Ocular Surface Disease in Glaucoma Patients

Leo Semes, OD

Ocular surface disease is common among glaucoma patients who manage their condition with topical drops. Understanding contributing factors and options for management benefits patients by potentially improving quality of life, adherence to treatment, and medical and surgical outcomes.

Ocular surface disease (OSD) is prevalent among patients treated with topical medications for ocular hypertension and glaucoma, affecting between 20% and 59% of patients according to recent studies.

Since the focus of glaucoma management is controlling intraocular pressure (IOP) and maintaining optic nerve health, eye care providers may regard the ocular surface as secondary and may overlook or dismiss OSD in their glaucoma patients. Others may regard OSD as an inevitable consequence of topical treatment that patients must accept, particularly since options for management are limited.

Both perspectives are unfortunate since an unhealthy ocular surface can significantly undermine quality of life and medication adherence. In addition, a poor quality ocular surface has the potential to jeopardize glaucoma surgery outcomes by exacerbating pre-existing inflammation and interfering with healing. Many patients tolerate IOP-lowering medications well without developing significant OSD; for those who do develop OSD, detecting the disorder in its early stages and offering management solutions—including alternative IOP-lowering therapies when necessary—can benefit patients.

Etiology

The ocular surface is a highly complex network of tissues that is subject to myriad stresses both internal and external to the eye. Among glaucoma and nonglaucoma patients alike, damage to the ocular surface may result from a wide range of conditions including allergy, blepharitis, dry eye disease (aqueous deficient and secondary to meibomian gland dysfunction [MGD] or other causes), or anatomical abnormality of the eyelid.

We see high prevalence rates of OSD among glaucoma patients in part because increased age is associated with both conditions; and there is some overlap in both prevalence and incidence simply due to chance. Independent of age, however, glaucoma increases patients' risk for OSD due to long-term ocular surface exposure to IOP-lowering medications, some of which have toxic effects on conjunctival and corneal epithelial cells (Figure 1).

The ocular surface effects of topically applied medications have been of interest to researchers since at least the 1990s. Basic research in the development of the first prostaglandin analogue (PGA) revealed that it induced ocular hyperemia via nitric oxide synthase activation, a well-described side effect of the PGA class. In 1996, Baudouin postulated that ocular exposure to a common IOP-lowering medication preservative,
benzalkonium chloride (BAK), may be related to inflammation as well as cytotoxicity and may contribute to glaucoma filtration surgery failure.6

The side effects of topical treatment—in particular BAK—on the ocular surface appear to be dose-dependent. In 1997, Ariturk showed that tissue from glaucoma filtration surgery patients who used multiple agents for longer durations showed higher concentrations of subepithelial inflammatory cells on histopathology compared to lesser exposed and unexposed tissue.7 Since then, many studies have confirmed that treatment with topical agents causes a dose-dependent increase in OSD signs and symptoms.8-10 Specifically, being on multiple medications (polypharmacy vs monotherapy), frequent dosing (BID or TID vs QD), and longevity of treatment—all of which contribute to total cumulative exposure—are risk factors for tear film abnormalities and medication-related OSD.7,9,10

On a cellular level, studies have shown that eyes with higher exposure to IOP-lowering medication (longer duration and/or multiple medications) have more evidence of inflammation (eg, overexpression of inflammatory marker human leukocyte antigen HLA-DR and immune cellular infiltration) and cellular abnormalities (including squamous metaplasia and decreased goblet cell density).11,12

**Ingredients and Mechanisms**

Ocular surface disease culprits may include the drug’s preservative (eg, BAK-induced cytotoxicity), active ingredient (eg, beta-blocker or prostaglandin analog effects), or even inactive excipients.

