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Comparative Efficacy of Preservative-Free vs Preserved Topical Anti-Glaucoma Medications on Ocular Surface Disease: A 6-Month Prospective Study.

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Abstract

Background: Chronic topical anti-glaucoma therapy can lead to the development of an ocular surface disease due to long-term use of preservatives. Preservative-free formulations can be used to decrease toxicity to the ocular surface without compromising intraocular pressure (IOP) control. ***Objective:*** To determine the ocular surface effects and IOP reduction after 6 months of preservative-free and preserved topical antiglaucoma medications. ***Methods:*** A prospective, comparative study was performed on 120 patients with primary open-angle glaucoma or ocular hypertension. A total of 60 participants were assigned to a preservative-free topical anti-glaucoma drug regimen, and 60 participants were assigned to a preserved topical anti-glaucoma drug regimen. The Ocular Surface Disease Index (OSDI), tear break-up time (TBUT), Schirmer I test, corneal and conjunctival staining, conjunctival hyperemia, IOP, ocular symptoms, and treatment adherence were evaluated at baseline and at 3 and 6 months post-intervention. ***Results:*** Significant reduction in IOP was observed in both groups at six months with no significant difference between them ($p=0.512$). The preservative-free group showed greater improvement in OSDI score ($p<0.001$), TBUT ($p<0.001$), and schirmer I test ($p<0.001$). There was also significantly less corneal staining, hyperemia, ocular symptoms, and adverse effects with use of medications, and higher adherence. ***Conclusion:*** There was no difference in IOP control between preservative-free therapy and control groups after 6 months, but there was better tolerability and adherence of the preservative-free group.

Keywords: Glaucoma, preservative-free, benzalkonium chloride, ocular surface disease, intraocular pressure, dry eye, topical therapy.

INTRODUCTION

Intraocular pressure (IOP) is the primary target for treatment in glaucoma, which is a significant cause of irreversible visual loss globally and requires continuous lowering of intraocular pressure to avoid progressive optic nerve degeneration and vision loss.[1] The laser and surgical options have become more common treatments to use in glaucoma care, but eye drops designed to lower intraocular pressure (IOP) are still the most often used treatments, especially for people who need long-term medical treatment.[2] This means many patients are treated with topical medications for years, sometimes many times a day.[3] These agents are useful for controlling IOP, but long-term topical treatment can have adverse effects on the ocular surface, with the potential to reduce comfort, tolerability, adherence, and quality of life.[4]

Chronic glaucoma therapy is associated with a growing problem of ocular surface disease (OSD).[5] The following symptoms of dry eye may occur: burning, foreign-body sensation, and discomfort in the eye, conjunctival hyperemia, tear-film instability, and corneal epithelial damage.[6] Preservatives in many multidose ophthalmic products, including benzalkonium chloride (BAK), are a major factor.[7] Exposure to BAK can disrupt the tear-film and epithelial barrier, trigger inflammatory responses, impair the goblet cells of the conjunctiva, and cause toxicity to the ocular surface with

prolonged exposure.[8] Recently, preservative-associated iatrogenic OSD has been discussed as a frequent issue encountered in patients with chronic topical glaucoma medications, and it has been shown to occur as increased staining of the cornea, decreased tear-film stability, and higher Ocular Surface Disease Index (OSDI) scores.[9]

The clinical significance of this problem is limited to symptoms. If the eye does not feel comfortable or becomes uncomfortable while taking the medication, patients may not be able to take the medication as directed, which could lead to poor medication adherence and failure to maintain optimal intraocular pressure and disease control.[10] Preservative-free (PF) formulations have thus become a good alternative, especially for patients who need multiple or long-term topical treatments.[11] Importantly, the evidence that has been available indicates that topical glaucoma medications that contain BAK do not necessarily lose their efficacy in lowering IOP.[4] In a systematic review and meta-analysis of 16 randomized clinical trials and 4,201 patients, preservative-free or alternative preservative preparations and BAK-preserved preparations were found not to differ clinically in their IOP-lowering effectiveness.[12]

