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# Ocular surface disease incidence in patients with open-angle glaucoma

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**SUMMARY**

**Introduction** Ocular surface disease (OSD) is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbances, tear film instability with potential damage to the ocular surface, accompanied by increased tear film osmolarity and inflammation of the ocular surface. It is a consequence of disrupted homeostasis of lacrimal functional unit. The main pathogenetic mechanism stems from tear hyperosmolarity and tear film instability. The etiological classification is hyposecretory (Sy-Sjögren and non-Sjögren) and evaporative (extrinsic and intrinsic) form. Delphi panel classification grades disease stages. Antiglaucoma topical therapy causes exacerbation or occurrence of symptoms of dry eye due to main ingredients or preservatives (benzalkonium chloride – BAK), which are dose- and time-dependent. BAK reduces the stability of the lipid layer of tears, the number of goblet cells, induces apoptosis and inflammatory infiltration.

**Objective** The aim of this study was the analysis of the OSD incidence in open-angle glaucoma patients caused by topical medicamentous therapy.

**Methods** Retrospective analysis of examined patients with open-angle glaucoma was used.

**Results** Increased incidence of moderate and advanced OSD Index degrees in the group of primary open-angle glaucoma (POAG) and pseudoexfoliative glaucoma. According to the Delphi Panel Scale the most common grade is IIb (POAG and pseudoexfoliative glaucoma). Evaporative form of OSD prevailed in all treatment groups. High percentage of dry eye in patients with higher concentrations of preservatives applied was noticed.

**Conclusion** OSD should be timely diagnosed and treated. Dry eye has an impact on surgical outcome and postoperative visual acuity, and in order to improve patient compliance and quality of life, symptoms of dry eye should be addressed and medications with lower concentrations of preservatives should be applied.

**Keywords**: glaucoma; ocular surface disease; dry eye; preservative

## INTRODUCTION

There are many definitions and synonyms explaining entity of dry eye in accordance with the change of knowledge of pathomechanisms referring to these multifactorial disorders. In 1995 Lemp defined dry eye as qualitative and quantitative disorder of the tear film that occurs as a result of the deficiency or increased tear evaporation and results in damaging of interpalpebral surface of the eye, with symptoms of ocular discomfort [1]. Most often used terms in the explanation of dry eye are the following: keratoconjunctivitis sicca, dysfunctional tear syndrome, ocular surface disease (OSD), dry eye syndrome. In accordance with the latest revision of the International Panel of Experts, Dry Eye Workshop (DEWS) 2007, dry eye is a chronic, multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbances, and tear film instability with potential damage of the ocular surface, accompanied by increased osmolarity of the tear film, and inflammation of ocular surface [1].

Dry eye syndrome is a very common disorder in adults, with an average prevalence of about 30% (5.5–57.1%). Etiology is multifactorial and may arise due to the use of medicines (antihistamines), nutritional factors (vitamin A, omega acids), age, diseases of the connective tissue, hormonal deficiencies, surgery of the anterior segment of the eye, trauma, sensory block in contact lens users, Ro therapy [2].

Tear production in healthy eyes depends on neuronal feedback. Disruption of the normal nerve control in tearing causes the dry eye disorder. The proposed mechanism that explains the occurrence of the OSD is feedback model that includes the lacrimal functional unit. It consists of the following three components: 1. ocular surface that is formed by the cornea, conjunctiva and meibomian gland; 2. lacrimal gland; 3. their mutual sensomotor innervation and innervation of the central nervous system.

Environmental stimulus (wind, low humidity) produces afferent impulses from the surface of the eye via the trigeminal nerve (n. V1) to the mesencephalon, cortical synapses, activates the parasympathetic efferent impulses (n. VII) to the lacrimal gland, resulting in tear secretion in a healthy eye. This reflex arc in a healthy eye is an example of positive feedback in response to stimuli from the environment [1, 3].

Damage of any component of the lacrimal functional unit interrupts the reflex arc, which

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results in damaging of the lacrimal gland and/or the surface of the eye. The consequence is a negative feedback with induced damage of the surface of the eye, disrupted secretomotor innervation that cause lacrimal gland dysfunction. Lacrimal gland cytokines continue to damage the conjunctiva and cornea due to activated inflammatory cascade. Released cytokines on the surface of the eye further interrupt signal generation in the secretory component. Secondary disruption of efferent signals to the lacrimal gland causes its further damage due to Ly infiltration, T-cell activation and cytokine release on the ocular surface [4].

Damage to any of the components of the lacrimal functional unit is presented as inflammation and hyperosmolar stress. The inflammatory process is essential in pathophysiology of the OSD. The mediators released in the highest concentration in inflamed lacrimal functional unit are as follows: IL-1, IL-6, IL-8, IL-1β, substance P, TNF-α, and MMP-9. Hyperosmolarity promotes inflammation as the main pathogenetic mechanism in all types of the dry eye. Healthy lacrimal functional unit produces the following protective mediators: androgen-dependent TGF-ß, EGF, IL-1ra, lysozyme and lactoferrin [4, 5].

