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REVIEW

Glaucoma and Ocular Surface Disease: More than Meets the Eye

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Abstract: Understanding the association between ocular surface disease and glaucoma is important for improving adherence to treatment and introducing practical solutions. While topical antihypertensive medications for glaucoma are well tolerated according to short-term studies, there is little evidence on their long-term effects. Since they are often required for many years, the effects of these drops on the ocular surface become important in regard to quality of life and adherence. In this nonsystematic review performed in April 2022, we summarize what is known about the relationship between glaucoma and ocular surface disease. Specifically, we examine how each class of topical glaucoma drops affects the ocular surface. We then review the treatment of ocular surface disease for patients on topical glaucoma therapy. Finally, we discuss treatments that may reduce or eliminate the burden of topical medications.

Keywords: glaucoma, ocular surface disease, adherence

Introduction

Glaucoma is the leading cause of irreversible blindness in the world.[1] The number of people living with glaucoma worldwide was estimated to be 64.3 million in 2013, with 3.36 million residing in North America.[1] By 2040, a projected increase by 74% will nearly double the number of people with glaucoma to about 111.8 million worldwide. Topical antihypertensive agents are generally first-line therapy for glaucoma. These agents have proven to be effective in decreasing intraocular pressure (IOP) as shown in many long-term studies.[2,3] In general, prospective clinical trials have demonstrated tolerability of topical glaucoma therapy,[4,5] but these studies are limited by short follow-up duration. However, topical treatment of glaucoma is often required for years or decades. Long-term glaucoma drop use has consistently demonstrated low adherence: one study demonstrated that merely 50% of the patients continued their prescribed medications after 6 months, and only 37% persisted on therapy after 3 years.[6] A big reason for these high attrition rates may be ocular surface disease: a study examining barriers in glaucoma medication adherence found that nearly a third (32%) of patients cited difficulties with side effects, medication costs, or regimen complexity[7] as the reason for discontinuation. Moreover, ocular discomfort increases with the number of medications used, which is noteworthy as approximately 50% of glaucoma patients require 2 or more topical medications.[3,8] In fact, the severity of ocular surface disease increases with increasing glaucoma severity, while quality of life score decreases consequently.[9] Importantly, ocular surface disease and patient symptoms may not only decrease adherence to treatment, but also negatively impacts glaucoma filtration surgery outcomes. Several studies have shown that ocular surface inflammation secondary to glaucoma medication use intensifies the wound healing response to incisional surgery, increasing the risk of filtration bleb fibrosis and failure.[10–13] Understanding the relationship between glaucoma therapy and ocular surface disease is critical for ophthalmologists treating glaucoma patients.

The purpose of this review is to raise awareness of ocular surface disease among comprehensive ophthalmologists. We feel that this knowledge may provide an evidence-based treatment algorithm for the general ophthalmologist.

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Epidemiology and Overlapping Demographics

Dry eye is a common condition with prevalence rates in the US ranging from 5% to 18%, which increases with age.[14,15] Glaucoma also affects older individuals with a prevalence of 3.54% among adults aged 40–80 years.[1] Several prospective observational studies of patients treated with topical glaucoma therapy have demonstrated significantly higher rates of dry eye signs and symptoms compared to the general population.[8,16] According to the German Glaucoma and Dry Eye Register, the prevalence of clinically significant dry eye, as determined by tear meniscus, fluorescein staining, tear break up time (TBUT), and Schirmer's test, was 52% in primary open-angle glaucoma.[17] A large prospective, multi-center study with 630 patients on glaucoma therapy demonstrated that 48.4% of the patients had at least mild dry eye symptoms, while 27% showed moderate-to-severe disease as measured with the Ocular Surface Disease Index (OSDI).[8] This is more than double the rate of clinically diagnosed dry eye disease in the general population, which is estimated to be around 6.8% of all adults in the US and 18% among patients 75 or older.[15] The impact of ocular surface disease on quality of life has also been well documented in the literature and remains a significant source of morbidity in this population and arguably the main source of non-compliance.[18]