**Preservatives and Excipients**

Long-term exposure to BAK-containing IOP-lowering medication has been shown to disrupt the tear film; induce toxic, inflammatory, and detergent effects on ocular surface cells and the tear film; and cause degenerative changes to trabecular meshwork (TM) cells similar to that seen via glaucoma mechanisms themselves.13-17 A cross-sectional study by Leung and colleagues showed that among patients being treated for glaucoma, 27% had severe ocular surface symptoms as measured by the Ocular Surface Disease Index (OSDI), 35% had severe tear deficiency as measured by Schirmer testing, and 78% had poor tear quality as indicated by abnormal tear break up time (TBUT).18 In that same study, corneal and conjunctival lissamine green staining was present in 22% of patients and correlated with BAK exposure (Figure 2).18 In a separate study, use of a BAK-containing medication was associated with nearly three times the odds ratio for significantly abnormal OSDI score.11

Drug vehicle ingredients included for purposes other than preservation, ie,
excipients, may also interact with and cause harm to the ocular surface with repeated exposure. Researchers recently demonstrated in vitro effects of several preservative-free PGAs—including increased blinking frequency, macrophage infiltration of the eyelids, and goblet cell damage—that might be induced to excipients in the formulation.\(^19\)

**Active Ingredients**

While BAK has received the most scrutiny with regard to ocular surface effects, active ingredients of glaucoma medications, particularly PGAs and beta-blocking agents, have also been associated with unwanted ocular surface changes.\(^16\),\(^20\) The body’s prostaglandins are known to be an essential link in the inflammatory chain of events; by extension, prolonged PGA glaucoma therapy could be expected to incite some degree of ocular surface inflammation over time.

Indeed, research seems to bear this out. Prospective studies have shown that conjunctival cells and tears of patients exposed to as few as several months of latanoprost demonstrate markedly increased concentrations of proinflammatory molecules, including matrix metalloproteinases (MMP-1 and MMP-9) and HLA-DR, compared with similarly preserved non-PGA medications or vehicle.\(^21\),\(^22\) The authors concluded that PGA exposure is specifically responsible for subclinical ocular surface inflammation.

Further, inflammatory ocular surface conditions, including blepharitis and MGD, occur with increased frequency among patients on long-term topical PGA medication compared with untreated patients and patients treated with non-PGA glaucoma medications.\(^20\) MGD has been demonstrated in 80% of patients on long-term hypotensive therapy and 96% of patients on PGA therapy specifically.\(^16\),\(^23\)

Beta-blocking IOP-lowering agents have been associated with decreased tear production and reduced TBUT, and may also contribute to MGD and corneal toxicity.\(^24\),\(^25\) One study showed that BAK-induced corneal epithelial effects were significantly worse among beta-blocker-treated patients compared with similarly exposed PGA-treated patients.\(^8\)

**Consequences for Patients**

Unchecked OSD compromises quality of life for patients who are already bearing the substantial psychological burden that comes with having an unpredictable, incurable, vision-threatening disease. In my experience, patients with ocular surface symptoms can typically pinpoint the start of their discomfort to the beginning of treatment or the addition of a new medication to their regimen, contributing to a perception among early-stage patients that the treatment is worse than the disease. Naturally, risk for treatment lapses or discontinuation is heightened in such patients.

For patients whose disease progresses on medical therapy and who may require invasive surgery, a healthy ocular surface is desirable, as it may facilitate better post-surgical healing, reduce risk for complications, and lead to better overall outcomes.

**Detect OSD Early**

Eye care providers should be vigilant for OSD symptoms and/or signs among their patients on topical hypotensive treatments, since disease detected in early stages is more amenable to successful therapy. Listen for symptoms of irritation, foreign body sensation, transiently blurred vision, and increased frequency of blinking; and cultivate the practice of administering a standardized symptom survey such as the OSDI. On examination of symptomatic patients, look for classic signs of OSD, including superficial punctate keratopathy (by ocular surface staining with fluorescein or lissamine green), meibomian gland inspissation, shortened TBUT, and increased tear osmolarity. Be sure to perform a close inspection of the ocular surface, as even subtle fluorescein staining may indicate an abnormality and warrant investigation.

