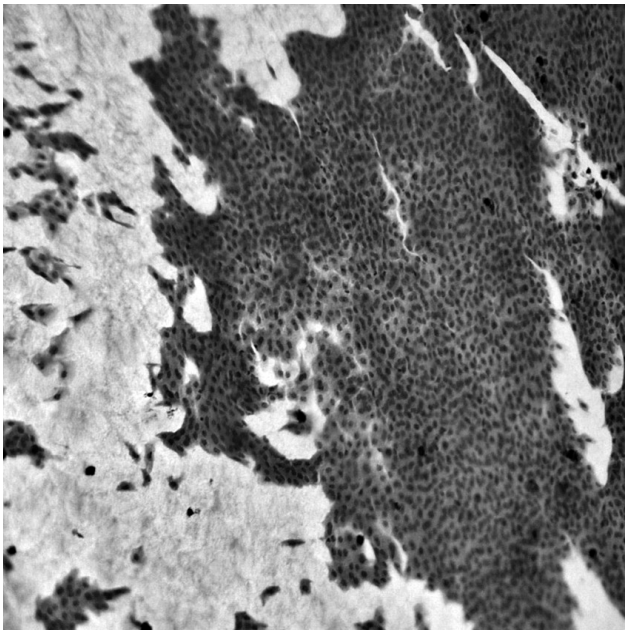

Fig. 3. Study group 2, Nelson's grade 1 (hematoxylin-eosin stain, original magnification 100×).

Table 2. Cytological findings in the study and control groups

Cytological characteristics		Study group 1 (n=21)		Study group 2 (n=15)		Control group (n=21)		p-value
Nelson's grade	0-1	5	23.8%	6	40.0%	18	85.7%	p_{1-c}=0.0001 p_{2-c}=0.0103 p_{1-2}=0.4646
	2	10	47.6%	8	53.3%	3	14.3%	p_{1-c}=0.0431 p_{2-c}=0.0255 p_{1-2}=1.000
	3	6	28.6%	1	6.7%	0	0	p_{1-c}= 0.0207 p_{2-c}=0.4167 p_{1-2}=0.2003
Presence of inflammatory cells		9	42.8%	1	6.6%	0	0	p_{1-c}= 0.0014 p_{2-c}=0.4167 p_{1-2}=0.0279

Note. $p < 0.05$ has been considered statistically significant; p_{1-c} – difference between study group 1 and controls; p_{2-c} – difference between study group 2 and controls; p_{1-2} – difference between study groups 1 and 2; n – number of cases

margin of the layers. Goblet cells are oval and round in shape, and are at a concentration of up to 15 cells per high power field. The nuclear-cytoplasmic ratio varies from 1:1 (in round cells) to 1:3 (polygonal).

The control group demonstrated a significant difference from the study groups ($p<0.05$), which reflects the effect of DED and glaucoma on conjunctival cytology in itself (Table 2).

Almost half of the patients in study group 1 had Nelson's grade 2; similarly, the vast majority of study group 2, 47.6% and 53.3%, respectively (Fig. 4).

Although study group 1 had a slightly larger percentage of patients with grade 2 metaplasia, there was no significant difference between study groups.

The same pattern was observed for patients with Nelson's grade 3. The data suggest that use of anti-glaucoma medication without or with a preservative does not significantly affect the cytological landscape of the bulbar conjunctiva. However, our further analysis has revealed the presence of inflammatory cells in 42.8% of patients receiving latanoprost with BAK and in 6.6% of patients taking the medication without preservatives ($p=0.0279$) (Fig. 3). Patients in study group 1 had 10.5 times the odds of presence of inflammatory cells than those in study group 2 (OR = 10.5; 95% CI [1.15 -95.25], P = 0.0366). These results show the potential role of preservatives in stimulating lymphocyte migration and causing subclinical inflammation in patients taking anti-glaucoma medications.

