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ORIGINAL RESEARCH

Ocular Surface Changes After Switching from Other Prostaglandins to Tafluprost and Preservative-Free Tafluprost in Glaucoma Patients

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Purpose: To study ocular surface disease (OSD) changes after switching from preserved prostaglandin analogues monotherapy to preserved tafluprost and preservative-free (PF) tafluprost in primary open-angle glaucoma patients.

Methods: Glaucoma patients treated with preserved prostaglandins (except tafluprost) monotherapy for at least 6 months, intraocular pressure (IOP) ≤22 mmHg, and diagnosed of OSD [≥1 criterion; tear break-up time (TBUT) ≤10 seconds, corneal fluorescein staining ≥grade 1] in both eyes were enrolled in a prospective, randomized, single-blinded study. All eligible patients were switched from preserved prostaglandin analogues monotherapy (latanoprost, bimatoprost, travoprost) to preserved tafluprost in one eye (group I) and PF-tafluprost in the other eye (group II) of the same patient by randomization. The symptoms of OSD were evaluated using the visual analogue scale, and lid inflammation, conjunctival hyperemia, TBUT, corneal fluorescein staining, and Schirmer I test were applied to assess the clinical signs. All parameters were evaluated before and then 6, 12, 24 weeks after switching the medications.

Results: Thirty patients (80% women; mean age: 61.2 ±11.5 years) were included. Baseline parameters were not different between the treatment groups. After switching therapies, TBUT was significantly increased in both groups ($p = 0.002$, $p = 0.004$, respectively); however, group II had better tear quality. Other symptoms and clinical signs of OSD were improved and IOP was controlled in both groups.

Conclusion: Treatment with PF-tafluprost improves TBUT better than preserved tafluprost, suggesting that PF-tafluprost should be especially beneficial for patients with pre-existing OSD. Less or no preservative anti-glaucoma eye drops can restore and enhance the ocular surface in glaucoma patients.

Keywords: glaucoma, ocular surface disease, preservative-free, tafluprost, tear break-up time

Introduction

Glaucoma, a chronic progressive optic neuropathy, is the second leading cause of blindness in Thailand and worldwide, which proportionately affecting women and Asians.[1–3] It is predicted that the number of glaucoma people worldwide will escalate to 79.6 million in the year 2020 mostly due to the rapidly aging population.[1] Glaucoma treatment can be provided by medications, laser, and drainage procedures or intracameral implants. Mostly, topical intraocular pressure (IOP) lowering therapy is the mainstay of the treatment in the initial stage of glaucoma.

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Most patients with glaucoma can be controlled by long-term use of topical medications and some patients may require life-long treatment. However, long-term treatment can adversely affect the ocular surface. Ocular surface disease (OSD) is a multifactorial disease, which is characterized by tear film instability, inflammation, and hyperosmolarity.[4,5] Many studies report a prevalence of OSD more than 50% in patients with glaucoma, which is considerably higher than in individuals who are not under topical anti-glaucoma therapy.[6–8] All the components of anti-glaucoma eye drops, including the active ingredients, the preservatives as well as the excipients, may be involved in the occurrence of ocular surface toxicity.[9–11] They have the potential for inducing at least some cellular toxicity and ocular surface changes.[12] A large multicenter epidemiology survey conducted in Europe revealed that OSD of patients using PF glaucoma medication was less severe than that of the preserved topical medication.[13] This study suggests that the active ingredients may also have a negative effect on the ocular surface. However, until recently, the published evidence that active ingredients cause OSD is scant. Currently, there is compelling evidence that preservatives significantly contribute to the development of OSD in glaucoma patients, in particular, after long-term treatment.[14–18]

Benzalkonium chloride (BAK), a preservative in almost of anti-glaucoma eye drops, has been shown to have various forms of ocular surface toxicity. Baudouin et al[14] reported that long-term use of BAK-containing eye drops might induce ocular surface changes that include tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial cell loss, and corneal surface impairment. Also, BAK has been reported to induce OSD which results in irritating symptoms such as itching, sting/burning, foreign-body sensation, redness, and tearing.[19] The symptoms of OSD usually affect the patient's quality of life and require additional supplementary treatment.[20] These ocular surface changes from BAK are both dose- and time-dependent resulting from its quantity and cumulative impact.[11,17,21] Using IOP-lowering eye drops with least preservative or preservative-free (PF) can be considered as a better choice for glaucoma patients, especially for those who need a long-term medication.[11,16,22–24]

