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Original Article

# Comparative Evaluation of Ocular Surface Health among Patients using Preserved and Preservative-Free Topical Anti-Glaucoma Medications: A Cross-Sectional Observational Study

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## ABSTRACT

**Objective**: To evaluate and compare the effects of preserved and preservative free topical antiglaucoma therapy on ocular surface health.
**Methods**: 40 glaucoma patients were divided into preserved and preservative-free groups (n=20 each). All patients with at least six months of topical anti-glaucoma therapy prior to enrollment in the study, were evaluated. Tear break-up time (TBUT), Schirmer I and II tests, and Ocular Surface Disease Index (OSDI) were assessed. Subgroup analysis based on single versus combination therapy was performed. Statistical analysis used independent t-tests or Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables.
**Results**: Baseline demographic and clinical characteristics were comparable between groups. Patients receiving preserved medications demonstrated significantly lower TBUT, Schirmer I, and Schirmer II values compared to the preservative-free group ($p < 0.01$). The preserved group showed significantly reduced TBUT (7.0 vs 8.0 sec), Schirmer I (10.0 vs 17.0 mm), and Schirmer II (6.45 ± 3.28 vs 9.75 ± 1.97 mm) compared to the preservative-free group. Median OSDI scores were higher in the preserved group (31.13 vs 16.6). Combination therapy was associated with significantly worse Schirmer test values and OSDI scores compared to single-drug therapy, while TBUT showed a declining trend but was statistically insignificant.
**Conclusion**: Long-term use of preserved topical antiglaucoma medications was associated with significantly greater ocular surface impairment compared to preservative-free formulations. Combination therapy further increased ocular surface impairment. Use of preservative-free formulations and minimizing polypharmacy may help improve ocular surface health.

***Keywords***: antiglaucoma medications, glaucoma, dry eyes, preservatives, tear film.

## INTRODUCTION

Glaucoma is a chronic, progressive optic neuropathy characterized by irreversible visual field loss and remains one of the leading causes of blindness worldwide, necessitating long-term or lifelong medical therapy in most patients [1]. Topical antiglaucoma medications constitute the first-line treatment for reducing intraocular pressure (IOP), the only modifiable risk factor known to slow disease progression. However, the chronic nature of glaucoma therapy requires sustained and often multidrug regimens, which may adversely affect the ocular surface, leading to a spectrum of disorders collectively termed ocular surface disease (OSD). Increasing evidence suggests that both the active compounds and, more significantly, the preservatives used in these formulations contribute to ocular surface toxicity [2].

Preservatives are added to multidose ophthalmic solutions to prevent microbial contamination and ensure drug stability. Among these, benzalkonium chloride (BAK) is the most commonly used preservative due to its potent antimicrobial properties. However, BAK has been extensively implicated in causing dose-dependent and time-dependent cytotoxic effects on the ocular surface. It disrupts the tear film, induces apoptosis of conjunctival and corneal epithelial cells, reduces

goblet cell density, and promotes inflammatory changes [3]. These alterations may manifest clinically as symptoms of dryness, burning, foreign body sensation, redness, and fluctuating vision, significantly impairing patient comfort and adherence to therapy. Moreover, chronic inflammation induced by preservatives can lead to subconjunctival fibrosis, which may adversely affect the success of future glaucoma filtration surgeries [4].

In contrast, preservative-free (PF) formulations have been developed to minimize ocular surface toxicity while maintaining therapeutic efficacy. These formulations are typically available in single-dose units or advanced multidose systems that prevent contamination without the need for preservatives [5]. Several studies have demonstrated that PF antiglaucoma medications are associated with improved tear film stability, reduced conjunctival inflammation, and better patient-reported comfort compared to preserved formulations [6]. Additionally, switching from preserved to PF therapy has been shown to improve signs and symptoms of OSD without compromising IOP control [7].

