

Research Article

Comparative Evaluation of Preservative-Free and Preserved Antiglaucoma Eye Drops

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Received: 10.09.2026, Revised: 02.10.2026, Accepted: 26.10.2026

ABSTRACT

Background: Long-term topical therapy is central to glaucoma management, but repeated exposure to preservatives, particularly benzalkonium chloride (BAK), may contribute to ocular-surface symptoms and signs. Preservative-free (PF) formulations may improve tolerability while maintaining intraocular-pressure (IOP) control.

Objective: To compare longitudinal IOP and ocular-surface measures, recorded adverse events, and treatment discontinuation among patients receiving PF or BAK-preserved antiglaucoma eye drops.

Methods: This prospective comparative observational study included 130 patients in the dataset: 78 receiving BAK-preserved drops and 52 receiving PF drops. Outcomes were summarized at baseline and months 1, 3, 6, and 12. Measures included IOP, Ocular Surface Disease Index (OSDI), tear-film break-up time (TBUT), Schirmer test, Oxford staining grade, conjunctival hyperemia, adverse events, and discontinuation. The study summary provides descriptive data but no dispersion estimates or inferential test results.

Results: Mean IOP decreased from 23.4 to 16.0 mmHg in the BAK group and from 24.4 to 17.6 mmHg in the PF group by month 12. In the BAK group, OSDI increased from 17.1 to 26.4, TBUT declined from 8.9 to 6.0 seconds, Schirmer values declined from 13.6 to 11.1 mm, Oxford grade increased from 0.79 to 1.54, and hyperemia score increased from 0.87 to 1.70. In the PF group, OSDI decreased from 20.2 to 18.0, TBUT increased from 8.3 to 9.0 seconds, Schirmer values were 12.8 and 13.2 mm, Oxford grade changed from 0.92 to 0.78, and hyperemia score from 0.90 to 0.68. Recorded adverse-event counts were 85 and 22, respectively. Adverse-event-related discontinuation was recorded for 16/78 (20.5%) in the BAK group and 3/52 (5.8%) in the PF group.

Conclusion: PF treatment was associated with more favorable ocular-surface trends and fewer recorded adverse-event-related discontinuations. Both groups showed lower mean IOP, with no statistically significant between-group difference in IOP change. These observational findings do not establish causality; active ingredients, baseline ocular-surface differences, and incomplete follow-up should be considered.

Keywords: Glaucoma, Benzalkonium Chloride, Preservative-Free Eye Drops, Ocular Surface Disease, OSDI, Tear-Film Break-Up Time, Intraocular Pressure, Tolerability.

INTRODUCTION

Glaucoma and ocular hypertension often require long-term topical treatment to reduce intraocular pressure and limit the risk of progressive optic-nerve damage. In routine care, effectiveness depends not only on pressure reduction but also on tolerability and the ability to continue therapy. Ocular-surface symptoms may reduce quality of life and complicate long-term treatment [1–4].

Benzalkonium chloride is a quaternary ammonium compound used in many multidose ophthalmic preparations. Experimental and clinical literature has raised concerns that repeated exposure may affect corneal and

conjunctival epithelium, tear-film stability, and ocular-surface inflammation. The clinical impact may depend on concentration, duration of exposure, dosing frequency, number of topical agents, and pre-existing ocular-surface disease [2,3,5]. Clinical observations and experimental work have also documented ocular symptoms with preserved formulations and differential effects of preservatives on ocular epithelial cells [7–9].

Preservative-free formulations reduce exposure to preservatives. Published studies and reviews suggest that IOP-lowering efficacy can often be maintained with PF formulations, although findings for ocular-

surface outcomes vary by drug, formulation, assessment method, and follow-up [1,4,6]. Real-world comparisons are useful, but treatment groups may differ in active ingredients, fixed combinations, disease severity, and baseline symptoms. Observed differences therefore cannot be attributed to preservative status alone when these factors are not controlled. A randomized two-year evaluation further examined ocular-surface responses to preserved and non-preserved glaucoma medications [10].

