Ocular surface conditions in Asian glaucoma patients with existing corneal disorders switching from preserved prostaglandin analogue monotherapy to preservative-free tafluprost

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Abstract

Introduction: Glaucoma medications are often preserved with agents such as benzalkonium chloride, which commonly lead to ocular surface diseases. Purpose: To investigate the effect of switching to a preservative-free prostaglandin analogue, tafluprost 0.0015% on treatment tolerability and ocular surface diseases. Study design: This was a prospective, open-label, non-randomised, observational study performed in a single hospital. Materials and methods: This study involved patients of Asian descent diagnosed with primary open-angle glaucoma and ocular hypertension (n = 28), who received preserved prostaglandin monotherapy for longer than 3 months and had a National Eye Institute ocular surface staining scale score higher than 1. Patients were switched from preserved prostaglandin monotherapy to preservative-free tafluprost 0.0015%. Patients were analysed at baseline (Visit 0), 1 month (Visit 1), and 3 months (Visit 2). The main parameter measured is the change in the fluorescein staining score at Visit 2. Results: There was a significant improvement in the fluorescein staining score,

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with a mean reduction score of 1.96 (standard deviation, SD = 1.53; \( p < 0.0001 \)), and significant reductions in conjunctival hyperaemia (bulbar, \( p < 0.0001 \); palpebral, \( p < 0.05 \)) from baseline to Visit 2. The Ocular Surface Disease Index questionnaire also showed a mean reduction of 4.14 from baseline to visit 2 (SD = 8.20; \( p < 0.05 \)). The intraocular pressure and tear breakup time were maintained from baseline to Visit 2.

**Conclusion:** Switching patients to preservative-free tafluprost 0.0015% showed significant improvements in ocular surface disease with minimal side effects and similar intraocular pressure reduction rates.

**Keywords:** glaucoma, ocular surface diseases, preservative-free, prostaglandin analogues, tafluprost

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**Abstrak**

**Pengenalan:** Ubat titis untuk penyakit glaukoma biasanya mengandungi bahan pengawet seperti benzalkonium klorida, yang kerap kali menyebabkan penyakit permukaan okular.

**Tujuan:** Untuk menyiasat toleransi terhadap rawatan dan kewujudan penyakit permukaan okular berikutan peralihan rawatan kepada prostaglandin analog tanpa bahan pengawet: tafluprost 0.0015%.

**Reka bentuk kajian:** Kajian pemerhatian prospektif tanpa rawak secara label terbuka yang dijalankan di satu pusat kajian.

**Kaedah kajian:** Kajian ini melibatkan pesakit yang menghidap glaukoma sudut terbuka primer (primary open-angle glaucoma) dan hipertensi okular (n = 28), berketurunan Asia yang sedang menerima rawatan ubat titis glaukoma monoterapi: prostaglandin yang mengandungi bahan pengawet selama lebih daripada tiga bulan dan mencatatkan skor bagi skala pewarnaan permukaan mata National Eye Institute (NEI) yang melebihi dari 1. Rawatan kepada pesakit ini kemudian ditukarkan kepada ubat titis prostaglandin tanpa bahan pengawet: tafluprost 0.0015%. Analisa kajian terutama perubahan skor ke atas skala perwarnaan permukaan mata dicatatkan awal kajian (Lawatan 0), sebulan (Lawatan 1), dan tiga bulan (Lawatan 2) selepas rawatan. Dapatan utama kajian ini adalah perbezaan skor skala ini di antara lawatan 0 dan lawatan 2.

**Hasil kajian:** Terdapat perbezaan yang signifikan dalam skor pewarnaan permukaan mata dimana min skor pengurangan sebanyak 1.96 (sisihan piawai, SP =1.53; \( p < 0.0001 \)), dan penurunan yang signifikan hiperemia konjunktiva (bulbus, \( p < 0.0001 \); palpebra, \( p < 0.05 \)) di antara lawatan 0 dan 2.

Terdapat juga penurunan dari skor soal selidik indeks penyakit permukaan okular (Ocular Surface Disease Index questionnaire) dengan penurunan min sebanyak 4.14 di antara lawatan 0 dan lawatan 2 (SP = 8.20; \( p < 0.05 \)). Manakala
Introduction

Glaucoma is a progressive optic neuropathy disease which has been well documented as a significant reason behind irreversible blindness globally.\(^1\)\(^2\) Although glaucoma is a multifactorial disease, the only way to slow disease progression and preserve the visual field as proven in literature at the moment is by reducing the intraocular pressure (IOP).\(^3\) For patients with primary open-angle glaucoma (POAG) and ocular hypertension (OH), eye drops are typically used as initial therapy to reduce IOP levels.