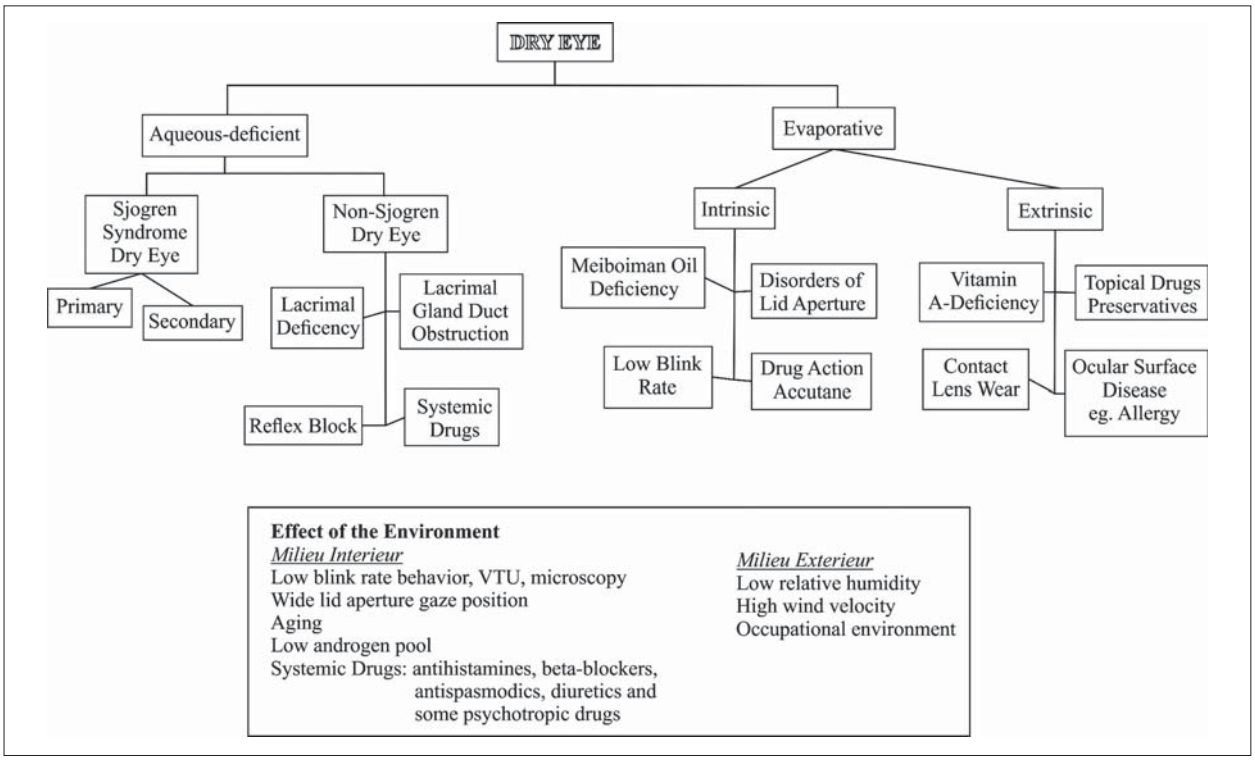
Based on the Triple Classification (SOE 2005, Berlin) and Delphi panels, DEWS in 2007, the three-part classification of dry eye was revised based on etiology, mechanisms and stages of the disease [1]. Etiologic classification system distinguishes two basic categories of dry eye: I. hyposecretory (Sy-Sjögren and non-Sjögren), and II. evaporative (extrinsic and intrinsic mechanism). A more detailed classification is shown in Scheme 1.

Although the scheme differentiates two basic forms of the disease, most people have mixed type, which can have a severe clinical presentation. Meibomian gland dysfunction has a significant role in the development of predominantly evaporative intrinsic form of the disorder. The first definition (Ocular Surface Society Workshop, 2011) states that meibomian gland dysfunction is chronic, diffuse abnormality characterized by obstruction of excretory ducts and/or qualitative and quantitative changes of glandular secretion.

Classification of dry eye toward the pathogenesis includes I. tear hyperosmolarity, and II. tear film instability. Hyperosmolarity (>300 mOsm/l) is essential in pathogenesis in all types of dry eye. Tear film instability in any of the three layers (lipid, aqueous, and mucous) is the key factor, and alteration of the regulatory mechanisms of the ocular surface results in activation of the inflammatory cascade. Inflammation is an underlying pathophysiological process in dry eye but not the primary one – it is a consequence of disrupted, already mentioned homeostatic mechanisms and exacerbation of pre-existing processes [5, 6, 7].

DEWS approved Delphi Panel classification of stages and disease severity according to clinical signs and symptoms is shown in Table 1 [3].