This study descriptively compares IOP, ocular-surface measures, recorded adverse events, and discontinuation over 12 months among patients receiving PF or BAK-preserved antiglaucoma drops.

MATERIALS AND METHODS

Study Design and Population

Clinical records were reviewed and analyzed during April–May 2026. The dataset contained longitudinal follow-up observations through month 12; April–May 2026 therefore represents the record-review and analysis period rather than the patient recruitment period. The analysis included 130 patients with available records: 78 receiving BAK-preserved antiglaucoma drops and 52 receiving preservative-free (PF) drops. Clinical data were verified by the author.

Exposure Groups and Follow-Up

The BAK-preserved group included latanoprost, bimatoprost, travoprost, timolol, and fixed combinations including dorzolamide/timolol, latanoprost/timolol, or bimatoprost/timolol. The PF group included latanoprost, tafluprost, bimatoprost, timolol, and combinations including dorzolamide/timolol and latanoprost/timolol. Scheduled observations were summarized at baseline and months 1, 3, 6, and 12. Measures were IOP (mmHg), OSDI score, TBUT (seconds), Schirmer test (mm), Oxford ocular-surface staining grade, and conjunctival hyperemia score. The study does not specify

measurement instruments, grading anchors, eye-level aggregation, or examiner masking.

Safety and Statistical Analysis

Patient-level visit records were parsed and linked to the patient roster by study code. Scheduled observations were summarized by group and month. For longitudinal comparison, complete cases with a recorded month-0 and month-12 value for the relevant outcome were analyzed using within-group paired t-tests and between-group Welch t-tests on individual change scores (month 12 minus month 0). These are exploratory, unadjusted comparisons; no correction for multiple testing was applied. Categorical discontinuation outcomes were compared using two-sided Fisher exact tests. Available month-12 complete cases were 37 in the PF group and 52 in the BAK group. Records contained inconsistent visit-type labels, so scheduled month values—not the text labels “baseline” or “scheduled”—were used to identify month-0 and month-12 observations. The heterogeneous active ingredients, nonrandom treatment allocation, and incomplete follow-up limit causal interpretation.

Ethics

Ethical approval for the study was obtained in writing. The study was conducted in accordance with the applicable institutional requirements and ethical principles for clinical research.

RESULTS

Participant Characteristics and Follow-Up

The cohort included 78 patients receiving BAK-preserved drops and 52 receiving PF drops. Mean age was 64.8 and 62.4 years, respectively. Women represented 48/78 (61.5%) in the BAK group and 29/52 (55.8%) in the PF group. Dry-eye history was recorded in 19/78 (24.4%) and 22/52 (42.3%), respectively; baseline dry-eye history was therefore more common in the PF group.

Characteristic	BAK-preserved (n=78)	PF (n=52)
Mean age, years	64.8	62.4
Female, n (%)	48 (61.5%)	29 (55.8%)
Dry-eye history, n (%)	19 (24.4%)	22 (42.3%)
Completed follow-up, n (%)	53 (67.9%)	37 (71.2%)
Discontinued, n (%)	18 (23.1%)	12 (23.1%)
Lost to follow-up, n (%)	7 (9.0%)	3 (5.8%)
Recorded adverse-event count	85	22

Stopped due to adverse event, n (%)	16 (20.5%)	3 (5.8%)
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The completion, discontinuation, and loss-to-follow-up categories sum to the respective group totals. Month-12 observation counts were 52 and 37, respectively. Incomplete follow-up may affect the composition of patients contributing to later group means.

Intraocular Pressure

Mean IOP declined in both groups. In the BAK group, the reported mean decreased from

23.4 mmHg at baseline to 16.3 mmHg at month 1 and remained between 16.0 and 16.3 mmHg through month 12. In the PF group, mean IOP decreased from 24.4 mmHg at baseline to 17.1 mmHg at month 1; the reported mean was 17.6 mmHg at months 6 and 12. These descriptive data do not establish equivalence or superiority.

