International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Effect of Monotherapy and Multiple Topical Antiglaucoma Drug Therapy on Tear Film Stability and Tear Secretion

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Received: 21-06-2026
Accepted: 15-07-2026
Available online: 27-07-2026

ABSTRACT

Purpose: To study the effect of topical antiglaucoma medications on tear film stability and secretion in glaucoma patients, and to compare the effect of single-drug versus multiple-drug topical therapy on tear film parameters. **Methods**: A hospital-based prospective study was conducted on 88 eyes of 46 newly diagnosed glaucoma patients (age 20–60 years) at the Department of Ophthalmology, Andhra Medical College, Visakhapatnam, between January and October 2021. Patients were started on either a single topical antiglaucoma drug (timolol maleate 0.5%, brimonidine 0.15%, bimatoprost 0.03%, or travoprost 0.004%) or a fixed combination of two drugs (brimonidine + timolol or travoprost + timolol), all containing benzalkonium chloride (BAK) as preservative. Tear film assessment — Ocular Surface Disease Index (OSDI) questionnaire, Schirmer 1 test (S1T), tear film break-up time (TBUT), and Oxford ocular surface staining — was performed before starting medication and at 1, 3, and 6 months thereafter. **Results**: The mean age of patients was 49.5 ± 7.14 years, with a female preponderance (54.3%) and predominantly bilateral involvement (89.1%). OSDI scores rose progressively in all groups, with the greatest increase seen in the timolol (monotherapy) and brimonidine + timolol (bitherapy) groups. TBUT declined significantly in the bimatoprost, travoprost, and travoprost + timolol groups ($p = 0.0001$). Schirmer 1 values fell significantly in the timolol, brimonidine + timolol, and travoprost + timolol groups. Comparison between monotherapy and bitherapy groups showed the bitherapy group had significantly higher OSDI ($p = 0.0001$) and lower TBUT ($p = 0.001$) at 6 months, while Schirmer 1 values were comparably reduced in both groups ($p = 0.709$). Oxford staining grade 4 (severe) changes were more frequent in the bitherapy group (26.7%) than the monotherapy group (8.6%) at 6 months. **Conclusion**: Long-term use of BAK-preserved topical antiglaucoma medication is associated with progressive deterioration of tear film stability and ocular surface health, and this effect is more pronounced with multiple-drug therapy than with monotherapy. Clinicians should weigh the ocular surface burden of multi-drug regimens and consider preservative-free alternatives where appropriate, particularly in patients requiring long-term multi-drug therapy.

Keywords: *Glaucoma, benzalkonium chloride, ocular surface disease, tear film break-up time, Schirmer test, OSDI.*

INTRODUCTION

Glaucoma is a progressive, multifactorial optic neuropathy characterised by loss of retinal ganglion cells and their axons, producing characteristic optic nerve head changes and corresponding visual field defects. It is the second leading cause of blindness worldwide, and elevated intraocular pressure (IOP) remains its only established modifiable risk factor. Topical IOP-lowering medications — beta blockers, prostaglandin analogues, alpha-2 agonists, and carbonic anhydrase inhibitors — are the mainstay of glaucoma management and are typically required lifelong.

Most topical antiglaucoma preparations contain benzalkonium chloride (BAK), a quaternary ammonium preservative used in roughly 70% of eye drops. While effective at maintaining sterility, BAK has detergent-like properties that destabilise the tear film lipid layer, damage corneal and conjunctival epithelium, reduce goblet cell density, and promote chronic inflammation of the ocular surface. Chronic exposure — particularly with multiple daily instillations or multiple concurrent medications — has been linked to a high prevalence of ocular surface disease (OSD) among glaucoma patients, which can in turn affect treatment adherence, visual comfort, and quality of life, and may even compromise the success of future filtering surgery.