Long-term combined antiglaucoma therapy causes exacerbation of subclinical symptoms of dry eye or their occurrence due to preservatives or main substances. Clinical signs of OSD caused by antiglaucoma medications are not rare and cause suboptimal glaucoma control in noncompliant patients. Hyperemia and irritation due to the combined antiglaucoma therapy worsens OSD, disrupting patient's quality of life. Dry eye "screening" is not a part of glaucoma observation, but provides valuable data in assessing the OSD. POAG patients' complaints about the symptoms of OSD are present in more than 50% of




**Scheme 1.** Classification of dry eye

**Table 1.** Delphi Panel Scale grading of dry eye

| DEWS Dry Eye Severity Grading Scheme | | | | |
|---|---|---|---|---|
| Dry eye severity level | 1 | 2 | 3 | 4* |
| Discomfort, severity and frequency | Mild and/or episodic, occurs under environ. stress | Moderate, episodic or chronic stress or no stress | Severe, frequent or constant without stress | Severe and/or disabling and constant |
| Visual symptoms | None or episodic mild fatigue | Annoying and/or activity limiting episodic | Annoying, chronic and/or limiting activity | Constant and/or possibly disabling |
| Conjunctival injection | None to mild | None to mild | +/- | +/++ |
| Conjunctival staining | None to mild | Variable | Moderate to marked | Marked |
| Corneal staining (severity/ location) | None to mild | Variable | Marked/central | Severe punctate erosions |
| Corneal/tear signs | None to mild | Mild debris, meniscus | Filamentary keratitis, mucus clumping, tear debris | Filamentary keratitis, mucus clumping, tear debris, ulceration |
| Lid/meibomian glands | Meibomian gland dysfunction (MGD) variably present | MGD variably present | Frequent | Trichiasis, keratinization, symblepharon |
| Fluorescein tear break-up time | Variable | ≤ 10 seconds | ≤ 5 seconds | Immediate |
| Schirmer score | Variable | ≤ 10 mm/5 min. | ≤ 5 mm/5 min. | ≤ 2 mm/5 min. |

(Source: The Ocular Surface, April 2007, vol 5, No 2)
* Must have signs and symptoms; ↓ – increased; ↑ – decreased

patients. Also, symptoms increase with each drop containing the preservative benzalkonium chloride (BAK). The most common reason for using preservatives in ophthalmic drugs is the inhibition of microbial growth. BAK is a quaternary ammonium molecule, a cationic surfactant with detergent characteristics that disrupt tear lipid layer. This compound has been shown to cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues [8–12].

A healthy eye surface is an essential finding in successful drug treatment and surgery outcomes (accurate keratometry, IOL calculations, and refractive outcomes). About 50% of patients already have preoperatively manifested dry eye and 50% are asymptomatic [7, 13]. In planning glaucoma surgery as a therapeutic option in the treatment of this chronic progressive optic neuropathy which may result in blindness, diagnosing and treating the problem of dry eye also has a significant role [14, 15].

## OBJECTIVE

The aim of this study was retrospective analysis of the OSD incidence in open-angle glaucoma patients treated with topical medicamentous therapy in different disease stages, different combinations of drugs, treatment duration and intraocular pressure compensation as potential candidates for surgical glaucoma treatment in refractory cases and disease progression.

## METHODS

The retrospective study included 80 patients or 160 eyes, out of which 40 eyes with diagnosed primary open-angle glaucoma (POAG), 40 eyes suffering from pseudoexfoliative glaucoma (XFG), 40 open-angle glaucoma eyes treated with tafluprost solution, and 40 healthy eyes without topical medicamentous treatment. Inclusion criteria were that all respondents were older than 30 years, previously diagnosed glaucoma in medicamentous treated groups with different duration, and no previous glaucoma surgery. Also, OSD was not previously diagnosed, none of them used artificial drops and there was no concomitant anterior segment pathology, including blepharitis chronica. None of the respondents were contact lens wearers. OSD screening and diagnostic tests were performed during glaucoma patient follow-up.

Performed ophthalmological examination included a questionnaire about experiencing dry eye symptoms that was presented and expressed results through OSD index score. The resulting score of the questions from the three groups related to the presence of symptoms of dry eye (A), symptoms in daily activities (B), and response to environmental factors (C) was added and expressed by the value of D, which is multiplied by 25 and divided with the number of questions with given answers, according to the following formula: OSD index = sum response × 25 / number of questions answered [16] (Figure 1).

The grading was performed according to the displayed color coded map or numerical scale of results as follows: normal finding (0–12), an incipient (13–22), moderate (23–32), and advanced (≥33) dry eye (Figure 2) [16, 17, 18].

