UPDATE/REVIEW

Ocular surface disease in glaucomatous patients

Francisco Pérez Bartolomé, MD1; Pedro Arriola Villalobos, MD, PhD1; Pouya Alaghband, MD2; José M. Benítez-del-Castillo, MD, PhD1

ABSTRACT: This review presents an exhaustive analysis of the current literature on ocular surface disease (OSD) in glaucoma. OSD in this population mainly manifests in the cornea and conjunctiva as superficial punctate keratitis and tear film instability, aggravated by the chronic use of intraocular pressure–lowering medications; this could account for poor treatment adherence and worsening of the patient's quality of life. A large body of literature has found increasing evidence implicating preservatives as the main factor, through both in vitro and clinical studies, especially in regard to benzalkonium chloride. However, the impact of preservatives on clinical practice varies in different studies. The decision to use preservative-free medication or alternative preservatives should therefore be assessed on an individual basis, whereby some subpopulations with abnormal tearing, decreased tear break-up time (TBUT) or corneal staining could benefit. Clinical assessment with validated quality of life questionnaires, corneal and conjunctival staining, TBUT and Schirmer's test is mandatory in these populations.

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Glaucoma is a chronic, progressive optic neuropathy in which increased intraocular pressure (IOP) is the most significant risk factor1,2. IOP reduction in the treatment of glaucoma has already been confirmed to be beneficial in large prospective randomised clinical trials3-7, and can decelerate or halt disease progression. Topical IOP-lowering drugs remain the first line therapy and, considering that IOP is the only controllable risk factor, the majority of patients receive medical treatment throughout their lifetime. Ocular surface disease (OSD) is a general term to describe a wide spectrum of diseases such as dry eye syndrome (DES), eyelid disease, conjunctivitis and keratitis8. OSD is a well-known comorbidity in glaucomatous patients that has been found to be aggravated by the chronic use of IOP-lowering medications9,10, thus accounting for poor treatment adherence and concordance11 and a decline in the patient's quality of life (QoL)12,13. Nonetheless, both OSD and glaucoma are age-related diseases14-18 that can occur as separate entities. Thus, the role of each component —whether age or medical treatment— must be assessed on an individual basis for each patient to optimise the treatment outcome. OSD induced by hypotensive therapy can result from the effect of the active ingredients of the medical treatment or the preservative agents, particularly benzalkonium chloride BAK9,19. Of these two factors, the preservative element of IOP-lowering drugs is one of the most relevant features in OSD9,20.

The role of active ingredients

The main topical hypotensive eye drops are timolol (non-selective adrenergic beta-blocker), carteolol (non-selective adrenergic beta-blocker with intrinsic sympathomimetic activity), carbonic anhydrase inhibitors such as dorzolamide or brinzolamide, brimonidine (adrenergic agonist alpha-2 selective) and prostaglandin analogues (latanoprost, bimatoprost, travoprost, tafluprost)15. Among these, prostaglandin analogues and beta-blockers are considered first-line therapies15,21,22. Common symptoms of OSD in glaucomatous patients include redness, dryness, irritation, tearing, burning and foreign body sensation,
photophobia and blurred vision\textsuperscript{23-24}. Clinical features of OSD for each hypotensive treatment are shown in Table\textsuperscript{1,23-34}. Corneal epithelial chemical toxicity (CECT) is one of the major clinical signs related to glaucoma therapy, most commonly associated with topical prostaglandin analogs\textsuperscript{25,26}, cholinergic agonists\textsuperscript{34} and beta-blockers\textsuperscript{25}. European multicenter studies found a CECT prevalence of up to 18\%\textendash{}31\%, data which overlapped with the prevalence found in smaller Asian trials (20\%\textendash{}54\%)\textsuperscript{35-37}. Tear-film functionality has been shown to be altered in treated glaucoma patients by objective tests such as the tear film break-up time (TBUT), Schirmer’s test, osmolarity and meibomian gland score, although the severity of the tear film disruption varies widely among studies\textsuperscript{38,39,40,41}. In a case-control study, the effect of timolol maleate on TBUT was evaluated in 192 eyes of 96 subjects\textsuperscript{42}. The authors found statistically significant differences in the mean break-up time between cases (10.45 s) and controls (30.18 s). One large cross-sectional study performed in our centre, which enrolled 211 glaucoma patients under topical hypotensive treatment and 51 controls without glaucoma eye drops, did not show statistically significant differences for TBUT between groups, using non-invasive first-TBUT scores assessed by Keratograph 5M\textsuperscript{43}. Blondin et al.\textsuperscript{44} demonstrated that preservative-free betaxolol, timolol, carteolol or latanoprost did not activate the complement system, which is considered an early inflammatory response mediator. Nielsen and Eriksen reported that 7 of 64 cohort patients treated with timolol developed a transitory sensation of dry eyes\textsuperscript{45}. However, in the current literature, there are no large clinical trials comparing preservative-free treatments with matched patients without topical hypotensive therapy to prove that active glaucoma agents alone can lead to OSD.

