Original Article

# Effect of Long-Term Topical Antiglaucoma Medication Use on the Ocular Surface

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## Abstract

**Purpose:** The purpose of this study was to describe the prevalence and pattern of ocular surface disease (OSD) in glaucoma patients using preserved topical antiglaucoma medications in a Nigerian population. **Methodology:** A comparative study of patients who had used topical preserved antiglaucoma medications for 6 months or more with age- and sex-matched individuals who were not on any other form of topical eye medication was carried out using fluorescein tear breakup time (FTBUT), Schirmer I test, and ocular surface staining with fluorescein and lissamine green. The right eyes of 103 eligible patients with primary open-angle glaucoma and that of 103 age- and sex-matched individuals (controls) were included in the study. **Results:** The prevalence of OSD among users of preserved topical antiglaucoma medications was significantly higher than among nonusers as assessed by FTBUT (83.5% vs. 57.3%; $P < 0.001$), Schirmer I (30.1% vs. 17.5%; $P = 0.033$), and ocular surface staining (62.1% vs. 31.1%; $P < 0.001$). Users of preserved topical antiglaucoma medications also had worse grades of OSD evaluated by FTBUT ($P = 0.001$), Schirmer I ($P = 0.023$), and ocular surface staining ($P < 0.001$). **Conclusion:** The prevalence of subjective OSD was significantly higher among users of topical antiglaucoma medications than nonusers. Hence, preserved topical medication use is a serious concern for increased ocular surface morbidity among glaucoma patients. This calls for more attention to be paid to the consequences of OSD among glaucoma patients on topical medications.

**Keywords:** Benzalkonium chloride, dry eye, glaucoma, ocular surface disease

## Introduction

The ocular surface comprising the corneal and conjunctiva epithelium with underlying subepithelial fibrous tissue is important for structural protection of the eye and optical clarity. For the cells of the ocular surface to perform these functions effectively, it has to be covered sufficiently by a stable tear film in the open-eye state. Ocular surface disease (OSD), often referred to as dry eye disease, is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[1] The tear film helps to provide lubrication of the ocular surface and protects the superficial cellular layers as well as provides a smooth air-corneal refractive interface for optimal vision.

OSD and glaucoma are both prevalent in the elderly and are common comorbidities in the same patient.[2] OSD has an age-dependent prevalence, affecting approximately 11% of patients between the ages of 40 and 59 while also affecting 18% of those older than age 80 years in the general population.[3] Several epidemiological studies have reported that the prevalence of glaucoma increases dramatically with age.[4-7] Patients with glaucoma and ocular hypertension tend to suffer OSD at a higher prevalence rate than in the normal population.[8-10] The etiology of OSD in glaucoma is thought to be multifactorial. The incidence of OSD is related to glaucoma itself, age of the patient, concomitant diseases including hypertension and diabetes, and the patient's antiglaucoma medications.[2,11]

Preservatives are frequently used in topical ophthalmic medications dispensed in multidose containers to maintain

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the efficacy of the active agent and sterility of the formulation before and during the period of use.[12,13] Multiple glaucoma medications are often used in combination to adequately lower intraocular pressure[14,15] with attendant multiple drop instillation and exposure of the ocular surface to the active agent, preservatives, and excipients. This has been linked to irritative ocular symptoms, drug use compliance, and increased risk of filtration surgery failure.[16,17] In ocular pathologies such as glaucoma and dry eye (a component of OSD), ophthalmic formulations need to be administered for a long time to sustain their therapeutic effect. Frequent use of preserved formulations is associated with alterations in the precorneal tear film, while in patients suffering from dry eye, they tend to aggravate the already existing problem.[18] Preservatives have also been found to be associated with ocular surface changes accompanied by inflammation in glaucoma patients.[19]

This study assessed some of the changes to the ocular surface environment in patients who have been exposed to preserved antiglaucoma medications over a considerable period of 6 months and more in comparison to age- and sex-matched healthy individuals.