While the ocular surface effects of individual antiglaucoma agents have been described, comparative data on tear film stability and secretion between single-drug and multiple-drug regimens remain limited, especially from South Asian populations. This study was undertaken to prospectively evaluate tear film stability and secretion in newly diagnosed glaucoma patients started on topical monotherapy or bitherapy, and to compare the magnitude of ocular surface change between the two treatment strategies.

Aims and Objectives

- To study the effect of topical antiglaucoma medications on tear film stability and secretion in glaucoma patients.
- To evaluate the effect of single topical drug therapy versus multiple topical drug therapy on tear film stability and secretion.

MATERIALS AND METHODS

Study design and setting: A hospital-based prospective study conducted in the Department of Ophthalmology, Andhra Medical College, Dr. R.S.P.R. Government Regional Eye Hospital, Visakhapatnam, from January 2021 to October 2021, after approval by the Institutional Ethics Committee, Andhra Medical College (Reg. No. EC/NEW/INST/2019/397). Written informed consent was obtained from all participants.

Sample: 88 eyes of 46 newly diagnosed glaucoma patients.

Inclusion criteria: Newly diagnosed glaucoma; age 20–60 years, both sexes; willingness to give consent.

Exclusion criteria: Active ocular inflammation or allergy; lid margin disease; ocular trauma; pre-existing dry eye symptoms or treatment; prior glaucoma surgery; contact lens wear; refractive surgery within the preceding 12 months; systemic disease such as diabetes mellitus or systemic medication known to cause dry eye; age > 60 years; concurrent topical medication other than the antiglaucoma drug; secondary glaucoma.

Grouping: Patients were allocated to a single-medication group — timolol maleate 0.5%, brimonidine 0.15%, bimatoprost 0.03%, or travoprost 0.004% — or a double-medication group — brimonidine 0.15% + timolol 0.5%, or travoprost 0.004% + timolol 0.5%. All preparations contained BAK as preservative.

Assessments: Baseline evaluation included visual acuity, slit-lamp examination, applanation tonometry, gonioscopy, and fundus examination. Tear film assessment was performed before starting medication and repeated at 1, 3, and 6 months, comprising:

- OSDI questionnaire — a validated 12-item instrument scored 0–100, with higher scores indicating greater disability.
- Schirmer 1 test (S1T) — Whatman No. 41 filter paper strip placed at the junction of the middle and lateral third of the lower lid for 5 minutes without anaesthesia; wetting <10 mm/5 min was considered borderline dry eye and <5 mm/5 min hyposecretive dry eye.
- Tear film break-up time (TBUT) — time between the last blink and appearance of the first dry spot in a fluorescein-stained tear film under cobalt-blue illumination; <10 seconds was taken as indicating dry eye.
- Oxford ocular surface staining — corneal and conjunctival staining graded 0 (normal) to V (severe) using the standard Oxford scheme panels.

Statistical analysis: Data were analysed using Microsoft Excel and SPSS version 25. Repeated-measures ANOVA was used to compare parameters across time points and between groups. Results were expressed as means ± SD and percentages; $p < 0.05$ was considered statistically significant.

RESULTS

A total of 88 eyes of 46 newly diagnosed glaucoma patients were studied.

Demographic profile

The mean age was 49.5 ± 7.14 years (range 30–60 years); 45.7% were aged 41–50 years and 43.5% were aged 51–60 years. Females (54.3%) outnumbered males (45.7%). Glaucoma was bilateral in 89.1% and unilateral in 10.9% of patients.

Distribution by drug regimen

In the single-medication group, 8 patients (17.4%) each used timolol and brimonidine, and 7 patients (15.2%) each used bimatoprost and travoprost. In the double-medication group, 8 patients (17.4%) used brimonidine + timolol and 8 (17.4%) used travoprost + timolol.