Have your antennae up for complaints that seem discordant with expected side effects, both at the onset of treatment and over the long term. For example, conjunctival hyperemia associated with a bedtime dose of PGA should dissipate overnight; redness that persists through the day may be an early sign of medication-related toxicity or inflammation. To optimize medication adherence, educate patients about potential side effects so they have an idea of what to expect, and encourage them to contact you with questions or concerns as they arise.

**Management**

**Strategies to Reduce Toxicity**

A number of approaches may be useful in the management of OSD among

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Key Issues in Ocular Surface Disease

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glaucoma patients. In one sense, OSD occurs when the eye is given too little time between insults to restore homeostasis; thus, the first goal is to reduce the burden of medications and preservatives on the eye without effecting the IOP-lowering potency of the regimen. Reducing the number of medications, number of doses, or switching to an alternative IOP-lowering medication or combination formulation that can be dosed less frequently reduces cumulative BAK exposure and may improve healing between doses. Alternatives to BAK include the preservatives SofZia®, a boric acid-based ionic buffered system, and polyquaternium-1 (Polyquad®), used in multipurpose saline solutions for contact lens care. SofZia and Polyquad have demonstrated significantly less cytotoxicity (better corneal, conjunctival, and trabecular meshwork cell viability) in vitro compared with BAK.26,27 Multiple studies have shown that substituting BAK-free antiglaucoma medications (either preserved with compounds other than BAK or preservative-free formulations) for BAK-containing ones reduces OSD signs and symptoms without compromising IOP control.28,31 For example, one prospective study showed that switching from a BAK-preserved latanoprost to a SofZia-preserved travoprost improved corneal staining, TBUT, and OSDI scores within 8 weeks.29 For some patients, laser or surgical trabeculoplasty may be effective in reducing or eliminating dependence on topical antiglaucoma medication and is an attractive option for controlling IOP. However additional risks must be weighed against the potential benefit.

Treatments for Dry Eye

Measures to lubricate and protect the ocular surface, reduce surface inflammation, and improve meibum quality and outflow may also be useful in the management of OSD among glaucoma patients. Preservative-free tear supplements; lid warming, hygiene and manual massage; and in-office lipid flow-enhancing treatments may be indicated. Tear supplements containing osmoprotectants, eg, sodium hyaluronate, carboxymethylcellulose, or hydroxypropyl methylcellulose, have been shown to improve dry eye symptoms, surface cell viability, tear film quality, corneal and conjunctival staining, and other parameters in glaucoma patients with medication-related OSD.32-34 Treatment with topical cyclosporine 0.05% twice daily for 6 months concomitantly with IOP-lowering medication has also been shown to markedly reduce signs and symptoms of OSD.35 Other options for the treatment of OSD related to topical IOP-lowering medications may include cyclosporine topical drops (Restasis®, Allergan), which has been FDA-approved for over a decade to enhance tear production in patients diagnosed with aqueous-deficient dry eye, and, lifitegrast (Xiidra®, Shire), which was recently FDA-approved to treat signs and symptoms of dry eye. In addition, omega-3 supplementation has been documented in epidemiological studies to be beneficial for dry eye sufferers.36

Conclusion

Topical ocular hypotensive medications can disrupt the normal balance of the ocular surface and lead to OSD. In addition to traditional measures for treating dry eye, efforts to reduce medication and preservative burden may reduce patient symptoms and optimize their odds for successful glaucoma management.

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REFERENCES

Dry Eye Disease in Ocular Surgery Patients

Walter Whitley, OD, FAAO

A significant proportion of patients seen every day in optometric practice have undiagnosed dry eye disease (DED). Identifying and managing DED in affected patients prior to surgical referral optimizes patients’ chances for excellent visual outcomes, maximal comfort, and overall surgical success.

