Preserved Prostaglandin Analog and Ocular Surface Disorders in Open-Angle Glaucoma

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Abstract

Purpose: Long-term use of topical ocular medications may affect ocular surface health. Purpose of this study was to evaluate the influence of BAK-preserved prostaglandin analog (bimatoprost 0.03%) treatment on the ocular surface health in patients with newly diagnosed POAG.

Methods: 40 newly diagnosed POAG patients were included in this prospective study. Intraocular pressure (IOP), tear break-up time (TBUT), and ocular surface disease index (OSDI) were assessed at baseline and 3-month after starting treatment with BAK-preserved bimatoprost 0.03% ophthalmic solution.

Results: IOP decreased in all patients from baseline to 3-month final visit (24.70 ± 1.65 mmHg versus 15.68 ± 1.68 mmHg). Mean TBUT decreased from 10.71 ± 1.85 seconds at baseline to 7.25 ± 1.21 seconds at 3-month final visit (p < 0.001). Mean OSDI score increased from 31.63 ± 18.48 to 44.41 ± 16.48 (p < 0.001).

Conclusions: BAK-preserved bimatoprost 0.03% is an effective medication in newly diagnosed POAG patients, but its long-term use may negatively influence ocular surface health by disrupting the tear film stability.

Key Words: BAK benzalkonium chloride – IOP intraocular pressure – TBUT tear break up time – OSDI ocular surface disease index – POAG Primary open angle glaucoma – IOP Intraocular pressure.

Introduction

OPTIC nerve damage in glaucoma is associated with elevated intraocular pressure (IOP) [1,2]. Medical and surgical treatments that decrease IOP thus may prevent or slow the progression of visual impairment and blindness [3].

These patients require lifelong treatment and follow-up care to preserve vision, so long-term patient compliance and medication persistence are essential; otherwise they risk developing elevated IOP levels and additional progressing visual impairment to blindness. Among topical ophthalmic medications, prostaglandin analogs (PGA) show several advantages over other medical treatments and are nowadays the initial medications of choice [4]. However, some prostaglandin-treated patients experience conjunctival hyperemia or ocular discomfort including burning, stinging, pain, dry eye, or foreign body sensation and these conditions are of concern because these side effects may have a negative effect on whether the patient takes the medication as directed (compliance) and/or continues to use the medication over time (persistence) [5].

Many prostaglandin analogs contain preservatives which have been associated with an increase in the prevalence of ocular signs and symptoms [6]. The most commonly used preservative is benzalkonium chloride (BAK) [7]. BAK is a quaternary ammonium compound whose antimicrobial activity arises from its ability to disrupt cell membranes and potentiate cell death. Along with its antimicrobial activity, BAK has a high affinity for membrane proteins and may accumulate in ocular tissues, inducing cell toxicity and/or cell death in a dose- and time-dependent manner. BAK-induced changes in corneal and conjunctival cell membranes may manifest as symptomatic ocular surface disease (OSD) in medically treated glaucoma patients.

OSD presents a group of disorders that affect various components of the ocular surface. The common consequence of ocular surface disease is dysfunction of the ocular tear film and/or the integrity of the ocular surface. These changes may result in a wide range of ophthalmic symptoms and signs including discomfort, burning, fatigue, fluctuating visual acuity, ulceration, and scarring of the ocular surface. Although OSD is seen in nearly 15% of general population [8,9], it has been
reported to occur in 48% to 59% of patients with medically treated glaucoma [10]. A higher incidence and severity of OSD has been reported in patients who received multiple BAK-preserved medications concomitantly than in patients who were treated with only one BAK-preserved medication.

The purpose of this study was to evaluate the influence of BAK-preserved prostaglandin analog treatment on the ocular surface health in patients with newly diagnosed POAG. To quantify the changes in the IOP level, tear break-up time (TBUT), and ocular surface disease index (OSDI) after starting treatment with BAK-preserved bimatoprost 0.03%.

Material and Methods

40 newly diagnosed primary open-angle glaucoma (POAG) patients were included in the study. POAG was defined as characteristic GON and visual field loss, with IOP >21mmHg on two separate occasions and a widely open angle. Typical GON was defined as a vertical cup-to-disc ratio (C/D) greater than 0.5, asymmetry of the C/D >0.2 between eyes, presence of localized RNFL defects, optic disc haemorrhages, and/or neuroretinal rim defects in the absence of any other abnormalities that could explain such findings. Assessment of GON was based on stereoscopic indirect slit lamp fundus examination and color fundus photographs of both eyes taken with a suitable 45° fundus camera (VISUCAM, Zeiss).