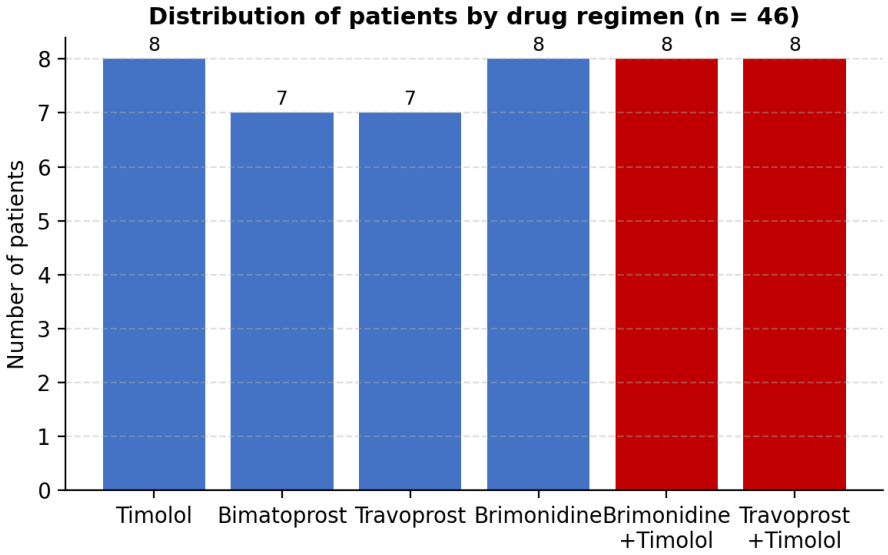

Figure 1. Distribution of patients by drug regimen.

Ocular Surface Disease Index (OSDI)

OSDI scores increased progressively with duration of treatment in all groups. In the single-medication group, the rise was statistically significant for timolol (4.80 ± 2.31 at baseline to 18.27 ± 2.55 at 6 months; p = 0.0001), while increases with bimatoprost, travoprost, and brimonidine did not reach significance. In the double-medication group, brimonidine + timolol showed a significant rise (6.93 ± 4.15 to 22.27 ± 2.25; p = 0.0001). Overall, the double-medication group had significantly higher mean OSDI than the single-medication group at every time point (p = 0.0001; Table 1).

Group	Baseline	1 month	3 months	6 months
Single medication	5.33 ± 3.06	7.91 ± 2.42	10.95 ± 2.70	16.02 ± 3.55
Double medication	7.07 ± 3.53	13.87 ± 3.75	19.87 ± 2.05	24.43 ± 2.06

***Table 1.* Comparison of mean OSDI between single- and double-medication groups (p = 0.0001).**

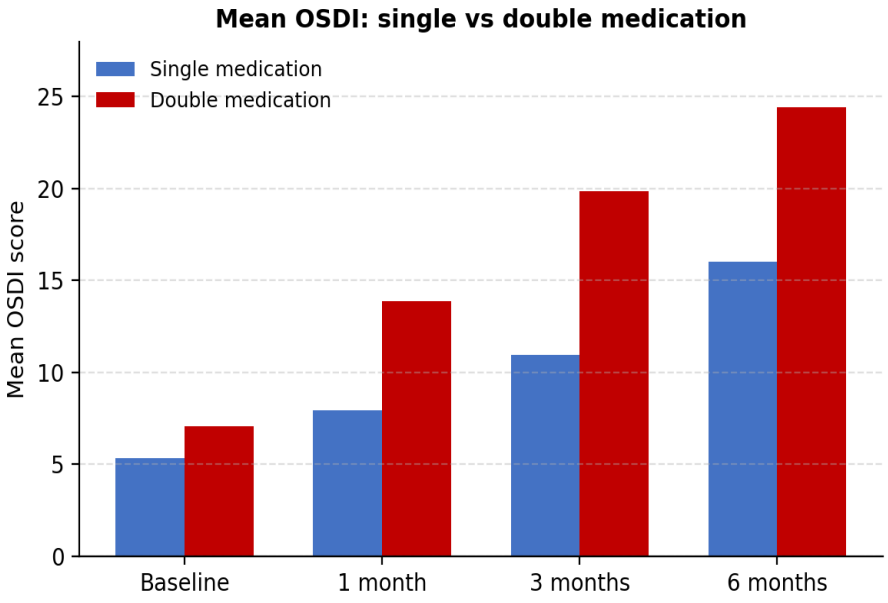

Figure 2. Trend in mean OSDI score over 6 months, single vs double medication.

