DOI: 10.4274/tjo.galenos.2021.20726
Turk J Ophthalmol 2022;52:302-308

Original Article

Prevalence of Ocular Surface Disease and Associated Risk Factors in Glaucoma Patients: A Survey Study of Ophthalmologists

Nilgün Yıldırım*, Banu Bozkurt**, Nurşen Yüksel***, Halil Ateş****, Rana Altan-Yaycıoğlu*****, Özcan Ocakoğlu******, Ayşe Burcu*******, Ilgaz Yalvaç********, Özlem Evren Kemer*********, Mehmet Orhan**********

*Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey
**Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey
***Kocaeli University Faculty of Medicine, Department of Ophthalmology, Kocaeli, Turkey
****Independent Practice, Turkey
*****Medline Adana Hospital, Clinic of Ophthalmology, Adana, Turkey
******İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
*******University of Health Sciences Turkey, Ankara Training and Research Hospital, Clinic of Ophthalmology, Ankara, Turkey
********Yeditepe University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
*********University of Health Sciences Turkey, Ankara City Hospital, Clinic of Ophthalmology, Ankara, Turkey
**********Güven Hospital, Clinic of Ophthalmology, Ankara, Turkey

Abstract

Objectives: This survey study of ophthalmologists investigated the prevalence and clinical manifestations of ocular surface disease (OSD) in glaucoma patients, assessment methods used, risk factors, glaucoma drugs considered responsible, and treatment approaches.

Materials and Methods: A questionnaire prepared jointly by the Turkish Ophthalmological Association Cornea and Ocular Surface Society and Glaucoma Society using SurveyMonkey was sent to ophthalmologists via e-mail. The distribution of parameters was compared with chi-square test and $p<0.05$ was considered statistically significant.

Results: Forty-five percent of the ophthalmologists reported that OSD was evident in least 25% of their patients. The most common symptom was redness (91.9%), while the most common ocular surface finding was conjunctival hyperemia (75.6%). The tests considered to be the most important in ocular surface assessment were ocular staining (38.7%) and tear film break-up time (TBUT) (21.9%). Ninety percent of the physicians stated that the main cause of OSD was benzalkonium chloride (BAC) in medications. Prostaglandin analogs and alpha-2 agonists were reported to be the most common medications causing OSD. In case of OSD, the ophthalmologists often switch to a glaucoma drug from a different group (38%), a non-preservative glaucoma drug (33.7%) or a drug with a preservative other than BAC (20.4%). Most physicians prescribed artificial tears (84.6%).

Conclusion: In this cross-sectional survey study, ophthalmologists detected varying rates of OSD in glaucoma patients depending on chronic drug use and BAC exposure. Although ocular surface examination was performed by physicians, tests such as TBUT and ocular surface staining were rarely used. Detecting OSD in glaucoma patients and planning personalized treatment increase patient comfort, drug compliance, and treatment effectiveness. For this reason, it is important to prepare an algorithm for the management of comorbid OSD in glaucoma patients.

Keywords: Glaucoma, ocular surface disease, medical treatment, benzalkonium chloride, survey study

Address for Correspondence: Nilgün Yıldırım, Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey
E-mail: nyyildirim@yahoo.com **ORCID-ID:** orcid.org/0000-0001-6266-4951
Received: 23.03.2021 **Accepted:** 24.10.2021

Cite this article as: Yıldırım N, Bozkurt B, Yüksel N, Ateş H, Altan-Yaycıoğlu R, Ocakoğlu Ö, Burcu A, Yalvaç I, Evren Kemer Ö, Orhan M. Prevalence of Ocular Surface Disease and Associated Risk Factors in Glaucoma Patients: A Survey Study of Ophthalmologists. Turk J Ophthalmol 2022;52:302-308

Introduction

Glaucoma is a neurodegenerative optic nerve disease characterized by peripapillary retinal nerve fiber loss, ganglion cell apoptosis, and progressive visual field loss and is the leading cause of blindness worldwide.[1] High intraocular pressure (IOP) is the main treatable risk factor responsible for the occurrence and progression of glaucomatous damage.[2] The first-line treatment is IOP-lowering medical treatment. Patients use topical antiglaucoma drugs continuously for life unless they undergo a laser or surgical procedure. In most cases, the desired level of IOP reduction cannot be achieved with a single drug, and patients have to instill multiple glaucoma drugs two or more times per day.[3]

