Evaluation of Ocular Surface Disease Associated with Glaucoma Patients

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Abstract

The relationship between glaucoma medications and ocular surface disease (OSD) has been investigated for a long time by ophthalmologists. It has been well known that all preservatives used in topical medications have the potential to cause corneal and conjunctival changes, including dry eye. It is important to also consider the toxicity of the active ingredients. Objective tests for evaluating OSD are the Schirmer Test, Tear Break Up Time (TBUT), Fluorescein Clearance Test (FCT), impression cytology, confocal microscopy – the most common subjective test is Ocular Surface Disease Index (OSDI). Adverse effects associated with topical medication may have a negative effect on patient adherence to medical treatment, the patient's life quality and the doctor–patient relationship. A favourable adherence to treatment will lead to more effective intraocular pressure (IOP) lowering and resultant decrease of glaucomatous vision loss.

Keywords

Glaucoma medications, ocular surface disease, ophthalmic preservatives

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Ocular surface disease (OSD) is an umbrella term that includes both dry eye and non-dry eye disease (e.g. lid disease, conjunctivitis and keratitis).[1] OSD can severely and negatively affect visual function, the ability to perform daily tasks, such as reading, watching TV and driving. Symptoms may include dryness, irritation, tearing, photophobia, foreign body sensation, grittiness, itching, burning, blurry vision, discomfort or pain, redness and, in severe cases, blindness due to corneal scarring.[2,3]

Glaucoma is a group of diseases that damage the optic nerve and can result in vision loss and blindness. Topical intraocular pressure (IOP)-lowering medication is the initial option in the treatment of glaucoma.[4] Patients with glaucoma and ocular hypertension have been shown to suffer OSD at a higher prevalence rate than patients without these ocular disorders.[5] Development of OSD resulting in dry eye may cause discontinuation and poor adherence with glaucoma treatment,[6,7] and it can cause irreversible vision loss due to glaucomatous optic nerve damage.

Wong et al. compared tear protein profile in patients receiving long-term glaucoma medication and in those with primary dry eye. They suggested that duration of use of anti-glaucoma medications longer than 1 year might start to induce changes in ocular surface inflammation.[8]

Jaenen et al. evaluated 9,658 patients who were on anti-glaucoma treatment in a multicentre cross-sectional epidemiological survey in four European countries.[9] When they compared preservative-free eyedrops with preserved eyedrops, the former were significantly less associated with ocular symptoms and signs of irritation.

Ophthalmic Preservatives

All preservatives used in topical medications have the potential to cause corneal and conjunctival changes, including dry eye. Most of the IOP-lowering agents contain the preservative benzalkoniumchloride (BAK). BAK is a quaternary ammonium compound that is used to inhibit microbial growth in the bottle. It disrupts cell membranes, increases membrane permeability and causes cell death.[10] After instillation, eye drops interact with ocular surface tissues.[11] Several studies showed that BAK has also a toxic effect on the corneal epithelium as well as conjunctival epithelium and stroma, and therefore can trigger or exacerbate OSD.[12–14] In animal models, BAK-free travoprost 0.004 % did not affect goblet cell numbers[15] or corneal epithelial cells,[16,17] whereas BAK-preserved latanoprost 0.005 % was shown to cause losses of goblet cells[15] and pathological changes in the corneal epithelium.[16,17] Studies have also shown that preservative-free drugs caused less ocular toxicity and damage to ocular surface compared with preserved drugs.[18–20]

Other studies have shown that BAK does not have important negative effects on cornea.[21–24] Alternative oxidising preservatives agents have been developed, such as sofZia™ (Alcon Laboratories), which contains borate, zinc and sorbitol. These oxidising agents may cause less cell damage than detergent preservatives such as BAK.[25] Also Purite is an oxidative preservative that is used in brimonidine and artificial tears.[26] In a study by Katz et al., brimonidin-purite 0.15 % showed the most favourable safety and tolerability profile with a reduced incidence of allergic conjunctivitis and better satisfaction and comfort rating.[27] Polyquad® is an another alternative polycationic preservative. Labbe et al. showed that Polyquad causes less toxicity than BAK *in vivo*.[28]

OSD and inflammation have long been associated with the chronic use of IOP-lowering medications and especially those that include preservatives.[13,29] Pisella et al. evaluated 4,107 patients prospectively to determine the incidence of ocular toxicity of preservatives with glaucoma medications.[30] All symptoms were more prevalent with preserved drugs than with preservative-free drugs (p<0.001). These symptoms were discomfort upon instillation, and symptoms between instillations such as burning-/stinging, foreign body sensation, dry eye sensation, tearing and eyelid itching. A reduction in the symptoms and signs was observed when patients changed from preserved to preservative-free drugs (p<0.001).

While the antiseptic concentrations of BAK are cytotoxic, it is important to also consider the toxicity of the active ingredients. It has been shown that non-preserved IOP-lowering medications, such as timolol, can increase the expression of human leukocyte antigen-DR region (HLA-DR), interleukin (IL)-6 and IL-8 in the conjunctival epithelium of glaucoma patients.[31] A 100-fold dilution of a therapeutic dose of PGAs can increase the release of cytosolic proteins from corneal endothelial cells, while a 1:100 dilution of 0.01 % BAK does not.[32] Similarly, undiluted beta-blocker in a preservative-free formulation causes a 40–60 % reduction in viability of human conjunctival cells.[33]

Evaluating Ocular Surface Disease in Glaucoma Patients

In the literature there are several objective measurement methods that have been used for assessing ocular surface health in glaucoma patients. These tests are: Schirmer Test, Tear Break Up Time (TBUT), Fluorescein Clearance Test (FCT), impression cytology and confocal microscopy.