A glaucomatous visual field defect in the standard automated perimetry (Octopus 101, G2 program, HAAG-STREIT International) was defined according to the Hodapp classification [11]. Exclusion criteria were previous history of ocular trauma, intraocular surgery, corneal refractive surgery, wearing contact lenses, or having clinically significant ocular surface diseases at baseline such as blepharitis or ocular seasonal allergy, secondary glaucoma, progressive retinal or optic nerve disease, or severe central visual field loss. Patients receiving any ocular medications, oral cortico steroids, or cytostatics, patients with immunologic, infectious inflammatory diseases, and pregnant women were not included in the study.

At the baseline visit, complete ophthalmic examination including best corrected visual acuity (BCVA), tear break-up time (TBUT), Goldmann applanation tonometry, slit lamp biomicroscopy of the anterior eye segment, binocular indirect slit lamp funduscopy, and fundus photography, and the ocular surface disease index (OSDI) was evaluated completely. At the conclusion of the baseline visit, enrolled patients were started glaucoma treatment with BAK-preserved bimatoprost 0.03% once daily in the evening. All patients were required not to use any other topical ophthalmic medications, other than given study medication, for the duration of the study. Patients returned 3 months after starting glaucoma treatment for the final study visit, which was scheduled at approximately the same time of day as the baseline visit for each patient. At 3 months final visit, an interval medical history was obtained and any side effects were assessed, an ophthalmic examination including slit lamp biomicroscopy of the anterior eye segment, tear break-up time (TBUT), and Goldmann applanation tonometry was performed, and the OSDI was evaluated completely.

Tear Break-Up Time (TBUT): This is a method of determining the stability of the tear film and checking for evaporative dry eye. It was obtained by placing 5 µL of 2% preservative free sodium fluorescein (NaFl) to the inferior fornix using a fixed volume micropipette. To carefully mix the NaFl with the tear film, the patients were instructed to blink three times. The slit lamp was set at a magnification of 16x using cobalt blue illumination and a stopwatch was used to time the occurrence of the first break in the fluorescein-stained tear film. The timer was started immediately after the last blink and stopped at the first break in fluorescein. This was measured three consecutive times and an average of these measurements was used to calculate the final TBUT. Despite the wide variation in TBUT among individual subjects, there is general agreement that a TBUT shorter than 10 seconds reflects tear film instability, whereas a TBUT shorter than 5 seconds is a marker of dry eye [12].

Ocular Surface Disease Index (OSDI): This is a confirmed, self-administered instrument for assessing the presence and severity of OSD symptoms [13]. The OSDI questionnaire includes 12 questions about the patient’s past-week experience with ocular symptoms, vision-related functioning, and environmental triggers [13,14].

Questions assessed whether patients had eyes that felt gritty, painful, sore, or sensitive to light; whether they had blurred or poor vision; whether they experienced limitations with reading, driving at night, watching television, or working with a computer or bank machine; and whether their eyes felt uncomfortable in windy conditions, in areas with low humidity or in air-conditioned places. Answer options for each question were “all of the time” (score=4), “most of the time” (score=3),
Mean tear break-up time (s)  
15  
13  
11  
9  
7  
5  

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“half of the time” (score=2), “some of the time” (score=1), and “none of the time” (score=0) [13]. The total OSDI score was calculated for each patient using the methods described by the OSDI originators [13], as follows:

OSDI = (Sum of Score of All Questions Answered) / X25 / Total Number of Questions Answered.

The total OSDI score could range from 0 to 100, with the OSDI scores classified as ≤12= Normal, 13-22=Mild OSD, 23-32=Moderate OSD, and ≥33=Severe OSD.

In each patient the “worse” eye was classified using the baseline IOP and TBUT values and later statistically analyzed. Statistical analysis was performed using Microsoft Excel Program. Results are presented as mean ± standard deviation (SD), numbers and percentages. Differences in distributions of continuous data were determined by Student’s t-test. Differences in distributions of categorical data were evaluated by chi-square test. p value of less than 0.05 was considered statistically significant.

The study done in Magrabi Hospital from 2012-2013.