The Role of Benzalkonium Chloride

Benzalkonium chloride (BAK) is the most commonly used preservative in ophthalmic pharmaceuticals. It is a non-specific antiseptic detergent that acts by disrupting lipid bilayers. BAK is used to prevent colonization by gram positive and negative bacteria and fungi.[19] However, this same property can also injure the ocular surface cells. When exposed to BAK in vitro, epithelial cells swell, desquamate, and lose cellular borders, likely from a loss of tight junction stability.[20] Although the in vitro effects of BAK are well documented, the in vivo effects are less defined. This may be due to the lower residence time of the drops on the ocular surface due to tear film clearance. Nevertheless, keratocyte activation, loss of microvilli, and reduced density of the superficial corneal epithelium have been shown to occur after long-term treatment with BAK compared to non-BAK or non-preserved controls.[21,22] It is thought that epithelial toxicity may result in an inflammatory cascade, decreasing subepithelial nerve plexus density and further reducing tear secretion.[21,23,24] The conjunctiva may also be damaged by BAK in both structure and function. Multiple studies have shown a decrease in goblet cell density, an increase in fibroblasts, and keratinization of the conjunctiva in patients taking BAK-preserved eye drops.[25,26] This may be a result of chronic changes in the conjunctiva including up-regulation of inflammatory factors resulting in metaplasia and subepithelial fibrosis.

Clinical findings related to BAK and the ocular surface include reduced TBUT, reduced Schirmer's score, and conjunctival staining with lissamine green.[27,28] Other reports have shown improvements in dry eye symptoms after switching from BAK-preserved drops to non-BAK preserved drops for those with mild symptoms, but not for those with moderate or severe symptoms.[29–31] One study reported a significant improvement in ocular symptoms but not function as measured by the Glaucoma Symptom Scale after switching from preserved to preservative free drops.[32] However, there are conflicting reports; some studies demonstrated no difference in conjunctival hyperemia, corneal staining, Schirmer's score, tear production, or TBUT between patients using BAK and non-BAK preserved prostaglandin analogues.[33,34] Several reasons may account for the large variability between these studies. Many of them examined a non-uniform population with varying ages and did not control for other causes of dry eye such as autoimmune disease, previous cataract surgery, and diabetes, all of which are known to cause clinically significant dry eye disease.[35,36] Importantly, the studies reporting no difference in dry eye from BAK-preserved and non-BAK preserved drops had short-term follow-up. Regardless of the underlying mechanism and the specific role of BAK, multiple large population-based studies have demonstrated an increase in ocular surface morbidity among patients taking preserved glaucoma medications, although the exact mechanism has yet to be fully elucidated.[37,38]

Topical Antihypertensives and Pseudo-Ocular Cicatricial Pemphigoid

Ocular cicatricial pemphigoid (OCP), a subtype of mucous membrane pemphigoid, is a progressive cicatrizing ocular surface disease caused by immune-mediated inflammation of the conjunctiva and other mucous membranes. Pseudo-OCP is an umbrella term that encompasses diseases causing cicatrizing conjunctivitis without other mucosal surface

involvement and a negative immunofluorescein conjunctival biopsy.[39] Though rare, a retrospective study of 145 patients with pseudo-OCP reported the most common (28.3%) presumed cause to be glaucoma treated with long-term topical anti-hypertensives.[39] The majority of patients with glaucoma medication-induced pseudo-OCP used multiple agents, with the most common being beta-blockers (87.8%), timolol (73.3%), and epinephrine/alpha-agonists (61%).[39] In another study, 27 of 29 glaucoma patients with OCP had a history of long-term glaucoma medication use.[40] Due to the polymodal treatment regimens, it is difficult to determine which drugs contribute to disease. Histologically, patients on long-term topical glaucoma medications have reduced goblet cells, increased fibroblast-like cells, and increased inflammation in the conjunctiva as compared with patients without a history of topical drug use.[41] It remains unclear whether the cicatrization process is due to the effects of preservatives or the actual active ingredients. The conjunctival and ocular surface changes associated with pseudo-OCP can lead to vision loss and impact the effectiveness of glaucoma filtration surgery if not addressed.[42] While termination of topical medication is the first step in pseudo-OCP therapy, many will require systemic immunomodulating therapy to halt progressive scar formation.