Visit	BAK visits	BAK IOP (mmHg)	PF visits	PF IOP (mmHg)
Baseline	78	23.4	52	24.4
Month 1	74	16.3	50	17.1
Month 3	69	16.3	45	17.0
Month 6	63	16.3	43	17.6
Month 12	52	16.0	37	17.6

Ocular-Surface Measures

In the BAK group, OSDI increased from 17.1 at baseline to 26.4 at month 12, while TBUT decreased from 8.9 to 6.0 seconds. Schirmer values declined from 13.6 to 11.1 mm, Oxford grade increased from 0.79 to 1.54, and hyperemia score increased from 0.87 to 1.70.

In the PF group, OSDI decreased from 20.2 to 18.0, TBUT increased from 8.3 to 9.0 seconds, Schirmer values were 12.8 mm at baseline and 13.2 mm at month 12, Oxford grade changed from 0.92 to 0.78, and hyperemia score decreased from 0.90 to 0.68.

Measure	Group	Baseline	M1	M3	M6	M12
OSDI	BAK	17.1	20.0	22.3	25.5	26.4
OSDI	PF	20.2	19.8	19.2	18.0	18.0
TBUT (s)	BAK	8.9	8.2	7.1	6.9	6.0
TBUT (s)	PF	8.3	8.6	8.7	9.0	9.0
Schirmer (mm)	BAK	13.6	13.0	12.0	11.5	11.1
Schirmer (mm)	PF	12.8	12.5	13.2	12.7	13.2
Oxford grade	BAK	0.79	1.01	1.29	1.52	1.54
Oxford grade	PF	0.92	0.98	0.84	0.74	0.78
Hyperemia score	BAK	0.87	1.19	1.43	1.59	1.70
Hyperemia score	PF	0.90	0.92	0.79	0.73	0.68

The patient-level complete-case analysis showed statistically significant between-group differences in change from baseline to month 12 for the ocular-surface measures (unadjusted $p < 0.001$ for each outcome). These findings should be interpreted in the context of baseline dry-eye imbalance, heterogeneous active ingredients, incomplete follow-up, and the observational design.

Adverse Events

The source recorded 85 adverse-event occurrences in the BAK group and 22 in the PF group. The most frequent listed events in the BAK group were burning/stinging (20), foreign-body sensation (15), conjunctival hyperemia (14), dry-eye symptoms (12), and allergic blepharoconjunctivitis/eyelid itching (11). In the PF group, dry-eye symptoms were

recorded 9 times; allergic blepharoconjunctivitis/eyelid itching 3 times; and burning/stinging, hyperemia, headache, blurred vision, and periocular pigmentation/eyelash changes 2 times each.

Recorded event	PF count	BAK count
Burning/stinging on instillation	2	20
Dry-eye symptoms	9	12
Conjunctival hyperemia	2	14
Foreign-body sensation	0	15
Allergic blepharoconjunctivitis/eyelid itching	3	11
Headache	2	4
Blurred vision	2	3
Periocular pigmentation/eyelash changes	2	2
Superficial punctate keratitis	0	3
Bradycardia/fatigue (beta-blocker effect)	0	1
Total recorded events	22	85

Treatment discontinuation. Adverse events were recorded as the reason for discontinuation in 16 BAK-group patients and 3 PF-group patients. Patient decision accounted for 1 and 5 discontinuations, respectively, while lack of efficacy accounted for 1 and 4. Overall

discontinuation was 18/78 (23.1%) in the BAK group and 12/52 (23.1%) in the PF group. The data therefore suggest a difference in recorded reasons for discontinuation, not a difference in overall crude discontinuation proportion.

Reason	PF (n=52)	BAK (n=78)
Adverse event	3 (5.8%)	16 (20.5%)
Patient decision	5 (9.6%)	1 (1.3%)
Lack of efficacy	4 (7.7%)	1 (1.3%)
Total discontinued	12 (23.1%)	18 (23.1%)

Statistical note: Month-12 analyses use complete cases only (n=37 PF; n=52 BAK). All p-values are unadjusted; multiple testing and confounding were not addressed. Table 3. Patient-level comparison of change from month 0 to month 12 among complete

cases. Change is calculated as month 12 minus month 0; negative values indicate reductions. Between-group difference is PF change minus BAK change. Welch tests and confidence intervals are unadjusted.