Historically, dry eye disease (DED) has been shown to be prevalent in middle-aged and older patient populations, including in many patients who are seeking refractive surgery (eg, LASIK, PRK, small incision lenticule extraction [SMILE], and corneal inlays), cataract surgery, and other types of ocular surgery (eg, anti-glaucoma, blepharoplaasty). While estimation methods vary and the exact DED prevalence within surgical populations cannot be stated as fact, evidence suggests that at least 60% of patients in evaluation for penetrating keratoplasty have DED, as do 27% of LASIK patients, 78% of glaucoma patients, and 26% of blepharoplasty patients. In a study by Trattler and co-workers looking at DED among patients presenting for cataract surgery, 77% had positive fluorescein staining of the cornea, and 63% had abnormal tear break-up time (TBUT); only 22%, however, were aware they had DED.

It is easy to ask, why aren’t more eye care providers identifying and managing DED? Within the OD community, tasks related to the refractive side of practice—for example, the art and science of fitting contact lenses and/or progressive addition lenses—are more practical, yet managing chronic diseases is becoming an optometrist’s mainstay in some practices. However, time constraints and loss of income from refractive sales might also factor into the challenges of the medical model. Regardless, DED is an optometric condition; failing to prioritize it as such does patients a disservice.

DED Implications

Recognizing and treating DED prior to referral is a fundamental part of presurgical care that serves several key functions. First, a smooth ocular surface and stable tear film enable accurate presurgical corneal topography and biometry. Surface aberrations skew corneal measurements, increasing the potential for suboptimal visual outcomes and reduced quality of life postoperatively. Studies show that cataract surgery outcomes are within 1.0 diopters (above or below) of the intended target only 71% of the time.

To extrapolate from those data for discussion purposes, outcomes could be substantially improved in more than one in four cataract surgeries. While many variables influence outcomes, including factors related to the surgeon and technique, factors related to the patient likely also play a role in missing the target; ocular surface irregularity, which can be caused by DED, is a plausible (and, in my mind, likely) culprit in many cases.

A second reason it is important to address ocular surface health, including DED, prior to surgery is so that the best type of surgery and, in the case of cataract surgery, the best type of intraocular lens (IOL) can be recommended. Of the more than 4 million cataract replacement surgeries performed every year, patients with significant long-standing ocular surface disease (OSD) may find that, come time for cataract surgery, they have fewer IOL options compared to patients with healthy ocular surfaces. In general, the more sophisticated the IOL, the more critical it is that the ocular surface is perfect to get desired visual outcomes and patient satisfaction. Patients with an unhealthy ocular surface that does not respond to presurgical treatment may be poor candidates (or not a candidate) for a toric, multifocal, or extended depth-of-focus IOL. This limits their options to a monofocal IOL and greatly diminishes their chances for spectacle-independence following cataract surgery.

Most patients seeking refractive surgery are good candidates for LASIK, as presurgical OSD and inflammation, when present, can usually be controlled through proper treatment prior to and after LASIK. However, patients with persistent corneal staining despite treatment, or those whose OSD takes a long time to clear, may be advised against refractive surgery or recommended for PRK rather than LASIK, since PRK has been associated with lower rates of postoperative dryness. Where newer technologies, including SMILE—a novel flapless laser vision correction modality—and corneal inlays—a monocular implant technology for treatment of presbyopia—fall on the continuum of potential for postoperative dryness is as yet unclear. There is some

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Patients should be counseled regarding the importance of identifying and treating any ocular surface abnormality—from symptomatic dryness to ocular surface damage—prior to surgery in order to reduce the risk for postoperative DED or other complications and to optimize visual outcomes. In my experience and practice, most patients are perfectly amenable to delaying surgery when they know that preparing the ocular surface will help their chance for achieving an excellent visual outcome.