Nowadays there are many kinds of IOP-lowering eye drops, and prostaglandin is deemed as the most effective one for reducing IOP for 25–35%. In addition, prostaglandins can be used once daily which encourages patient adherence. Therefore, prostaglandins are widely used for glaucoma treatment. Although prostaglandins are effective in reducing IOP, adverse effects are often found such as prostaglandin-associated periorbitopathy (PAP), eyelash growth, iritis, and OSD.[18,25,26] Tafluprost, a recent prostaglandin $F_{2\alpha}$ derivative, has demonstrated long-term intraocular pressure-lowering effects regardless of treatment patterns or diagnosis.[27] Tafluprost 0.0015% was formulated into two preparations; preserved and PF. Currently, preserved tafluprost is a prostaglandin eye drop, which contains the lowest concentration of BAK (0.001%) compared to other prostaglandin formulations containing preservatives. Tafluprost 0.0015% was the first topical prostaglandin approved by the Food and Drug Administration for treatment of open-angle glaucoma and ocular hypertension containing no preservative. Until recently, PF-tafluprost is the only available PF-prostaglandin monotherapy in Thailand, other prostaglandin analogues monotherapy is provided with preservatives.

Accordingly, the primary aim of the current study was to evaluate the ocular surface changes after switching from other preserved prostaglandin analogues monotherapy to preserved tafluprost and PF-tafluprost in glaucoma patients. The secondary objective was to compare the ocular surface changes between preserved tafluprost and PF-tafluprost in the same patient.

Methods

Study Design

This prospective, randomized, investigator-masked, single-blinded, open-label study was conducted at Siriraj Hospital, the largest national tertiary referral center in Thailand. The study was approved by the Committee for the Protection of Human Participants in Research, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand [Si 011/2017], and was registered at the Thai Clinical Trials Registry (www.clinicaltrials.in.th) (TCTR20170420001). Written informed consent was obtained from all participants before enrollment into the study. The study complied with the principles of the Declaration of Helsinki.

Study Population

Inclusion Criteria

Patients were diagnosed with primary open-angle glaucoma, age between 18 and 80 years, C:D <0.8, and visual acuity ≥20/200. They were treated with preserved prostaglandin analogues monotherapy (latanoprost or bimatoprost

or travoprost) for at least 6 months, intraocular pressure (IOP) ≤22 mmHg. Patients who were included had no history of allergy to medications used in this study. Patients diagnosed with ocular surface disease [≥1 criterion; tear break-up time (TBUT) ≤10 seconds, corneal fluorescein staining ≥ grade 1], never received other types of eye drops within 3 months before enrollment. If patients have used concomitant artificial tear eye drops, they were asked to discontinue their use at least 2 weeks before enrollment into the current study. All inclusion criteria had to be met for both eyes.

Exclusion Criteria

The exclusion criteria included secondary glaucoma from known causes, immunocompromised status, active or recent ocular infection, known allergies to any components of the study medications, pregnancy or lactation, contact lens usage, and patients who were not able to follow the study instructions. Patients who used cyclosporine, steroids, or topical ocular nonsteroidal anti-inflammatory drugs within 3 months of the study and patients with the previous history of corneal or conjunctival surgery within 6 months were also excluded.

Study Procedures

All study patients were asked initially for OSD symptoms in terms of itching, burning, redness and tearing by using the visual analogue scale. They were graded from 0 to 10, with 0 indicating no symptom, 1–4 = mild, 5–8 = moderate and 9–10 = severe symptom. Subjective OSD symptoms of all patients in every visit were graded by only one investigator for consistency.

The five objective clinical tests of OSD were performed in the following sequence: inspected lid margin inflammation first, and then followed by conjunctival hyperemia. Lid margin inflammation (0–3) was evaluated and scored as previous studies.[28,29] Conjunctival hyperemia (0–4) was graded as follows: 0 = no injection, 1= trace, 2 = mild, 3 = moderate, and 4 = severe injection.[30,31] TBUT was recorded by a stopwatch and averaged 3 times per each eye. Corneal fluorescein staining was analyzed using the scale from Oxford grading of corneal staining in the context of dry eye tests (0–5).[31–34] After about 30 minutes, Schirmer I test (without anesthesia) was lastly performed to avoid reflex tearing due to ocular irritation caused by the preceding dye staining test.[34] Then, the IOP measurement and complete eye examination were followed. All study procedures were performed in the morning (9–11 am).