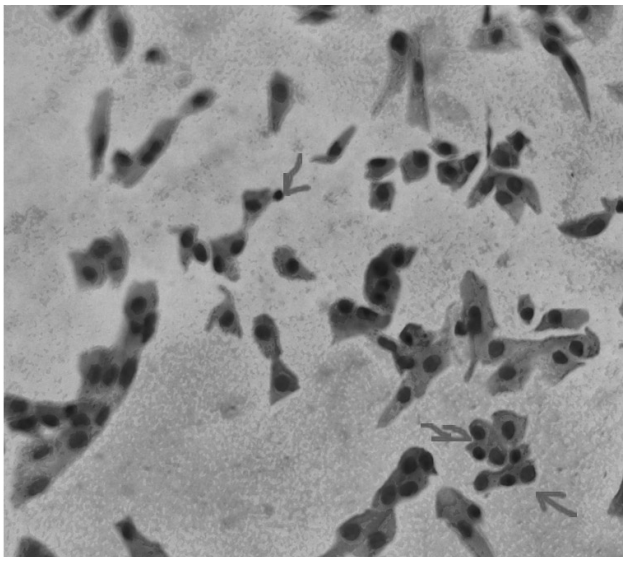

Fig. 4. Study group 1, Nelson's grade 2, groups of 3-8 polygonal cells, nuclear-cytoplasmic ratio 1:3, loss of intercellular junctions, 0-3 goblet cells. Note 0-5 lymphocytes (red arrow) (hematoxylin-eosin stain, original magnification 400×).

Rates of blinking were similar between study group 1 and healthy controls ($p=0.14327$), although the former group had higher scores of Nelson's grades. In contrast, this parameter was significantly higher in study group 2 (Table 3).

Table 3. Blinking rates in study groups and controls

Parameter \ Group	Study group 1 (n=21)	Study group 2 (n=15)	Control group (n=21)	p-value
Blinking rate (per min.)	12.43±3.38	16.67±4.30	13.76±2.30	p_{1-c}= 0,14327 p_{2-c}=0,01298 p_{1-2}= 0,00223

Note. $p < 0.05$ has been considered statistically significant; p_{1-c} – difference between study group 1 and controls; p_{2-c} – difference between study group 2 and controls; p_{1-2} – difference between study groups 1 and 2

As the continuous use of preservatives can cause neuropathy, blinking rates may not reflect the real cytological changes of the conjunctiva and lead to deactivation of the mechanical defense system of the lacrimal unit in this cohort of patients.

Discussion

The present study demonstrates that patients with glaucoma and mild dry eye disease (DED) receiving latanoprost therapy exhibit impaired tear production and reduced tear film stability compared with healthy controls, with more pronounced alterations in those treated with preservative-containing formulations. Although mean OSDI scores did not differ significantly between the study groups, conjunctival impression cytology revealed substantial epithelial damage, including higher Nelson's grades and a markedly increased presence of inflammatory cells in patients using latanoprost preserved with BAC. These findings suggest that preservatives may contribute to subclinical ocular surface inflammation, even in the absence of pronounced subjective symptoms. Furthermore, blinking rates did not correlate with the severity of cytological changes, indicating a possible preservative-induced impairment of neurosensory or protective mechanisms of the ocular surface.

Our findings are consistent with other studies reporting improved ocular comfort after switching to preservative-free therapy. Abegão Pinto et al. (2014) demonstrated a significant clinically relevant improvement in ocular symptoms, though not in functional complaints measured by the Glaucoma Symptom Scale, following a switch from preserved to preservative-free glaucoma medications [13]. In contrast, several studies have reported no significant differences in conjunctival hyperemia, corneal staining, Schirmer test results, tear production, or TBUT between patients using BAK-preserved and preservative-free prostaglandin analogues [14,15]. Importantly, these studies were characterized by relatively short follow-up periods, potentially underestimating the cumulative effects of long-term preservative exposure.

Regardless of the specific mechanisms involved, large population-based studies have consistently demonstrated an increased prevalence of ocular surface disease among patients treated with preservative-containing antiglaucoma medications [16,17]. Reported adverse effects include conjunctival hyperemia, eyelash growth, and ocular discomfort associated with topical prostaglandin analogues such as latanoprost, bimatoprost, and travoprost [18,19]. Conjunctival hyperemia is the most frequently reported adverse event and occurs significantly more often with travoprost and bimatoprost than with latanoprost, which shows the lowest incidence of adverse events among prostaglandin analogues.

