Tear clearance and ocular symptoms in patients treated with preservative-free prostaglandins


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Abstract

Objectives: To assess the effects of switching from a prostaglandin with a preservative to a preservative-free prostaglandin on dry eye symptoms and tear dynamics.

Material and methods: Fourteen patients (N = 28 eyes) with open-angle glaucoma and dry eye symptoms, treated with preserved latanoprost, travoprost or bimatoprost were included in this uncontrolled prospective study. Ocular symptoms were analyzed using a validated ocular surface disease questionnaire and ocular signs were assessed with tear clearance, Schirmer and tear function index test (TFI = Schirmer/clearance). Patients were assigned to preservative-free tafluprost treatment, and measurements were repeated 4 weeks after change of medication. Wilcoxon test and Spearman correlation coefficient were used in the statistical analysis.

Results: No statistically significant difference in intraocular pressure (IOP) was observed after switching to tafluprost. Mean IOP at baseline was 20.4 mmHg (SD 2.2) and after 4 weeks 19.9 mmHg (SD 2.6) (p > 0.05). The mean questionnaire score significantly decreased from 9.7 (SD 3.7) at baseline to 5.4 (SD 2.7) after one month (p < 0.001). No significant differences in tear clearance, Schirmer or TFI were found (p > 0.05). At baseline, it was found that tear clearance was 0.13 (SD 0.07), Schirmer = 10.7 mm (SD 6) and TFI = 80 (48–156), while after 4 weeks, it was found that tear clearance was 0.1 (SD 0.07), Schirmer = 9.5 mm (3.9) and TFI = 104 (48–216). A significant association between questionnaire score and tear clearance after 4 weeks was observed (Spearman coefficient = 0.62; p = 0.014).

Conclusions: Switching from preservative prostaglandin with a preservative to preservative-free tafluprost treatment improves dry eye symptoms and suggests an improvement in TFI.
Aclaramiento lagrimal y sintomatología ocular en pacientes tratados con prostaglandinas sin conservantes

RESUMEN

Objetivos: Evaluar el efecto en los síntomas de sequedad ocular y en la dinámica lagrimal que se produce al sustituir una prostaglandina con conservante por una prostaglandina sin conservante.

Material y métodos: Estudio prospectivo no controlado en el que se seleccionaron 28 ojos de 14 pacientes con síntomas de ojo seco en tratamiento con latanoprost, travoprost o bimatoprost con conservante. Se evaluaron los síntomas oculares con un cuestionario validado de enfermedad de la superficie ocular y los signos mediante el test de aclaramiento lagrimal, el Schirmer y el índice de función lagrimal (TFI, TFI = Schirmer/Aclaramiento). En todos los pacientes se cambió el tratamiento hipotensor a tafluprost sin conservante. Al mes, se repitieron los tests. En el análisis estadístico se utilizó el test de Wilcoxon y el coeficiente de correlación de Spearman.

Resultados: No encontramos diferencias en la presión intraocular (PIO) al cambiar a tafluprost. La PIO inicial era 20,4 mmHg (DE 2,2) y la PIO al mes era 19,96 mmHg (DE 2,6) (p > 0,05). La puntuación del cuestionario disminuyó de forma significativa desde 9,7 (DE 3,7) a 5,4 (DE 2,7) al mes del tratamiento (p < 0,001). No encontramos diferencias significativas en el aclaramiento, en el Schirmer, ni en el TFI (p > 0,05). Inicialmente, Aclaramiento = 0,13 (DE 0,07), Schirmer = 10,7 mm (DE 6) y TFI = 80 (48-156). Al mes, Aclaramiento = 0,1 (DE 0,07), Schirmer = 9,5 mm (DE 3,9) y TFI = 104 (48-216). Hemos encontrado una asociación significativa entre la puntuación del cuestionario y el aclaramiento al mes (coeficiente de correlación = 0,62; p = 0,014).

Conclusiones: La sustitución de una prostaglandina con conservante a tafluprost sin conservante mejora los síntomas de sequedad ocular y sugiere una mejora en el test de función lagrimal.