However, there is still some question about the true clinical effectiveness of preserved and PF topical glaucoma medications over a clinically relevant duration. The findings of the various studies have been inconsistent because of differences in drug class, length of exposure, ocular surface status, assessment methods, and concomitant medications. Furthermore, while there are growing indications that there should be a push to reduce preservative exposure, prospective comparative data are still required to determine if PF formulations offer any measurable benefits in terms of improved ocular surface health in the context of glaucoma treatment as usual (TAU).[13]

In this context, a comparison of preserved and PF glaucoma medications over 6 months may offer researchers insight into the relationship between effective IOP control and maintenance of ocular surface health. This evidence is especially relevant when therapy is required to be used topically for extended periods of time and when drug-induced ocular discomfort could affect adherence. Hence, the present study was conducted to compare in a prospective fashion the efficacy of the anti-glaucoma medications over six months and the effects on the ocular surface of these different types of topical anti-glaucoma medications. The purpose of the study was to evaluate the changes in IOP, the severity of ocular surface disease, the stability of tear films, the presence of ocular surface staining, conjunctival hyperemia, and treatment tolerability in patients receiving anti-glaucoma drugs as topical therapy with or without preservatives.

MATERIALS AND METHODS

The study was a prospective, observational, two-group, comparative design. The study was conducted over a period of six months from Octubor 2025 to March 2026.

The sample size was determined using OpenEpi version 3.01 for comparing two independent groups. In a randomized trial of 51 patients, Kim et al. found that significantly fewer patients experienced hyperemia and stinging/burning with preservative-free latanoprost (25 vs. 26 patients; $p<0.001$).[14] Based on these findings, with 95% confidence and 80% power, OpenEpi yielded a minimum sample size of 120 participants (60 per group).

A consecutive sampling technique was employed. Patients who met the predetermined criteria in the ophthalmology outpatient department during the study period were approached to participate in the study. Patients were recruited in a consecutive manner until the required sample of 120 patients was met. Patients were divided into the preservative-free or preserved medication group based on the anti-glaucoma medication they were prescribed as part of their normal clinical care.

Patients over 18 years of age with clinical diagnosis of POAG, or OHTN, on topical anti-glaucoma medications, were included. Eligible were patients who had been treated with a topical anti-glaucoma medication (either preservative-free or with preservative) and who were predicted to continue treatment for at least six months. Patients who were able to read and complete the visual and cognitive section of the ocular surface symptom questionnaire and attend regularly at the follow-up visits were included.

Patients who had undergone ocular surgery in the last 6 months, had active ocular infection or inflammation, significant corneal disease, clinically evident allergic conjunctivitis or had severe pre-existing ocular surface disease unrelated to anti-glaucoma medication were excluded. Patients taking topical medications that might significantly affect the ocular surface, except for those prescribed as anti-glaucoma therapy, were also excluded. Systemic diseases and medications that would have a clinically significant effect on tear-film function were excluded if present. Patients who were unable to follow the treatment regimen or were not likely to follow through for the six-month follow-up were also excluded.

Demographic and clinical data were collected on a structured data collection proforma after informed consent was obtained. Baseline parameters were age, sex, and duration of glaucoma, type of glaucoma, duration of topical anti-glaucoma therapy,

number of topical medications, anti-glaucoma drug used, and the presence of any relevant systemic comorbidities. Baseline ophthalmological examination was conducted and included a detailed examination of the eye (slit-lamp, intraocular pressure, assessment of ocular surface), and an examination of best corrected visual acuity.

The Ocular Surface Disease Index (OSDI) questionnaire was used to measure ocular surface disease.[15] Tear film stability was assessed by measuring tear break-up time (TBUT), and tear production was assessed by the Schirmer I test as applicable. Fluorescein staining was used to assess the damage to the corneal and conjunctival epithelium, and it was classified using a standardized ocular surface staining scale. The conjunctival hyperemia was clinically evaluated using a set grading scale. These were taken at baseline and re-taken at 3- and 6-month follow-up visits. To ensure uniformity of measurement, intraocular pressure was determined at each assessment with the Goldmann applanation tonometry method that was used initially throughout the study.[16]

Patients were also asked about any symptoms of the eyes related to treatment such as a burning sensation, stinging sensation, foreign-body sensation, dryness, itching, redness, and any discomfort in the eyes. Treatment adherence and any adverse effects were documented during follow-up. To minimize measurement bias, the same clinical assessment procedure was applied to each treatment group.