The following clinical ophthalmological testing was used in the examination: TBUT test (tear breakup time, time of interrupted precorneal tear film), Schirmer's test I of tear volume production and vital staining (rose bengal) with grading according to Oxford scale after slit-lamp examination [19]. TBUT test is a measure of adequate tear film stability and mucus production. It is expressed as a period of time in seconds from the last blink until the breakup of the fluorescein stained tear film at random positions on the cornea. In evaluation, more than 10 seconds

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| Have you experienced any of the following *during the last week?* | All of the time | Most of the time | Half of the time | Some of the time | None of the time |
|---|---|---|---|---|---|
| 1. Eyes that are sensitive to light? .. | 4 | 3 | 2 | 1 | 0 |
| 2. Eyes that feel gritty? ..... | 4 | 3 | 2 | 1 | 0 |
| 3. Painful or sore eyes? ..... | 4 | 3 | 2 | 1 | 0 |
| 4. Blurred vision? ..... | 4 | 3 | 2 | 1 | 0 |
| 5. Poor vision? ..... | 4 | 3 | 2 | 1 | 0 |

Subtotal score for answers 1 to 5 (A)

| Have problems with your eyes limited you in performing any of the following *during the last week?* | All of the time | Most of the time | Half of the time | Some of the time | None of the time | N/A |
|---|---|---|---|---|---|---|
| 6. Reading? ..... | 4 | 3 | 2 | 1 | 0 | N/A |
| 7. Driving at night? ..... | 4 | 3 | 2 | 1 | 0 | N/A |
| 8. Working with a computer or bank machine (ATM)? ..... | 4 | 3 | 2 | 1 | 0 | N/A |
| 9. Watching TV? ..... | 4 | 3 | 2 | 1 | 0 | N/A |

Subtotal score for answers 6 to 9 (B)

| Have your eyes felt uncomfortable in any of the following situations *during the last week?* | All of the time | Most of the time | Half of the time | Some of the time | None of the time | N/A |
|---|---|---|---|---|---|---|
| 10. Windy conditions? ..... | 4 | 3 | 2 | 1 | 0 | N/A |
| 11. Places or areas with low humidity (very dry)? ..... | 4 | 3 | 2 | 1 | 0 | N/A |
| 12. Areas that are air conditioned? ... | 4 | 3 | 2 | 1 | 0 | N/A |

Subtotal score for answers 10 to 12 (C)

**Figure 1.** Ocular Surface Disease Index Questionnaire (part I) [16]

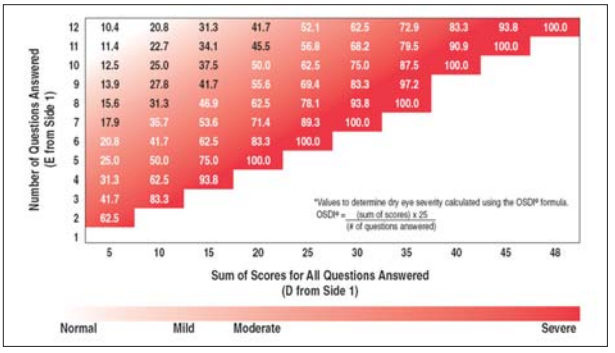



**Figure 2.** Ocular Surface Disease Index Questionnaire (part II) [16]

is a normal finding, less than 10 seconds is abnormal, and less than five seconds is clearly abnormal. It is standardized that TBUT is taken as mean value of three consecutive measurements.

Schirmer's test I is performed without topical anesthesia via a standardized filter paper strip and measures tear volume (basal and reflex) secretion. According to the test protocol, if more than 15 mm is measured during 5 minutes of testing, the value is considered normal. Length of moisture less than 10 mm is abnormal, and is evaluated as clearly abnormal if less than 5 mm [3, 20, 21, 22].

Ocular surface damage of the exposed eye is assessed by staining with vital dyes and graded against standard charts. There are three standard schemes used to estimate surface damage in dry eye, and in this study Oxford grading scale was used, showed in Figure 3.

Staining is represented by punctate dots on a series of panels (A–E). Staining ranges 0–5 for each panel and 0–15 for the total exposed inter-palpebral conjunctiva and cornea.

Dyes that could be used are lissamine green, fluorescein sodium and rose bengal, which we used. Estimation is made using slit-lamp to observe ocular surface. To grade