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Introduction

At present, prostaglandin analogues constitute the basis of medical treatment for glaucoma due to their efficiency and systemic safety profile. However, there is a growing evidence about the negative effects of anti-glaucoma medication on the ocular surface. These adverse negative effects include ocular dryness symptoms such as conjunctival hyperemia and foreign body feeling. These symptoms are related to the effects of antiglaucoma drugs and their preservatives on the stability of the lachrymal film which could reduce corneal toxicity. As mentioned medical treatment is long-term, and these symptoms could worsen with time and lead to noncompliance. Therefore, it is recommended to utilize preservative-free eyedrops, particularly in patients having pre-existing damages in the ocular surface and those experiencing adverse effects.

Tafluprost is a prostaglandin analogue with high selectivity for the FP-prostaglandin receptor which is marketed without preservatives.

The main objective of this paper is to assess whether the substitution of hypotensor treatment with prostaglandin with preservatives with prostaglandin without preservatives improves ocular dryness symptoms and lachrymal dynamics. The secondary objective is to analyze the relationship between dryness symptoms and lachrymal dynamics.

Subjects, materials and methods

A quasi-experimental noncontrolled prospective study was conducted, which selected 28 eyes of 14 patients with dry eye symptoms in treatment with latanoprost (Xalatan®, Pfizer, Madrid, Spain), travoprost (Travatan®, Alcon Cusi, El Masnou, Barcelona, Spain) or bimatoprost (Lumigan®, Allergan, Tres Cantos, Madrid, Spain), with benzalconium chloride (BAK) preservative.

A validated ocular surface disease symptom questionnaire was filled in by the patients who visited the practice during treatment with latanoprost, travoprost or bimatoprost and who referred ocular dryness symptoms. The patients having a score of 4 or higher were included in the study.

The above-mentioned questionnaire was designed for the diagnosis and follow-up of patients with symptoms of ocular surface disease. Higher scores indicate higher ocular dryness symptoms and comprises 18 items, i.e., ocular reddening, inflamed eyelid edges, palpebral edge scaling, eyelids stuck to each other when awakening, secretions, eye dryness, foreign body or sandy feeling, itching, discomfort in the eyes, acute pain, tearing, crying eyes, photophobia, temporary blurred vision, tired eyes and feeling of heaviness.

The patients included in the study were submitted to Schirmer’s test, lachrymal clearing and lachrymal function test (TFI; TFI = Schirmer/clearing).
Clearing was analyzed by means of Fluotest® eyedrops (Alcon, Barcelona, Spain) to which we added 0.5 ml fluorescein. One drop was instilled in the inferior conjunctival sac fundus of the patient, after which the patient was made to wait for 5 min, and then the Schirmer test was performed for an additional 5 min. The clearing value was read on the strip according to fluorescein dilution scale. Possible values that clearing can reach are: 1, 1/2, 1/4, 1/8, 1/16, 1/32, 1/64, 1/128 and 1/256. Clearing is better with lower quotient values. As clearing is the denominator of the TFI formula, there is a reverse relationship between both variables, i.e., higher TFI represents better clearing.

In all the patients the hypotensor treatment was combined with tafluprost (Saflutan®, Merck Sharp & Dohme, Madrid, Spain), one drop every 24 h. After one month, the questionnaire and the tests were repeated. Due to the small sample size, nonparametric tests were used for the statistical analysis. The Wilcoxon test and Spearman’s correlation coefficient were utilized. The study included both eyes of each patient because data analysis was paired, i.e., the comparison was made on the same sample before and after substitution of the drug. For the statistical analysis the SPSS Version 15.0 for Windows was utilized (SPSS Inc., Chicago, IL, USA). The study was approved by the Ethical Committee of the Reina Sofia hospital of Córdoba, Spain.

Results

The mean age of our patients was 71.1 years (SD 7.2). The sex distribution was as follows: 42.8% males and 57.2% females. Initially, 69.2% of patients were treated with latanoprost and 30.8% with travoprost.

Intraocular pressure (IOP) remained stable: baseline IOP = 20.4 mmHg (SD 2.2), IOP at month one = 19.96 mmHg (SD 2.6). This difference was not statistically significant (p = 0.26).