At present, prostaglandin analogues (PGA) are the recommended first-line treatment, as there is evidence demonstrating their efficacy in lowering IOP and tolerable safety profile. The most commonly used PGAs are latanoprost, travoprost, bimatoprost, and tafluprost.\(^4\) However, despite their efficacy, these medications are usually preserved with agents such as benzalkonium chloride (BAK), a quaternary ammonium compound with a detergent effect that leads to lysis of bacterial walls and membranes.\(^5\) BAK was first used as a germicide in the 1910s, and then in the 1940s as a preservative in hard contact lens solutions within the ophthalmic industry. It is currently commonly used in most ophthalmic solutions, including artificial tears and glaucoma medications.\(^6\) Latanoprost 0.005% and bimatoprost 0.01% each contain 0.02% BAK, and travoprost 0.004% contains 0.01% polyquaternium-1 (a detergent class of preservative that acts on cell membranes) or a preservative system consisting of zinc, borate, propylene glycol, and sorbitol.\(^7\)

These ophthalmic drops are not a cure for glaucoma; therefore, POAG and OH patients need to consistently remain on prolonged treatment in order to achieve their target IOPs. However, several experimental and clinical studies have demonstrated the association between prolonged exposure to the preservatives (e.g., BAK) in these eye drops and changes in the ocular surface, e.g., tear film lipid layer interference, as well as many ocular surface diseases (OSD), e.g., hyperaemia, dry eyes, or punctate keratitis.\(^8\)\(^-\)\(^10\)

Preservative-free (PF) PGAs have been developed to improve long-term toler-
ability. One of them is PF taf luprost 0.0015%, which has been approved by both the US Food and Drug Administration and the European Medicines Agency. There have been a number of studies demonstrating the efficacy of PF taf luprost as an effective IOP-lowering agent.\textsuperscript{11} However, only a few studies have evaluated the effect of switching from preserved topical glaucoma medications to PF taf luprost on the ocular surface.\textsuperscript{11-16} These studies were comprised of Western patients switching from preserved drops to PF taf luprost and showed a reduction in OSD while maintaining the IOP.

The purpose of this study was to investigate the effect of switching from commonly used preserved PGAs to PF taf luprost on OSD in an Asian population. To evaluate this effect, changes in the fluorescein staining score using the National Eye Institute/Industry (NEI) scale were measured at baseline and subsequently at 4 weeks and 12 weeks after switching to PF taf luprost. Other OSD symptoms were also observed at each visit, along with the IOP-lowering effects.

**Materials and methods**

This study is registered in the ClinicalTrials.gov Registry under identifier number NCT04654611. This was a prospective, single-centre, open-label, nonrandomised, observational study carried out at the Tun Hussein Onn National Eye Hospital, Petaling Jaya, Malaysia between January 2019 and December 2019. The sample size was calculated using the G*power software, based on the intended paired t-test analysis in answering the primary study objective. Based on 80% power with a 0.05 two-sided significance level, a minimum of 24 participants were needed, with the assumption of effect size of 0.6.

Twenty-eight POAG or OH patients with OSD caused by preserved PGA therapy were recruited for the study. Recruited patients were required to have a score above 1 on the NEI scale and to have been on PGA monotherapy for more than 3 months. All patients provided their written consent following detailed explanation of the study methodology. This study complied with the principles of the Declaration of Helsinki and the local ethics committee.

First, a thorough anamnesis was established including age, gender, duration of glaucoma diagnosis, type of glaucoma, history of ocular and non-ocular concomitant diseases, and history of ocular surgeries, followed by a detailed ocular examination. Patient compliance was documented at each visit, where patients were asked if they complied every day, most days, some days, or rarely to the study medication.