Results

This study included 40 patients with newly diagnosed primary open-angle glaucoma (20 male, 20 female) with a mean age 53.63 ± 10.37 years (range 37 to 70). The average best corrected visual acuity (BCVA) of included patients was 0.87±0.13, and the average cup-to-disc ratio (C/D) was 0.54±0.12. Table (1) presents descriptive statistics of demographic characteristics and basic ophthalmologic parameters of newly diagnosed POAG patients included in the study. The mean IOP decreased from 24.70±1.65mmHg at baseline to 15.68±1.68mmHg at 3 months of starting glaucoma treatment (p<0.001). Subjective symptoms like ocular discomfort, itching, pain, dry eye, or foreign body sensation occurred at an incidence between 2% and 5%. The most common side effect was hyperemia. Eight patients (20%) complained about mild to moderate degree of hyperemia a week after starting treatment, but five patients (12.5%) had moderate degree of hyperemia at final 3 months visit. Systemic tolerability was also noted and most patients did not report any complications. The mean TBUT in enrolled patients at baseline was 10.71±1.85 seconds. At the final visit, 3 months after starting treatment with BAK-preserved bimatoprost 0.03%, the mean TBUT decreased to 7.25±1.21 seconds (p<0.001) (Fig. 1). The mean OSDI increased from moderate category at baseline to severe category at 3 months after starting glaucoma treatment with BAK preserved bimatoprost 0.03% ophthalmic solution (31.63±18.48 versus 44.41±16.48; p<0.001), (Table 2, Fig. 2) and changes of OSDI by end of 3th month (mild, moderate and severe) (Fig. 3, Table 3) explains the category of OSDI.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>POAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.63±10.37</td>
</tr>
<tr>
<td>Sex</td>
<td>50% male</td>
</tr>
<tr>
<td>BCVA</td>
<td>0.87±13</td>
</tr>
<tr>
<td>C/D</td>
<td>0.54±12</td>
</tr>
</tbody>
</table>

Table (2): TBUT, OSDI at baseline and after three months of bimatoprost 0.03% treatment.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBUT</td>
<td>10.71±1.85</td>
<td>7.25±1.21</td>
</tr>
<tr>
<td>OSDI</td>
<td>31.63±18.48</td>
<td>44.41±16.48</td>
</tr>
</tbody>
</table>

Table (3): OSDI category at baseline and 3 months after starting treatment.

<table>
<thead>
<tr>
<th>OSDI category</th>
<th>Baseline</th>
<th>After 3 months</th>
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<tbody>
<tr>
<td>Normal</td>
<td>12 (30%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (10%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (28%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (32%)</td>
<td>24 (60%)</td>
</tr>
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Fig. (1): Mean tear break-up time (TBUT) of newly diagnosed POAG patients assessed at baseline and after 3 months.
mean ocular surface disease index (OSDI)

Fig. (2): Ocular surface disease indexes.

Severity of ocular surface disease by OSDI score

Fig. (3): Percentage of newly diagnosed POAG patients with ocular surface disease index (OSDI) scores indicating normal ocular surface or the presence of mild, moderate, or severe ocular surface disease assessed at baseline and after 3 months.

Discussion

Benzalkonium chloride is a detergent and quaternary ammonium compound with a broad range of antimicrobial activity. It was first introduced as a germicide in the 1910s and became more widely used in the 1940s [15]. In the ophthalmic industry, BAK was first used in the 1940s as a means to preserve hard contact lens solutions. Since then, BAK has been used in nearly all classes of ophthalmic solutions, from antiglaucoma medicines to over-the-counter artificial tear solutions.

Benzalkonium chloride is the most frequently used preservative in ophthalmic solutions today [16], and its concentration in glaucoma formulations ranges from 0.004 to 0.02%. The reasons for the frequent use of BAK as a preservative includes its extreme efficacy in combating microbial contamination of bottles, its ability to break cell-cell junctions in the corneal epithelium, thus allowing for antimicrobial and antiglaucoma drops to enter the anterior chamber. While the efficacy of BAK is well known, there is a multitude of published studies that document the detrimental effects of BAK [17-21]. Benzalkonium is known to induce necrosis (at concentrations of 0.05-0.1%) and cellular apoptosis (at concentrations of 0.01%) by way of disturbing the cellular membrane in bacterial cells [18]. However, human ocular surface cells can also absorb this detergent, and effects on ocular surface cells are similar to those seen in bacterial cells. The effects of the detergent are cumulative and become more severe with more concentrated and frequent exposures [18]. Breakdown of the corneal epithelium and increased permeability of the cornea as a result of BAK toxicity is well documented [19]. Higher concentrations of BAK (as can be induced through repeated exposure and subsequent accumulation of BAK in ocular surface tissues) can reduce tear break-up time by causing disruption of the lipid component of the tear film and hence causes tear-film instability [20]. This is especially problematic in glaucoma patients, as they inherently have a decreased rate of basal tear turnover [22]. In one study, it has been shown that ocular cells repeatedly exposed to BAK can over-express the cell marker Apo 2.7, which has been implicated in apoptosis [21].