Beta Blockers and the Ocular Surface

The active ingredients in ocular anti-hypertensives also have been implicated in ocular surface abnormalities, of which the most well established are beta-blockers.[43–45] As a glaucoma therapy, topical application of beta-blockers lowers IOP by inhibiting sympathetic activation of the ciliary body and decreasing aqueous humor production.[46] Considering the ubiquity of beta receptors throughout the body, it is unsurprising that the main and accessory lacrimal glands also contain them and blocking them may result in reduced tear production.[47] Additionally, animal studies have shown that beta-blockers impair corneal wound healing through inhibiting sympathetic activity of limbal stem cells.[46] One clinical study compared the ocular surface side effects of beta blockers (e.g, timolol, timolol maleate) to prostaglandin analogues (eg, latanoprost, bimatoprost, and travoprost).[43] An increase in conjunctival staining scores, conjunctival epithelial metaplasia, and a reduction in goblet cells by impression cytology were seen in both preserved and preservative-free timolol groups at 3 and 6 months. In comparison, these changes were not seen with topical prostaglandin analogues.[43] A larger retrospective study of 300 eyes with strict exclusion criteria (including a history of intraocular surgery, diabetes, and autoimmune disease) studied whether BAK or the active ingredient in the various glaucoma medications accounted for corneal toxicity.[48] Timolol, brimonidine, latanoprost, dorzolamide, and combination drops were included. After adjusting for the cumulative age-adjusted BAK toxicity, beta-blockers were found to have a significant negative impact on the ocular surface, more than can simply be attributed to the concentration of BAK. The effects included reduced TBUT and higher corneal punctate erosion scores compared to the other medications. The actual mechanisms involved remain unclear.[47]

Alpha Agonists, Carbonic Anhydrase Inhibitors, and the Ocular Surface

Alpha 2 receptors are widely distributed throughout the body and cause anti-hypertensive effects, dry mouth, sedation, and bronchodilation.[49] Local toxicity of brimonidine, an alpha 2-agonist, is well established and can result in a follicular conjunctivitis and conjunctival hyperemia in up to 30% of patients.[50] A randomized controlled trial (n=22) of 0.2% brimonidine demonstrated that 9% of the participants had Schirmer's scores below 10mm at the end of 1 year compared to none at baseline.[51] A comparative study of brimonidine-purite 0.2%, brimonidine-purite 0.15%, and brimonidine 0.2% demonstrated no differences in IOP reduction among the 3 groups. However, the 0.2% formulations had >14% incidence of allergic conjunctivitis compared to a 9% incidence in the 0.15% formulation, suggesting that the active ingredient may play a role in the process.[52] An animal study showed brimonidine, beta blockers, and latanoprost, increased levels of matrix metalloproteinase (MMP)-3 activity in rat eyes after instillation of the drops twice daily for 2 weeks compared to BAK controls.[53] MMP-3 contributes to extracellular matrix degradation, indicating that the active ingredient may result in the loss of subepithelial connective tissue.[54] More studies are warranted to examine the specific effects of this agent on tear production, ocular surface toxicity, and symptoms of dry eye.