The primary endpoint was to observe changes in the NEI fluorescein staining score at Visit 2 (week 12). The secondary endpoints included changes in the tear breakup time (TBUT), Ocular Surface Disease Index (OSDI) patient questionnaire, hyperaemia score, IOP, and adverse drug reactions.
To be considered for inclusion, patients were required to be 21 years or older, able to provide informed consent, have OSD due to PGA usage (at least one eye with a score above 1 on the NEI scale), have an IOP of ≤ 21 mmHg in the study eye at the screening examination (under treatment; the eye with a higher NEI score was selected for evaluation), and have received pretreatment monotherapy with any of the following preserved ophthalmic solutions: latanoprost, bimatoprost, tafluprost (these three preserved with BAK), or travoprost (preserved with polyquarternium-1) for a period longer than 3 months. Additional eligibility criteria were best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score of +0.6 logMAR (Snellen equivalent of 6/24) in each eye. Those with severe visual field disorder (mean deviation of 15 dB or worse), history of ocular surgeries within 6 months prior to study initiation, severe dry eye, ocular allergy, ocular infection or ocular inflammation, or history of drug allergy were excluded from the study. In addition, patients on systemic or ophthalmic steroids, female patients who were pregnant, nursing, or lactating, contact lens users during the study period, patients with corneal abnormalities or other conditions which could impede accurate applanation tonometry measurements, as well as those with uncontrolled systemic disease such as hypertension or diabetes, were also excluded from the study.

Figure 1 outlines the study design. At baseline (Visit 0), eligible patients who were already on preserved PGAs such as latanoprost 0.005%, bimatoprost 0.01%, tafluprost 0.0015% (these three preserved with BAK), travoprost 0.004% or travoprost 0.003% (these two preserved with polyquarternium-1), for a period longer than 3 months were switched to PF tafluprost 0.0015%. Patients were reviewed again at 4 weeks (Visit 1) and at 12 weeks (Visit 2). During the treatment period, patients were advised to instil PF tafluprost 0.0015% either unilaterally or bilaterally, one drop, once daily, as indicated. The drops were applied at the same hour of the day during the treatment period.
At each follow-up visit (Visit 1 and Visit 2), patients underwent IOP measurement, OSD evaluation (National Eye Institute/Industry [NEI/I] method, TBUT, hyperaemia score), and completed the OSDI questionnaire. Patient compliance and adverse drug reactions were also documented at each visit.

**OSD evaluation**

**NEI/I method**
At every visit, fluorescein dye was instilled in the conjunctival sac of the eye and the fluorescein-stained area of the cornea was measured. The staining degree in each of the five areas of the cornea (central, superior, inferior, temporal and nasal) were scored as follows: none = 0; sparse = 1; dense = 2; coalesced = 3.

**TBUT**
After instilling fluorescein stain, the time (in seconds) until the tear film breaks and the corneal surface is exposed was measured using a slit-lamp microscope. The measurement was conducted three times for one eye and the average of the three scores was recorded as the result.

**IOP measurement**
IOP was measured with Goldmann applanation tonometer at each visit, twice for each measurement. If the two readings differed by ≤ 2 mmHg, the average was recorded as the IOP measurement. If the two readings differed by > 2 mmHg, then a third reading was performed and the median reading was documented.

*Table 1. The Japanese Guideline for Allergic Conjunctival Diseases clinical evaluation criteria for bulbar and palpebral conjunctiva*

| Bulbar conjunctiva | | |
|--------------------|-------------------------|
| i                  | None                    | No manifestations |
| ii                 | Mild                    | Several vessels dilated |
| iii                | Moderate                | Many vessels dilated |
| iv                 | Severe                  | All vessels dilated |

| Palpebral conjunctiva | | |
|-----------------------|-------------------------|
| i                     | None                    | No manifestations |
| ii                    | Mild                    | Several vessels dilated |
| iii                   | Moderate                | Many vessels dilated |
| iv                    | Severe                  | Individual blood vessels indistinguishable |

Adapted from Takamura et al.17
Hyperaemia score
Bulbar and palpebral conjunctiva was examined and scored using reference photographs and a four-step scale. This four-step scale is cited from the clinical evaluation criteria of the Japanese Guideline for Allergic Conjunctival Diseases (Table 1).17

OSDI questionnaire
The OSDI questionnaire was used to evaluate OSD symptoms. It is a 12-item questionnaire frequently used to evaluate OSD severity.18 OSD symptoms, limitations in function related to vision, and environmental factors were assessed and scored from 0 (none) to 4 (all the time). The OSDI score was then obtained as follows:

\[
\text{Total score} = \frac{\text{Sum of the score for all the questions answered} \times 100}{\text{Number of questions answered} \times 4}
\]

The total score ranges from 0 to 100. A score of 0–12 points indicated normal ocular surface, 13–22 points mild disease, 23–32 points moderate disease, and ≥ 33 points severe disease.19 The primary and secondary endpoints in this study were analysed both descriptively and inferentially using the parametric paired t-test. Wilcoxon signed rank test was applied when the assumptions for paired t-test were not fulfilled. \( P < 0.05 \) was considered statistically significant.