After enrollment, the treatment for each patient was switched from other preserved prostaglandin analogue monotherapy to preserved tafluprost in one eye and PF-tafluprost in the other eye of the same patient by randomization into group A and B. Group A applied preserved tafluprost on the right eye and PF-tafluprost on the left eye; group B applied preserved tafluprost on the left eye and PF-tafluprost on the right eye (Figure 1). All eligible patients were scheduled to follow up at 6, 12, and 24 weeks after the enrollment. The study was open-label as there were two preparations of study medication; preserved tafluprost in the bottle and PF-tafluprost in a single usage unit. Only one investigator (KC), who knew which patients belonged to group A or group B, instructed the patients during every visit to use the correct eye drop in each eye. Symptoms and clinical signs were examined and monitored in a blind manner by two investigators independently. All OSD symptoms and clinical sign tests were recorded at every visit by co-researchers, who did not know which type of medications were used in each eye (investigator-masked, single-blinded study). Subjective symptoms and clinical sign tests were recorded at the baseline and then followed at week 6, 12, and 24 respectively after switching to preserved tafluprost and PF-tafluprost. When the study was completed, all study eyes were re-classified into two groups; group I (preserved tafluprost eyes) and group II (PF-tafluprost eyes). Then, both groups were statistically analyzed (Figure 1).

Demographic information such as gender, age, medical history, topical IOP-lowering eye drops (type and duration of glaucoma treatment), central corneal thickness, the severity of glaucoma (mean deviation in Humphrey visual field test) and other parameters were obtained from the patients and medical records.

Statistical Analyses

Data were presented as mean ± standard deviation (SD). Variable scores from OSD symptoms with numerical rating scale (0–10), lid inflammation (0–3), conjunctival hyperemia (0–4), and corneal fluorescein staining (0–5), Wilcoxon's signed-rank test was applied to test change from baseline and week 24 in preservative-containing tafluprost group (group I) and PF-tafluprost group (group II). TBUT, Schirmer test and IOP, paired *t*-test was performed to analyze the difference between the two groups from baseline and week 24.