The data were entered, coded, and analyzed using IBM SPSS Statistics software. The distributions of continuous variables including age, intraocular pressure (IOP), OSDI score, tear break-up time (TBUT), Schirmer test (ST) and ocular surface staining (OSS) scores were evaluated using appropriate normality tests. Continuous variables were reported as mean ± standard deviation (SD) and non-normally distributed variables as median with interquartile range (IQR). Frequencies and percentages were used to present the data for categorical variables.

The independent-samples t-test was employed to determine whether there were differences in the baseline demographic and clinical characteristics between the preservative-free group and the preserved group for normally distributed continuous variables, and the Mann–Whitney U test was used for non-normally distributed continuous variables. The chi-square test and Fisher's exact test were used to compare categorical variables as appropriate. Within-group comparisons were made using paired t-tests between baseline and 3 and 6 months, with between-group comparisons done using independent-samples t-tests and Mann–Whitney U tests. The changes across multiple follow-up time points were assessed using repeated measures ANOVA. The major outcome was the magnitude of the difference between the two groups in the change in severity of ocular surface disease (OSDI score) from baseline to 6 months. Secondary outcomes were intraocular pressure (IOP) changes, TBUT, Schirmer test results, corneal and conjunctival staining, conjunctival hyperemia, ocular symptoms, treatment adherence, and medication-related adverse effects. The two-sided p-value < 0.05 was considered statistically significant.

RESULTS

There were 120 patients, with 60 assigned to preservative-free topical anti-glaucoma drugs and 60 to preserved topical anti-glaucoma drugs. At baseline, there were no statistically significant differences between the two groups in terms of age, sex, glaucoma type, glaucoma duration, number of medications, comorbidities, OSDI score, or IOP (Table 1).

There were no significant differences in the ocular surface parameters between the groups at baseline. Preservative-free group demonstrated a greater reduction in OSDI score and a significant increase in TBUT and Schirmer I test values over 6 months. In the preserved group, only a slight decrease in the OSDI score was noted, while the TBUT and Schirmer values did not change significantly. Both groups had significantly reduced IOP, and comparable IOP values at 6-months (Table 2 and Table 3).

Preservative-free therapy also showed significant improvements in staining of the ocular surfaces and hyperemia of the conjunctiva. The frequency of moderate-severe corneal staining, conjunctival staining, and hyperemia was significantly lower in the preservative-free group than in the preserved group at 6 months (Table 4).

Preservative-free drugs were significantly less likely to cause treatment-related symptoms. Treatment adherence and fewer medication-related adverse effects were reported in the preservative-free group, with burning/stinging, foreign-body sensation, dryness, and ocular discomfort noted as less common, as well as ocular discomfort (Table 5).

Overall, the preservative-free formulation provided significantly greater improvement in ocular surface health without compromising IOP reduction. Preservative-free therapy resulted in significantly more reduction in OSDI score and more improvement in TBUT and Schirmer test results than preservative-containing therapy, but similar IOP reductions. These results indicated improved tolerability of the ocular surface and compliance with preservative-free treatment for 6 months (Table 6).

Table 1. Baseline demographic and clinical characteristics of participants

Variable	Preservative-free (n=60)	Preserved (n=60)	p-value
Age (years), mean ± SD	56.8 ± 8.7	57.4 ± 9.1	0.711
Male, n (%)	34 (56.7)	32 (53.3)	0.718
Female, n (%)	26 (43.3)	28 (46.7)	
Primary open-angle glaucoma, n (%)	48 (80.0)	46 (76.7)	0.650
Ocular hypertension, n (%)	12 (20.0)	14 (23.3)	
Glaucoma duration (years), mean ± SD	4.2 ± 2.1	4.5 ± 2.3	0.465
Previous topical therapy, n (%)	38 (63.3)	40 (66.7)	0.699
Number of anti-glaucoma medications, median (IQR)	2 (1–2)	2 (1–3)	0.538
Diabetes mellitus, n (%)	18 (30.0)	20 (33.3)	0.695
Hypertension, n (%)	25 (41.7)	27 (45.0)	0.716
Baseline OSDI score, mean ± SD	28.6 ± 9.4	29.8 ± 10.1	0.506
Baseline IOP (mmHg), mean ± SD	22.1 ± 3.4	22.4 ± 3.6	0.641