Dry eye disease is a multifactorial disease of the ocular surface characterized by loss of tear homeostasis and ocular symptoms.[4] Tear film instability, hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities are involved in the etiology.[4] The prevalence of dry eye and ocular surface disease (OSD) varies between studies in the literature, ranging from 5% to 50%.[4] Older age, female sex, systemic diseases, and medications used are risk factors for dry eye and OSD. Patients often experience eye redness, burning, stinging, foreign body sensation, watering, and less commonly, itching. The presence and severity of dry eye symptoms are assessed using questionnaires such as the Symptom Assessment in Dry Eye and Ocular Surface Disease Index (OSDI).[5] Eye examination includes biomicroscopic examination of the eyelash margin, meibomian glands, conjunctiva, and cornea, and clinical diagnosis is made using ocular surface staining, tear film break-up time (TBUT), and Schirmer tests.[5]

Glaucoma and dry eye disease increase in incidence with age. Age-related dry eye disease and meibomian gland dysfunction are seen in the majority of glaucoma patients. In addition, the active molecules and preservatives in antiglaucomatous drops cause ocular surface toxicity, tear film layer instability, epithelial damage, and inflammation with long-term use, leading to exacerbation of the existing OSD.[6,7,8,9,10,11,12,13] Rates of dry eye and OSD increase with the number of glaucoma drugs used.[14,15,16] In patients using multiple glaucoma drugs, high OSDI scores, low mean Schirmer and TBUT values, and high ocular surface staining scores were observed, and dry eye and OSD findings were found to be associated with decreased central subbasal nerve fiber layer density.[17]

Many studies have shown that glaucoma drugs that are unpreserved or contain low concentrations of preservatives lead to less dry eye and OSD signs and symptoms and enhance patient quality of life compared to drugs that contain high concentrations of preservatives.[9,15,18,19,20,21] In a meta-analysis reviewing 720 articles on glaucoma therapy and OSD published from 1972 to 2018, the results of 102 articles implicated ocular surface toxicity from preservatives rather than antiglaucoma drugs, and the authors recommended reducing the use of preservatives, treating underlying dry eye, and if necessary, performing laser trabeculoplasty and conjunctiva-sparing minimally invasive glaucoma surgery (MIGS).[9] It was concluded that treatment success and satisfaction of both patient and physician will improve if physicians consider the ocular surface symptoms that may occur and the risk factors for the development of OSD when prescribing anti-glaucoma drugs.[9]

As a joint study by the Cornea and Ocular Surface Society and Glaucoma Society of the Turkish Ophthalmological Association (TOA), a questionnaire for ophthalmologists was prepared to evaluate the prevalence and treatment approaches of OSD associated with chronic drug use in glaucoma patients in our country. This questionnaire aimed to make a general evaluation of glaucoma patients in our country by questioning the frequency of OSD, the most common eye complaints, ocular surface findings, preferred dry eye tests, antiglaucoma drugs that cause OSD, and treatment approaches used in glaucoma patients examined by ophthalmologists.

Materials and Methods

The "Prevalence and Treatment of Ocular Surface Disease in Glaucoma" questionnaire prepared jointly by the TOA Cornea and Ocular Surface Society and Glaucoma Society on SurveyMonkey was sent to TOA member ophthalmologists via e-mail (Appendix 1) (http://glns.co/nl20c). The questionnaire consisted of a total of 14 items about the ophthalmologists' years of professional experience, the type of institution they worked in, their active TOA society memberships, the number of patients with glaucoma they examined weekly, the percentage of their glaucoma patients with complaints related to drug therapy and common ocular surface symptoms, whether and at what frequency they assess the ocular surface in glaucoma patients, which tests are most important in ocular surface assessment, frequently detected ocular surface disorders and risk factors for OSD in glaucoma, which glaucoma drugs were more often associated with OSD, the drugs most frequently used in the treatment of OSD, and their preferred treatment approach (within the circumstances of our country) to patients who develop OSD because of glaucoma drugs.

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Statistical evaluations were based on the number of physicians who responded to each question. Since all of the parameters in the study were categorical variables, chi-square test was used for comparisons. A p-value <0.05 was considered statistically significant.