## Methodology

This was a hospital-based comparative study of patients on long-term topical antiglaucoma medications and healthy age- and sex-matched controls, which was carried out at the outpatient Eye clinic, Eye Care Centre, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria, between January and May 2014. One hundred and three patients with primary open-angle glaucoma (POAG) and another 103 age- and sex-matched healthy volunteers were enrolled in this study. Informed consent was obtained from all participants after ethical approval was obtained from the hospital's Ethical Review Committee. The research was conducted in accordance with the tenets of the Helsinki Declaration. Eligible participants in the study group were individuals aged 18 years or more with POAG and had been exclusively on one or more topical antiglaucoma medications for at least 6 months before enrollment. The control group was age- and sex-matched individuals and had not been on any topical medication in the preceding 2 months. Individuals with antecedent corneal or conjunctival surgery, topical corticosteroid or contact lens wear, and/or current use of dry eye therapeutic agents were excluded from the study. The number of antiglaucoma formulations and preservative of the topical medication(s), as well as systemic comorbidities of each participant, were noted.

Eligible consenting participants were evaluated for signs of OSD using a triad of objective tests in the following order: Schirmer I test (without anesthesia), fluorescein tear breakup time (FTBUT), and ocular surface staining with fluorescein and lissamine green. All the participants were evaluated by the same ophthalmologist.

Schirmer I test was conducted using a graduated Whatman 41 filter (Schirmer strip) with the rounded end bent at the zero mark and carefully applied into the inferior fornix for 5 min. Participants were asked to keep their eyes open and blink as necessary with ambient room illumination maintained during the test. A diagnosis of OSD based on Schirmer I test was taken as advancing solvent line reading of <10 mm on the Schirmer strip.

The FTBUT was evaluated by wetting a sterile dye-impregnated fluorescein 1 mg strip with three drops of freshly opened nonpreserved 0.9% saline using a tuberculin syringe and needle. Excess fluid was removed by gently shaking the wet strip after about 10 seconds. The wet end was gently applied to the inferior fornix to avoid inducing reflex tearing. A digital stopwatch was used to record the time between the last complete blink and the first appearance of growing micelle (tear film breakup). For each eye, the FTBUT was determined as the average of 3 consecutive breakup times.

Ocular surface staining was determined by comparing the combined corneal and conjunctival staining appearance with the panels on the Oxford grading scheme[2,20] following consecutive instillations of fluorescein and lissamine green dyes for corneal and conjunctival epithelial staining, respectively. The lissamine green dye was generated from sterile strips impregnated with 1.5 mg of lissamine green. A diagnosis of OSD based on ocular surface staining was taken as Oxford scheme grade I or higher.

Data analysis was conducted with the IBM® SPSS® Statistics version 21 (IBM Corporation, Armonk, NY, USA) for Windows version 21.0. Mean, standard deviation, and range were used to describe quantitative variables and proportion and percentages for qualitative variables. Chi-square test was used to assess the relationship between categorical variables. Data were presented using tables and charts.

## Results

Data of 206 participants (103 cases and 103 age- and sex-matched controls) were analyzed. The age range of both the study groups was 31–84 years. The mean age was 63.1 ± 9.7 years for cases and 64.5 ± 10.1 years for controls ($P = 0.307$, $t = -1.024$). Age group and sex distribution are shown in Table 1. Only nine (8.7%) of cases and 14 (13.6%) of controls had diabetes mellitus ($P = 0.269$). Figure 1 shows the significantly higher prevalence of OSD using all three objective tests. Glaucoma patients on topical antiglaucoma medications had significantly worse OSD than the controls across all the three objective tests [Table 2]. Majority of the glaucoma patients were using 2 or more topical antiglaucoma medications [Figure 2]. Figure 3 shows that the majority of glaucoma patients were using timolol-based or timolol-only medications. All the brands of topical medications used by the patients were preserved with benzalkonium chloride (BAC), as stated in the drug information sheet or drug package. It was noticed that some manufacturers of some brands did not state the concentration of the preservative. Further data analysis showed that the severity of OSD across all test

**Table 1: Age and sex distribution of participants**

| | Frequency (%) | | *P* |
|---|---|---|---|
| | Glaucoma | Control | |
| Age group (years) | | | |
| <50 | 6 (5.8) | 6 (5.8) | 0.964 |
| 50-59 | 30 (29.1) | 28 (27.2) | |
| 60-69 | 38 (36.9) | 35 (34.0) | |
| 70-79 | 24 (23.3) | 28 (27.2) | |
| >80 | 5 (4.9) | 6 (5.8) | |
| Sex | | | |
| Male | 49 (47.6) | 49 (47.6) | 1.000 |
| Female | 54 (52.4) | 54 (52.4) | |