Carbonic anhydrase is an ubiquitous enzyme found in red blood cells, kidneys, and the ciliary body.[49] Inhibiting this enzyme results in systemic effects including alkalinization of the urine, metabolic acidosis, and central nervous system side effects such as drowsiness and paresthesias. The low pH of carbonic anhydrase inhibitors such as dorzolamide may

also be associated with damage to the ocular surface. A rabbit study compared brimonidine, dorzolamide, timolol, and latanoprost found that dorzolamide with the lowest concentration of BAK (0.0075%) induced more damage than either latanoprost or timolol, both of which had higher concentrations of BAK.[22] Further studies specifically examining the active ingredient in dorzolamide, preferably without BAK, would help delineate the role of each.

Prostaglandins and the Ocular Surface

Prostaglandins are oxygenated metabolites of unsaturated fatty acids found in the phospholipids of cell membranes.[49] They reduce IOP by increasing uveoscleral outflow and are often first-line agents for IOP lowering due to their safety profile and once-a-day dosing.

There is evidence that the active ingredient in the prostaglandin analogues may also play contribute to ocular surface disease. One trial comparing bimatoprost 0.1% with four times the amount of BAK compared to bimatoprost 0.3% showed higher rates of stinging/burning, foreign body sensation, and eye dryness at 6 months and 12 months in the 0.3% concentration group.[55] However, the baseline goblet cell density in both groups was lower than average known controls, which may be due to prior treatment with bimatoprost 0.3% in all patients.

Other studies show a possible protective effect of PGAs. A prior study demonstrated an increase in goblet cell density in the conjunctiva after instillation of travoprost 0.004%–timolol 0.5%, bimatoprost 0.03%–timolol 0.5%, and latanoprost 0.005%–timolol 0.5%.[56] The authors theorized that this increase may be a reaction to external insults rather than a protective effect of the PGA. There is also some evidence that the PGAs may have a protective effect against BAK on conjunctiva-derived cells in vitro.[57] Guenoun et al compared commercial preparations of latanoprost, travoprost, and bimatoprost to their corresponding concentrations of BAK and found that there was less apoptosis in the PGAs, theorizing an antioxidant effect of PGAs.[57] Considering the high degree of variability between the aforementioned studies, studying the effects of multiple factors contributing to the complex mechanisms of ocular surface damage remains challenging.

Newer Glaucoma Agents and the Ocular Surface

Newer topical anti-hypertensives such as latanoprostene bunod and netarsudil also affect the ocular surface. Two Phase III clinical trials showed that netarsudil dosed 1 to 2 times daily caused conjunctival hyperemia in 50–59% of the patients compared to 8–11% of the patients on 0.5% timolol dosed twice daily. Patients on netarsudil also experienced higher rates of conjunctival hemorrhage (15–17%) and corneal deposits (4–15%) compared to patients on 0.05% timolol.[58] In a Phase IV trial of netarsudil, adverse events reported by >5% of the patients included conjunctival hyperemia, vision blur, conjunctival hemorrhage, and instillation site pain.[59] Phase III studies of latanoprostene bunod dosed once daily revealed higher incidences of conjunctival hyperemia (5.9% vs 1.1%), eye pain (3.6% vs 2.2%), and irritation (4.6% vs 2.6%) compared to 0.5% timolol dosed twice daily.[60,61] The majority of reported adverse events during clinical trials for both netarsudil and latanoprostene bunod were mild to moderate in severity.[58,61] While these agents have been a boon for glaucoma patients, the long-term side effects as well as patient adherence to treatment of these drops remains to be seen.

The Newer Preservatives and the Ocular Surface

Newer preservatives include stabilized oxychloro complex (Purite®) (Allergan Inc., Irvine, CA), polyquaternium-1 (polyquad 0.001%,) sodium perborate, and edetate disodium, as well as SofZia® (Alcon, Inc. Fort Worth, Texas, USA), which contains ion-buffered borate, zinc, and sorbitol.[52]

These preservatives have consistently demonstrated greater safety for the corneal epithelium than BAK in rabbit models.[22,62] One study compared membrane integrity, cell viability, and barrier function between the known preservatives including polyquad, Purite®, and edetate disodium and sorbic acid.[62] All of the BAK-preserved solutions had more unfavorable effects on enzyme activity, membrane integrity, and apoptosis.