Results

Demographic Characteristics

Of the 442 ophthalmologists who participated in the survey, 125 worked in university hospitals (28.3%), 114 in training and research hospitals (25.6%), 113 in private hospitals (25.6%), 86 in public hospitals (19.5%), and 22 in eye clinics (5%); 18 of the participants (4.1%) worked in two different places. Years of professional experience was reported as over 15

years by 39.4% of participants, 10-15 years by 16.2%, 5-10 years by 20.1%, 2-5 years by 16.7%, and less than 2 years by 7.6% of the participants. Table 1 shows the distribution of professional experience according to employing institution. Of the 442 physicians, 134 (30.3%) reported active TOA society membership and 67 (15.16%) were members of more than one society. The distribution by society was 52 participants (25.9%) in the Cataract and Refractive Surgery Society, 40 (19.9%) in the Corneal and Ocular Surface Society, 37 (18.4%) in the Glaucoma Society, and 72 (35.8%) in other societies.

The number of glaucoma patients examined per week was reported as 9 of fewer by 36.4% of the ophthalmologists, 10-25 by 43.9%, 26-50 by 13%, and more than 50 by 6.6% of the participants (Table 1). The number of glaucoma patients per week was similar in all employing institutions and was most commonly 10-25 patients (Table 1).

OSD Prevalence

When the prevalence of glaucoma patients with OSD was evaluated, 45% of the ophthalmologists reported that they detected OSD in at least 25% of patients. The majority of physicians with active society memberships (36.6%) reported drug-induced complaints and OSD in 26-50% of their patients (Table 2). Society members were more likely to report that over 26% of their patients had ocular surface-related complaints than participants who were not society members (Table 2).

The most commonly observed symptom was eye redness (91.9%), followed by stinging/foreign body sensation (24.2%) and burning (18.3%). Patients generally had more than one complaint. There was no difference in the frequency distribution of complaints between employing institutions ($p>0.05$).

Assessment Methods

Ninety-four percent of the physicians evaluated the ocular surface in glaucoma patients and more than half (59.6%) said they performed this evaluation at each examination. The tests considered most important in ocular surface assessment were ocular staining (38.7%), TBUT (21.9%), meibomian gland examination (17.5%), OSDI scoring (17.5%), and Schirmer test (5.2%).

The most common ocular surface finding was conjunctival hyperemia (75.6%), followed by punctate epitheliopathy (55.7%), contact dermatitis (34.6%), blepharitis/meibomian gland dysfunction (25.1%), and follicular conjunctivitis (14.5%). There was no difference in the incidence of OSD findings among employing institutions ($p=0.88$). Among patients with multiple findings, the most common combination was conjunctival hyperemia, punctate epitheliopathy, and contact dermatitis.

Table 1. Demographic data of the physicians and number of glaucoma patients examined per week

Institution	n (%)	Active society member, n (%)	Professional experience†	Weekly glaucoma patients†
University hospital	125 (28.3%)	89 (71.2%)	>15 years (33.6%)	10-25 (46.4%) <10 (28%)
Training and research hospital	114 (25.6%)	39 (34.2%)	5-10 years (27.2%)	10-25 (40.4%) <10 (34.2%)
Private hospital	113 (25.6%)	63 (55.8%)	>15 years (71.7%)	<10 (57.5%) 10-25 (33.6%)
Public hospital	86 (19.5%)	11 (12.8%)	5-10 years (39.5%)	10-25 (57%) <10 (20.9%)
Eye clinic	22 (5%)	11 (50%)	>15 years (100%)	<10 (40.9%) 10-25 (40.9%)
Two institutions	18 (4.1%)	12 (66.7%)	>15 years (59.1%)	<10 (36.4%) 10-25 (36.4%)
Total	442 (100%)	134 (30.3%)	>15 years (39.4%)	10-25 (43.9%) <10 (36.4%)

*Members can be registered in more than one society. †Mean values not available; the most common ranges are indicated

Table 2. OSD prevalence in glaucoma patients reported by active society members and non-members

OSD prevalence (%)	Society members, n (%)	Non-members, n (%)	Total, n (%)
<10	20 (14.9%)	66 (21.4%)	86 (19.6%)
11-25	37 (27.6%)	118 (38.3%)	155 (35.4%)
26-50	49 (36.6%)	91 (29.5%)	140 (32%)
51-75	18 (13.4%)	24 (7.8%)	42 (9.6%)
>76	6 (4.5%)	9 (2.9%)	15 (3.4%)