Tear function results (Schirmer, clearing and TFI) are shown in Table 1. Even though Schirmer test and clearing exhibited reductions and TFI increased, said difference was not significant (p > 0.05).

The initial score of the questionnaire was 9.7 (SD 3.7). At month 1 a significant improvement was observed in dry eye symptoms, with a final score = 5.4 (SD 2.7) (p < 0.001).

A significant and moderate correlation was found between the questionnaire score at month 1 with the initial clearing (Spearman coefficient = 0.59; p = 0.019) (Fig. 1) and between the score at month 1 with final clearing (Spearman = 0.62; p = 0.014) (Fig. 2). In addition, the existence of an association between symptom changes (final score – initial score) and clearing (final clearing – initial clearing) was also analyzed. In this analysis, a nonsignificant correlation was observed (r = 0.46; p = 0.1).

Furthermore, a significant association was found between IOP and clearing before the treatment was modified (r = 0.56; p = 0.002) and between baseline IOP and baseline TFI (r = −0.48; p = 0.01). Similarly, a significant correlation was observed between IOP and clearing after the treatments were modified (r = −0.4; p = 0.03) and between final IOP and TFI (r = 0.4; p = 0.03).

Discussion

In this study, a significant improvement of symptoms has been found when hypotensor treatment with preservatives by another without preservatives was substituted. Two recently published articles describe improvement of symptoms as well as signs when switching from latanoprost and travoprost to tafluprost. The most frequent reason for said substitution was conjunctival hyperemia, achieving a reduction in the percentage of patients with moderate/severe hyperemia from 43.2% to 1.9%.

In what concerns the lachrymal function parameters, neither Schirmer test or TFI exhibited significant changes in our sample. However, in the case of TFI the increased values were in the limits of statistical significance. Accordingly, it would be convenient to increase sample sizes in a subsequent study to confirm said significance. Terai studied in healthy subjects the effect of prostaglandins on lachrymal function and found a significant baseline lachrymal secretion reduction of 30% 90 min after the application of brimonidine and of 20% after the application of latanoprost. In addition, said authors described a reduction of 51% in the tear breakup time (BUT) after the administration of latanoprost.

Several articles have compared the efficacy of preservative-free tafluprost with other prostaglandins.
Hommer describes IOP reductions when switching patients who had previously been treated with latanoprost or travoprost to tafluprost. Said reduction is significant at 1 and 3 months, reaching 8.6% in IOP at week 12. In contrast with said study, we did not find significant differences in IOP, matching the results published by Usitalo et al. and Stirbu et al.

It could be considered whether clearing has any effect on IOP. In our study, the patients who exhibited the best IOP control were those with the best clearing. Perhaps a well-maintained ocular surface with lower inflammation could contribute to enhance the effectiveness of the treatment. Experimental studies in animals have shown that the expression of inflammatory markers such as CD45 and TNF is greater with latanoprost or BAK than with tafluprost. Another possible explanation could be better compliance by patients who have less symptoms and better clearing.

The relationship between clearing and ocular symptoms has already been demonstrated. However, a possible relationship between clearing and symptoms after substituting a preservative-carrying prostaglandin by a preservative-free prostaglandin should be analyzed in new studies, including other techniques such as lachrymal osmolarity determination and flow cytometry.

To conclude, the substitution of preservative-carrying prostaglandin by tafluprost without preservatives improves ocular dryness symptoms and suggests improvements in lachrymal function test. Therefore, it would be convenient to increase the sample size in subsequent studies.

Conflict of interests

No conflict of interests has been declared by the authors.

REFERENCES


Table 1 – Lachrymal dynamics parameters before and after changing treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before changing treatment</th>
<th>One month after changing treatment</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (range)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Schirmer (mm)</td>
<td>10.76</td>
<td>9 (7–12)</td>
<td>9.4 (3.8)</td>
</tr>
<tr>
<td>Clearing</td>
<td>0.13 (0.07)</td>
<td>0.12 (1/16–1/8)</td>
<td>0.1 (0.07)</td>
</tr>
<tr>
<td>TFI</td>
<td>133.5 (134.3)</td>
<td>80 (48–156)</td>
<td>151.3 (145.5)</td>
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SD: standard deviation; TFI: tear function index.