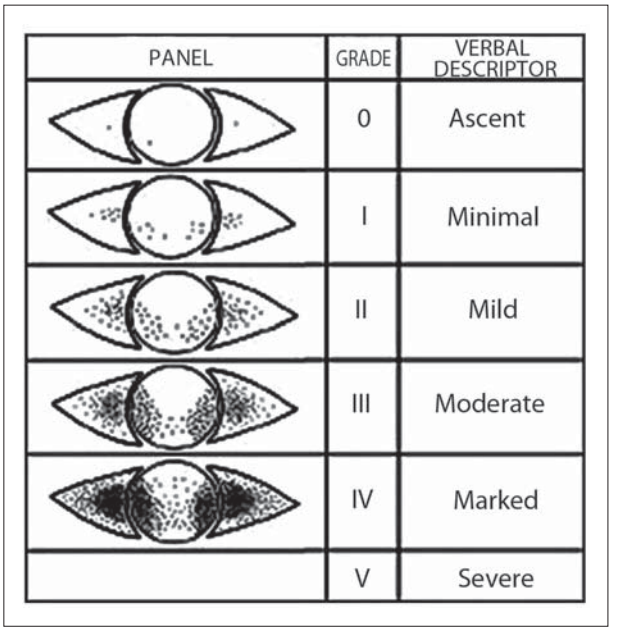



**Figure 3.** Vital dye (rose bengal) ocular surface disease staining according to Oxford Scale (source: The Ocular Surface, April 2007, vol 5, No 2)

the temporal zone of the conjunctiva, respondent looks towards their nose, and in grading the nasal zone of the conjunctiva, the subject looks to the opposite side, temporal bone [1, 20–23].

Delphi panel grading scale was used in estimation of the disease stages according to Table 1 [1]. More detailed subclassification of stage II is applied and differentiates dry eye as moderate (IIa) and moderately severe (IIb). The main differences are in TBUT values and epithelial integrity. In stage IIa, TBUT values are 10–15 seconds with punctiform epithelial staining; in stage IIb, TBUT values are 5–10 seconds with marked epithelial damage. In both stages, values of Schirmer's test are less than 10 mm [3].

The two groups of treated patients (POAG, XFG) already received antiglaucoma therapy as mono- or therapy combined of two or three drugs with different active substance or contained preservatives in different concentrations available in our country. The drugs contained Purite, which is not harmful, and BAK in different concentrations. These concentrations of preservatives were added if two or three drugs were applied. The third group was treated with monotherapy by tafluprost solution in single-dose containers, comprising EDTA and polysorbate 80. The fourth group did not use any drops, not even artificial tear drops.

Obtained results were analyzed by descriptive statistical analysis, tabular and graphical presentation of cumulative frequency curve in MS Office Excel, and by using SPSS 19 statistical software package (IBM Corp., Armonk, NY, USA) for testing proportions for categorical variables through $\chi^2$ test.

## RESULTS

Of all surveyed individuals, 65% were female and 35% were male. Similar sex ratio in POAG and XFG groups

**Table 2.** Distribution according to sex

| Sex | Number of patients (number of eyes) | | | | Total |
|---|---|---|---|---|---|
| | POAG group | XFG group | Group on tafluprost | Control group | |
| Female | 12 (24) | 9 (18) | 16 (32) | 15 (30) | 52 (65.0%) |
| Male | 8 (16) | 11 (22) | 4 (8) | 5 (10) | 28 (35.0%) |
| Total | 20 (40) | 20 (40) | 20 (40) | 20 (40) | 80 (100.0%) |

POAG – primary open-angle glaucoma; XFG – pseudoexfoliative glaucoma

**Table 3.** Age structure in tested groups

| Age (years of life) | Number of patients (number of eyes) | | | |
|---|---|---|---|---|
| | POAG (gl. simplex) group | XFG group | Group on tafluprost | Control group |
| 30–40 | 1 (2) | / | 4 (8) | 5 (10) |
| 41–50 | / | / | 3 (6) | 6 (12) |
| 51–60 | 7 (14) | / | 8 (16) | 3 (6) |
| 61–70 | 6 (12) | 5 (10) | 3 (6) | 3 (6) |
| 71–80 | 5 (10) | 8 (16) | 2 (4) | 3 (6) |
| 81–90 | 1 (2) | 7 (14) | / | / |
| Total | 20 (40) | 20 (40) | 20 (40) | 20 (40) |

**Table 4.** Classification of symptoms according to Ocular Surface Disease Index (OSDI) questionnaire

| OSDI grade | Number of patients (%) | | | |
|---|---|---|---|---|
| | POAG group | XFG group | Group on tafluprost | Control group |
| Normal | 8 (40.0) | 3 (15.0) | 18 (90.0) | 16 (80.0) |
| Mild | 5 (25.0) | 3 (15.0) | 2 (10.0) | 2 (10.0) |
| Moderate | 3 (15.0) | 3 (15.0) | 0 | 2 (10.0) |
| Severe | 4 (20.0) | 11 (55.0) | 0 | 0 |

**Table 5.** Distribution of dry eye according to the Delphi panel scale

| Delphi panel scale | Number of eyes (%) | | | |
|---|---|---|---|---|
| | POAG group | XFG group | Group on tafluprost | Control group |
| Normal | 2 (5.0) | / | 19 (47.5) | 26 (65.0) |
| Grade I | 13 (32.5) | / | 15 (37.5) | 6 (15.0) |
| Grade IIa | 10 (25.0) | 10 (25.0) | 4 (10.0) | 3 (7.5) |
| Grade IIb | 15 (37.5) | 24 (60.0%) | 2 (5.0) | 5 (12.5) |
| Grade III | / | 6 (15.0) | / | / |
| Grade IV | / | / | / | / |
| Total | 40 (100) | 40 (100) | 40 (100) | 40 (100) |

was found, but more prevalent female sex in the control and the tafluprost treated group is evident (Table 2).