OSD: Ocular surface disease

Table 3. Risk factors for ocular surface disease in glaucoma

Risk factors / Institution	Age (n)	Gender (n)	Drug number (n)	Duration of use (n)	BAC (n)	Additional ocular disease (n)	Systemic disease (n)
University hospital	32	72	106	82	110	94	46
Training and research hospital	33	16	90	75	102	95	45
Public hospital	13	6	61	57	77	69	23
Private hospital	28	12	76	61	93	78	43
Eye clinic	4	2	15	14	18	17	5
Total (%)	110 (25%)	43 (9.7%)	348 (78.7%)	289 (65.4%)	400 (90.5%)	353 (79.9%)	162 (36.6%)

BAC: Benzalkonium chloride

Risk Factors

When questioned about risk factors, 90% of physicians regardless of employing institution stated that the main cause of OSD was the benzalkonium chloride (BAC) in drugs (Table 3). Other risk factors were concomitant ocular disease (80%), number of antiglaucoma drugs (79%), and duration of use (65%). There was no difference in risk factors according to the participants' employing institutions (p=0.93).

When all physician responses were evaluated, the glaucoma drugs most commonly implicated in the development of OSD were prostaglandin analogs (56.4%) and alpha-2 agonists (43.6%). However, active Glaucoma Society members considered alpha-2 agonists (81.1%) to be riskier.

Treatment Approaches

In patients who develop OSD due to glaucoma medication, drug change was recommended as the initial approach (98.3%), with participants mostly preferring a glaucoma drug from a different group (38%), a glaucoma drug with no preservatives (33.7%), or a drug containing a preservative other than BAC (20.4%). A small number of participants recommended selective laser trabeculoplasty (1.1%), MIGS (0.2%), and trabeculectomy or other surgeries (0.2%).

Artificial tears were most preferred for the symptomatic treatment of OSD (84.6%). The use of topical steroids (6.7%), topical antihistamines (4.9%), topical cyclosporine (2.4%), and topical non-steroid anti-inflammatory drugs (1.4%) was also reported. The treatments used did not differ significantly according to the physicians' employing institutions (p=0.06). However, it was noted that topical cyclosporine was especially preferred by physicians working in university-affiliated institutions.

Discussion

The results of this survey study revealed that 442 ophthalmologists working in various centers frequently encountered OSD symptoms and signs in glaucoma patients in their daily practice. Most participants reported the frequency of OSD complaints among their glaucoma patients as 11-25% or 26-50%. Redness was the leading symptom of the patients, while conjunctival hyperemia was the most common examination finding. Preservation of drugs with BAC was most cited as the most important risk factor for OSD, followed by the number of drugs used and the duration of use. The top two drugs implicated in the development of OSD were prostaglandin analogs and alpha-2 agonists. Physicians generally preferred to switch the current medical therapy to treat OSD, while artificial tears were the most commonly used symptomatic treatment.

In glaucoma patients, long-term use of multiple BAC-containing glaucoma drugs leads to OSD or exacerbates age-related dry eye and meibomian gland dysfunction.[6,7,8,9,10,11,12,13,14,15,16] Reducing the number of eye drops containing BAC and switching to glaucoma drugs with lower concentrations of BAC or no preservatives have been reported to reduce or eliminate patients' dry eye symptoms.[10,11,12,15,18,19,20,21] An epidemiological study including 4,107 patients with glaucoma showed that 57% of patients had least one OSD symptom after using antiglaucoma drops.[10] Patients often had discomfort, followed by OSD symptoms such as burning, stinging, foreign body sensation, dry eye sensation, watering, and itching. When ocular findings were evaluated, conjunctival hyperemia was the most common (38%), followed by conjunctival follicles and superficial punctate keratitis.[10] In the same study it was reported that ocular symptoms and signs were more common among patients using preserved drops compared to those using preservative-free drops, the frequency of OSD increased with the number of preserved drops used, and signs and symptoms decreased significantly after switching to preservative-free drops or reducing the number of preserved drops used.[10] In a multicenter epidemiological study conducted in Europe, it was reported that glaucoma patients using preserved beta-blocker drops had more OSD symptoms than those using unpreserved beta-blocker drops (pain/discomfort during instillation: 48% vs. 19%, foreign body sensation: 42% vs. 15%, stinging/burning: 48% vs. 20%, and dry eye sensation: 35% vs. 16%).[19] Ruangvaravate et al.[15] observed that patients using preserved prostaglandin analogs had significant ocular surface changes and reported that after switching to low-BAC or no-BAC tafluprost therapy, there was