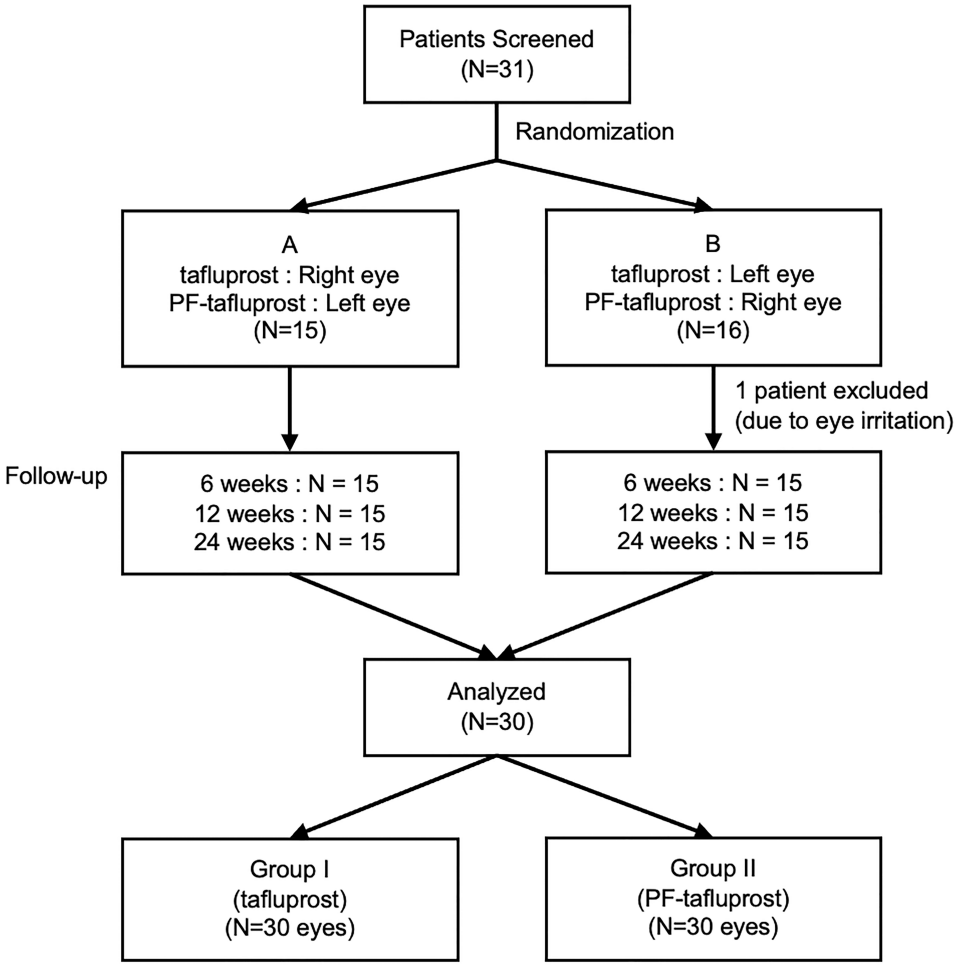

Figure 1 Study design of a randomized, single-blinded trial. The glaucoma patients were treated with preservative tafluprost in one eye and PF-tafluprost in the other eye of the same patient by randomization. Ocular surface symptoms and signs were evaluated at baseline and then followed at week 6, 12, and 24 respectively after the enrollment.
Abbreviation: PF, preservative-free.

Results

Thirty-one patients (62 eyes) were enrolled and completed all the tests at baseline visit. One patient in group B refused to follow the study protocol in week4 after enrollment due to eye irritation from study medications. Thirty patients (60 eyes) (80% women; mean age: 61.2 ±11.5 years; mean central corneal thickness: 526.3±31.7 μm) completed the study and were analyzed. Twenty-two patients were treated with latanoprost, two patients with bimatoprost and six patients with travoprost.

After completing follow-up visits in 6, 12 and 24 weeks, all randomized eyes, 30 eyes in group I (preserved tafluprost) and 30 eyes in group II (PF-tafluprost) were statistically analyzed. Baseline symptoms and clinical sign tests of OSD in both groups are shown in Table 1. Similar results were seen in both groups. The results composing between first visit (week 0) and week 24 are shown in Table 2. All subjective OSD symptoms improved in both groups. Statistically significant improvement was observed for both burning and redness symptoms. Other symptoms also improved, although the difference between week 0 and week 24 and between groups was not statistically significant. All clinical sign tests were improved in both groups, except for conjunctival hyperemia. There was no statistically significant change in IOP (Table 3 and Figure 2A). TBUT showed a statistically significant increase in both groups at week 24 (P=0.002, P=0.004, respectively) with better improvement in group II (PF-tafluprost) than in group I (preserved tafluprost) (Figure 2B). Schirmer test was minimally improved in group I with no statistically significant difference from baseline. However, there was no statistically significant difference in clinical sign tests between groups.

Table 1 Baseline Symptoms and Clinical Sign Tests of Ocular Surface Disease

Symptoms and Clinical Sign Tests (Range of Scores or Units)	Mean ± SD (Min,Max)	
	Group I (Tafluprost) (n=30)	Group II (PF-Tafluprost) (n=30)
Itching (0–10)	1.73 ± 2.10 (0,6)	1.67 ± 2.04 (0,6)
Burning (0–10)	2.43 ± 2.30 (0,8)	2.20 ± 2.40 (0,8)
Redness (0–10)	1.77 ± 2.41 (0,10)	1.60 ± 2.44 (0,10)
Tearing (0–10)	1.13 ± 1.78 (0,8)	1.47 ± 2.05 (0,8)
Lid inflammation (0–3)	2.17 ± 0.70 (0,3)	2.20 ± 0.67 (0,3)
Conjunctival hyperemia (0–4)	1.27 ± 0.52 (0,2)	1.27 ± 0.52 (0,2)
Corneal staining (0–5)	0.97 ± 0.96 (0,5)	0.93 ± 1.02 (0,4)
TBUT (seconds)	5.21 ± 2.46 (2.17,13.34)	5.38 ± 2.16 (2.49,11.97)
Schirmer test (mm)	5.45 ± 6.97 (0,23)	7.63 ± 8.29 (0,29)

Abbreviations: PF-tafluprost, preservative-free tafluprost; TBUT, tear break-up time.

