Effects of switching from BAC-containing latanoprost to BAC-free latanoprost in patients diagnosed with glaucoma: Effectiveness and dry eye parameters

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ABSTRACT

Purpose: To compare the effects of switching from Benzalkonium Chloride (BAC)-containing latanoprost to BAC-free Latanoprost on intraocular pressure (IOP) and tear break up time test (TBUT).

Materials and Methods: 43 glaucoma patients (43 right eyes) who were switched from BAC-containing latanoprost to BAC-free formulations between June 2022 and February 2025 were retrospectively analyzed. At the time of switching to a BAC-free formulation, IOP and TBUT were recorded and compared with the follow up assessments conducted and 1st, 6th and 12 months.

Results: After the treatment switch, a significant difference was observed in IOP between 1st and 6th months. However, no significant difference in IOP changes was observed between the treatment switch-first month and 6th and 12th month ($p>0.05$). Additionally, a statistically significant difference was noted in the measurements for TBUT (treatment switch-1st month, 1st month-6th month and 6th month-12th month) ($p<0.001$).

Conclusion: In this study, switching from BAC-containing to BAC-free latanoprost was associated with no clinically significant difference in IOP, suggesting similar effectiveness. Additionally, the transition to BAC-free latanoprost was linked to an improvement in TBUT, indicating a potential benefit for tear film stability. Although this study did not include other dry eye parameters or patient-reported outcomes, the observed TBUT improvement may contribute to better ocular comfort and treatment adherence. To our knowledge, this is the first study in Turkey to evaluate the clinical effects of BAC-free latanoprost on IOP control and tear film stability.

Key words: Benzalkonium Chloride, Glaucoma, Intraocular pressure, Topical latanoprost treatment

INTRODUCTION

Glaucoma is a chronic, progressive optic neuropathy characterized by damage to the optic nerve and the retinal nerve fibre layer, ultimately leading to retinal ganglion cell loss and potentially irreversible visual field loss.[1-2] Elevated intraocular pressure (IOP) is the main risk factor for disease progression and remains the only modifiable target for therapeutic intervention.[3-5] Topical medications aimed at lowering IOP are widely accepted as first-line therapy for most types of adult glaucoma.[6] Prostaglandin analogs (PGAs) are among the most effective and commonly prescribed medications for lowering IOP due to their efficacy and convenient once-daily dosing.[7-10] Latanoprost, an ester prodrug of prostaglandin F2 alpha, was the first PGA approved for clinical use and has become a cornerstone of glaucoma pharmacotherapy.[11-15] It is generally well tolerated but may cause ocular side effects such as conjunctival hyperemia, pigmentation of iris and periorbital tissue, eyelash changes, and, rarely, uveitis or cystoid macular edema.[16-20]

Preservatives are commonly added to multidose ophthalmic solutions to maintain sterility; however, they can cause

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ocular surface toxicity with long-term use, potentially leading to patient discomfort, reduced tear film stability, and poor adherence.[21-23] Benzalkonium chloride (BAC) is by far the most frequently used preservative in antiglaucomatous eye drops but has been shown to disrupt the corneal epithelium and tear film, contributing to dry eye symptoms and ocular surface inflammation.[24-26] As a result, preservative-free (PF) or BAC-free formulations have been developed to reduce these adverse effects while maintaining similar IOP-lowering efficacy.[27-30]

The aim of the present study is to evaluate the effects of switching from BAC-containing latanoprost to BAC-free latanoprost on IOP control and tear film stability, as measured by tear break-up time (TBUT), in a cohort of glaucoma patients.

MATERIALS AND METHODS

This was a longitudinal, retrospective cohort study conducted at a single centre. The University of Health Sciences Ankara Etlik City Hospital Ethics Committee approved the study undertaken at the Diskapi Yildirim Beyazit Training and Research Hospital, which was conducted in compliance with the Helsinki Declaration. The study population was recruited over a period of two and a half years, from June 2022 to February 2025, from the Diskapi Glaucoma Clinic Registry. The study was approved by the Ethics Committee (Ethics committee approval number: AEŞH-BADEK-2025-0202).