a significant increase in TBUT but patients using unpreserved tafluprost had better tear quality. They attributed the ocular surface improvement with BAC-preserved tafluprost to the lower BAC concentration in this drop compared to other prostaglandin analog drops.[15] In a similar study, a reduction in complaints and clinical signs was observed in patients who switched to low-dose BAC-preserved tafluprost therapy after at least 3 months of using latanoprost drops.[20] Ramli et al.[12] found that there was a three-fold increase in OSDI score and a significant decrease in TBUT in patients using BAC-containing drops compared to those who used Purite-preserved or preservative-free drops.

In a review of preservatives in glaucoma drugs, it was noted that there is no evidence that OSD findings occur in patients using drops with a low BAC concentration, so expensive unpreserved drugs should generally be preferred only for glaucoma patients who use multiple drugs or have OSD.[22]

In another observational study, dry eye disease was reported to be associated with the number of drugs used by glaucoma patients, with rates 11% in those using one drop, 39% in those using two drops, and 43% in those using three drops.[14] In a study evaluating OSD in glaucoma patients in Thailand, a significant positive relationship was observed between the number of drugs used and corneal fluorescein and Rose Bengal staining.[18] Baudouin et al.[23] reported in their study that the high number of daily drops used by patients with advanced glaucoma and high IOP increased the degree of OSD. Similarly, the physicians participating in our survey study stated that greater number of drugs and long duration of use were the most common causes of OSD after the BAC content of drugs.

Stalmans et al.[16] stated that all glaucoma patients should be asked whether they have any tolerance problems related to their treatment and that even patients with no complaints may have signs of OSD that might require treatment changes. Therefore, ocular surface assessment is recommended for glaucoma patients at each follow-up visit. Most physicians in our survey study (94%) evaluated the ocular surface in glaucoma patients and more than half (59.6%) performed this evaluation at each examination.

Leung et al.[13] observed dry eye symptoms in a total of 59% of glaucoma patients (severe in 27%), reduced Schirmer test values in 61% of patients, decreased TBUT in 78% of patients, and ocular surface staining in 22% of patients. In our survey study, surface staining tests were reported most frequently (38.7%), while 21.9% reported evaluating TBUT. Using the study by Leung et al.[13] as a reference, evaluating TBUT can be recommended as a priority in glaucoma patients.

In our survey results, the drug group most frequently responsible for OSD was alpha-2 agonists according to active members of the Glaucoma Society, whereas prostaglandin analogs were the leading group according to other participants. Apart from the preservative agent in alpha-2 agonist drops, the drug is believed to contribute to OSD via its allergic and/or proinflammatory properties.[24,25] There are also case reports in the literature that alpha-2 agonists cause allergic inflammation and allergic conjunctivitis resembling vernal conjunctivitis, as well as increased IOP.[26,27] Conjunctival hyperemia is the most common adverse effect associated with the use of prostaglandin analogs, but OSD, dry eye disease, and meibomian gland dysfunction can also be seen. Prostaglandin-induced conjunctival hyperemia is not considered to be associated with BAC toxicity and is believed to be a result of nitric oxide-mediated vasodilatation.[28,29] The fact that latanoprost drops with the highest BAC concentration cause less conjunctival hyperemia than other prostaglandin analogs also supports this.[30]

The DEWS II report recommends determining the role of the primary drug as the first step in managing glaucoma patients with OSD when late-onset adverse effects occur after initiating treatment, when multiple drugs or molecules are used, and when concomitant OSD is present or treatment cannot be discontinued.[31] Patients using drugs containing BAC can be switched to a preservative-free drug. As BAC causes dose-dependent toxicity, the side effect profile can be reduced by reducing the number of medications or by administering fixed combination drugs in patients using of multiple BAC-preserved drops.[19,32] In addition, laser trabeculoplasty or surgery is an alternative option when OSD is severe and affects the quality of life.[33]

Su et al.[34] monitored the development of OSD in patients using BAC-preserved latanoprost and observed that Schirmer test values decreased less in patients using artificial tears together with their glaucoma medication than in those who did not. Therefore, the use of artificial tears with glaucoma therapy can be regarded as good clinical practice not only in patients who have OSD but also to avoid OSD in patients with multiple drug use or OSD risk factors. According to our survey results, we found that physicians mostly preferred artificial tears (84.6%) for symptomatic treatment of OSD.