Despite these advantages, preserved formulations continue to be widely used due to their lower cost, greater availability, and convenience in multidose packaging, especially in resource-limited settings [8]. This creates a clinical dilemma where the benefits of cost-effective treatment must be balanced against the risk of long-term ocular surface damage. Furthermore, many patients are on combination therapy involving multiple preserved drugs, thereby increasing cumulative preservative exposure and exacerbating ocular surface compromise [9].

The prevalence of OSD among glaucoma patients is significantly higher than in the general population, with studies reporting rates ranging from 40% to 60% [10]. The severity of OSD correlates with the duration of therapy, number of medications, and total preservative load . Objective findings such as decreased tear breakup time (TBUT), reduced Schirmer's test values, punctate epithelial erosions, and conjunctival hyperemia are commonly observed in patients on long-term preserved antiglaucoma therapy [11]. In contrast, patients using PF medications generally demonstrate better ocular surface parameters and lower inflammatory markers.

Given the chronicity of glaucoma management and the increasing emphasis on patient quality of life, it is crucial to evaluate the long-term impact of preserved versus preservative-free antiglaucoma medications on ocular surface health [12]. Understanding these differences is essential not only for optimizing therapeutic outcomes but also for improving patient compliance and minimizing treatment-related morbidity [13]. Therefore, this comparative study aims to assess and analyze the effects of long-term use of preserved and preservative-free topical antiglaucoma medications on various clinical and functional parameters of the ocular surface, thereby providing evidence to guide more patient-centered and safer glaucoma management strategies.

## METHODOLOGY

### Study Design

The present study was conducted as a hospital-based, cross-sectional, comparative, observational study carried out in the Department of Ophthalmology of a tertiary care teaching hospital (Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha).

### Ethical Considerations

We obtained Institutional Ethics Committee clearance (KIIT/KIMS/IEC/1518). The study adhered to the ethical principles of the Declaration of Helsinki. The study period was from March 2025 to December 2025.

### Inclusion and Exclusion Criteria

The study included patients diagnosed with any form of glaucoma requiring topical therapy, aged 18 years or older, who had been using topical antiglaucoma medications for a minimum duration of 6 months. Only patients who were able to reliably complete the publicly available Ocular Surface Disease Index (OSDI) questionnaire, were included in the study [14]. The study excluded patients with pre-existing ocular surface disorders unrelated to glaucoma therapy, a history of ocular surgery within the last six months, or contact lens use were excluded from the study. Patients with systemic diseases known to affect tear secretion, such as Sjögren's syndrome, as well as those using systemic or topical medications known to affect the ocular surface, were also excluded.

### Study Sampling

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{d^2}$$

where Zα/2 = 1.96 for 95% confidence interval, Zβ = 0.84 for 80% power, σ represents pooled standard deviation, and d represents the expected mean difference between groups. Based on the study by Awe et al., [15], assessing ocular surface parameters among glaucoma patients on topical therapy, an expected mean difference of approximately 3 mm in Schirmer II values with pooled standard deviation of 2.7 mm was considered. The minimum calculated sample size was 12.7, rounded to 13, participants per group. To improve statistical validity and account for possible data loss, 20 participants were included in each group.

**Study Sample Size**
A total of 40 patients were included in the study, divided equally into two groups: preserved and preservative-free medication users. The sample size was determined based on feasibility, patient availability, and prior similar studies assessing ocular surface parameters. Each group comprised 20 patients, ensuring balanced comparison and statistical validity.

**Study Groups**
Based on our study design, which was cross-sectional, comparative, two study groups were made. According to the calculated sample size, the first group consisted of twenty patients who were on anti-glaucoma medications containing the preservative Benzalkonium Chloride. The second group also consisted to twenty patients who were on preservative-free anti-glaucoma medications for more than six months. Two predefined comparative analyses were performed. One between preserved and preservative-free medication groups and the other between single and combination therapy. Additionally, a subgroup analysis was performed based on therapy type, wherein the Combination Therapy Group included patients receiving more than one topical medication, and the Single Therapy Group included patients receiving a single topical medication. Topical medications included drugs from Prostaglandin Analogues, Beta blockers and Carbonic Anhydrase Inhibitor groups or a fixed dose combination of Beta Blocker and Carbonic Anhydrase Inhibitors. Care was taken not to include patients who were on multiple drugs with both Preserved and Preservative-free formulations in the same group. Baseline comparability between groups was ensured, with no significant differences in age, gender, intraocular pressure (IOP), or best-corrected visual acuity (BCVA).