Uusitalo et al. showed that abnormal corneal fluorescein staining reduced statistically significantly from 81.6 % to 40.6 % of cases and TBUT improved statistically significantly from 4.5±2.5 seconds to 7.8±4.9 seconds after changing medication from a BAK-preserved to a preservative-free prostaglandin analogue.[34]

Leung et al. examined the prevalence of OSD in 101 glaucoma and ocular hypertensive patients.[35] Schirmer testing showed 62 (61 %) patients with a decrease in tear production in at least one eye. Severe tear deficiency was presented in 35 (35 %) patients. Corneal and conjunctival lissamine green staining showed positive results in 22 (22 %) patients. TBUT showed abnormal tear quality in 79 (78 %) patients and a severe decrease in tear quality was found in at least one eye in 66 (65 %) patients. In a study of 20,506 adults in Germany, 53 % of the patients with glaucoma were also diagnosed with dry eye based on Schirmer test, corneal fluorescein staining and TBUT.[36] Baudin et al. compared topical 2 % carteolol with and without benzalkonium chloride. Reductions in TBUT were observed both 3 hours and 3 days after using BAK-preserved carteolol.[37] Martone et al. evaluated long-term effects of preservative-free and preservative-containing antiglaucoma medications on the tear secretion and ocular surface.[38] The preserved medication groups showed reductions in Schirmer test I scores, TBUT, number of superficial corneal epithelial cell and subbasal nerves compared with the preservative-free medication group and normal patients. Another study by Arici et al. showed that hazardous tear film function changes with Schirmer test and TBUT after the long-term use of antiglaucoma medication.[39] Yalvac et al. studied the long-term effects of topical anti-glaucoma medications using Schirmer's test, TBUT, conjunctiva impression cytology and goblet cell density.[40] They determined lower Schirmer test scores, TBUTs and reduced goblet cell densities for patients who were treated with BAK-timolol combination.

A multicentre, investigator-masked, parallel group study of patients treated with latanoprost for at least 4 weeks were randomised to receive bimatoprost with BAK (n=35), latanoprost with BAK (n=38) or travoprost with SofZia (n=33).[41] The outcome measures were conjunctival hyperaemia at month 3 and corneal staining with fluorescein and TBUT. There were no significant differences among bimatoprost with 0.005 % BAK, latanoprost with 0.02 % BAK and travoprost with sofZia in conjunctival hyperaemia, corneal staining and TBUT after 3 months of treatment.

As well as objective methods there are several subjective survey instruments that determine ocular surface health.[42] One of them is the Ocular Surface Disease Index (OSDI), which identifies subclinical dry eye cases.

OSDI is a validated, self-administered tool for assessing the presence and severity of OSD symptoms.[43] The OSDI questionnaire includes 12 questions about the respondent's experience with ocular symptoms, vision-related functioning and environmental triggers.[43,44] Response options for each question were graded as 0 = none of the time; 1 = some of the time; 2 = half of the time; 3 = most of the time; 4 = all of the time. Questions about vision-related functioning of environmental triggers can also be answered with 'non applicable', so that question is not factored into the final score calculation. The total OSDI score is calculated using this method: OSDI = ([sum of scores for all questions answered] x 100)/([total number of questions answered] x 4). The final total OSDI score is based on a range from 0 to 100, which is classified as ≤12 = normal; 13–22 = mild OSD; 23–32 = moderate OSD and ≥33 = severe OSD.[42,45] Fechtner et al. found a good correlation between OSDI symptoms and the number and duration of glaucoma treatments used.[46]

Rossi et al. found that the use of multiple antiglaucoma medications is associated with a significantly increased rate of moderate and severe dry eye.[47] Garcia-Feijoo et al. evaluated patients who were using anti-glaucoma medications with OSDI in a multicentre, international study,[48] concluding that there was a statistically significant correlation between increased time since glaucoma diagnosis and worsening of OSD symptoms.

Henry et al. performed a multicentre study with patients who changed from latanoprost or bimatoprost monotherapy to travoprost with SofZia.[49] Overall OSDI scores were 12.0 for latanoprost, 13.2 for bimatoprost and 8.7 for travoprost after 8 weeks of treatment (p<0.0001). In 70.2 % of 235 patients with OSD symptoms, symptoms were reduced in severity by at least 1 level.

A prospective, 8-week, single centre study of 40 eyes of 20 patients who were switched from latanoprost to travoprost-Z found a significant increase (p<0.001) in mean TBUT and a significant decrease (p<0.001) in the mean OSDI score. Schwartz et al. conducted a retrospective analysis of three large databases. They revealed that latanoprost with BAK or travoprost-Z with SofZia did not statistically in rates of coding for dry, ocular infection or OSD during the first year post-index.[50]

Katz et al. determined OSDI in patients who treated with latanoprost with BAK at least 1 month.[45] The patients' OSDI scores were ≥13. Then they were randomly separated into groups as patients who continued with latanoprost and patients who switched to travoprost with SofZia. OSDI scores were calculated again at 6 and 12 weeks. When patients

with mild OSD at baseline were assessed after 12 weeks, the mean OSDI score was significantly lower (p= 0.04) in the BAK-free travoprost group (score = 11.6±10.8) than in the BAK-preserved latanoprost group (score = 14.4±11.9).

In conclusion, it is well known that adverse effects linked with topical medication may have a negative effect on patient adherence to medical treatment, patient's life quality and the doctor–patient relationship.[51] Patients who have less ocular irritation may be more likely to be adherent to their treatment. This will lead to more effective IOP lowering and resultant decrease of glaucomatous vision loss. Further prospective and randomised studies are required to better understand relationship with OSD and anti-glaucoma treatment to enhance patient compliance. ■

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