Results

Demographics and clinical characteristics
A total of 28 patients were enrolled, with 24 patients (85.7%) completing this study. The sociodemographic characteristics analysis revealed that the majority of the participants were male (\( n = 19; 67.9\% \)) and of Chinese descent (\( n = 24; 85.7\% \)). Age ranged from 45 to 84 years old, with an average age of 65.5 (standard deviation, SD = 9.55) years. Analysing the clinical characteristics of the participants, the study involved more of right-eye patients than left-eye patients (\( n = 17; 60.7\% \) versus \( n = 11; 39.3\% \)) (Table 2). Most participants were diagnosed as POAG (\( n = 26; 92.9\% \)) followed by OH (\( n = 2; 7.1\% \)), as shown in Figure 2.

Primary endpoint
Changes in NEI corneal fluorescein staining score at Visit 2
There was an overall mean reduction in the corneal fluorescein staining (CFS) scoring of 1.96 from baseline to Visit 2 (SD = 1.53) when compared to the entire cornea (Fig. 3). The maximum CFS scoring reduction from baseline to Visit 2 was 6, while the minimum CFS scoring reduction from baseline to Visit 2 was 0 (Fig. 3). No increased CFS scoring was noted at Visit 2 compared to baseline. The differences
Table 2. Baseline demographic and clinical characteristics ($n = 28$)

| Variables        | Frequency (%) |
|------------------|---------------|
| Gender           |               |
| Male             | 19 (67.9)     |
| Female           | 9 (32.1)      |
| Ethnicity        |               |
| Chinese          | 24 (85.7)     |
| Indian           | 3 (10.7)      |
| Malay            | 1 (3.6)       |
| Age (years)      |               |
| Mean             | 65.5 (SD = 9.55) |
| Minimum          | 45            |
| Maximum          | 84            |
| RE/LE            |               |
| RE               | 17 (60.7)     |
| LE               | 11 (39.3)     |

LE: left eye; RE: right eye; SD: standard deviation

Fig. 2. Distribution of patient diagnosis. OH: ocular hypertension; POAG: primary open-angle glaucoma.
in CFS scoring between these two points were found to be statistically significant ($p < 0.0001$) based on the Wilcoxon signed rank test.

**Secondary endpoints**

*Changes in TBUT at Visit 2*
There was an overall mean reduction of TBUT scoring by 0.22 from baseline to Visit 2 (SD = 2.41). The maximum TBUT scoring reduction from baseline to Visit 2 was 7. The maximum increase in TBUT scoring was 4 at Visit 2 compared to baseline. The differences in TBUT scoring between these two points were not found to be statistically significant ($p > 0.05$; 95% confidence interval, CI: -0.73–1.18) based on paired t-test.

*Changes in OSDI patient questionnaire at Visit 2*
The OSDI questionnaire was used to evaluate OSD symptoms. There was an overall mean reduction of OSDI scoring by 4.14 from baseline to Visit 2 (SD = 8.20). The maximum OSDI scoring reduction from baseline to Visit 2 was 31. The maximum increase in OSDI scoring was 2 at Visit 2 compared to baseline. The differences in OSDI scoring between these two points were found to be statistically significant ($p < 0.05$) based on the Wilcoxon signed rank test.
Fig. 4. (a) Mean bulbar and (b) mean palpebral hyperaemia scores at baseline (Visit 0) and after switching patients from preserved prostaglandin analogue monotherapy to preservative-free tafluprost (Visits 1 and 2). Standard deviations are indicated by error bars. * indicates $p < 0.0001$ vs Visit 0; ** indicates $p < 0.05$ vs Visit 0.
Changes in hyperaemia at Visit 2

Bulbar conjunctiva
There was an overall mean reduction of hyperaemia scoring by 1.04 from baseline to visit 2 (SD = 1.26) (Fig. 4a). The maximum hyperaemia scoring reduction from baseline to Visit 2 was 6, with minimum score reduction of 0 from baseline to visit 2. No increase in hyperaemia was noted at the end of Visit 2. The differences in hyperaemia scoring between these two points were found to be statistically significant ($p < 0.0001$) based on the Wilcoxon signed rank test.