The results of this prospective study demonstrate that bimatoprost 0.03% ophthalmic solution dosed once daily in the evening provides a good intraocular pressure control. It decreased IOP in patients significantly at 3 months after starting treatment (p<0.001). Among the 40 patients included in our study, BAK-preserved bimatoprost 0.03% ophthalmic solution was generally well tolerated, and most side effects were mild to moderate in severity and required no intervention. Ocular hyperemia was the most common side effect. (20%) complained about mild to moderate degree of hyperemia a week after starting treatment, but only (12.5%) had moderate degree of hyperemia at final 3 months visit. Other common side effects including ocular discomfort, itching, pain, dry eye, or foreign body sensation were rare and occurred at an incidence of 2% to 5%.

No systemic side effects were reported among patients in the study. There is a significantly lower mean TBUT in patients 3 months after starting treatment with BAK-preserved bimatoprost 0.03% ophthalmic solution.

According to general guidelines for TBUT [12], the category of the tear film stability in patients decreased from normal at baseline to tear film
instability at 3 months after starting glaucoma treatment. There is significant increase of the mean OSDI score, from moderate category at baseline to severe category at 3 months after initiating glaucoma treatment with BAK-preserved bimatoprost 0.03% ophthalmic solution. The percentage of patients within each OSDI category (normal ocular surface, mild, moderate, and severe ocular surface disease) was changed from baseline to final visit at 3 months after starting treatment. Significant changes were observed in the normal OSDI category ($p<0.001$) and in the severe OSDI category ($p=0.025$). Some previous studies have found similar results [23-25]. Crichton et al., reported tear film instability in patients with open-angle glaucoma and ocular hypertension after 12-week treatment with different preservative prostaglandin analogs, but with no differences in TBUT between the medication groups (TBUT in seconds: Bimatoprost with 0.02% BAK 9.7±5.7; latanoprost with 0.02% BAK 9.3±4.0; $p=0.379$) [24]. Horsley and Kahook observed the mean TBUT of 2.02±0.71 seconds and the mean OSDI of 26.31±8.25 in open-angle glaucoma patients treated with BAK 0.02%-preserved latanoprost [25]. Ammar et al., found that BAK has significant in-vitro cytotoxicity to cultured ocular epithelial cells. This toxicity of the prostaglandin analogs latanoprost, tafluprost and travoprost preserved with BAK was similar to the toxicity observed in their respective BAK concentrations [26,27]. Broadway et al., assessed that a significant in vitro cytotoxicity of topical antiglaucoma medications is a result of an increase in inflammation, as presented by significant decrease in goblet cells, increase in pale cells, macrophages, and lymphocytes within the epithelium, and increase in fibroblasts, macrophages, mast cells, and lymphocytes in the substantiapropria [23,28].

Conclusively BAK-preserved bimatoprost 0.03% ophthalmic solution dosed once daily in the evening in patients with newly diagnosed primary open-angle glaucoma is an effective drug for intraocular pressure control. It is well tolerated, associated with few side effects which are mild in severity and require neither intervention nor disruption of treatment. Among side effects the most common is ocular hyperaemia. However, its long-term use may negatively influence ocular surface health in patients presented by decreasing in the tear break-up time and increasing in the ocular surface disease index score.

Therefore, while choosing the medication for glaucoma or ocular hypertension, both the efficacy and the tolerability of medication should be considered, especially in patients who already have ocular surface disease symptoms and clinical signs or who are at high risk of developing them due to use of BAK-preserved medication.

References


13. F. OZCURA, S. AYDIN and M.R. HELVACI: “Ocular surface disease index for the diagnosis of dry eye syn-
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