Although rabbit models have been generally consistent in their results, clinical studies in humans have some degree of variability. Purite®, used in Alphagan-P® can oxidize microbial cellular components without a significant effect on human ocular tissues. Several studies have demonstrated an increased tolerability compared to BAK-preserved brimonidine.[52,63] However, there may be some question about the antimicrobial efficacy compared to BAK.[19]

SofZia®, a preservative used in Travatan-Z® has also demonstrated increased tolerability compared to BAK-preserved PGAs in patients switching from latanoprost to Travatan-Z®,[64] but larger clinical trials have failed to demonstrate this.[65] The discrepancy in study design and the difficulty in testing the particular ingredients in these compounds remain a challenge in comparing the effects of these drops.

Topical Treatment versus Selective Laser Trabeculoplasty

Selective laser trabeculoplasty (SLT) is an alternative to topical drops for reducing IOP by increasing aqueous outflow through the trabecular meshwork.[66] By decreasing or removing the need for topical medications, SLT may reduce the ocular and systemic side effects associated with chronic topical therapy. One large randomized controlled trial (n = 167) comparing SLT versus topical medication as an initial glaucoma treatment found that more participants in the medication group had eyelid erythema at 2 years and conjunctival hyperemia at both 1 and 2 years compared to the SLT group.[67] The Laser in Glaucoma and ocular HyperTension (LiGHT) study compared quality of life and side effect profiles of SLT versus topical glaucoma medication. It found that topical drops had worse side effects including burning/smarting/stinging, tearing, dryness, itching, soreness/tiredness, feeling of something in the eye, and more at multiple time points over 3 years.[68] Both of these studies suggest that patients susceptible to ocular surface disease may benefit from laser therapy before topical drops.

Treatment of Ocular Surface Disease in Patients on Topical Glaucoma Therapy

Artificial tears are often concurrently recommended to patients on topical glaucoma medications. One 5-year retrospective study of 500 patients with glaucoma showed that 54% used artificial tears.[69] One randomized double-masked, controlled study compared two types of preservative-free artificial tears: sodium hyaluronate and hydroxypropyl methylcellulose (HPMC)/dextran.[70] HPMC is a conventional ingredient of artificial tears, while sodium hyaluronate is a naturally lubricating viscoelastic solution that has demonstrated a reduction in the ocular toxicity of BAK with in vitro studies.[71] The authors found that patients experienced a significant relief in dry eye symptoms (as measured using OSDI), improved TBUT, and decreased conjunctival and lid hyperemia compared to baseline with both treatments, but sodium hyaluronate was more effective. The currently commercially available preparations of sodium hyaluronate include Hyalein®, Vismed®, Vislube®, Opticalm®, Hylabak®, Hylovis®, and Blink®. Aside from Blink®, these drops are not readily available in the US, where carboxymethylcellulose, glycerin, and polysorbate preservative-free drops are used more often. Additionally, sodium hyaluronate is listed only as a low concentration inactive ingredient in Blink® and may not be pharmacologically significant.

In addition to artificial tears, topical cyclosporine 0.05% (Restasis) has been shown to improve OSDI scores, corneal and conjunctival staining scores, TBUT, and sub-basal nerve fiber layer density after 6 months in patients taking two or more glaucoma agents (timolol, brimonidine, or latanoprost) for at least 6 months.[72] These findings suggest that the inflammatory pathways of topical glaucoma-related therapy may parallel those of aqueous-deficiency. Newer anti-inflammatory agents, such as lifitegrast and varenicline, have not been specifically studied in patients with glaucoma-related ocular surface disease.