Palpebral conjunctiva
There was an overall mean reduction of hyperaemia scoring by 0.81 from baseline to visit 2 (SD = 0.96) (Fig. 4b). The maximum hyperaemia scoring reduction from baseline to Visit 2 was 3. The maximum increase in hyperaemia scoring was 1 at Visit 2 compared to baseline. The differences in hyperaemia scoring between these two points were found to be statistically significant ($p < 0.05$) based on the Wilcoxon signed rank test.

Changes in IOP at Visit 2
There was an overall mean increase of IOP by 0.30 mmHg from baseline to Visit 2 (SD = 2.22). The maximum IOP reduction from baseline to Visit 2 was 5 mmHg. The maximum increase in IOP was 4 mmHg at Visit 2 compared to baseline. The differences in IOP between these two points were found to be not statistically significant ($p > 0.05$; 95% CI: -1.17-0.58) based on paired t-test. Switching drops did not cause harmful fluctuations or alter the patients’ IOP overall.

Adverse drug reactions
Three out of 28 patients (10.7%) recorded drug reactions in this study. The reactions were itchiness ($n = 3$), redness ($n = 1$), and burning sensation ($n = 1$). No systemic adverse reaction was recorded. All adverse reactions were mild and resolved after discontinuing the medication.

Discussion

IOP is typically the only variable that is treated or controlled in glaucoma patients. Due to the chronic and progressive nature of the condition, patients are usually on long-term topical drops that typically contain high levels of preservatives.

The purpose of this study was to investigate the effect of switching patients from commonly used preserved PGAs to PF tafluprost on OSD in an Asian population. Previous switch studies conducted on Asian eyes have been retrospective studies looking at varying glaucoma diagnoses, or prospective studies involving patients
switched from different classes of medications or from a specific eyedrop only.\textsuperscript{20,21} This study has the advantage of being a prospective study specifically evaluating POAG and OH patients switching from preserved PGA class to PF tafluprost in a multiethnic Asian population. Even though most glaucoma patients can tolerate preserved PGAs, a large number of patients do suffer from OSD caused by preservatives, specifically BAK. BAK contains a combination of alkylbenzyldimethylammonium chlorides, which are toxic to microorganisms as well as eukaryotic cells. This may contribute to ocular surface side effects such as conjunctival hyperaemia, tear film instability, dry eye, and burning sensation.\textsuperscript{22,23}

A significant reduction in the number of patients exhibiting subjective symptoms during PF tafluprost treatment was noted, evidenced by the OSDI questionnaire showing a mean reduction of 4.14 from baseline to Visit 2 (SD = 8.20; \( p < 0.05 \)). PF tafluprost maintained IOP with no significant change from baseline throughout the treatment period of 3 months. There were no significant changes noted for TBUT as well; this could have been attributed to the short study duration, as longer observations would be needed to see improvement in TBUT. There was a significant improvement in the NEI CFS score with a mean score reduction of 1.96 (SD = 1.53; \( p < 0.0001 \)) and significant reductions in conjunctival hyperaemia (bulbar, \( p < 0.0001 \); palpebral, \( p < 0.05 \)). Itchiness was the most common adverse effect documented. It was also found that 89.3\% of the patients were compliant to the treatment and rarely missed doses. We hypothesise that the high compliance rate could be directly related to the tolerability and reduced ocular side effects of the PF eye drop.

It should also be pointed out that this study had some limitations, as the sample size was small and the treatment period was only 12 weeks. A longer treatment period may be necessary to evaluate potential long-term benefits of the PF tafluprost preparation, such as visual field stability and enhanced ocular blood flow.\textsuperscript{24-26} The study was not blinded and this could have led to investigator bias in the results. However, the patient outcomes were reported in accordance to the protocol, which was adhered to by the investigator and his team.

In conclusion, PF tafluprost was better tolerated than commercially available preserved PGA formulations in patients recruited in this study. The high compliance rate of patients also provides an indication of improved adherence in those switching from preserved drops. PF tafluprost 0.0015\% showed significant improvements in OSD with minimal side effects and similar IOP reduction rates.

**Declarations**

**Ethics approval and consent to participate**
This study is registered in the ClinicalTrials.gov Registry under identifier number NCT04654611. All patients provided their written consent following detailed
explanation of the study methodology. This study complied with the principles of
the Declaration of Helsinki and the local ethics committee.

**Competing interests**
The authors declare no competing interests.

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