Table 2 Results of Symptoms and Clinical Sign Tests of Ocular Surface Disease at Baseline and 24 Weeks After Switching

Symptoms and Clinical Sign Tests (Range of Scores or Units)	Duration of Therapy	Mean ± SD		
		Group I (Tafluprost) (n=30)	Group II (PF-Tafluprost) (n=30)	
Itching (0–10)	Week 0 Week 24 *P*-value	1.73±2.10 1.30±1.78 0.216	1.67±2.04 1.43±1.89 0.348	0.552
Burning (0–10)	Week 0 Week 24 *P*-value	2.43±2.30 1.07±1.55 **0.007***	2.20±2.40 1.27±1.64 0.059	0.097
Redness (0–10)	Week 0 Week 24 *P*-value	1.77±2.41 0.50±1.33 **0.011***	1.60±2.44 0.57±1.38 **0.049***	0.141
Tearing (0–10)	Week 0 Week 24 *P*-value	1.13±1.78 0.90±1.56 0.425	1.47±2.05 1.13±1.74 0.334	0.719
Lid inflammation (0–3)	Week 0 Week 24 *P*-value	2.17±0.70 2.07±0.64 0.439	2.20±0.67 2.10±0.66 0.439	1.000
Conjunctival hyperemia (0–4)	Week 0 Week 24 *P*-value	1.27±0.52 1.40±0.56 0.248	1.27±0.52 1.37±0.56 0.405	0.564
Corneal staining (0–5)	Week 0 Week 24 *P*-value	0.97±0.96 0.87±0.63 0.681	0.93±1.02 0.87±0.73 0.922	0.315
TBUT (seconds)	Week 0 Week 24 *P*-value	5.21 ± 2.46 7.45 ± 3.09 **0.002***	5.38 ± 2.16 8.10 ± 4.01 **0.004***	0.518
Schirmer test (mm)	Week 0 Week 24 *P*-value	5.45 ± 6.97 6.18 ± 6.98 0.60	7.63 ± 8.29 7.13 ± 7.75 0.71	0.370

Note: **P*-value < 0.05 indicates statistical significance which provides in bold.
Abbreviations: PF-tafluprost, preservative-free tafluprost; TBUT, tear break-up time.

Discussion

Current therapies aim to target OSD as it is a multifactorial disease impairing tear film and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, all of which are associated with potential damage to the ocular surface.[4,35] Symptoms of OSD include dryness, irritation, burning, foreign-body sensation, photophobia, fatigue, and fluctuation of visual acuity. Age, gender, and race are factors that can influence the prevalence of OSD.[36] Patients with glaucoma are considered to be at higher risk for developing OSD, as both of these conditions are common in elderly patients.[37]

A recent study has shown that glaucoma patients have a high prevalence of OSD, which is more prevalent in Asians than in Westerners.[8] In addition, the use of preserved anti-glaucoma eye drops has also been associated with the development of OSD.[7,8,18,38] Most topical anti-glaucoma medications contain benzalkonium chloride (BAK) as a preservative. The long-term usage of medications containing BAK might induce OSD or worsen pre-existing disorders.[11,18,38–40]

In Thailand, current prostaglandins monotherapy contain preservative as follows; latanoprost 0.005% (Pfizer, Inc., New York, NY, USA) (BAK0.02%), bimatoprost 0.03% (Allergan, Inc., Irvine, CA, USA) (BAK 0.005%), travoprost 0.004% (Alcon, Inc., Fort Worth, TX, USA) (polyquad 0.001%). Recent prostaglandin eye drops, which contain tafluprost 0.0015% (Santen, Osaka, Japan) have commercially available in two forms: preserved tafluprost (in bottle: BAK0.001%) and PF-tafluprost. Preserved tafluprost contains the lowest BAK concentration when compared to other preserved prostaglandins. Before enrollment, all participants in this study used preserved prostaglandins, and most of them used latanoprost (73.3%), the others used bimatoprost (6.7%) and travoprost (20%). Despite the fact that the concentration of preservative, which the patients received each day seem to be low, the treatments were repeated every day for more than 6 months. So, the effect of preservative and active ingredient could damage the ocular surface.

According to the primary objective of this study, the authors aimed to compare OSD changes after switching

Table 3 Mean Intraocular Pressure in Relation to the Duration of Therapy

Duration of Therapy	IOP mean ± SD		P-value
	Group I (Tafluprost)	Group II (PF-Tafluprost)	
Week 0	13.5 ± 2.73	13.4 ± 2.97	0.71
Week 6	14.00 ± 2.95	14.07 ± 3.21	0.82
Week 12	13.93 ± 2.90	14.00 ± 2.68	0.79
Week 24	14.5 ± 2.66	14.43 ± 2.50	0.79
P-value (Week 0–24)	0.52	0.12	0.92

Abbreviations: IOP, intraocular pressure; PF-tafluprost, preservative-free tafluprost.

from other preserved prostaglandin analogues monotherapy (latanoprost, bimatoprost, and travoprost) to preserved tafluprost and PF-tafluprost in glaucoma patients. The enrolled patients in this study were mild or moderate glaucoma who could be controlled intraocular pressure (IOP) by only preserved prostaglandin monotherapy. All enrolled eyes were previously exposed with one drop of preserved prostaglandin per day for more than 6 months. So, baseline symptoms and clinical signs of OSD were mild as shown in Table 1. Moreover, the authors randomized patients to use preserved tafluprost in one eye (group I) and PF-tafluprost in the other eye (group II) of the same patient. As our secondary objective was to compare the results of the study between two groups and the same patient usually had a similar baseline of ocular symptoms and signs between eyes.