**Study Parameters**
The study evaluated both clinical and functional ocular surface parameters. Tear film break-up time (TBUT) was assessed according to the method described by Norn et al. [16]. Schirmer I and II tests were performed using the original Schirmer technique [17]. Intraocular pressure was measured using Goldmann applanation tonometry and best-corrected visual acuity (BCVA) was recorded using standardized Snellen charts as per Snellen et al. [18,19]. BCVA was converted to logMAR units for standardization. The Ocular Surface Disease Index (OSDI) questionnaire validated by Schiffman et al. was used to assess subjective symptoms. These parameters were selected to assess tear film stability, tear production, and subjective symptom severity.

**Study Procedure**
All participants underwent a comprehensive ophthalmic evaluation. After obtaining informed consent, a detailed history was recorded, including duration and type of antiglaucoma medication use. Visual acuity was assessed using a standardized Snellen chart and converted to logMAR for analysis. Intraocular pressure was measured using Goldmann applanation tonometry.

Ocular surface evaluation was performed in a standardized sequence to avoid interference between tests. TBUT was measured using fluorescein dye under slit-lamp examination (Normal > 10sec; Mild – Moderate Dry Eye: 5-10 sec; Severe Dry Eye: <5 sec). Schirmer I test was conducted without anesthesia to assess basal and reflex tear secretion, followed by Schirmer II test with topical anesthesia to evaluate basal secretion (Normal: >15mm; Mild dry eye: 10-15mm; Moderate Dry eye: 5-10mm; Severe Dry eye: <5mm). The publicly available Ocular Surface Disease Index (OSDI) questionnaire, developed by Allergan and validated by Schiffman et al., was administered to assess subjective symptoms related to ocular discomfort and dryness (0-12: Normal; 13-22: Mild Dry eye; 23-32: Moderate Dry eye; 33-100: Severe Dry eye). Only findings of the right eye of all patients were used to analysis for uniformity.

The groups using combination therapy had a maximum of two drugs in each vial and all preserved medications taken for analysis had Benzalkonium Chloride (BAK) as a preservative.

**Study Data Collection**
Data were collected using a structured case record form (CRF) designed specifically for the study. All demographic details, clinical findings, and ocular surface parameters were recorded systematically. The data collection process ensured uniformity and minimized observer bias. Measurements were performed using standardized instruments and techniques across all participants.

**Data Analysis**
Data were entered into Microsoft Excel and analyzed. We used IBM SPSS Statistics Version 26.0 (Released 2018; IBM Corp., Armonk, New York, United States) software for data collection, tabulation and statistical analysis [20]. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on data distribution. Categorical variables were expressed as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro-Wilk test; variables conforming to a normal distribution (Schirmer II, IOP, Age) were reported as Mean ± SD and compared using the independent samples t-test, while variables deviating from normality (TBUT, Schirmer I, OSDI, BCVA) were reported as Median [Q1, Q3] and compared using the Mann-Whitney U test. Box-and-whisker plots in Figures 1 and 2 display all variables in a unified visual format, which is considered appropriate regardless of distributional

assumption. Comparison between groups were performed using independent t-tests or Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

A total of 40 patients with 20 patients in each group were included in the study and the baseline parameters were compared. No statistically significant differences were observed between the preserved and preservative-free groups in age (53.8 ± 4.2 vs 55.9 ± 5.4 years; p = 0.188), gender (40% vs 50% females; p = 0.751) distribution, intraocular pressure, or best-corrected visual acuity (16.1 ± 3.2 vs 14.8 ± 3.3 mmHg; p = 0.234) (p > 0.05 for all). The groups were well-matched at baseline (Table 1).