Conjunctival hyperemia is generally considered a mild and transient effect of prostaglandin therapy and is thought to result primarily from vasodilation rather than overt inflammation [20]. Nevertheless, severe hyperemia is more commonly associated with prostaglandin analogues than with other antiglaucoma agents [21], although its intensity often decreases with continued treatment [22]. Our cytological findings, however, suggest that inflammatory changes may occur at a subclinical level, even when clinical signs appear mild.

Morphological evidence supporting this hypothesis was provided by a study by Zhmud et al. (2023) [23], where they demonstrated significant structural alterations of the bulbar conjunctival epithelium in patients with open-angle glaucoma receiving long-term preserved topical therapy. Squamous metaplasia grades II–III (Nelson's classification) were identified in 90% of cases, accompanied by goblet cell loss, disruption of intercellular junctions, and degenerative epithelial changes. The severity of metaplasia correlated significantly with treatment duration, whereas the number of medications used had minimal impact. Notably, even a single preserved medication was sufficient to induce epithelial alterations, although signs of reactive basal cell hyperplasia suggested preserved regenerative potential in patients receiving shorter-term monotherapy [23].

Additional evidence of preservative-associated inflammation was provided by Guglielminetti et al (2002), who reported increased human leukocyte antigen (HLA-DR) expression in conjunctival epithelial cells of patients treated with 0.005% latanoprost, indicating activation of local immune responses despite good clinical tolerability [24].

Increased HLA-DR expression may reflect an underlying inflammatory milieu and could potentially increase the risk of excessive postoperative scarring, highlighting its value as a biomarker of ocular surface inflammation.

In line with these observations, our study identified inflammatory cells in 42.8% of patients using BAK-preserved latanoprost, further supporting the role of preservatives in inducing subclinical ocular surface inflammation. The use of conjunctival impression cytology allowed detailed morphological assessment of the bulbar conjunctiva, providing objective cellular-level evidence of ocular surface damage and reinforcing the rationale for preservative-free formulations in long-term glaucoma management.

This study has several limitations, including a relatively small sample size, variability in treatment duration, and the lack of objective assessment of corneal neuropathy and its potential influence on blinking rate. In addition, only patients with mild DED were included. Future studies should involve larger cohorts, longer follow-up periods, and a broader spectrum of DED severity to further elucidate the inflammatory and neurotrophic effects of preserved versus preservative-free antiglaucoma therapy.

Conclusion. Eyes of patients with POAG and mild DED treated with topical BAK-preserved latanoptost showed significantly impaired tear production and stability, as evidenced by significantly reduced Schirmer's and TBUT scores, compared to those treated with preservative-free latanoptost and healthy controls.

Conjunctival impression cytology found more advanced cytological changes in this group, including higher

Nelson's grades and a significantly increased presence of inflammatory cells, indicating subclinical inflammation.

These findings support the preferential use of preservative-free antiglaucoma eye drops, particularly in patients with pre-existing or suspected ocular surface damage, to minimize cytological changes and subclinical inflammation during long-term therapy

Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by T. Zhmud and G. Drozhzhyna. The first draft of the manuscript was written by T. Zhmud and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Disclaimers

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this work.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of The Filatov Institute of Eye Diseases and tissue therapy of the National Academy of Medical Sciences of Ukraine, Odessa, Ukraine (approval number 08.11.2024 № 1).

The authors affirm that human research participants provided informed consent for publication of the images in Fig. 1.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Due to institutional policy and patient confidentiality, raw data are not publicly available.

Abbreviations

OR – odd ratio; CI – confidence interval; IOP – intraocular pressure; OSD – ocular surface diseases; DED – dry eye disease; BAC – Benzalkonium chloride; TBUT – tear break-up time; OSDI – Ocular Surface Disease Index; CIC – conjunctival impression cytology.

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