### The role of preservatives

In recent years, a large body of literature has found increasing evidence that preservative-containing medications can lead to worsening of signs and symptoms of OSD. BAK was one of the first preservatives introduced, and today remains the most common ophthalmic excipient. Several in vitro and animal studies have shown corneal neurotoxicity, tear film disruption and trabecular meshwork damage with BAK-preserved solutions\textsuperscript{46-56}. Tomić et al.\textsuperscript{57} reported a significant decrease in TBUT in 40 patients with newly diagnosed primary open-angle glaucoma (POAG) after 3 months of treatment with BAK-preserved travoprost 0.004\%. Barabino et al.\textsuperscript{58} reported in an experimental study with mice with dry eye that BAK had negative effects on the ocular surface under normal and dry eye conditions, but that BAK-free travoprost eye drops showed increased tear secretion and corneal protection.

In a prospective longitudinal study that included 132 patients with POAG, Lester et al.\textsuperscript{59} reported a significant improvement in patient QoL using preservative-free 0.1 timolol for 3 months, after having switched from preservative-containing beta-blockers. The authors reported a significant decrease in dryness, hyperaemia, follicular hyperplasia, and foreign body sensation. These types of clinical trials (cross-over trials) today represent the majority of recent clinical studies on preservatives\textsuperscript{59,60,61,65}.

Other preservatives have been evaluated in vitro. Polyquaternium 1 (Polyquad\textsuperscript{®} [PQ]) was marketed with travoprost 0.004\% ophthalmic solution. Labbé et al.\textsuperscript{62} evaluated this compound compared to BAK, and concluded that PQ induced fewer toxic effects, with less destruction of goblet cells, than similar concentrations of BAK. Liang et al.\textsuperscript{63} reported a greater safety advantage

### Table 1. Clinical manifestations of OSD from antiglaucoma therapies.

<table>
<thead>
<tr>
<th>Common symptoms described for all ingredients</th>
<th>Redness, dryness, irritation, tearing, burning and foreign body sensation, photophobia and blurred vision\textsuperscript{23,24}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandins</td>
<td>Eyelid and eyelash hyperpigmentation, hypertrichosis, iris cysts, uveitis, macular edema\textsuperscript{25}, recurrence of herpes simplex keratitis\textsuperscript{36}.</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Contact dermatitis\textsuperscript{27}, blepharitis, conjunctivitis, superficial punctate keratitis\textsuperscript{25}, pseudopenphigoid syndrome\textsuperscript{28}.</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Allergic conjunctivitis and dermatitis\textsuperscript{25}, corneal edema\textsuperscript{29,30}.</td>
</tr>
<tr>
<td>Alpha-adrenergic agonists</td>
<td>Granulomatous anterior uveitis, allergic conjunctivitis and dermatitis\textsuperscript{25,51,52}.</td>
</tr>
<tr>
<td>Parasympathomimetic agonists</td>
<td>Spasm of accommodation, miosis and myopization, poor night vision, iritis\textsuperscript{33,34}.</td>
</tr>
</tbody>
</table>