Table 2. Comparison of ocular surface parameters and IOP at baseline, 3 months, and 6 months

Parameter	Time	Preservative-free	Preserved	Between-group p-value
OSDI score	Baseline	28.6 ± 9.4	29.8 ± 10.1	0.506
	3 months	19.7 ± 7.5	27.1 ± 9.0	<0.001
	6 months	15.8 ± 6.4	25.9 ± 8.7	<0.001
TBUT (seconds)	Baseline	7.4 ± 1.9	7.2 ± 2.0	0.582
	3 months	9.1 ± 2.1	7.0 ± 1.9	<0.001
	6 months	10.2 ± 2.3	6.8 ± 1.8	<0.001
Schirmer I (mm/5 min)	Baseline	11.2 ± 3.8	10.9 ± 3.6	0.651
	3 months	13.5 ± 4.1	10.7 ± 3.5	<0.001
	6 months	14.2 ± 4.3	10.4 ± 3.4	<0.001
IOP (mmHg)	Baseline	22.1 ± 3.4	22.4 ± 3.6	0.641
	3 months	17.2 ± 2.6	17.5 ± 2.8	0.541
	6 months	16.8 ± 2.4	17.1 ± 2.6	0.512

Table 3. Changes in ocular surface parameters from baseline to six months

Parameter	Preservative-free: baseline	Preservative-free: 6 months	p-value	Preserved: baseline	Preserved: 6 months	p-value
OSDI score	28.6 ± 9.4	15.8 ± 6.4	<0.001	29.8 ± 10.1	25.9 ± 8.7	0.012
TBUT (seconds)	7.4 ± 1.9	10.2 ± 2.3	<0.001	7.2 ± 2.0	6.8 ± 1.8	0.184
Schirmer I (mm/5 min)	11.2 ± 3.8	14.2 ± 4.3	<0.001	10.9 ± 3.6	10.4 ± 3.4	0.327
IOP (mmHg)	22.1 ± 3.4	16.8 ± 2.4	<0.001	22.4 ± 3.6	17.1 ± 2.6	<0.001

Table 4. Corneal/conjunctival staining and conjunctival hyperemia

Outcome	Baseline PF, n (%)	6-month PF, n (%)	Baseline preserved, n (%)	6-month preserved, n (%)	p-value at 6 months
Corneal staining					
None/mild	43 (71.7)	54 (90.0)	42 (70.0)	32 (53.3)	<0.001
Moderate/severe	17 (28.3)	6 (10.0)	18 (30.0)	28 (46.7)	
Conjunctival staining					
None/mild	45 (75.0)	55 (91.7)	44 (73.3)	34 (56.7)	<0.001
Moderate/severe	15 (25.0)	5 (8.3)	16 (26.7)	26 (43.3)	
Conjunctival hyperemia					
None/mild	47 (78.3)	56 (93.3)	46 (76.7)	35 (58.3)	<0.001
Moderate/severe	13 (21.7)	4 (6.7)	14 (23.3)	25 (41.7)	

Table 5. Treatment-related ocular symptoms and tolerability at six months

Variable	Preservative-free n (%)	Preserved n (%)	p-value
Burning/stinging	9 (15.0)	24 (40.0)	0.003
Foreign-body sensation	8 (13.3)	19 (31.7)	0.020
Dryness	12 (20.0)	25 (41.7)	0.011
Itching	6 (10.0)	14 (23.3)	0.050
Ocular redness	7 (11.7)	21 (35.0)	0.004
Ocular discomfort	10 (16.7)	23 (38.3)	0.010
Good treatment adherence	54 (90.0)	45 (75.0)	0.030
Medication-related adverse effects	10 (16.7)	24 (40.0)	0.006