Tear film break-up time (TBUT)

TBUT declined progressively in all groups. The decline was statistically significant for bimatoprost, travoprost (both p = 0.0001), and, in the double-medication group, travoprost + timolol (p = 0.0001). The decline in timolol, brimonidine, and brimonidine + timolol groups did not reach significance individually. Comparing overall groups, the double-medication group showed significantly lower TBUT than the single-medication group at 6 months (9.97 ± 1.33 vs 11.55 ± 2.28 seconds; p = 0.001; Table 2).

Group	Baseline	1 month	3 months	6 months
Single medication	17.72 ± 2.53	16.48 ± 2.33	14.10 ± 2.37	11.55 ± 2.28
Double medication	18.80 ± 2.52	15.37 ± 1.69	12.93 ± 1.66	9.97 ± 1.33

Table 2. **Comparison of mean TBUT (seconds) between single- and double-medication groups (p = 0.001).**

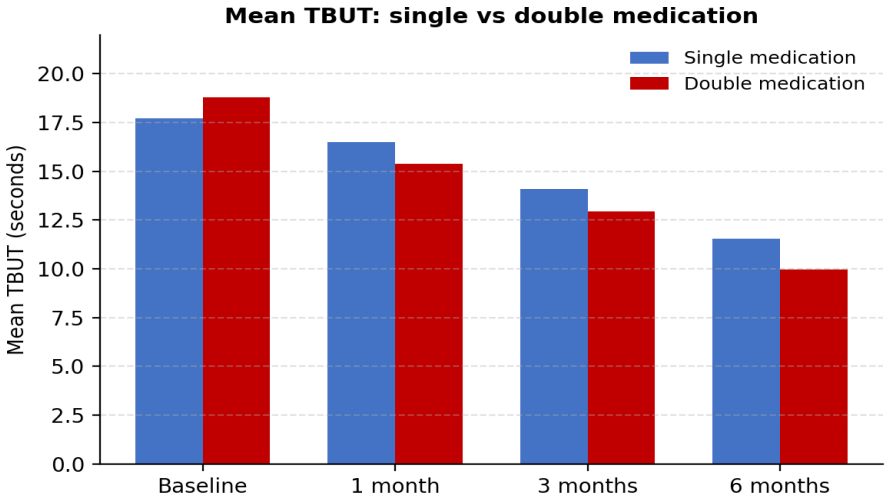

Figure 3. Trend in mean TBUT over 6 months, single vs double medication.

Schirmer 1 test (S1T)

Schirmer 1 values fell significantly with timolol (24.93 ± 4.95 to 19.40 ± 3.76 mm; p = 0.04) in the single-medication group, and with both brimonidine + timolol and travoprost + timolol (both p = 0.0001) in the double-medication group. Overall, mean S1T declined similarly in both groups over 6 months (single: 22.67 ± 3.91 to 15.48 ± 3.55 mm; double: 21.8 ± 2.73 to 15.23 ± 1.1 mm), and this between-group difference was not statistically significant (p = 0.709; Table 3).

Group	Baseline	1 month	3 months	6 months
Single medication	22.67 ± 3.91	20.41 ± 3.38	17.90 ± 3.35	15.48 ± 3.55
Double medication	21.80 ± 2.73	19.77 ± 2.27	17.43 ± 1.63	15.23 ± 1.10

Table 3. **Comparison of mean Schirmer 1 test (mm) between single- and double-medication groups (p = 0.709, not significant).**