Outcome	PF n	PF mean change	BAK n	BAK mean change	Between-group difference (95% CI)	p-value
IOP (mmHg)	37	-7.51	52	-7.42	-0.09 (-1.23 to 1.05)	0.874
OSDI score	37	-2.04	52	+10.51	-12.54 (-14.44 to -10.64)	<0.001
TBUT (s)	37	+0.54	52	-2.90	+3.44 (2.94 to 3.94)	<0.001
Schirmer (mm)	37	+0.38	52	-2.46	+2.84 (2.12 to 3.56)	<0.001

Oxford staining	37	-0.22	52	+0.77	-0.99 (-1.22 to -0.75)	<0.001
Hyperemia score	37	-0.28	52	+0.84	-1.12 (-1.29 to -0.95)	<0.001

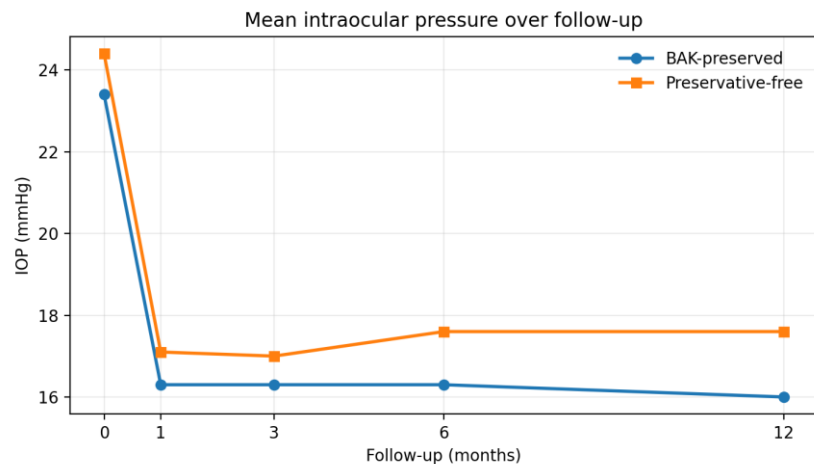


Figure 1. Mean Intraocular Pressure at Scheduled Visits.

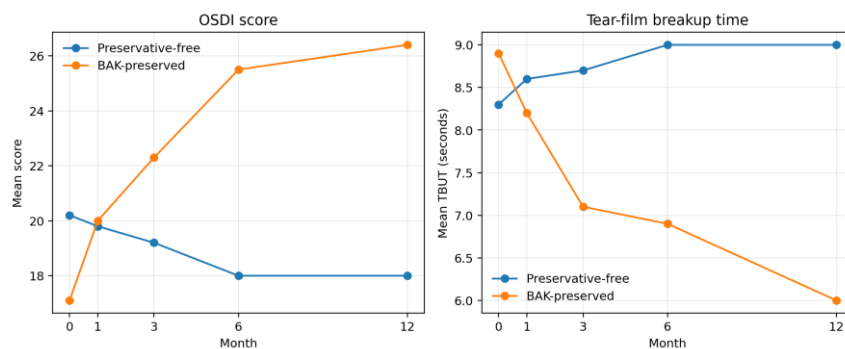


Figure 2. Ocular-Surface Outcomes at Scheduled Visits: OSDI Symptom Scores and Tear-Film Breakup Time (TBUT). Values are Group Means from the Summary; Error Bars are not Shown.