**Table 1: Comparison of Baseline Characteristics Between Preserved and Preservative-Free Group**

| Parameter | | Preserved | Preservative-Free | Test Statistic | P-value |
|---|---|---|---|---|---|
| Age (in years) - Mean ± SD | | 53.8 ± 4.2 | 55.9 ± 5.4 | t = - 1.341 | 0.188* |
| Gender (in %) | Male | 12 (60%) | 10 (50%) | $X^2$ = 0.101 | 0.751# |
| | Female | 8 (40%) | 10 (50%) | | |
| IOP (in mmHg) - Mean ± SD | | 16.1 ± 3.2 | 14.8 ± 3.3 | t = 1.209 | 0.234* |
| BCVA (log MAR) - Median [Q1, Q3] | | 0.1 [0.0, 0.2] | 0.1 [0.0, 0.2] | U = 245.0 | 0.672$ |
| IOP - Intraocular pressure, BCVA - Best Corrected Visual Acuity<br>* Independent t test, # Chi- Square test, $ Mann-Whitney U Test | | | | | |

Age, intraocular pressure, and BCVA were comparable between combination and single therapy groups (p > 0.05) (Table 2). The comparison between combination and single therapy groups revealed no significant differences in IOP (15.3 ± 3.4 vs 15.6 ± 3.1 mmHg; p = 0.738) and BCVA [0.1 (0.0, 0.2) vs 0.1 (0.0, 0.1); p = 0.584].

**Table 2: Comparison of Baseline Characteristics Between Combination and Single Medication Groups**

| Parameter | Combination | Single | Test Statistic | P-value |
|---|---|---|---|---|
| IOP (in mmHg) - Mean ± SD | 15.3 ± 3.4 | 15.6 ± 3.1 | t = -0.093 | 0.738* |
| BCVA (logMAR) - Median [Q1, Q3] | 0.1 [0.0, 0.2] | 0.1 [0.0, 0.1] | U = 272.0 | 0.584$ |
| IOP - Intraocular pressure, BCVA - Best Corrected Visual Acuity<br>* Independent t test, $ Mann-Whitney U Test | | | | |

Table 3 showed comparison of Ocular surface parameters between preserved and preservative free drug groups. Preserved medications were associated with significantly worse ocular surface parameters compared to preservative-free medications. The preserved group demonstrated shorter tear break-up time, reduced tear secretion on both Schirmer I and II testing, and higher OSDI scores (indicating greater symptom burden). All differences were statistically significant (p < 0.01 for all parameters).

**Table 3: Comparison of Ocular Surface Parameters Between Preserved and Preservative-Free Groups**

| Outcome | Preserved | Preservative-Free | Test Statistic | P-value |
|---|---|---|---|---|
| TBUT (in sec) - Median [Q1, Q3] | 7.0 [4.7, 8.0] | 8.0 [8.0, 8.0] | 85.0 | 0.001$ |
| Schirmer I (in mm) - Median [Q1, Q3] | 10.0 [5.7, 15.2] | 17.0 [15.5, 18.0] | 87.0 | 0.002$ |
| Schirmer II (in mm) - Mean ± SD | 6.45 ± 3.28 | 9.75 ± 1.97 | -3.853 | <0.001* |
| OSDI - Median [Q1, Q3] | 31.1 [23.0, 35.4] | 16.6 [13.3, 16.6] | 398.0 | <0.001$ |
| TBUT – Tear film Break Up Time; OSDI – Ocular Surface Disease Index<br>* Independent t test, $ Mann-Whitney U Test | | | | |

Combination therapy was associated with worse ocular surface outcomes compared to single medication therapy. Statistically significant differences were observed for Schirmer I, Schirmer II, and OSDI scores (p < 0.05). TBUT showed a clinically lower value in the combination group, though this did not reach statistical significance (p = 0.095), suggesting a trend toward poorer tear film stability with multiple medications (Table 4).