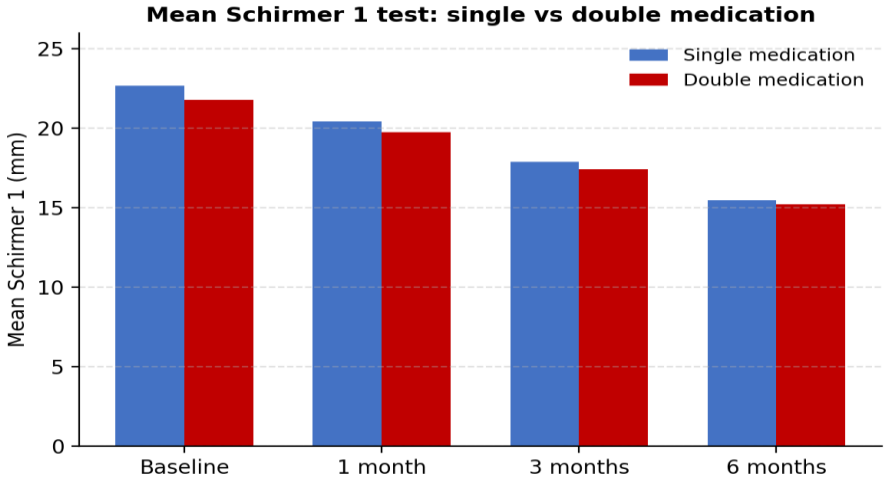

Figure 4. Trend in mean Schirmer 1 test over 6 months, single vs double medication.

Oxford ocular surface staining

At baseline, grade 0 (normal) staining was present in 65.5% of the single-medication group and 66.7% of the double-medication group, with the remainder showing grade 1 changes. Staining severity increased with duration of treatment in both groups. By 6 months, severe (grade 4) staining was seen in 8.6% of eyes in the single-medication group — most often with timolol — compared with 26.7% of eyes in the double-medication group, seen with both brimonidine + timolol and travoprost + timolol (Table 4).

Time point	Grade 1	Grade 2	Grade 3	Grade 4 (severe)
Baseline	34.5% / 33.3%*	–	–	–
1 month	84.5% / 63.3%	10.3% / 36.7%	1.7% / 0%	–
3 months	51.7% / 23.3%	41.4% / 46.7%	6.9% / 30.0%	–
6 months	12.1% / 0%	48.3% / 43.3%	31.0% / 30.0%	8.6% / 26.7%

Table 4. **Oxford ocular surface staining grade distribution over time (single-medication % / double-medication %).**

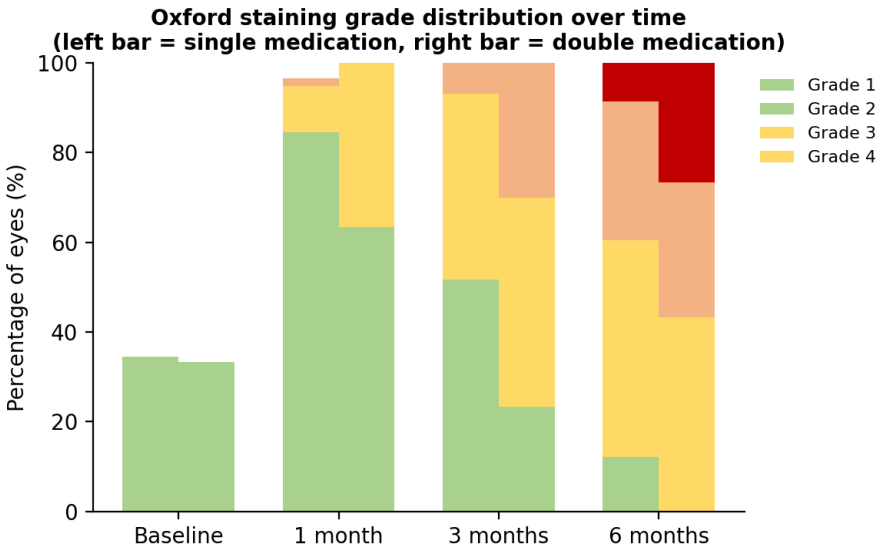

Figure 5. Oxford ocular surface staining grade distribution over time.