The present study included a total of 46 eyes of 46 patients — 22 with primary open-angle glaucoma (POAG), 14 with pseudoexfoliation glaucoma (PEXG), and 10 with narrow-angle glaucoma (NAG) — who were enrolled between June 2022 and February 2024 and switched from benzalkonium chloride (BAC)-containing latanoprost (Xalatan®, Pfizer Ophthalmics, New York, USA) to BAC-free latanoprost (Latafree®, VEM İlaç, Istanbul, Turkey) at a tertiary referral hospital; follow-up data for these patients were collected until February 2025. A complete ophthalmic examination was conducted for all patients at each visit, encompassing visual acuity, slit-lamp biomicroscopy, the TBUT, IOP measurement with Goldmann applanation tonometry (GAT), iridocorneal angle measurement with a Goldmann three-mirror lens, and fundoscopy with dilated pupil.

The inclusion criteria comprised a best-corrected visual acuity (BCVA) of 20/40 or better, spherical refraction of ≤ 5 diopters, and cylinder correction of ≤ 3 diopters. Patients diagnosed with glaucoma who had been administered BAC-free latanoprost for a minimum period of 12 months subsequent to topical treatment alteration were also included. Conversely, cases involving the utilisation of alternative topical ocular medications, excluding BAC-free latanoprost, during the follow-up period, as well as those with coexisting ocular surgical procedures, uveitis, trauma, or any corneal pathology, were excluded from the study. Additionally, patients with systemic diseases known to cause or exacerbate ocular surface disorders, such as Sjögren's syndrome, uncontrolled diabetes mellitus, rheumatoid arthritis, or other autoimmune conditions affecting tear production, were excluded to minimize confounding effects on tear film stability. Furthermore, patients who exhibited an allergic reaction to BAC-free latanoprost eye drops following a treatment switch were also excluded from the study. In order to circumvent the effects of diurnal variations in IOP and TBUT, all measurements were performed between 9am and 12pm using a GAT for IOP and TBUT for ocular surface health. IOP was measured using GAT after TBUT. The assessment, incorporating IOP and TBUT, was conducted at the baseline, as well as at one-month, six-month and 12-month intervals following the switch.

TBUT Application

TBUT has been used to assess tear film instability. Following a complete blink, the upper eyelid completes its journey, causing the tear film to gradually thin before breaking up, resulting in the formation of dry areas that are randomly distributed. After fluorescein instillation, the time interval between the final blink and the emergence of the initial dry area is defined as the break-up time. This index is used to express the stability of the tear film. The use of a cobalt blue filter has been shown to enhance the visibility of the break-up of tear film fluorescence. The cut-off value for TBUT was < 10 seconds.

Statistical analysis

The statistical software package SPSS v.18.0 for Windows (SPSS Inc., IBM Corp., Chicago, IL, USA) was used to analyse the data. The mean ± standard deviation (mean ± SD) and 95% confidence interval (95% CI) were utilised

to represent the collection of measurements. Statistically significant results were defined as those with a p-value less than 0.05. The IOP and TBUT measurements were taken concurrently for all glaucoma patients. The findings revealed a substantial correlation between these values for both right and left eyes. Consequently, the right eye measurements were utilised in the subsequent statistical analysis. The normal distribution of the variables was tested using the Shapiro-Wilk test. Repeated-measures analysis of variance (ANOVA) test was employed to evaluate changes in normally distributed IOP and TBUT values across the four time points. Levene's test for equality of variances and the post-hoc Bonferroni test were used. Furthermore, the Wilcoxon signed-rank test was applied for non-normally distributed paired comparisons to determine significant changes in IOP and TBUT over time. Finally, the sample size was calculated using G*Power software (version 3.1.9.4; University of Düsseldorf). The objective was to detect a significant interaction in normally distributed IOP values across the four designated time points (baseline, 1 month, 6 months and 12 months). The IOP data among the measurements was analysed, and the effect size (Cohen's f value) was determined to be 0.25. The power of the study was then calculated using this effect size, and the result was found to be 95.1% for the total sample size of 43 patients. The significance level employed for this calculation was set at 0.05.