**Table 4: Comparison of Ocular Surface Parameters Between Combination and Single Medication Groups**

| Outcome | Combination | Single | Test Statistic | P-value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| TBUT (in sec) - Median [Q1, Q3] | 7.0 [6.0, 8.0] | 8.0 [7.5, 8.0] | 140.0 | 0.095$ |
| Schirmer I (in mm) - Median [Q1, Q3] | 10.0 [8.0, 16.0] | 17.0 [12.5, 19.0] | 125.0 | 0.044$ |
| Schirmer II (in mm) - Mean ± SD | 7.14 ± 2.76 | 9.16 ± 3.29 | -2.087 | 0.044* |
| OSDI - Median [Q1, Q3] | 31.0 [20.8, 35.41] | 16.67 [16.6, 20.8] | 314.5 | 0.002$ |
| TBUT – Tear film Break Up Time, OSDI – Ocular Surface Disease Index<br>* Independent t test, $ Mann-Whitney U Test | | | | |

**DISCUSSION**

The present study provides a comprehensive evaluation of the long-term impact of preserved versus preservative-free topical antiglaucoma medications on ocular surface health, with additional insights into the effects of combination therapy, indicating that subsequent differences in ocular surface parameters were attributable to medication-related factors rather than baseline disparities. The baseline comparability between study groups strengthens the validity of the findings, as no statistically significant differences were observed in age, gender distribution, intraocular pressure, or best-corrected visual acuity. Similar findings were in the baseline parameters were observed by previous studies by Kim KE, et al. and Harasymowycz P et al. [21,22]. The most notable findings of this study were the significantly poorer ocular surface parameters observed in patients using preserved antiglaucoma medications. Tear film stability, as assessed by tear break-up time (TBUT), was significantly reduced and furthermore, subjective symptom burden, as measured by OSDI, was significantly higher in the preserved group compared to the preservative-free group. These findings clearly indicate that preserved formulations are associated with compromised tear film stability, reduced tear secretion, and increased symptom severity, suggesting significant ocular surface dysfunction.

These results are in strong agreement with the findings of Awe et al., which reported a significantly higher prevalence of ocular surface disease among users of preserved antiglaucoma medications compared to nonusers, with abnormal FTBUT observed in 83.5% versus 57.3% ($P < 0.001$) and reduced Schirmer I values in 30.1% versus 17.5% ($P = 0.033$) [15]. Additionally, ocular surface staining was significantly higher in medication users (62.1% vs 31.1%; $P < 0.001$), indicating greater epithelial damage. The similarity between the present study and Awe et al.'s findings reinforces the evidence that preserved medications play a substantial role in ocular surface deterioration.

Further support is provided by the study by Khan et al., which demonstrated that although baseline TBUT and Schirmer values were comparable between preserved and preservative-free groups, a greater decline was observed in the preserved group after 3 months (TBUT reduced to 9.62 sec vs 10.18 sec; Schirmer's reduced to 11.81 mm vs 13.18 mm) [23]. Uusitalo et al. also reported that with preservative free formulations, TBUT was increased and Schirmer's Test values were more in comparison to preserved medication [24]. While the absolute values in the present study are lower—likely due to longer duration of exposure, the trend remains consistent, suggesting cumulative toxicity associated with preserved medications over time. This highlights the progressive nature of ocular surface damage with chronic exposure to preservatives.

The present study also demonstrated that combination therapy was associated with greater ocular surface impairment. Although TBUT was lower in the combination group compared to the single therapy group, this difference did not reach statistical significance ($p = 0.095$), suggesting a trend toward reduced tear film stability. However, significant differences were observed in tear production, with Schirmer I ($p = 0.044$), and Schirmer II values ($p = 0.044$) in the combination group versus single therapy group. Subjective symptoms were also significantly worse, in the combination group compared to the single therapy group ($p = 0.0018$) in the present study. These findings, similar to the study by Kim DW et al., suggest that increased medication burden, and consequently higher cumulative preservative exposure are associated with worsening of ocular surface parameters [25].