In a study by Muzychuk et al.[35] in which 36 glaucoma specialists scored their responses on a Likert scale from 1 (strongly disagree) to 7 (strongly agree), nearly all of the participants agreed that treating OSD would substantially improve quality of life in glaucoma patients and improve glaucoma outcomes because of better patient adherence to glaucoma treatment. However, only 22% agreed that OSD was adequately treated in glaucoma practice. Most (86.1%) of the participants said that they routinely evaluated the ocular surface in glaucoma patients. The most commonly used assessment methods were evaluation of conjunctiva (91%), lid health (88.6%), and lid position (80%), and fluorescein staining of the ocular surface (80%). The percentage of experts who performed TBUT, OSDI, and Schirmer tests were 62.9%, 5.7%, and 2.9%, respectively. Approximately 75% of the participants stated that they sometimes, frequently, or always referred glaucoma patients to an OSD specialist. In addition, 83.3% of the participants agreed that ocular surface health should be considered in the treatment of glaucoma and 66.7% agreed that personalized treatment is needed. When the treatment approaches were examined, 100% of the participants considered themselves knowledgeable about the necessity of modifying topical glaucoma treatment (selecting a fixed combination, preservative-free, or non-BAC preserved

drug), while about 60% stated that they were knowledgeable about topical immunomodulatory, steroid, and omega fatty acid therapy and 31% about autologous serum. The 3 most common treatments used in the approach to OSD were reported to be artificial tears (94.4%), optimization of topical glaucoma medications (66.7%), and lid hygiene (55.6%). Nearly all (92%) of the participants stated that a recommended algorithm would improve the treatment of OSD in glaucoma.

Treating OSD has been shown to reduce IOP in addition to the signs and symptoms of dry eye.[24,36] This has been attributed to decreased inflammation in the trabecular network or better adherence to glaucoma therapy as a result of reduced discomfort.[36] It should be kept in mind that eye drops such as topical antihistamines and steroids used to relieve dry eye symptoms also contain preservatives and may exacerbate existing OSD symptoms. In this respect, topical cyclosporine is a good alternative for the treatment of OSD.[37] Saini et al.[38] demonstrated decreases in ocular surface staining score and OSDI and significant increases in Schirmer's test, corneal sensitivity, and subbasal nerve fiber layer density in patients with chronic glaucoma after 6 months of topical cyclosporine therapy. OSD reduces the quality of life and treatment adherence of patients with glaucoma, can lead to glaucoma progression, and also causes national economic losses.[39,40] In Australia, 39% of patients with glaucoma were found to have significant dry eye, resulting in an economic burden of 330.5 million Australian dollars annually.[39]

Conclusion

This cross-sectional survey study demonstrated that ophthalmologists have high awareness of concomitant OSD in patients with glaucoma and consider the presence of BAC and the number and duration of drugs as risk factors for the development of OSD. Although most physicians stated that they assessed the ocular surface, their use of tests such as TBUT and ocular surface staining was found to be low. Switching to a different drug group and using artificial tears were common approaches to treatment. Due to the extremely limited number of non-BAC glaucoma drugs in our country, preference rates for BAC-free or non-BAC preserved drugs were extremely low. Considering the high incidence of OSD, it is clear that there is a serious need for preservative-free glaucoma drugs in our country. Detecting OSD in glaucoma patients and planning personalized treatment increase patient comfort, drug adherence, and treatment effectiveness. Therefore, it is essential to create an algorithm for the approach to OSD that occurs in glaucoma patients because of chronic drug use.

Acknowledgements: The authors thank Dr. Onur Özalp for his contribution to the writing of this article and Dr. Muzaffer Bilgin for his contributions during statistical analyses.

Ethics

Ethics Committee Approval: It was not necessary because it was a survey study and it was not conducted on patients.