It is also useful to counsel patients with regard to what to expect after surgery. Most patients have dryness in the immediate postoperative period that resolves in a majority of cases within weeks to months of the procedure. Chronic DED following PRK or LASIK is rare (occurring in fewer than 5% of patients) and is, to some extent, predicted by preoperative ocular surface status, for example, a lower presurgical Schirmer score. Knowing a patient’s baseline state of ocular surface health or disease may be useful in the management of any postoperative complaints that may arise.

**Detect and Diagnose**

Busy eye care providers who have yet to incorporate DED screening into their practices and who are wondering where to start might look to a very practical set of recommendations put forward by the 2014 Dry Eye Summit. A protocol for evaluating the ocular surface should include assessment of symptoms and signs of ocular surface distress and underlying conditions of DED, lid disease, and meibomian gland disease (MGD). An assessment would ideally start with the administration of a written questionnaire that quantifies symptoms, such as the Standard Patient Evaluation of Eye Dryness (SPEED) or the Ocular Surface Disease Index (OSDI), which patients can complete in the waiting room. Incorporating a symptom survey into daily practice is easy to do and would almost certainly reveal a surprisingly high proportion of patients suffering from DED. Alternatively, asking patients three or four questions (verbally or written) would suffice, such as the four key questions that emerged from the Dry Eye Summit:

1. Do your eyes ever feel dry or uncomfortable?
2. Are you bothered by changes in your vision throughout the day?
3. Are you ever bothered by red eyes?
4. Do you ever use or feel the need to use drops?

In addition to general ocular surface symptoms (eg, burning, itching, foreign body sensation, irritation, grittiness, photophobia, and contact lens intolerance), patients with anterior blepharitis sometimes report excessive crusting or eyelids sticking together, especially in the morning. Affirmative findings on surveys or during the patient interview should be followed by testing for DED.

An OSD evaluation need not include every available test, but patients suspected of DED should at a minimum undergo 1) eyelid examination, including of the meibomian glands; 2) corneal staining; and 3) an assessment of tear film stability, such as TBUT or osmolarity testing. Other tests may also be performed, including MMP-9 assessment via InflammaDry® (RPS, Sarasota, FL), a point-of-service test for an inflammatory marker in tears. For patients with suspected or confirmed MGD, meibography using an instrument such as LipiScan™ (TearScience, Morrisville, NC) or Keratograph® 5M (Oculus, Arlington, WA) is not only useful for diagnosis, but the resultant images are a powerful visual aid for patient education and counseling (Figure 1).

**Treatment**

In presurgical patients, DED treatment is aimed at reducing signs and symptoms and interrupting inflammation. Underlying conditions such as MGD or lid disease should also be addressed, when present.

According to the Dry Eye Summit,
DED treatment should include 1) eyelid hygiene, 2) ocular lubrication, 3) omega fatty acid supplementation, and 4) a topical anti-inflammatory agent. Patients with more advanced disease may also benefit from punctal plug placement or, if MGD is causing the dryness, thermal lid margin treatments such as LipiFlow® (TearScience, Morrisville, NC).

Follow-up should be scheduled for 4 to 6 weeks (sooner if warranted) following the initiation of therapy and include the same tests as initially performed. If sufficient ocular surface healing is demonstrated, one can confidently refer for surgery. If significant ocular symptoms or signs remain, additional therapies may be warranted. It is important to discuss both with the patient and the surgeon when the cataract evaluation and surgery should be performed based on medical necessity. An example would be someone in need of renewing his or her driver’s license but who still has chronic DED; that patient may need surgery sooner with a standard IOL.

**Post-surgical Follow-up**

Post-surgical follow-up should be tailored to the patient and the procedure and coordinated with the surgical team. My practice is to follow up with patients 1 day, 1 week, and 1 month following either cataract or refractive surgery in order to assess vision and rule out complications as patients complete each course of discharge medications (generally anti-inflammatory and antiinfectives). Occasionally, antiinflammatory medication may need to be restarted or changed.