**Table 2: Severity pattern of ocular surface disease**

| | Glaucoma (%) | Control (%) | *P* |
|---|---|---|---|
| FTBUT severity grade | | | |
| Normal | 17 (16.5) | 42 (40.8) | 0.001 |
| Mild to moderate | 35 (34.0) | 24 (23.3) | |
| Severe | 51 (49.5) | 37 (35.9) | |
| Schirmer I | | | |
| Normal | 72 (69.9) | 85 (82.5) | 0.023 |
| Mild to moderate | 15 (14.6) | 4 (3.9) | |
| Severe | 16 (15.5) | 14 (13.6) | |
| Ocular surface staining | | | |
| Normal | 39 (37.9) | 71 (68.9) | <0.001 |
| Mild to moderate | 48 (46.6) | 28 (27.2) | |
| Severe | 16 (15.5) | 4 (3.9) | |

modalities was neither significantly affected by the number of topical antiglaucoma medications nor the active agent in the medication [Table 3].

## Discussion

The prevalence of severe OSD reported by Leung *et al*. based on FTBUT (65%) and Schirmer I test (35%) among users of topical antiglaucoma medications[21] was higher than that of the index study [Table 2]. Aside from possible racial variations, Leung *et al*. study considered the eye with the worse result (for analysis in each specific test) for their study, unlike this study which considered the right eye of each participant. This could have accounted for their relatively higher prevalence. Racial and geographical differences have been reported in the prevalence of OSD among the normal population.[22] Surprisingly, Leung *et al*. study reported no case of severe OSD with lissamine green staining. Whereas this study found that 15.5% of glaucoma patients had severe ocular surface staining with lissamine green, it also identified a significant difference in the level of severity in both the study groups [Table 2]. Characteristic punctate ocular surface staining is an evidence of chronic tear film layer disruption and epithelial layer damage. These findings have largely been attributed to the preservative constituent and dose but less on the active agent/molecule. Some preservatives and active agents in topical antiglaucoma medications have been found to upregulate inflammatory markers in the epithelium of the ocular surface which results in epithelial and subepithelial changes in long-term users.[19]

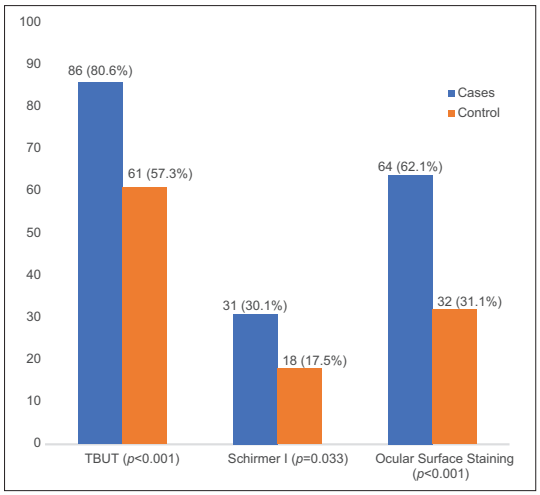


**Figure 1:** Prevalence of objectively-assessed ocular surface disease among long-term users of topical anti-glaucoma medications and control

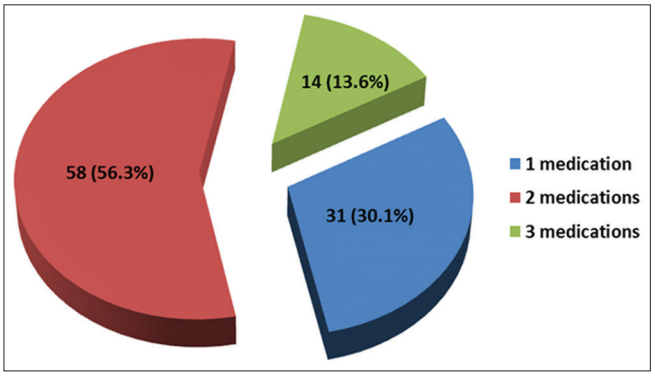


**Figure 2:** Distribution of number of topical antiglaucoma medications used by glaucoma patients

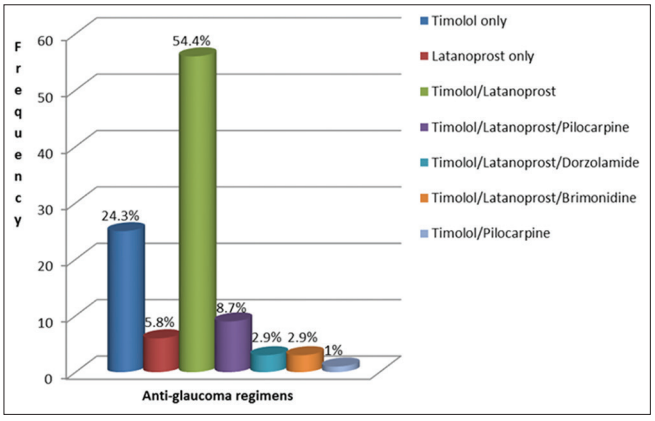


**Figure 3:** Distribution of antiglaucoma regimens

The prevalence of OSD using all three objective tests was not significantly affected by the number of medications. However, the prevalence of OSD based on the number of medications