Since glaucoma and OSD frequently occur in the elderly population, age structure in the investigated groups was analyzed and showed population older than 50 years in the POAG group and older than 60 years in the XFG group. In comparison to the tafluprost solution treated group, younger population was noticed, with approximate age distribution of 30–60 years, similar to the results in the control group (Table 3).

According to the symptoms and OSD index, the distribution in the POAG group was as follows (Table 4): 40% normal, 25% incipient, 15% moderate, and 20% had advanced symptoms. In the XFG group, the distribution was the following: 15% normal, 15% incipient, 15% moderate, and 55% of advanced symptoms. In the tafluprost treated group, 90% of the surveyed individuals showed normal findings, and 10% were incipient. OSD index distribution

**Table 6.** Classification based on types of dry eye

| Type of dry eye | Number of eyes (%) | | | |
|---|---|---|---|---|
| | POAG group | XFG group | Group on tafluprost | Control group |
| Normal | 16 (40.0) | 6 (15.0) | 19 (47.5) | 26 (65.0) |
| Hyposecretory | 4 (10.0) | 6 (15.0) | 4 (10.0) | 4 (10.0) |
| Evaporative | 10 (25.0) | 16 (40.0) | 13 (32.5) | 6 (15.0) |
| Mixed type | 10 (25.0) | 12 (30.0) | 4 (10.0) | 4 (10.0) |
| Total | 40 (100) | 40 (100) | 40 (100) | 40 (100) |

**Table 7.** Distribution of therapy duration among respondents

| Therapy duration | Number of eyes (%) | | |
|---|---|---|---|
| | POAG group | XFG group | Group on tafluprost |
| <1 year | 10 (25) | 4 (10) | 20 (50) |
| 1–5 years | 18 (45) | 36 (90) | 20 (50) |
| >5 years | 12 (30) | / | / |
| Total | 40 (100) | 40 (100) | 40 (100) |

**Table 8.** Distribution according to the number of drugs (bottles) among respondents

| Number of bottles | Number of eyes (%) | |
|---|---|---|
| | POAG group | XFG group |
| 1 | 14 (35) | 8 (20) |
| 2 | 12 (30) | 10 (25) |
| 3 | 14 (35) | 22 (55) |
| Total | 40 (100) | 40 (100) |

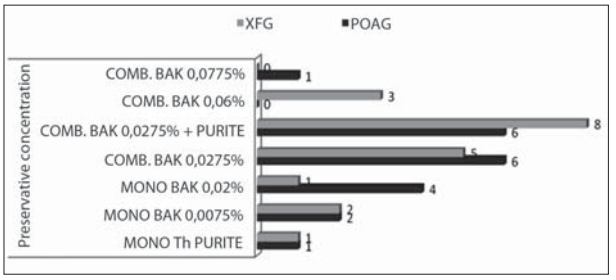
in the control group was as follows: 80% normal findings, 10% incipient, and 10% moderate symptoms of dry eye.

According to the Delphi panel scale in POAG (Table 5), the distribution was as follows: 32.5% grade I, 25% grade IIa, and 37.5% grade IIb. In the XFG group the distribution was as follows: 25% grade IIa, 60% grade IIb, and 15% grade III. In the tafluprost group the distribution was the following: 47.5% were healthy eyes, 37.5% grade I, 10% grade IIa, and 5% grade IIb. In the control group the distribution was as follows: 65% were healthy eyes, 15% grade I, 7.5% grade IIa, 12.5% grade IIb.

Classification according to the type of dry eye was done (Table 6). In the POA glaucoma group, 10% of hyposecretory, 25% of the evaporative, and 25% of mixed form was diagnosed. In the XFG group, 15% hyposecretory form, 40% of the evaporative, and 30% of mixed form was diagnosed. In the POAG group treated with tafluprost antiglaucoma solution, 10% hyposecretory, 32.5% evaporative, and 10% of mixed form was determined.

Manifestation of symptoms and signs of OSD depends on the duration of glaucoma therapy, on the number of antiglaucoma agents, and it is also estimated according to the type and concentration of preservatives. Distribution of therapy duration among respondents in therapy groups is shown in Table 7. The most prevalent time interval of applied antiglaucoma drugs in all three treated groups was between one and five years. Relation of applied number of antiglaucoma agents (bottles of drugs) in the treated groups of respondents to the type of glaucoma (POAG; XFG) is presented in Table 8.