RESULTS

In the present study, data from 46 eyes of 46 glaucoma patients were analyzed. Two patients (one with PEXG, one with NAG) were excluded due to an allergic reaction to BAC-free latanoprost, and an additional patient (one with NAG) was excluded because the patient underwent laser surgery during the follow-up period. Consequently, the final analysis included 43 eyes of 43 glaucoma patients. The mean age of the participants was 69.3 ± 10.4 years (range: 44–86 years). The mean duration of use of BAC-containing latanoprost before switching was 61.5 ± 14.9 months (range: 42–88 months). The mean central corneal thickness was 530.8 ± 30.2 µm (range: 477–587 µm).

The mean IOP and TBUT values at baseline (time of medication switch) and at the 1st, 6th, and 12th months after switching are presented in Table 1. The mean IOP slightly increased at the 1st month (16.44 ± 2.95 mmHg) compared to baseline (16.05 ± 3.12 mmHg), but this difference was not statistically significant ($p = 0.166$). Thereafter, IOP decreased to 15.58 ± 2.89 mmHg at the 6th month ($p = 0.001$) and to 15.40 ± 2.63 mmHg at the 12th month ($p > 0.05$). The reduction in IOP between the 1st and 6th months was statistically significant; however, the magnitude of this decrease (approximately 0.86 mmHg) is not considered clinically relevant. Furthermore, the lack of a statistically significant difference between the baseline IOP and the IOP at 6 months ($p = 0.176$) supports the conclusion that overall IOP control remained stable after switching to BAC-free latanoprost.

The mean TBUT improved progressively after the switch, increasing from 9.8 ± 1.1 seconds at baseline to 10.4 ± 0.8 seconds at the 1st month, 10.9 ± 0.7 seconds at the 6th month, and 11.4 ± 0.9 seconds at the 12th month ($p < 0.001$ for all comparisons).

Table 1. *Mean IOP and TBUT at baseline and 1, 6 and 12 months after switching from BAC-containing latanoprost to BAC-free latanoprost treatment.*

	Baseline (Mean ± SD)	Month 1 (Mean ± SD)	P value	Month 6 (Mean ± SD)	P value	Month 12 (Mean ± SD)	P value
IOP (mmHg)	16.05 ± 3.12	16.44 ± 2.95	0.166*	15.58 ± 2.89	**0.001***	15.4 ± 2.63	1.0*
TBUT (seconds)	9.8 ± 1.1	10.4 ± 0.8	**0.001****	10.9 ± 0.7	**0.001****	11.4 ± 0.9	**0.001****

IOP: Intraocular pressure; TBUT: Tear breakup time testing; BAC: Benzalkonium chloride; SD: Standard deviation
P* : Repeated measures ANOVA test for Baseline–1st month, 1st–6th month, and 6th–12th month comparisons.
P** : Wilcoxon signed ranks test for Baseline–1st month, 1st–6th month, and 6th–12th month comparisons.

DISCUSSION

Latanoprost is one of the primary treatment options for glaucoma. Nevertheless, noncompliance with medication due to adverse effects is a significant challenge for patients with glaucoma. BAC is the most commonly used preservative in antiglaucomatous drugs.[21] However, it has been demonstrated that this compound can exert toxic effects on the ocular surface, with the potential to impact patient adherence to treatment and result in irreversible visual consequences. To address this challenge, the development of BAC-free formulations has been a major focus in the last decade, with the aim of enhancing patient adherence to chronic medication regimens.