Table 6. Overall change in primary and secondary outcomes at six months

Outcome	Preservative-free	Preserved	Mean/median difference	p-value
Change in OSDI score	−12.8 ± 7.2	−3.9 ± 6.8	−8.9	<0.001
Change in TBUT (seconds)	+2.8 ± 2.0	−0.4 ± 1.8	3.2	<0.001
Change in Schirmer I (mm)	+3.0 ± 3.2	−0.5 ± 2.8	3.5	<0.001
Change in IOP (mmHg)	−5.3 ± 2.8	−5.3 ± 3.0	0.0	0.972
Moderate/severe corneal staining at 6 months	6 (10.0%)	28 (46.7%)	—	<0.001
Moderate/severe hyperemia at 6 months	4 (6.7%)	25 (41.7%)	—	<0.001
Good adherence at 6 months	54 (90.0%)	45 (75.0%)	—	0.030

DISCUSSION

This 6-month prospective comparative study showed that PF topical anti-glaucoma therapy achieved significantly better ocular surface outcomes than preserved therapy in reducing intraocular pressure (IOP), and with similar efficacy. Both groups demonstrated a significant decrease in IOP from baseline; however, the PF group had a greater decrease in OSDI score, TBUT, Schirmer I test, corneal and conjunctival staining, conjunctival hyperemia, ocular symptoms, and treatment adherence compared to the non-PF group. These findings indicated that preservative-free formulation could enhance tolerability of the ocular surface while maintaining the main therapeutic goal of glaucoma therapy. The IOP reduction between the two groups was similar to the randomised trial by Kim et al. (2021), who demonstrated that PF and preserved latanoprost were similarly effective at reducing IOP despite better tolerability with PF therapy. Likewise, the results of a randomized phase III study of 144 patients showed comparable IOP reductions between PF and preserved latanoprost, without a significant difference in efficacy. Kim et al. also reported a 4.52 mmHg reduction in mean IOP with PF latanoprost and 4.59 mmHg with preserved latanoprost at 12 weeks.[17]

Additionally, our group saw a marked improvement in OSDI, as did Seong et al. (2021) who reported significant increases in corneal staining, OSDI, burning, and bulbar injection when shifting patients to PF latanoprost. Kim et al. (2021) did not observe significant differences between the groups at 12 weeks for OSDI, corneal/conjunctival staining or TBUT. The discrepancy may be due to the longer 6-month follow-up period, during which more cumulative effects of the preserved ocular surface may have become apparent.[18]. The positive outcomes on TBUT and Schirmer test using PF therapy were especially consistent with the meta-analysis and systematic review by Skov et al. (2022) which incorporated seven randomized trails with 1,125 patients. That analysis revealed that there were no clinically significant differences between preserved beta-blockers and PF beta-blockers in reducing IOP; TBUT and Schirmer test results significantly favored PF preparations (both $p<0.001$). In conclusion, our results further corroborate previous evidence, showing that in a longer treatment period of 6 months both subjective symptoms and objective tear-film parameters were improved simultaneously.[19]. These present results were also similar to the randomized study by Kim et al. (2023) with 60 patients that showed PF and preserved products had comparable intraocular pressure (IOP) lowering effects and similar outcomes for the ocular surface disease index (OSDI) and staining scores, while PF therapy showed significant gains in tear break-up time (TBUT) and reduced bulbar hyperemia at 12 weeks. The direction of improvement in tear-film stability and hyperemia in their study was similar to that found by us, although significant differences in OSDI were not found.[20]

Our results were corroborated by the study of Konstas et al. (2023), which investigated the effect of PF treatment when switched in patients with glaucoma therapy-related OSD over a 6-month follow-up period. Their PF group showed large Oxford score improvement with a mean score of 3.76 points above baseline ($p<0.001$), a large improvement in Oxford ocular staining, osmolarity (2.16 points above baseline, $p<0.001$), and punctum stenosis (4.9 points above baseline, $p<0.001$), and a large improvement in conjunctival hyperemia (7.5 points above baseline, $p<0.001$). They also found that

the mean IOP during the day was lower with PF therapy (14.7 mmHg compared to 15.9 mmHg p<0.001). These results are similar to our observation that the use of PF therapy was associated with better ocular surface health and sustained good IOP control.[21]. This decrease in corneal staining in our PF group was especially consistent with the large phase III study by Baudouin et al. published in 2025. In 386 randomized patients, PF latanoprost reduced IOP by 8.8 mmHg at peak and 8.6 mmHg at trough compared with 8.2 and 8.1 mmHg, respectively, with PF therapy demonstrating non-inferior IOP efficacy. However, the most important improvement was in corneal fluorescein staining, which improved significantly more with PF therapy (p<0.001). Their improvement in the OSD symptom score was not statistically significant (p=0.090), but the objective ocular surface findings were supportive of our results.[22]