Informed Consent: Not obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.Y., B.B., N.Yü., H.A., R.A-Y., Ö.O., A.B., I.Y., Ö.E.K., M.O., Design: N.Y., B.B., N.Y., H.A., R.A-Y., Ö.O., A.B., I.Y., Ö.E.K., M.O., Data Collection or Processing: N.Y., B.B., N.Yü., Analysis or Interpretation: N.Y., B.B., N.Yü., Literature Search: N.Y., B.B., Writing: N.Y., B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kingman S. Glaucoma is second leading cause of blindness globally. Bull World Health Organ. 2004;82:887-888.
2. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268-1279.
3. No authors listed. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 3: Treatment principles and options Supported by the EGS Foundation: Part 1: Foreword; Introduction; Glossary; Chapter 3 Treatment principles and options. Br J Ophthalmol. 2017;101:130-195.
4. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, Na KS, Schaumberg D, Uchino M, Vehof J, Viso E, Vitale S, Jones L. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017;15:334-365.
5. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, Gupta PK, Karpecki P, Lazreg S, Pult H, Sullivan BD, Tomlinson A, Tong L, Villani E, Yoon KC, Jones L, Craig JP. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017;15:539-574.
6. Pérez-Bartolomé F, Martínez-de-la-Casa JM, Arriola-Villalobos P, Fernández-Pérez C, Polo V, García-Feijoó J. Ocular Surface Disease in Patients under Topical Treatment for Glaucoma. Eur J Ophthalmol. 2017;27:694-704.
7. Hollo G, Katsanos A, Boboridis KG, Irkec M, Konstas AGP. Preservative-Free Prostaglandin Analogs and Prostaglandin/Timolol Fixed Combinations in the Treatment of Glaucoma: Efficacy, Safety and Potential Advantages. Drugs. 2018;78:39-64.
8. Baudouin C, Aragona P, Messmer EM, Tomlinson A, Calonge M, Boboridis KG, Akova YA, Geerling G, Labetoulle M, Rolando M. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013;11:246-258.
9. Zhang X, Vadoothker S, Munir WM, Saeedi O. Ocular Surface Disease and Glaucoma Medications: A Clinical Approach. Eye Contact Lens. 2019;45:11-18.
10. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002;86:418-423.
11. Kumar S, Singh T, Ichhpujani P, Vohra S, Thakur S. Correlation of Ocular Surface Disease and Quality of Life in Indian Glaucoma Patients: BAC-preserved versus BAC-free Travoprost. Turk J Ophthalmol. 2020;50:75-81.
12. Ramli N, Supramaniam G, Samsudin A, Juana A, Zahari M, Choo MM. Ocular Surface Disease in Glaucoma: Effect of Polypharmacy and Preservatives. Optom Vis Sci. 2015;92:222-226.
13. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. J Glaucoma. 2008;17:350-355.
14. Rossi GC, Tinelli C, Pasinetti GM, Milano G, Bianchi PE. Dry eye syndrome-related quality of life in glaucoma patients. Eur J Ophthalmol. 2009;19:572-579.
15. Ruangvaravate N, Choojun K, Srikulsasitorn B, Chokboonpiem J, Asanatong D, Trakanwitthayarak S. Ocular Surface Changes After Switching from Other