BAC is by far the most frequently used preservative in antiglaucomatous eye drops. It is a quaternary ammonium agent belonging to a family of bipolar compounds. These compounds are highly water-soluble and have surfactant properties.[21] The mechanism of action of these compounds primarily entails the utilisation of their detergent properties, which facilitate the dissolution and destruction of bacterial cell walls and membranes.[22] Nevertheless, cumulative evidence indicates that ocular surface damage caused by BAC can result in toxicity, characterised by the disruption of the corneal epithelial barrier, the loss of epithelial cell microvilli, corneal stromal toxicity, and meibomian gland loss and loss of conjunctival goblet cells.[22-24] As a surfactant, BAC also interacts with the tear film lipid layer and degrade tear film, which may result in decreased TBUT in clinical practice.[22] It has been shown that BAC is not only toxic to the ocular surface but also affects deeper structures. The accumulation of these substances within the trabecular meshwork (TM) has been demonstrated to induce trabecular dysfunction and degeneration through the augmentation of proinflammatory cytokines. This, in turn, has the potential to inflict further damage to the TM, which may consequently lead to an impairment in outflow, thereby contributing to an escalation in IOP.[25] Finally, it is important to note that BAC cannot be neutralised by mammalian cells. In addition to irritation, BAC can also act as a hapten to induce an allergic response.[26] Conversely, alternative preservatives are available, including polyquad (PQ). PQ is also a detergent that was initially developed for contact lens solutions.[27] Although PQ and BAC are both classified as detergent-type preservatives, in vitro studies showed that PQ has less ability to penetrate mammalian cells due to its much greater molecular weight compared with BAC. Consequently, it is less likely to induce cytotoxic effects and is considered to have superior tolerability.[28]

Tafluprost 0.0015% is the first PF topical PGA to be approved by the Food and Drug Administration for the treatment of open-angle glaucoma and ocular hypertension. Notably, it is free from BAC.[31] In a meta-analysis of two phase IIIb clinical trials involving a total of 339 patients, switching from BAC-preserved latanoprost to PF tafluprost maintained IOP at the same level while reducing ocular signs and symptoms.[32] On the other hand, a prospective study involving twenty-two patients with POAG demonstrated that switching from BAC-preserved latanoprost to PF-latanoprost resulted in a significant reduction in anterior chamber flare over a period of three months. This finding provides further evidence that the toxicity of BAC is not limited to the ocular surface, but also affects the anterior chamber, inducing low-grade inflammation.[33] In a further study comparing PF 0.0015% tafluprost to the both PF and BAC-preserved 0.005% latanoprost, PF-latanoprost was associated with the best patient responsiveness and tolerability. However, despite the absence of BAC, PF 0.0015% tafluprost did not demonstrate significantly superior tolerability in comparison to BAC-preserved 0.005% latanoprost. Furthermore, it was emphasised that factors such as the pH of the formulations and the presence of carbomer can also influence patient tolerability.[34] Finally, Ranno et al. conducted a comparative analysis of PF tafluprost with all other preservative-containing PGAs (bimatoprost, latanoprost, travoprost) that are commercially available. The results demonstrated that switching to PF tafluprost resulted in an overall IOP-lowering effect that was similar to others preservative containing PGAs. However, when each PGA was compared with PF tafluprost, bimatoprost was found to provide a statistically significant additional IOP lowering effect.[35]