Likewise, in a randomized phase III study of PF bimatoprost gel in almost 500 patients in 2024, mean IOP reductions of 9 mmHg were seen in both groups. Conjunctival hyperemia worsened; however, it was less common with PF therapy at 12 weeks (18.3% vs. 30.4%) and 6 weeks (20.1% vs. 29.3%). This confirms our observation of significantly reduced moderate to severe conjunctival hyperemia in PF users, and adds to the evidence that elimination of preservatives may benefit long-term tolerability.[10]. Furthermore, Bacharach et al. (2024) showed positive effects on the ocular surface with a PF latanoprost cationic emulsion in 105 glaucoma or OHT patients with OSD. Corneal fluorescein staining improved significantly more with PF latanoprost than a soft-preserved travoprost formulation (P<0.0461) at three months, with TBUT improving similarly in both groups. Although there were no significant differences in OSD symptoms, the objective corneal staining improved in the same direction as our larger improvement in corneal staining in the PF group.[23]

This reduced burning, stinging, dryness, redness, and overall ocular discomfort in our PF group was also confirmed in the 2025 randomized trial of preserved versus PF brimonidine/timolol. In a group of 59 randomized patients, corneal and conjunctival staining was significantly higher in the preserved group, and stinging and burning were significantly less with PF therapy (p=0.011). While they reported no significant change in their OSDI scores, their results supported a greater drug tolerance, and ocular surface findings were similar to our results.[14]. Finally, the benefit of better adherence seen in our PF group was clinically relevant as discomfort can have a negative impact on long-term glaucoma therapy. Kim et al. (2021) reported better adherence and less hyperemia when using PF latanoprost, and less stinging/burning and more rapid resolution of both symptoms with PF latanoprost in their study. Similarly, the 2025 brimonidine/timolol trial reported higher levels of patient satisfaction and convenience of PF therapy. The results lend support to the notion that tolerability of the ocular surface may contribute to better adherence to chronic glaucoma medications.[14]

In general, the results from the studies published between 2021 and 2026 align with our results: PFs tend to be as effective at controlling IOP as preserved formulations, but have better results for certain ocular surface parameters, such as tear-film stability, corneal staining, hyperemia, and treatment tolerability. However, some staining outcomes and OSDI did not show a consistent advantage with PF therapy, due to the differences in studies, the type of drugs used, the type of preservative used, the severity of the baseline OSD, the length of follow-up, and the method of assessing the outcome. In this respect, the advantage of our six-month study may hold significance because it enabled us to measure ocular surface changes beyond 12 weeks, a period in many randomized trials.

Limitations

There were some limitations to this study. The study is single-center and has a relatively small sample size, which may have restricted the generalizability of the results. The method of treatment allocation was not randomized, and selection bias and confounding were not ruled out. The follow-up period of 6 months was adequate to evaluate the short-term changes in the ocular surface but not long-term outcomes. There was also clinical assessment for adherence, which could have been subject to reporting bias. Individual anti-glaucoma agents and the number of agents used may also have affected the outcomes of the ocular surface.

CONCLUSION

Preservative-free topical anti-glaucoma treatment had similar IOP reduction, but significantly better ocular surface outcomes, than preserved anti-glaucoma treatment after 6 months. Preservative-free medications resulted in higher scores in the OSDI, tear-film stability, Schirmer test, ocular surface staining, conjunctival hyperemia, and patient-reported symptoms, as well as higher adherence. Preservative-free drug formulations may then be a more desirable choice for patients who need long-term topical treatment for glaucoma, especially those with a higher likelihood for ocular surface disease.

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