A recent retrospective study has reported that tafluprost was safe and showed the effective IOP lowering, which was sustained up to 12 months post-treatment.[41] The previous studies also showed that preserved PF-tafluprost significantly decreased the symptoms and signs of OSD when compared to latanoprost.[11,22] The result of this current study was similar to these previous studies reported.[11,16,22] Even though the baseline OSD symptoms in this study were mild, all symptoms improved in both groups which statistically significant improvement in burning and redness symptoms. However, the difference in OSD symptoms between groups was not statistically significant. This may imply that relatively lesser preservative in group I and no preservative in group II could improve OSD symptoms in glaucoma patients.

All clinical sign tests in this study were improved in both groups, except for conjunctival hyperemia. Lid margin inflammation and corneal fluorescein staining both demonstrated improvement, even though there were no statistically significant differences. Studies demonstrated that inflammatory mechanisms may play a role in the propensity of dry eye, lid margin changes and corneal epithelial cells lost in patients receiving long-term topical anti-glaucoma medications.[38,42,43] In addition, the treated patients, especially those using preserved eye drops over a long time, consistently exhibited higher levels of inflammatory markers than age-matched controls.[44] However, the recent study suggests that adding a topical anti-inflammatory agent (such as cannabimimetic palmitoylethanolamide) may have a role to improve ocular surface inflammation attributable to chronic glaucoma treatment.[10] Also, the recent approval of cyclosporine 0.1% represents a novel medication for the management of dry eye, meibomian gland dysfunction and inflammatory OSD.[45] It is primarily beneficial for patients requiring immunomodulatory therapy and has the potential to improve the management of moderate to severe glaucoma therapy-related OSD.[45] Moreover, switching to lesser or no preservative eye drops may have a role in the improvement of lid inflammation and corneal fluorescein staining, which is in line with our study.

Meibomian gland dysfunction (MGD) is the main cause of evaporative dry eye. The core mechanisms of obstructive MGD are hyperkeratinization of the ductal epithelium and increase in meibum viscosity, which in turn are influenced by aging, hormonal changes, contact lens usage and topical anti-glaucoma medications. MGD is the major cause of lipid tear deficiency, which results in abnormal lipid tear layer and causes instability of tear film and reducing the TBUT.[28] The current study showed significant improvement in tear film stability in both groups. TBUT obviously increased when changing to preserved tafluprost, and changing to PF-tafluprost resulted in more improvement of tear quality (Figure 2B). These results were similar to previous studies reported.[11,16,22,26,46] This may suggest that preserved tafluprost and PF-tafluprost can potentially enhance the tear film quality in glaucoma patients. Furthermore, the recent study demonstrated that switching from preserved prostaglandins to PF-tafluprost leads to an increase in TBUT and tear film thickness, which are measured by ultrahigh-resolution optical coherence tomography.[16]

Schirmer test was also minimally improved, although no statistically significant, due to high variability. The change in light, humidity, and temperature may interfere with the tear reflex and result of this test.[47] A wide range of sensitivity and specificity values has been reported for the Schirmer

