Advances in the Diagnosis and Management of OSD

The role of preservatives and considerations before advancing glaucoma treatment.

By Jeremy B. Wingard, MD, and Francis S. Mah, MD

Ocular surface diseases (OSDs) such as keratoconjunctivitis sicca and blepharitis are extremely common among glaucoma patients. Except in cases of uveitic glaucoma and a few other specific diagnoses, the connection does not seem to be intrinsic to glaucoma but rather related to its treatment, both medical and surgical. A number of advances in glaucoma medications are aimed at decreasing the ocular surface complications of therapy, but many patients continue to suffer.

PRESERVATIVES

Benzalkonium Chloride

Although many patients tolerate a single topical agent or even a few daily eye drops relatively well, any glaucoma medication can cause intermittent or chronic ocular surface complaints. The more eye drops a patient is prescribed, the greater these concerns become. The drugs themselves are sometimes implicated as allergens or irritants, although it is often the preservatives that appear to increase the burden of OSD.[1]

Benzalkonium chloride (BAK), a common preservative used in many eye drops, has been specifically linked to symptomatic punctate epithelial staining of the cornea and conjunctival inflammation.[2] Changes to the ocular surface not only cause the patient to complain about dry eye or foreign body symptoms, but he or she may also notice a fluctuation of vision, tearing, and redness. Chronic corneal punctate erosions may also lead to anterior corneal scarring or haze. Rarely, they may be the starting point for corneal melting, ulceration, or infectious keratitis. Not only can the cornea and conjunctiva be changed by the inflammatory nature of BAK, but the eyelids and meibomian glands can be negatively affected as well. This inflammation can result in or aggravate blepharitis.

The problem related to BAK was significant enough in glaucoma patients that manufacturers altered several formulations of their drugs to improve their tolerability. Allergan, Inc., replaced its original brimonidine solution (Alphagan) with a version containing the company's proprietary preservative Purite (Alphagan P). Alcon Laboratories, Inc., replaced BAK in its travoprost solution (Travatan) with the company's Sofzia (Travatan Z). Both changes appear to have succeeded in increasing the drugs' tolerability.

Generics

Because glaucoma treatment will generally be lifelong, clinicians must find a stable regimen for their patients that provides long-term tolerability and thus enhances their adherence to prescribed therapy. One major concern involves an unlikely source. As more of the well-known glaucoma medications come off patent, many will be released with either a different preservative altogether or a different concentration of a particular preservative. This variation presents a risk to patients, especially if their physicians are unaware of the generic substitutions being made. In many cases, insurers may refuse to pay for the brand-name drug, or they may require a higher copayment. Physicians should track exactly which formulation of each medication their patients are using, especially those with OSD.

SURGICAL INTERVENTION

Eye drops for lowering IOP generally succeed in preventing or delaying surgical intervention for glaucoma in many patients. Those who are unable to tolerate medical treatment may need more invasive intervention earlier. Selective laser trabeculoplasty is a generally well-tolerated

intervention that physicians should probably consider earlier for patients with preexisting or treatment-related dry eye disease and/or blepharitis, because this modality may allow the elimination of one or more eye drops for a period of time.

In some cases, patients are so intolerant of topical therapy that they may require incisional surgery early in the course of their disease. It should be remembered, however, that a number of patients continue to complain of dry eyes after surgery. Either they had a preexisting problem with their ocular surface unrelated to their glaucoma treatment, or the surgery itself caused ocular surface problems. Specific causes are an irregular tear film related to drying at the limbal margin of a filtering bleb and effects on the limbal stem cells from surgery or antifibrotic medications.

Before advancing glaucoma therapy due to patients' intolerance of medical treatment, physicians can try a few approaches. First, when it is safe to do so, conducting a trial of one or more eye drops can help to establish the etiology of the OSD. Some preservative-free glaucoma drops are commercially available or can be extemporaneously formulated and can be the subject of a trial as well. At times, simply switching patients to a formulation with a different preservative can be beneficial. Fixed-combination eye drops that pair medications from different classes generally have a lesser total preservative load than two individual drops, so switching a patient to a combined agent may significantly relieve his or her symptoms. Preservative-free artificial tears are a mainstay of treatment for early symptomatic disease. They may be instilled 5 minutes after the glaucoma drop to help reform the tear film and wash away any residual preservative.

Standard dry eye treatment is important for the glaucoma patient to optimize the ocular surface for glaucoma medications. Aqueous tear deficiency can be treated with punctal occlusion or cyclosporine 0.05% eye drops (Restasis; Allergan, Inc.). An irregular tear film due to blepharitis can also make glaucoma medications more irritating. Warm compresses, lid hygiene, topical azithromycin (AzaSite; Merck & Co., Inc.), and even oral doxycycline may therefore help affected patients. In the authors' institution, a number of severely affected patients benefit from serum eye drops, which are made from the patient's own blood and used in the same way as artificial tears.

CONCLUSION

Although glaucoma is not inherently a cause of OSD, the treatments of the former—both pharmacologic and surgical—can initiate or aggravate the latter. OSD can also significantly affect the efficacy of glaucoma therapy and patients' perception of success. By modifying and optimizing individual therapy and treating the ocular surface, physicians can improve patients' adherence to therapy and their outcomes.

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Advice on diagnosing and managing dry eye and lid disease in the glaucoma population.


By Eric D. Donnenfeld, MD, and Allon Barsam, MD, MRCOphth

Glaucoma and ocular surface disease (OSD) are extremely common chronic ophthalmic diseases, the incidence of which increases with age. Both affect quality of life. Estimates suggest that 55 million Americans experience dry eye disease and that it is more prevalent in the glaucoma age group.[1] Glaucoma and OSD may occur independently, but surgical intervention for glaucoma and/or the long-term use of glaucoma medications may contribute to the worsening of OSD. In a recent multicenter study of 10 sites that involved 630 patients, almost half of those (305 patients) being treated with topical medications for glaucoma had concomitant OSD.[2] Risk factors included the preexistence of dry eye disease and the use of multiple glaucoma medications.[3]

Figure 1. Dry eye with conjunctival rose bengal staining in a patient on topical timolol for glaucoma.