**Table 3: Prevalence of ocular surface disease by number of medications among glaucoma patients**

| | Frequency (%) | | | *P* |
|---|---|---|---|---|
| | 1 medication (*n*=31) | 2 medications (*n*=58) | 3 medications (*n*=14) | |
| FTBUT | 25 (80.6) | 47 (81.0) | 11 (78.6) | 0.978 |
| Schirmer test | 8 (25.8) | 18 (31.0) | 5 (35.7) | 0.777 |
| Ocular surface staining | 17 (54.8) | 38 (65.5) | 9 (64.3) | 0.603 |

was generally higher than control for each corresponding test, irrespective of the number of topical medications [Table 3]. This suggests that the occurrence of ocular surface changes in long-term users of topical antiglaucoma medications is not necessarily dose dependent but rather a function of exposure. This is similar to findings reported by Leung *et al*. with the exception of ocular surface staining with lissamine green where the odds of OSD significantly increased with number of medications. The authors were of the opinion that this is due to poor specificity of the TBUT and Schirmer I tests.[21] Similarly, a recent studies have reported that the odds of OSD with ocular surface staining significantly increase with number of eye drops instilled per day.[23]

BAC has been particularly singled out for being responsible for signs of OSD in many glaucoma patients on topical medications, as demonstrated by clinical studies comparing the use of preserved, unpreserved, and new generation preservatives.[24,25] Since the preservative used in all the brands of topical antiglaucoma medications that were being used by the patients in our study was BAC, it is then likely that the higher prevalence of OSD might be as a result of the ocular surface exposure to the toxic effects of BAC in the ophthalmic formulations. This view is supported by the reports of some clinical studies, which suggests that changing to preservative-free topical antiglaucoma medications gives clinically relevant benefits.[26,27]

The prevalence of objective OSD in both the study groups varies widely across the modalities utilized for evaluation. The data from this study showed that OSD is more likely to be a consequence of evaporative/lipid layer deficiency of the precorneal tear film than aqueous deficiency as demonstrated by the wide disparity in the prevalence of OSD derived from FTBUT (83.5%), a measure of tear film instability, ocular surface staining (62.1%) which assesses the extent of damage to the ocular surface, and Schirmer I test (30.1%) which is a measure of aqueous production.[28,29] BAC commonly used as a preservative in majority of topical antiglaucoma eye drops is known to have detergent effect on the lipid layer of the tear film, thereby exposing the underlying aqueous layer of the tear film resulting in faster evaporation. Chronic breakdown of the tear film causes exposure of the cellular layers to adverse conditions that trigger the release of cytotoxic inflammatory mediators, which further impairs the tear film, thereby setting off a vicious circle, further fuelled by the continuous but necessary instillation of preserved eye drops.[30]

The significantly lower prevalence of OSD in the age- and sex-matched control group across all modalities of objective assessment suggests that other factors outside age and gender also significantly affect the ocular surface. The study also showed that such factors may affect the quality of the tear film, ocular surface cells as well as the quantity of aqueous production. In other words, some newly diagnosed glaucoma patients might have had some compromise of the ocular surface before the commencement of topical antiglaucoma medications. Such individuals are expected to have worsening of the ocular surface changes with the use of medications.

## Conclusion

The findings of this research showed that objectively assessed changes to the ocular surface in patients on long-term antiglaucoma medication are significantly more prevalent and worse than their age- and sex-matched counterparts. It cannot be overemphasized that the use of topical antiglaucoma medications, particularly the preserved forms, contributes significantly to the morbidity of ocular surface changes found to be more prevalent among glaucoma patients. More attention should, therefore, be given to the ocular surface status of patients on long-term antiglaucoma medications with consideration for alternatives that have a less toxic effect on the ocular surface.

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### Conflicts of interest

There are no conflicts of interest.

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