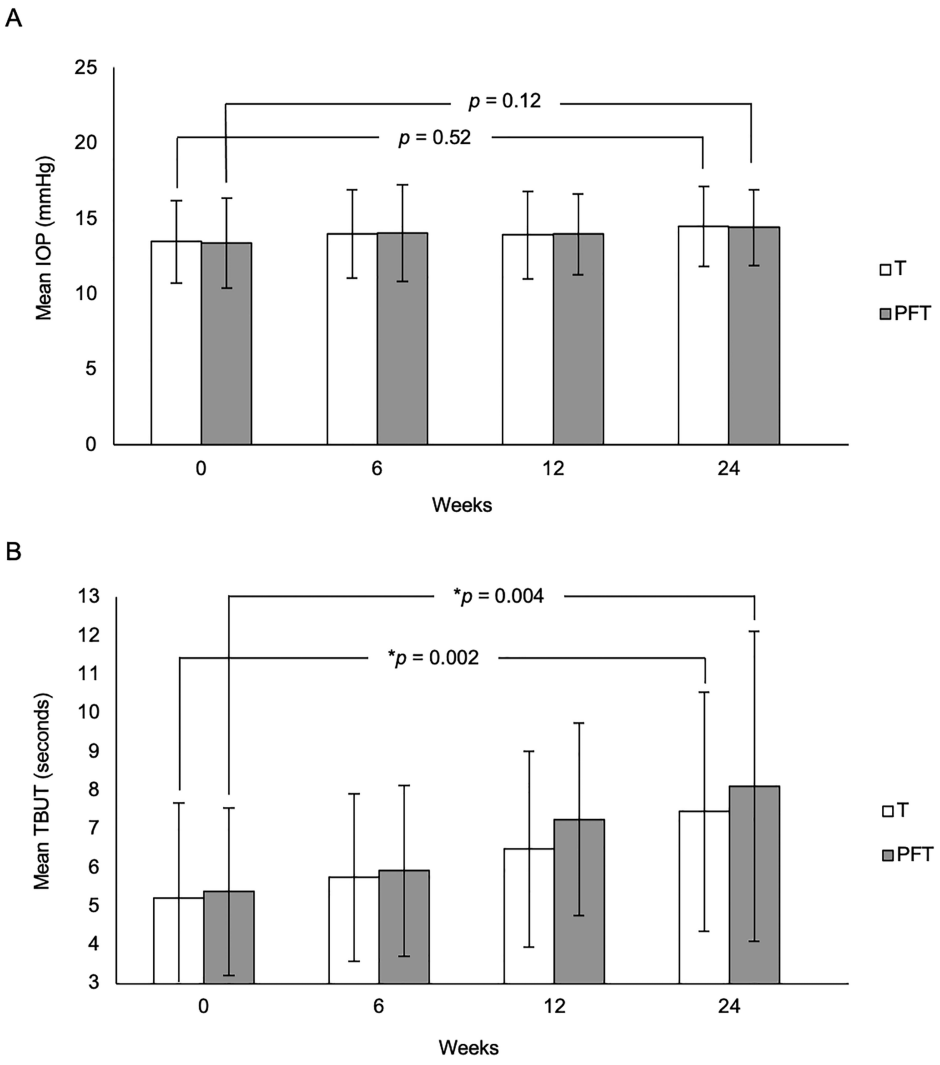

Figure 2 Intraocular pressure (IOP) (**A**) and tear break-up time (TBUT) (**B**) were demonstrated the outcomes of preservative tafluprost and preservative-free tafluprost treatments in relation to the duration of therapy.
Note: *$P < 0.05$.
Abbreviations: PFT, preservative-free tafluprost; T, tafluprost.

test.[48] The Schirmer I test can be reasonably considered for severe dry eye, but it lacks sufficient sensitivities and is too variable to be used for grading of milder dry eye.[48]

However, OSD/conjunctival hyperemia is empirically known to develop frequently during prostaglandin analogue use and often affect the adherence and/or persistence of topical instillation.[49,50] Previous studies in laboratory animal models have suggested that prostaglandin can trigger endothelial-derived factors released by perivascular sensory nerves, which may relax the veins and cause conjunctival hyperemia.[51] Moreover, prostaglandin E receptor stimulation has been reported to have a direct relaxant effect on vascular smooth muscle and cause hyperemia of ocular surface.[52] Conjunctival hyperemia did not show improvement in both groups of the current study. This is probably due to the effect of the active ingredient of the prostaglandin analogue. In addition, conjunctival hyperemia is an OSD sign that mostly manifests in glaucoma treating patients, especially with prostaglandin eye drops.[18,49] A recently published meta-analysis has shown that all prostaglandin analogues demonstrated a high incidence of conjunctival hyperemia.[53] Surprisingly, the data in this current study showed improvement of redness symptom, but the clinical sign of conjunctival hyperemia still unchanged. This may explain that the patients felt more comfortable after changing to preserved tafluprost and PF-tafluprost. So, the subjective symptom of redness showed improvement in both groups even though the clinical sign of conjunctival hyperemia remained unchanged. In addition, redness

symptom is subjective information, but conjunctival hyperemia is the clinical sign which is objective and more reliable.