Similarly, Richhariya et al., reported a progressive decline in ocular surface parameters with increasing number of medications [26]. In their study, Schirmer's test values decreased from 15.06 mm in single-drug users to 11.24 mm in triple-drug users ($p < 0.001$), while TBUT decreased from 9.84 seconds to 5.29 seconds ($p < 0.001$). OSDI scores also increased significantly from 25.93 in single therapy to 49.63 in triple therapy ($p < 0.001$). Similar findings were reported by Ramli et al. [27]. The present study mirrors these findings, demonstrating that combination therapy is associated with worse tear function and higher symptom burden, thereby reinforcing the concept of dose-dependent ocular surface toxicity. In addition, the findings of this study align with broader evidence summarized by Wasyluk et al., which concluded that preservative-free formulations are generally better tolerated and less burdensome for patients requiring long-term glaucoma therapy [28]. The chronic nature of glaucoma necessitates prolonged use of medications, often for decades, making the cumulative impact of preservatives clinically significant. Wasyluk emphasized the importance of minimizing preservative exposure to prevent long-term ocular surface damage, a conclusion strongly supported by the present study.

However, it is important to consider the observations of Figus et al., who noted that despite strong preclinical evidence of reduced toxicity with preservative-free formulations, the limited number of randomized clinical trials makes it difficult to definitively conclude superior efficacy or safety in clinical practice [29]. This highlights an important limitation in the existing literature and underscores the need for further large-scale, randomized studies. Nonetheless, the present study contributes valuable clinical evidence supporting the ocular surface benefits of preservative-free medications.

Overall, the findings of this study clearly demonstrate that long-term use of preserved antiglaucoma medications is associated with significant deterioration in ocular surface health, as evidenced by reduced TBUT, decreased tear secretion, and increased OSDI scores. Furthermore, the use of multiple medications exacerbates these effects, likely due to cumulative preservative exposure. These results have important clinical implications, emphasizing the need for clinicians to consider preservative-free formulations and minimize polypharmacy wherever possible. By doing so, it may be possible to improve patient comfort, enhance adherence to therapy, and ultimately optimize long-term outcomes in glaucoma management.

**Limitations**

The results of the study should be interpreted with a number of limitations in mind. The research design was single-center observational and it indicated a single-point assessment of ocular surface status, thus, it cannot be said to have identified the causes or evaluated the progression of ocular surface changes that occurred over time. Because of the cross-sectional observational design, causal relationships between antiglaucoma medication type and ocular surface changes cannot be definitively established. Also, the impact of screen time could not be assessed as patients who were selected had minimal screen use. There were small sample sizes in the subgroups of Preservative free and Preserved Combination and Single medications due to limited availability of Preservative-free medications in the market and this may have the effect of causing estimates to be less precise. In addition, the study did not use any advanced diagnostic methods such as meibography, tear osmolarity, inflammation markers, or impression cytology, which could have given a more profound mechanistic insight into the changes in the ocular surface that were observed.

## CONCLUSION

The present study demonstrates that long-term use of preserved topical antiglaucoma medications is significantly associated with deterioration of ocular surface health, as evidenced by reduced tear film stability, decreased tear secretion, and increased symptom burden compared to preservative-free formulations. Additionally, the use of combination therapy was associated with worse ocular surface parameters, likely due to cumulative preservative exposure and increased drug load. While both treatment modalities effectively maintain intraocular pressure and visual acuity, their differential impact on ocular surface parameters highlights the clinical importance of treatment selection. These findings suggest that, whenever feasible, the use of preservative-free medications and minimization of polypharmacy should be considered to enhance patient comfort, improve adherence, and reduce long-term ocular surface morbidity in glaucoma management.

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