OSD, Ocular surface disease
for the ocular surface of patients receiving chronic glaucoma treatment with PQ-preserved travoprost 0.004% ophthalmic solution, rather than with BAK-preserved travoprost 0.004% ophthalmic solution. Purite®, a new stabilized oxychloride complex, was studied by Noecker et al.64, concluding that glaucoma medications containing BAK resulted in greater corneal damage and conjunctival cell infiltration than medications preserved with Purite®. This preservative was marketed with brimonidine 1.5 mg/ml ophthalmic solution. SofZia® is a new ionic buffer solution that works as a microbicidal agent through oxidative properties. This compound was evaluated in a large prospective, randomized multicentre comparative study that enrolled 220 patients with open-angle glaucoma or ocular hypertension who had been treated with BAK-preserved latanoprost 0.005% monotherapy for at least 3 months65. After switching to SofZia®-preserved travoprost 0.004%, corneal and conjunctival disease significantly decreased and TBUT significantly increased, with no statistically significant differences for IOP and hyperaemia.

Thus, BAK is the most commonly-used preservative in glaucoma medications and is more toxic than other, newer preservatives. Although these new preservatives used after BAK resulted in significantly higher percentages of live conjunctival and corneal cells, further studies are needed to understand the clinical implications of these findings.

While clinical and in vitro studies have investigated the adverse effects of BAK, different BAK concentrations and exposure time on the ocular surface, concentrations have rarely been exceeded at high enough levels to be an effective bactericide, or to cause clinically relevant adverse effects66. The exposure time reported in vitro for ocular surface toxicity to occur is approximately 5 to 30 minutes66-68. Other clinical trials have also illustrated the safety of these excipients67,68. Thus, the impact of preservatives on clinical practice varies in different studies. Accordingly, the decision to use preservative-free medication or alternative preservative elements should be made on an individual basis, whereby some subpopulations with abnormal tearing, decreased TBUT or corneal staining could benefit.

Fixed combination therapies

Fixed-combination (FC) therapies offer several advantages to patients with glaucoma, such as convenience and compliance, decreased time requirements for eye drop application, reduced exposure to preservatives and reduced risk of medication washout69,70. Moreover, considering that the severity of OSD symptoms has been positively correlated to the number of IOP-lowering drugs71, FC could serve as a useful alternative, not only to control IOP, but also OSD signs and symptoms. Disadvantages would be the higher cost and greater implications of non-compliance60. In a recent review, Radcliffe stated that FC therapies that contain timolol maleate could have more favourable ocular surface tolerability compared to the non-timolol individual component69.

This effect appears to be most significant for latanoprost 0.005%, bimatoprost 0.03%, and brimonidine 0.2%. Ormrod et al.70 reported similar conclusions with FC dorzolamide 2%/timolol 0.5%. Brinzolamide 2%/timolol 0.5% appears to produce less discomfort than dorzolamide 2%/timolol 0.5%71,72. FC prostaglandins/timolol seem to induce less hyperaemia than the concomitant treatment.73 One 5-year multicentre clinical trial found that FC latanoprost-timolol produced iris hyperpigmentation in 30% of the patients, eyelash hyperpigmentation in 58% and eyelid hyperpigmentation in 5%-6%74. Among prostaglandin-timolol F Cs, bimatoprost/timolol seems to cause more hyperaemia and ocular discomfort75. FC travoprost/timolol is nowadays the only commercialized prostaglandin FC without BAK, which can be helpful in patients with previous OSD.