According to IOP-lowering efficacy, there was no statistically significant change of IOP in this study. This result is similar to previous reported studies.[16,22,46,54] However, our data were shown that mean IOP increased by 1 mmHg (from around 13.5 to 14.5 mmHg) after switching medications (Table 3). This may be explained by latanoprost has trough IOP in the daytime which was demonstrated in the previous studies of efficacy over 24 hours.[55,56] Most of the patients enrolled in the current study were on latanoprost at baseline, and IOP was performed only in the morning (10 am) with no 24-hour IOP measurement. Konstas et al[55] demonstrated that trough IOP of latanoprost was in the daytime, while that of tafluprost was at night. Latanoprost demonstrated significantly better 24-hour trough IOP whereas tafluprost provided significantly lower 24-hour IOP fluctuation.[55] They concluded that PF-tafluprost achieved similar 24-hour IOP reduction to latanoprost (mean 24-hour IOP difference was only 0.1 mmHg). A Systematic review and meta-analysis to compare the effectiveness of first-line medications for primary open-angle glaucoma, was concluded that bimatoprost, latanoprost, and travoprost are among the most efficacious drugs, although the within-class differences were small and may not be clinically meaningful.[57] The previous study from a pharmacodynamic analysis demonstrated that the reduction in IOP achieved by PF-tafluprost is equivalent to that obtained with the preserved formulation.[58] In addition, the recent studies indicated that PF-tafluprost is not inferior in its IOP-lowering potency.[16,46]

The previous study from Uusitalo et al showed that PF-tafluprost significantly decreased the symptoms and signs of OSD when compared to latanoprost.[22] This meta-analysis confirmed that PF-tafluprost eye drops offered clinical benefits to glaucoma patients that outweighed those of the BAK-preserved latanoprost eye drops, which PF-tafluprost significantly decreased the symptoms and signs of ocular surface disease. Moreover, the recent study by Hommer et al indicated that switching to PF-tafluprost is beneficial for ocular surface health in patients under long-term preserved prostaglandin eye drops.[16] They showed that changing to PF-tafluprost leads to improve tear film quality and an increase in tear film thickness. This current study is in line with these previous studies.[11,16,22,46] In addition, our secondary objective was to compare the ocular surface changes between preserved tafluprost and PF-tafluprost, in which the results showed no statistically significant difference. As preserved tafluprost has a lower concentration of BAK (0.001%), so this may be less effective to the ocular surface, resulting in no difference between groups. This may imply that lesser or no preservative tafluprost eye drops can restore and enhance the ocular surface in glaucoma patients under long term preserved prostaglandin formulations.

Some limitations of this study need to be taken into account. First, the sample size of the study was limited to 30 patients, which was too low to detect changes in clinical variables of OSD as well as in symptom scores. Second, the follow-up period should be longer than 24 weeks to represent the results of long-term treatment. Thirdly, this study did not have comparative age-matched controls. Finally, this study was an open-label. However, the authors conducted all procedures by investigator-masked, single-blinded to decrease observer bias. Therefore, further study to include more participants with long-term follow-up and age-matched control group should be warranted. In addition, in terms of active ingredient, the results of OSD from head-to-head of various PF-prostaglandin eye drops compared to age-matched controls should also be investigated to complete the assessment of OSD from topical prostaglandin therapies.

Conclusion

Both tafluprost and PF-tafluprost groups have shown significant improvement in tear film quality as a result of a significant increase of TBUT. Our data suggest that preserved tafluprost and PF-tafluprost can enhance the tear film quality in glaucoma patients. PF-tafluprost has demonstrated relatively further improved tear film quality versus preserved tafluprost; therefore, PF-tafluprost should be especially beneficial for patients with pre-existing OSD. Topical anti-glaucoma formulations with relatively lesser or no preservatives can restore ocular surface in glaucoma patients.

Abbreviations

BAK, benzalkonium chloride; IOP, intraocular pressure; OSD, ocular surface disease; PF, preservative-free; PAP, prostaglandin-associated periorbitopathy; TBUT, tear break-up time.

Data Sharing Statement

All de-identified clinical data are available and can be supplied upon reasonable request.

- The authors intend to share de-identified participant data.
- The authors intend to share all de-identified clinical data in the study.
- All de-identified study documents will be made available from the corresponding author on reasonable request.
- The de-identified clinical data will be accessible by the permission of the corresponding author on reasonable request.
- The de-identified clinical data will be made available in contact with the corresponding author by e-mail with unlimited time.

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Disclosure

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