The anti-inflammatory activity of omega-3 fatty acids also has shown promise in the treatment of both meibomian gland disease and aqueous deficiency.[73,74] One large, open-label, prospective, uncontrolled, multi-center study examined the effects of omega-3s on more than 1000 patients on anti-glaucoma therapy.[74] Patient-reported symptoms, Schirmer test scores, TBUT, and ocular surface staining score improved significantly over the course of a 12-week treatment. The study was limited by its open-label design, and the specific types of glaucoma therapy were not examined. The largest, double-masked randomized dry eye clinical trial supported by the National Eye Institute, the Dry Eye Assessment and Management study, did not demonstrate any difference in improvement in signs and symptoms of dry eye disease with oral omega-3s.[75]

Future of Glaucoma Treatment

Although IOP-lowering topical medications have been the mainstay of glaucoma treatment for decades, the future of combating glaucoma lies in alternate drug delivery systems and in minimally invasive glaucoma surgery (MIGS).

A novel microdroplet delivery system capable of delivering 8-µL microdoses of latanoprost was shown to achieve significant reductions in IOP 1 and 2 days post-administration. The system reduced drug dose and preservative delivery to the eye by 75% compared to highly variable eye drop delivery which can range from 30 to 50 µL, potentially reducing ocular and systemic toxicities as well.[76]

Several sustained drug delivery systems have also been developed in an effort to replace the need for daily topical drop treatment. In the field of nanomedicine, delivery vehicles including liposomes, niosomes, and nanoparticles are being investigated for biocompatibility and sustained drug delivery.[77] Clinical studies are actively examining subconjunctival depot injections of a polymeric system capable of delivering latanoprost continuously for 152 days in an animal model.[78] Drug-eluting contact lenses have shown better efficacy in lowering IOP while simultaneously decreasing drug and preservative load compared to topical drops in an animal model.[79] There are also many ongoing clinical trials for sustained-release implants including a biodegradable sustained-release pellet injected into the anterior chamber, a titanium intraocular implant, and a punctal plug which elutes drug into the tear film.[80,81] Although the field of sustained drug delivery is promising, there remains concerns regarding long-term safety and the duration of the IOP lowering effects.

MIGS also has shown promise in both ab-intero[82] and ab-externo[83] approaches to reduce dependence on drops; however, the majority of these studies are lacking in evidence based on large, randomized, comparative clinical trials. One prospective randomized trial comparing the Hydrus® (Ivantis Inc., Irvine, CA, USA) and iStent® (Glaukos Corporation, San Clemente, CA, USA) implants reported that the Hydrus reduced medication drop usage by a mean of 1.6 drops compared to 1 drop with iStent.[84] Another study reporting a reduction in drop use following iStent implantation noted significant improvements in the OSDI score, corneal and conjunctival staining, and TBUT.[85] Strikingly, the proportion of eyes that had moderate or severe OSDI scores was reduced from 73% preoperatively to 29% at 3 months post-op. Additionally, OSDI scores were normal in 57% of the eyes at 3 months post-op, versus 9% preoperatively. Finally, many of these interventions require the use of mitomycin C at the limbus, which may result in limbal stem cell deficiency. Well-designed prospective studies comparing both effectiveness and side effect profiles for topical drops vs MIGS for are needed.

Conclusion

The public health impact of glaucoma on our aging population is considerable. While short-term studies have demonstrated the safety and tolerability of topical glaucoma medications, there is extensive evidence of an association between the long-term use of these therapies and ocular surface disease with direct impact on adherence to regimen, patient quality of life and glaucoma surgery outcomes. Artificial tears should be widely utilized by glaucoma patients with drug induced ocular surface disease to help reduce irritation symptoms and improve medication adherence. Topical cyclosporine 0.05% and lifitegrast should be considered in cases of severe ocular surface disease. When possible, switching to preservative-free preparations should be considered in patients who are on multiple drops. Patients who require multiple agents may fare better by opting for laser trabeculoplasty or MIGS. Factors including patient age, compliance, stage of glaucoma, and degree of ocular surface disease should guide clinician management.

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