Prostaglandins to Tafluprost and Preservative-Free Tafluprost in Glaucoma Patients. Clin Ophthalmol. 2020;14:3109-3119.
16. Stalmans I, Lemij H, Clarke J, Baudouin C, GOAL study group. Signs and Symptoms of Ocular Surface Disease: The Reasons for Patient Dissatisfaction with Glaucoma Treatments. Clin Ophthalmol. 2020;14:3675-3680.
17. Saini M, Vanathi M, Dada T, Agarwal T, Dhiman R, Khokhar S. Ocular surface evaluation in eyes with chronic glaucoma on long term topical antiglaucoma therapy. Int J Ophthalmol. 2017;10:931-938.
18. Ruangvaravate N, Prabhasawat P, Vachirasakchai V, Tantimala R. High Prevalence of Ocular Surface Disease Among Glaucoma Patients in Thailand. J Ocul Pharmacol Ther. 2018;34:387-394.
19. Jaenen N, Baudouin C, Pouliquen P, Manni G, Figueiredo A, Zeyen T. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol. 2007;17:341-349.
20. Wong TT, Aung T, Ho CL. Ocular surface status in glaucoma and ocular hypertension patients with existing corneal disorders switched from latanoprost 0.005% to tafluprost 0.0015%: comparison of two prostaglandin analogues with different concentrations of benzalkonium chloride. Clin Exp Ophthalmol. 2018;46:1028-1034.
21. de Jong C, Stolwijk T, Kuppens E, de Keizer R, van Best J. Topical timolol with and without benzalkonium chloride: epithelial permeability and autofluorescence of the cornea in glaucoma. Graefes Arch Clin Exp Ophthalmol. 1994;232:221-224.
22. Steven DW, Alaghband P, Lim KS. Preservatives in glaucoma medication. Br J Ophthalmol 2018;102:1497-1503.
23. Baudouin C, Renard JP, Nordmann JP, Denis P, Lachkar Y, Sellem E, Rouland JF, Jeanbat V, Bouée S. Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension. Eur J Ophthalmol. 2012.
24. Dubrulle P, Labbé A, Brasnu E, Liang H, Hamard P, Meziani L, Baudouin C. Influence of Treating Ocular Surface Disease on Intraocular Pressure in Glaucoma Patients Intolerant to Their Topical Treatments: A Report of 10 Cases. J Glaucoma. 2018;27:1105-1111.
25. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol. 1997;115:847-852.
26. Shah AA, Modi Y, Thomas B, Wellik SR, Galor A. Brimonidine allergy presenting as vernal-like keratoconjunctivitis. J Glaucoma. 2015;24:89-91.
27. Bozkurt B, İrkeç M. Allergic Conjunctivitis and Elevated Intraocular Pressure Associated with The Use of Brimonidine Tartrate 0.2%. Glo-Kat. 2006;1:67-69.
28. Hollo G. The side effects of the prostaglandin analogues. Expert Opin Drug Saf. 2007;6:45-52.
29. Chen J, Dinh T, Woodward DF, Holland M, Yuan YD, Lin TH, Wheeler LA. Bimatoprost: mechanism of ocular surface hyperemia associated with topical therapy. Cardiovasc Drug Rev. 2005;23:231-246.
30. Guenoun JM, Baudouin C, Rat P, Pauly A, Warnet JM, Brignole-Baudouin F. In vitro study of inflammatory potential and toxicity profile of latanoprost, travoprost, and bimatoprost in conjunctiva-derived epithelial cells. Invest Ophthalmol Vis Sci. 2005;46:2444-2450.
31. Gomes JAP, Azar DT, Baudouin C, Efron N, Hirayama M, Horwath-Winter J, Kim T, Mehta JS, Messmer EM, Pepose JS, Sangwan VS, Weiner AL, Wilson SE, Wolffsohn JS. TFOS DEWS II iatrogenic report. Ocul Surf. 2017;15:511-538.
32. Goldberg I, Graham SL, Crowston JG, d'Mellow G; Australian and New Zealand Glaucoma Interest Group. Clinical audit examining the impact of benzalkonium chloride-free anti-glaucoma medications on patients with symptoms of ocular surface disease. Clin Exp Ophthalmol. 2015;43:214-220.
33. Banitt M, Jung H. Ocular surface disease in the glaucoma patient. Int Ophthalmol Clin. 2018;58:23-33.
34. Su CC, Lee YC, Lee PRC. Assessment of ocular surface disease in glaucoma patients with benzalkonium chloride-preserved latanoprost eye drops: a short-term longitudinal study. Graefes Arch Clin Exp Ophthalmol. 2021;259:1243-1251.
35. Muzychuk A, Racine L, Robert MC, Birt C, Penner V, Harasymowycz P, Crichton A, Ford B, Gooi P, Harissi-Dagher M. Management of Ocular Surface Disease in Glaucoma: A Survey of Canadian Glaucoma Specialists. J Glaucoma. 2020;29:1162-1172.
36. Mylla Boso AL, Gasperi E, Fernandes L, Costa VP, Alves M. Impact of Ocular Surface Disease Treatment in Patients with Glaucoma. Clin Ophthalmol. 2020;14:103-111.
37. Boboridis KG, Konstas AGP. Evaluating the novel application of cyclosporine 0.1% in ocular surface disease. Expert Opin Pharmacother. 2018;19:1027-1039.
38. Saini M, Dhiman R, Dada T, Tandon R, Vanathi M. Topical cyclosporine to control ocular surface disease in patients with chronic glaucoma after long-term usage of topical ocular hypotensive medications. Eye (Lond). 2015;29:808-814.
39. Chan CC, Crowston JG, Tan R, Marin M, Charles S. Burden of Ocular Surface Disease in Patients With Glaucoma From Australia. Asia Pac J Ophthalmol (Phila). 2013;2:79-87.
40. Pezzullo L, Streatfeild J, Simkiss P, Shickle D. The economic impact of sight loss and blindness in the UK adult population. BMC Health Serv Res. 2018;18:63.