Cumulative frequency of BAK preservative-applied combined therapy is illustrated in the diagram (Graph 1)




**Graph 1.** Benzalkonium chloride (BAK) concentrations in primary open angle glaucoma (POAG) and pseudoexfoliative glaucoma (XFG)

**Table 9.** Benzalkonium chloride (BAK) concentrations in primary open angle glaucoma (POAG) and pseudoexfoliative glaucoma (XFG)

| BAK concentrations | | Number of patients | |
|---|---|---|---|
| | | POAG glaucoma | XFG glaucoma |
| Monotherapy | Purite | 1 | 1 |
| | BAK 0.0075% | 2 | 2 |
| | BAK 0.02% | 4 | 1 |
| Combined therapy | BAK 0.0275% | 6 | 5 |
| | BAK 0.0275% + Purite | 6 | 8 |
| | BAK 0.06% | 0 | 3 |
| | BAK 0.0775% | 1 | 0 |

and in Table 9 and correlates to the types of dry eye in both POAG and XFG group and presents most frequently applied 0.0275% of cumulative BAK.

High correlation of dry eye type to different concentrations of applied BAK and number of applied drugs was determined using $\chi^2$ test ($\chi^2 = 0.087$, likelihood ratio $p < 0.021$).

## DISCUSSION

Both glaucoma and dry eye are multifactorial and very prevalent diseases. Glaucoma is the second most common cause of blindness in the world; on the other hand, OSD is one of the main diagnoses in ophthalmological practices. OSD prevalence shows large variation in general population of up to 33%, but in glaucoma patients was found to be present in more than 52.6% [2, 24, 25]. In our study group, OSD prevalence and characteristics were analyzed in glaucoma patients, starting with epidemiologic factors, female sex was more prevalent in all respondents (65% vs. 35%), and also more prevalent in the tree groups of glaucoma patients (POAG, XFG and open-angle glaucoma treated with tafluprost) excluding control group, with the ratio of 61.67% of females versus 38.33% of males. A similar sex distribution was found in a comprehensive study by Erb et al. [26] resulting with German Register for Glaucoma Patients with Dry Eye – 60.9% females vs. 39.1% males.

In relation to age, our study based on a small population sample was in accordance with evidence that glaucoma is a disease of elderly population and that dry eye prevalence increases with age. Purpose of the German Register was to determine the links between glaucoma, age, concomitant disease, medication, and dry eye in a large group of glaucoma patients, showing OSD incidence from 31.3% in people younger than 40 years, to 61.6% in patients older than 90 years, according to the German study [26]. Our respondents were mostly older than 60 years in the POAG and the XFG group, but younger than 60 years in open-angle glaucoma group treated with tafluprost, and the control group. Therefore, incidence of dry eye in glaucoma treated groups was expected to be higher than that in the control group.

Questionnaires about presence of dry eye symptoms are included in epidemiologic or clinical research to screen individuals for prevalence of dry eye or in clinical practice to assess the diagnosis, to grade disease severity and estimation of treatment. Increased incidence of moderate and advanced OSD index grades was noticed due to the presence of symptoms of dry eye in the of POAG and XFG groups of our respondents. Open-angle glaucoma group treated with tafluprost (medication without preservative) showed symptoms of dry eye similar to healthy control group, with 90% of normal results and 10% of mild symptoms. In our groups, experienced symptoms of ocular discomfort and dry eye grading to Ocular Surface Disease Index (OSDI) questionnaire were as follows: 60% in the POAG group patients, 85% in the XFG group, 10% in tafluprost treated patients, and 20% in the control group. OSDI score could be a good predictor of preservative toxicity and ocular surface damage, as our treated respondents indicated. Thus, as OSDI score is growing, a patient's quality of life is decreasing. [1, 21, 27].

The most prevalent grades of dry eye according to DEWS grading system are IIa and IIb in both glaucoma groups (POAG and XFG groups). This differs from the most prevalent grade I (37.5%) in tafluprost treated patients, and 65% of normal eyes in the control group. The highest percentages of grade IIb, based on Delphi panel scale in POAG and XFG treated groups, indicate not only high association with dry eye, but these values also indicate the type of glaucoma due to therapy response to topical medications. It is obvious that XFG in all these groups showed the most severe grades (60% IIb), with characteristic clinical signs and changes of the anterior segment of the eye. In addition to exfoliative keratopathy, tear function disorder was analyzed in a study by Kozobolis et al. [28, 29]. Schirmer's and TBUT test show reduced tear production and instability of tear film as disorder of reduced mucin [28]. Electron microscopy indicates that PEX material could be confirmed in conjunctival stroma [29]**.** This explains why XFG is in low proportion in general population of glaucoma patients (20% of open-angle glaucoma patients, or 5.2% of the population in the German study [26]), but with high incidence of OSD in these treated groups.

Evaporative form of OSD is the most common in all three treatment groups, and indicates disruption of lipid tear film layer, but mixed and evaporative form are more prevalent in therapeutic groups with preservative drops (POAG, XFG).