For example, following cataract surgery, some patients do not achieve best corrected 20/20 vision—the expected satisfactory outcome—with a light (or no) prescription by one month’s time. Possible causes may include cystoid macula edema, posterior capsular opacification, residual refractive error, or OSD. If ocular surface inflammation is the suspected underlying cause, treatment with topical ocular anti-inflammatory agent such as Xiidra® (lifitegrast ophthalmic solution 5%, Shire, Lexington, MA) or Restasis® (cyclosporine A ophthalmic emulsion 0.05%, Allergan, Irvine, CA) may be indicated.

Artificial tears are commonly prescribed for patients post-LASIK and post-cataract surgery to provide relief from dryness and support tear homeostasis and function. I stress to patients the importance of using the drops multiple times per day as prescribed irrespective of their perceived dryness, since patients with corneal desensitization may not perceive ocular surface symptoms.14,15

**Conclusion**

Evaluating and preparing the ocular surface prior to refractive or cataract surgery and LASIK referral improves patients’ chance for successful surgery and favorable postoperative visual outcomes. Eye care providers should screen patients for DED using a standardized symptom questionnaire and implement basic DED diagnostic and treatment protocols.

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**REFERENCES**

1. Sheppard JD. Prevalence of dry eye in planned penetrating or endothelial keratoplasty. World Cornea Conference VII; April 15-17, 2015; San Diego, CA. Poster #15668.


12. Expert Recommendations from The 2014 Dry Eye Summit. Dallas, TX.


**SEMS REFERENCES continued from page 4**


1. Which of the following parameters has NOT been shown to influence risk for OSD among glaucoma patients?
   A. Dosing frequency
   B. Timing of dosing
   C. Number of medications
   D. Duration of IOP-lowering management

2. A presurgical cataract patient reports symptoms of ocular grittiness, burning, crusting around the lashes, and eyelids stuck together upon awakening. What condition is most commonly associated with this constellation of symptoms?
   A. Anterior blepharitis
   B. Posterior blepharitis
   C. Meibomian gland disease
   D. None of the above

3. Which of the following may be an appropriate OSD management strategy for patients with glaucoma?
   A. Osmoprotectant tear supplements
   B. Topical drop “holiday”
   C. Consideration of a glaucoma surgical consultation
   D. A and C

4. Which of the following conditions is LEAST likely to be associated with medical antiglaucoma management?
   A. Blepharitis
   B. Keratopathy
   C. Bacterial conjunctivitis
   D. Dry eye

5. Which of the following questions were recommended by the Dry Eye Summit committee for screening of DED?
   A. Are you bothered by changes in your vision throughout the day?
   B. Do you ever feel the need to use drops?
   C. A and B
   D. Neither of the above

6. BAK-preserved IOP-lowering medications have been associated with which of the following effects?
   A. Decreased goblet cell density
   B. Increased corneal epithelial-cell compromise
   C. Increased tear film inflammatory markers
   D. All of the above

7. Which of the following is NOT a recommended first-line treatment for DED according to the Dry Eye Summit committee?
   A. Lid hygiene
   B. Omega-3-fatty acid supplementation
   C. Punctal plugs
   D. Topical cyclosporine A

8. Which of the following is NOT a role of ODs in perisurgical care of patients?
   A. Counseling patients
   B. Diagnosing DED
   C. Treating DED
   D. All of the above are OD roles

9. Which of the following is NOT a part of the rationale for addressing ocular surface health prior to surgery?
   A. Accuracy of presurgical measurements
   B. Lower risk for chronic DED after surgery
   C. To dissuade patients from undergoing surgery
   D. To improve IOL options for cataract patients

10. Which of the following is NOT an osmoprotectant available in artificial tears for the treatment of OSD?
    A. Boric acid
    B. Sodium hyaluronate
    C. Carboxymethylcellulose
    D. Hydroxypropyl methylcellulose