DISCUSSION

This prospective study evaluated tear film stability and secretion in newly diagnosed glaucoma patients started on BAK-preserved topical antiglaucoma monotherapy or bitherapy, and compared the magnitude of ocular surface change between the two regimens over 6 months.

The mean age of presentation (49.5 ± 7.14 years) and female preponderance (54.3%) observed here are broadly consistent with previous reports, though some studies (e.g., Ramesh Kumar et al., Manu Saini et al.) found an equal or male-predominant gender distribution, likely reflecting differences in the study populations. Bilateral involvement (89.1%) was similarly in keeping with the chronic, typically bilateral nature of glaucomatous optic neuropathy, and comparable to rates reported by Kurna et al. and Inoue et al.

OSDI scores worsened progressively with treatment duration across all drug groups, with the most marked deterioration seen in the timolol monotherapy group and the brimonidine + timolol bitherapy group. Comparison between the two treatment strategies showed a significantly greater rise in OSDI with bitherapy, consistent with the concept that exposure to a greater cumulative BAK load — whether via multiple drops or combination formulations — is an independent predictor of worsening symptom scores, as reported by Fechtner et al. and others.

TBUT, a marker of tear film stability, declined significantly with bimatoprost and travoprost monotherapy and with travoprost + timolol bitherapy, suggesting a more pronounced evaporative component with prostaglandin-analogue-containing regimens, a finding that parallels the observations of Kurna et al. The overall comparison confirmed significantly greater TBUT reduction in the bitherapy group, in agreement with prior reports linking higher eye-drop burden and BAK exposure to greater tear film instability (Cvenkel et al., Ramli et al.).

Schirmer 1 values, reflecting aqueous tear secretion, fell significantly with timolol monotherapy and with both combination regimens, consistent with earlier reports (Kumar Ramesh et al., Bonomi et al., Shimazaki et al.) that beta-blockers impair tear production and turnover. Notably, the magnitude of Schirmer 1 decline was similar between monotherapy and

bitherapy groups in this study, suggesting that aqueous secretion may be less sensitive than tear film stability or symptom scores to the number of concurrent medications used.

Oxford staining scores worsened progressively in both groups, with severe (grade 4) changes more than three times as frequent in the bitherapy group by 6 months. This is consistent with the literature demonstrating a dose-dependent relationship between the number of BAK-containing drops instilled daily and the severity of ocular surface staining (Leung et al., Pisella et al., Rossi et al.), and supports the broader principle that both the preservative and the active pharmacological agent contribute to cumulative ocular surface toxicity through reduced goblet cell density, corneal epithelial damage, and chronic low-grade inflammation.

Taken together, these findings reinforce that chronic topical antiglaucoma therapy — particularly multi-drug regimens — carries a measurable ocular surface burden that increases with duration of use. Since glaucoma treatment is typically lifelong, awareness of this burden may inform decisions about regimen simplification, preservative-free formulations, and adjunctive ocular surface therapy in patients requiring long-term multi-drug treatment.

CONCLUSION

Topical antiglaucoma medications, particularly when preserved with benzalkonium chloride, are associated with progressive deterioration of tear film stability, tear secretion, and ocular surface integrity over time. This effect is more pronounced with multiple-drug therapy than with single-drug therapy, most evidently in symptom burden (OSDI), tear film stability (TBUT), and ocular surface staining, while aqueous tear secretion (Schirmer 1) declines to a similar extent regardless of the number of drugs used. Since glaucoma management is typically lifelong, clinicians should be mindful of the ocular surface impact of multi-drug regimens and consider preservative-free alternatives or adjunctive ocular surface care where clinically appropriate.

Limitations of the study

1. The number of patients in each drug subgroup was limited.
2. No untreated control group was included.
3. Follow-up was limited to 6 months.
4. Only one preservative (BAK) was studied; no preservative-free group was included.
5. Only conventional clinical tests were used; no laboratory-based tear film biomarkers were assessed.

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