The duration of glaucoma also plays a role in OSD occurrence. OSD prevalence in POAG (60%), XFG (85%)

and tafluprost group (52.5%) in all treated patients corresponds to more than one year of therapy, respectively (75% vs. 90% vs. 50%), in treated groups. Similar distribution is in the applied number of drugs, more precisely bottles, because each bottle contains its own preservative in different concentration, which means that applied monotherapy and combined therapy affects ocular surface differently in POAG and XFG.

OSD prevalence increases with the number of antiglaucoma drugs and duration of their application.

Prevalence of OSD increases in relation to number of antiglaucoma agents due to active substance and mostly preservative containing drops. Preservatives could be analyzed by the type and concentration of preservative contained in a bottle of an antiglaucoma drug. Apart from preservative-free agents, most of glaucoma drops contain variable degrees of BAK, whose harmful effects – disturbed tear film, inflammation of conjunctiva, cytotoxicity to cornea – are well known. In a study by Leung et al. [2] after correcting for age and gender, every additionally administered BAK-containing anti-glaucoma agent resulted in a two-fold increase in the incidence of ocular surface lesions found on lissamine green staining.

A high percentage of dry eye in the treatment groups with high concentration of applied preservatives (mostly BAK) detects the causative factor. All our treated groups showed more than 50% prevalence of dry eye, similar to other authors and the mentioned German study [2, 26, 30, 31]. In our treated groups (POAG, 60%; XFG, 85%; tafluprost group, 52.5%), incidence of OSD correlates with higher BAK level, number of applied drugs (drops), and therapy duration.

Clinical and experimental studies have demonstrated that OSD is common in glaucoma patients receiving glaucoma drops, and that the preservatives in these drops play a major role in the occurrence of OSD [32].

## CONCLUSION

Ocular surface changes may induce both symptoms reported by patients and anterior segment clinical signs, detected by ophthalmologist, and should be systematically assessed during examination in all glaucoma patients. Preservative-free drops are associated with lower OSD incidence. In patients with OSD, reducing the amount of preservatives administered using fixed drug combinations should be advised. Adding artificial tear drops could be useful. According to the DEWS recommendations, preserved medications should be replaced by those without preservatives whenever possible. Generally, in order to improve compliance of patients, quality of life, and treatment, combinations of drugs with lower BAK concentrations, less toxic formulations (Purite, polyquaternium) or drops without preservatives are recommended. Also, timely diagnoses and treatment of dry eye is very important as well-timed indication for surgery treatment of glaucoma in certain situations for successful surgical outcome.

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## NOTES

The paper is part of Marija Radenković's master thesis and presents some of the results that will be processed and published in the thesis.

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# Инциденца болести површине ока код пацијената са глаукомом отвореног угла

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**КРАТАК САДРЖАЈ**

**Увод** Болест површине ока (БПО) мултифакторијелно је обољење суза и површине ока које резултује симптомима дискомфора, сметњама вида и нестабилношћу сузног филма са потенцијалним оштећењем површине ока. Ово обољење праћено је повећаном осмоларношћу сузног филма и инфламацијом површине ока. Последица је нарушене хомеостазе лакрималне функционалне јединице. Основни патомеханизам настанка је услед хиперосмоларности суза и нестабилности сузног филма. Етиолошки су класификоване две форме: хипосекреторна (Су Сјогрен и нон-Сјогрен) и евапоративна (*extrinsic* и *intrinsic*). Стадијуме градира Делфи панел класификација. Антиглаукомна терапија проузрокује егзацербацију или настанак симптома сувог ока услед дејства основне супстанце или конзерванса (бензалконијум – БАК), која је дозно и временски зависна. БАК редукује стабилност липидног слоја суза, број пехарастих ћелија, индукује апоптозу и инфламаторну инфилтрацију.

**Циљ рада** Циљ истраживања је била анализа инциденце БПО код пацијената са глаукомом отвореног угла на топикалној медикаментозној терапији.

**Методе рада** Ретроспективна анализа прегледаних пацијената са глаукомом отвореног угла.

**Резултати** Повећана је инциденца индекса БПО и то умерених и узнапредовалих градуса у групи примарног глаукома отвореног угла и псеудоексфолијативног глаукома. Делфи панел скала: најзаступљенији је градус *IIb* (у *POAG* и псеудоексфолијативном глаукому). Евапоративна форма БПО је најзаступљенија у све три терапијске групе. Високи проценат сувог ока потврђен је код пацијената са апликованом највишом концентрацијом конзерванса.

**Закључак** БПО би требало правовремено дијагностиковати и лечити. Суво око има утицаја на постоперативни хируршки исход и видну оштрину, те ради побољшања комплијансе и квалитета живота пацијената треба кориговати знаке сувог ока и применити лекове без конзерванса.

**Кључне речи:** глауком; болест површине ока; суво око; конзерванс

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