DISCUSSION

In this observational dataset, both treatment groups demonstrated lower mean IOP during follow-up, and the between-group difference in month-0 to month-12 IOP change was not statistically significant ($p=0.874$). The complete-case analysis found statistically significant unadjusted between-group differences in changes in OSDI, TBUT, Schirmer values, Oxford staining, and hyperemia, each favoring the PF group (all $p<0.001$). Adverse-event-related discontinuation was also less frequent in the PF group (5.8% versus 20.5%; Fisher's exact $p\approx 0.023$), although overall discontinuation was identical at 23.1%. These findings support a tolerability advantage in this dataset, but should be interpreted cautiously because treatment was not randomized, active

ingredients differed between groups, follow-up was incomplete, and analyses did not adjust for confounding or multiple comparisons. These patterns are biologically plausible in light of literature describing potential ocular-surface effects associated with repeated exposure to BAK. BAK is a surfactant preservative, and clinical and experimental reports describe possible effects on epithelial integrity, tear-film stability, and inflammation [2,3,5]. Reviews suggest that IOP-lowering efficacy can often be maintained with BAK-free formulations, while ocular-surface outcomes vary among studies and formulations [1,4,6]. The present findings are broadly compatible with this literature but should not be overstated. Related clinical and experimental studies likewise describe ocular-surface effects

associated with preserved topical glaucoma therapy [7–10].

The IOP trajectories indicate pressure reduction in both groups. The patient-level comparison of change from baseline to month 12 did not identify a statistically significant between-group difference. The observational design and heterogeneous medications mean that superiority, equivalence, or non-inferiority cannot be concluded.

Interpretation of ocular-surface differences also requires caution. Dry-eye history was more frequent in the PF group at baseline (42.3% versus 24.4%). Treatment selection may have reflected symptoms or clinician preference. Active ingredients and fixed combinations also differed; symptoms such as hyperemia may be related to the active molecule as well as the preservative. The observed association is between treatment groups as used in routine care, not a causal estimate of the independent effect of BAK.

The discontinuation findings are nuanced. Adverse-event-related discontinuation was more common in the BAK group, but overall discontinuation was identical as a proportion in both groups (23.1%). The PF group had more discontinuations attributed to patient decision or lack of efficacy. The dataset does not show a direct validated measure of adherence, dose-taking behavior, or refill history; therefore, improved adherence should not be claimed.

Strengths include patient-level longitudinal records, follow-up scheduled through 12 months, multiple symptom-based and clinical ocular-surface measures, and documentation of adverse events and discontinuation reasons.

Limitations

This observational study included heterogeneous active medications, baseline differences in dry-eye history, and incomplete follow-up. These factors may have influenced the findings, and residual confounding cannot be excluded. Treatment adherence was not directly measured.

CONCLUSION

In this comparative analysis of 130 patients, both preservative-free and benzalkonium chloride (BAK)-preserved antiglaucoma eye drops were associated with reductions in mean intraocular pressure over follow-up. The between-group difference in mean IOP change from baseline to month 12 was not statistically significant (−0.09 mmHg; 95% CI, −1.23 to

1.05; $p=0.874$). In contrast, the complete-case comparisons showed statistically significant differences in changes in ocular-surface measures, favoring the preservative-free group for OSDI, tear-film breakup time, Schirmer testing, Oxford staining, and conjunctival hyperemia (all $p<0.001$ in unadjusted analyses). Adverse-event-related discontinuation was also lower in the preservative-free group than in the BAK-preserved group (3/52 [5.8%] versus 16/78 [20.5%]; Fisher's exact $p\approx0.023$), whereas overall discontinuation was identical proportionally (23.1% in each group). Taken together, these findings support a statistically significant advantage for preservative-free formulations in the measured ocular-surface changes and adverse-event-related discontinuation, but not in IOP reduction. Because the study was observational, the groups used heterogeneous active medications, follow-up was incomplete, and analyses were unadjusted for confounding and multiple comparisons, the results should be interpreted as associations rather than proof that preservative status alone caused the differences.

Declarations

Ethics approval: Written ethical approval was obtained.

Informed consent: Consent procedures were conducted in accordance with the approved study protocol.

Funding: There is no funding for this study.

Conflicts of Interest: There is no conflict of interest.

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