Quality of life and clinical assessment

OSD and glaucoma are both known to affect QoL12,13,75. A study with 124 patients found that patients with OSD had a poorer QoL as assessed by the Glaucoma Quality of Life-15 questionnaire (GQL-15) and Ocular Surface Disease Index (OSDI). The strongest predictors of OSD were daily BAK, more than four daily drops and more than two topical glaucoma medications. More than 3 daily BAK drops was an independent predictor for OSD76. García Feijoó and Sampaolesi77 reported higher OSDI scores in patients with longer duration since diagnosis and increase in the number of medications. Pouyeh et al.75 found a statistically significant correlation between Dry Eye Questionnaire scores and the ability to perform daily activities and emotional well-being. Rossi et al.78 found a significant association between the number of instillations and QoL. However, other studies with large sample sizes have not concluded that OSD due to glaucoma medication has a high impact on patient QoL43,67,68. Identifying patients treated with a higher number of daily hypotensive eye drops, preservative therapy and longer treatment durations could provide long-term benefits by individualizing topical therapy.

We suggest that clinical assessment of OSD in patients on topical hypotensive treatment should include QoL with a validated questionnaire (Ocular Comfort Index [OCI]; OSDI questionnaires; Ocular Symptom Scale [OSS] questionnaires),
Schirmer’s test score, TBUT score with fluorescein 1%, corneal staining with fluorescein 1% and a validated corresponding grading scale (National Eye Institute [NEI]; SICCA ocular staining score; Industry Workshop Scale; Oxford Grading Scale), conjunctival staining preferably with lissamine green and a validated corresponding grading scale (NEI; Industry Workshop Scale; Oxford Grading Scale; SICCA ocular staining score)70-83.

Impact of the ocular surface disease on glaucoma treatment outcomes

Glaucoma and OSD together may predispose to failure of glaucoma filtering surgery84-86. Topical therapy causes a spectrum of cellular responses that may lead to chronic conjunctivitis after the use of multi-medication throughout long-term therapy. This chronic conjunctivitis may not only affect QoL, but is also attributed to a significant proportion of trabeculectomy failures due to bleb scarring87. Broadway et al.85,86 studied glaucoma patients with previous filtering surgery, and concluded that patients with less exposure time to medical hypotensive eye drops before the intervention presented a lower final IOP. The exact mechanism whereby topical medical therapy induces inflammation and predisposes to scarring of the bleb remains controversial87. There is currently a clear need to preserve the ocular surface as much as possible, by reducing the number of instillations or using less aggressive therapies like polyquaternium ammonium.

Recommendations

Glaucoma patients with OSD need to be treated with a stepladder approach. Having identified the problem, use of artificial tears is essential, with lubricating gel and ointment added if needed. Short-term use of mild corticosteroids, such as rimexolone or loteprednol, if available, should be considered, although it is essential to be watchful for steroid-induced elevation of IOP. Topical cyclosporine has recently been reported to be useful by improving Schirmer’s test, ocular surface staining scores, OSDI, and corneal sensations in chronic glaucoma patients after long-term use of topical ocular hypotensive medications88. If the OSD continues to deteriorate despite having introduced lubricant treatment, a high index of suspicion for ocular allergy must be considered. This condition should be treated by withdrawing the current medication and switching to a different class of active compound, although cross-reactivity is still possible. If there is intolerance to multiple therapies, allergy to the preservative should be suspected, and a preservative-free medication should be prescribed23. Although there is controversy regarding the real impact of preservatives in clinical practice, the weight of the evidence appears to support the notion that preservative-containing glaucoma medications can cause adverse effects on the ocular surface. Hence, nowadays it is imperative to consider preservative-free medications or FCs in patients with OSD prior to the instigation of glaucoma therapy. Clinical assessment with validated QoL questionnaires, corneal and conjunctival staining, TBUT and Schirmer’s test are mandatory in these populations.

REFERENCES


First author:
Francisco Pérez Bartolomé, MD

Department of Ophthalmology
H. Clínico San Carlos, Madrid, Spain.