A number of studies have been conducted in order to compare the effectiveness of BAC-containing latanoprost and PF-latanoprost. The majority of these studies have reported no significant differences in IOP between the two formulations. Baudin et al. conducted a phase 3 trial, the objective of which was to compare the IOP-reducing efficacy of BAC-containing latanoprost and PF-latanoprost. IOP was measured at baseline, week 4 and week 12, with tonome-

try performed twice daily. The study concluded that PF-latanoprost exhibited non-inferior IOP-lowering efficacy in comparison with preserved latanoprost.[36] Aptel et al. have compared the effectiveness of BAC-containing latanoprost and PF-latanoprost by assessing IOP four times a day on days 0, 42 and 84. The study's findings revealed that both treatments resulted in comparable IOP reductions, with the overall diurnal reduction being similar in both groups.[37] Furthermore, the initial prospective switch study was conducted by Hojlo et al., who evaluated the effects of transitioning from BAC-preserved latanoprost to PF-latanoprost in patients diagnosed with POAG. The study's findings, based on the evaluation of 140 patients at days 15, 45, and 90 following the switch, indicated that PF-latanoprost was as effective as BAC-preserved latanoprost with better ocular surface tolerability.[38] Moreover, an international, multicentre, randomised, investigator-masked, parallel-group clinical study was conducted in six countries (France, Belgium, Italy, Spain, Portugal and Tunisia) to compare the PF-latanoprost formulation with BAC-preserved latanoprost during a 3-month treatment period. The study demonstrated the non-inferiority of single-dose preservative-free latanoprost eye drops to multidose latanoprost in reducing IOP from the first assessment time (15 days after treatment initiation). Furthermore, the study established that hyperemia diminished over time in the BAC-free group, while it increased over time in the BAC-containing group.[39] Finally, Muñoz et al. conducted a switch study to assess both IOP reduction and patient satisfaction following a transition to PF-latanoprost. The study population included patients with varying treatment histories, with the majority having received glaucoma medications previously, some having been on PF treatments, and others being treatment naive. However, all patients were transitioned to PF-latanoprost. The study's findings revealed that the overwhelming majority of patients expressed satisfaction with the PF formulation. The findings of the study lend further support to the hypothesis that PF-latanoprost provides effective IOP reduction with improved tolerability, regardless of prior treatment history.[40]

The present study has several strengths. Firstly, it evaluated IOP over an extended follow-up period, enabling the observation of the sustained effects of switching to BAC-free latanoprost over a longer duration. Furthermore, the study demonstrated that both preservative-free and BAC-containing latanoprost formulations were equally efficacious in reducing IOP, with no clinically significant variation in treatment outcomes over a 12-month period. Secondly, in addition to comparing BAC-free and BAC-containing latanoprost in separate cohorts, evaluating treatment changes within the same patients provided valuable data by eliminating interpatient variability and minimizing confounding effects. Additionally, although preservative-free formulations are generally associated with improved tolerability, allergic or hypersensitivity reactions can still occur, as evidenced by the exclusion of two patients in our study due to allergic responses to BAC-free latanoprost. This finding is consistent with previous reports, which indicate that while rare, hypersensitivity to active compounds or excipients can impact treatment adherence and should be considered by clinicians when prescribing preservative-free options.[37,39-40]

This study has several limitations that should be considered. Firstly, its retrospective design inherently limits the control over data collection. Secondly, the study was conducted at a single centre, which may limit the applicability of the results to broader populations. Thirdly, as IOP fluctuates throughout the day, single time measurements may not fully capture treatment effects, which may have limited our ability to assess peak and trough variations. Furthermore, a key limitation is that the assessment of ocular surface health relied solely on TBUT measurements, without additional objective tests such as corneal staining, Schirmer test, or symptom-based questionnaires like OSDI. Future prospective studies should include a comprehensive dry eye evaluation to provide more robust conclusions.

In conclusion, the findings of this study demonstrate that switching from BAC-containing latanoprost to BAC-free latanoprost was associated with similar IOP control, suggesting comparable effectiveness within the limitations of the current study. Additionally, the transition to a BAC-free formulation was associated with a significant improvement in TBUT, suggesting reduced toxic effects on the tear film and enhanced tear film stability. Although not directly assessed in this study, this improvement in tear film stability could potentially contribute to better ocular comfort and treatment adherence, as reported in previous studies. To our knowledge, this is the first study in Turkey to evaluate the clinical effects of BAC-free latanoprost on IOP control and tear film stability.

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