Managing the ocular surface is an important part of ophthalmic care, and problems with the ocular surface are among the most common reasons why patients visit ophthalmology offices on a regular basis. Visual quality and ocular comfort start with a healthy tear film, and even minimal disruption of the ocular surface may cause significant discomfort and visual problems.

DRY EYE DISEASE

Diagnosis

Diagnosing dry eye disease in glaucoma patients is important. Although the number of symptoms and varying presentations among patients can complicate the diagnosis, visual fluctuation is diagnostic of OSD. If a patient's vision varies between blinks, from morning to evening, or after prolonged effort such as extended time at the computer, clinicians can assume that OSD is the culprit until proven otherwise.

The signs of dry eye disease can be evaluated with several diagnostic tests. Conjunctival staining with lissamine green or rose bengal can facilitate the diagnosis within seconds (Figure 1). Positive staining indicates that the ocular surface should be improved, because glaucoma treatment will likely worsen the condition. Other tests used in the diagnosis of dry eye disease include fluorescein corneal staining, Schirmer testing, assessment of the tear meniscus and debris, tear breakup time, and an evaluation of corneal sensation. Recently, tear osmolarity became a readily available clinical test that can be sensitive and specific in the diagnosis of dry eye disease (TearLab Osmolarity System; TearLab Corporation, San Diego, CA).

Treatment

Steps to avoid dry eye in patients with glaucoma include identifying those at risk and maximizing the stability of their tear film prior to treatment. Artificial tears are used universally, and individuals with severe dry eye should use unpreserved tears at least four times per day. Transiently preserved tears may be used up to three times per day for mild dry eye. Preserved tears may be used for very mild dry eye. Gels and ointments are available for overnight use.

Nutritional supplements can be very beneficial in optimizing the ocular surface and may be used routinely by all patients. The authors recommend a combination of flaxseed oil (omega-3 polyunsaturated fatty acids) to thin meibomian gland secretions[4] and fish oil (eicosapentaenoic and docosahexaenoic fatty acids) to reduce inflammation. Both are necessary for optimal results. Only medical-grade supplements should be taken, and fish oil supplements should be verified to be mercury-free.

An important therapeutic shift in recent years has allowed dry eye disease to be treated with the goal of reversing the condition, not merely providing palliative lubrication. The key to improving dry eye is immunomodulation. Cyclosporine treatment has been shown to significantly improve the ocular surface, and it can improve tear production, corneal staining, and meibomian gland function.[5,6] Concomitantly, this treatment significantly improves visual outcomes, reduces ocular burning and stinging, and enhances patients' satisfaction.[5] Cyclosporine is a potent T-lymphocyte modulator, and subconjuctival lymphocyte aggregation is a common finding after long-term topical glaucoma therapy.[7] Treating patients prior to glaucoma filtering surgery with topical cyclosporine (Restasis; Allergan, Inc.) may improve surgical results and reduce the incidence of failed blebs.

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LID DISEASE

OSD may result from aqueous deficiency or meibomian gland disease. Most commonly, it is a mixed-mechanism disease. In terms of management, hot compresses are an essential part of therapy, and nutritional supplements may be beneficial for all patients.[3] Topical antibiotics, in particular azithromycin (AzaSite; Merck & Co., Inc.), improve the lipid component of the tear film and meibomian gland secretions, thereby improving the ocular surface and quality of vision.[8] Because azithromycin can sometimes burn and sting, clinicians may wish to prescribe loteprednol (Lotemax; Bausch + Lomb) when initiating azithromycin therapy. Topical cyclosporine and the short-term use of corticosteroids can be an effective combination, but in severe cases, the addition of oral doxycycline may be warranted.

GLAUCOMA TREATMENT AND OSD

Often intrinsic to topical glaucoma medications are problems of tolerability, which may be exacerbated by the long-term use of preserved agents. Prostaglandin analogues can change the pigmentation of the iris and skin around the eye. They may also prolong post-surgical inflammation that, in turn, may increase the risk of cystoid macular edema.[9] Topical carbonic anhydrase inhibitors may cause a decrease in corneal endothelial function, which can result in corneal edema.[10] Locally, ß-blockers can cause corneal anesthesia as well as ocular irritation and dry eye symptoms.[11] One method of determining an individual's tolerance of a medication and the drug's effect on the ocular surface is to instill the glaucoma medication in one eye while allowing the second eye to serve as a control.

Some patients will not tolerate the preservatives in glaucoma medications, and specialty pharmacies can compound unpreserved medications that improve the ocular surface. For patients with significant OSD, the continued use of any topical medication may prevent the ocular surface from healing. A short trial of oral carbonic anhydrase inhibitors may allow them to discontinue the use of topical medications and enable the ocular surface to improve.

The surgical management of glaucoma may also permit the patient to discontinue topical medications or reduce their use. Laser intervention may be considered earlier than usual in the treatment algorithm of patients with glaucoma and OSD. Fortunately, new technologies have made glaucoma surgery less invasive and less risky, which allows surgery to be an option, rather than a last resort, for patients with mild or moderate disease.

CONCLUSION

Glaucoma and OSD are among the most common ophthalmic disorders. They interact with each other and can degrade patients' quality of vision and quality of life. Aggressive management of the ocular surface with the appropriate use of glaucoma treatment options can improve patients' comfort and visual prognoses. ❑

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