Getting beyond the surface in ocular surface disease

Eliminating inflammation has many implications for ocular surgery patients

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Ocular surface disease (OSD) is a prevalent, chronic, and progressive condition with an often multifactorial etiology. A comprehensive approach to detection, treatment, and monitoring is required.

In its most severe forms, OSD can be associated with blurred or fluctuating vision, foreign body sensation, photophobia, stinging, itching, watery eyes, grittiness, burning, and irritation.[1-3] Among cataract surgery patients, presence of even mild OSD can lead to variability in average keratometry, anterior corneal astigmatism, and IOL power calculations.[4]

Recent news: Shire's dry eye drug now available by prescription

In an era where patients are expecting more from their postsurgical vision, it behooves the ocular surgeon to take a proactive approach for managing the ocular surface.

OSD rarely presents as a solitary, easily identifiable entity, and there are often comorbidities and other factors present in patients with dry eye disease (DED) that contribute to or exacerbate the clinical presentation. For example, there is significant crossover in the signs and symptoms of dry eye disease and allergic conjunctivitis, blepharitis, and bacterial conjunctivitis.[5-7]

Related: How sleep habits may affect dry eye

Furthermore, blepharitis is known to be both a cause of ocular surface symptoms as well as a contributor to DED.[6] Meibomian gland dysfunction (MGD) can be a cause of blepharitis and a prominent underlying factor in DED.[8] MGD can manifest as pure MGD or combined MGD/aqueous-deficient dry eye in 86% of DED patients, as seen in a multi-center study of 299 subjects.[9]

A number of risk factors for DED have been identified, including systemic medical issues (i.e., thyroid, hypertension, hypercholesterolemia, diabetes), use of systemic medication, and lifestyle (i.e., stress, work environment, excess computer use, poor ergonomics, poor make up habits, etc.).[3,10-12]

Recent: Portable device offers rapid high-definition meibomian gland imaging

Prominently, inflammation plays an important role in DED, which "is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[3] Abnormal tear osmolarity has been

identified as a common feature of both aqueous deficient and evaporative dry eye.

Thus, while OSD (and DED in particular) warrants diligence in its own right, the associated impact of OSD inflammation pre- and postoperatively deserves consideration in cataract and other ocular surgeries.

Even gentle cataract surgery in eyes with mild forms of OSD can induce inflammatory responses that portend poor visual outcomes and exacerbation of symptoms that affect quality of vision and, in some cases, quality of life.

OSD: Epidemiology and pathophysiology

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DED is already one of the most prominent ocular diseases in the United States, affecting roughly 29 million individuals.[10] According to surveys, 40% of patients experience symptoms of DED on a regular basis,[13] and 14% self-report having DED.[14] Although classically thought to be age-related, emerging evidence has demonstrated a shift in the demographics of OSD.

The Beaver Dam Offspring Study showed that the prevalence of DED in the 21- to 49-year old age group is not statistically significantly different than the prevalence in the above age 50 group.[14] This corroborates many clinicians' observations that DED is affecting younger patients as well.

OSD is often a chronic and progressive entity, which is particularly true in the case of dry eye and MGD. Thus, the golden opportunity in these disease states is to identify the inflammation burden early in life and introduce interventions designed to quell the signs and symptoms in the short-term, while restoring the health of the tear film in the long-term.

There has been much research to contribute to the understanding of DED, particularly in highlighting its inflammatory nature. The lacrimal functional unit (LFU) is a tightly integrated system designed to maintain tight homeostatic control of the normal, protective tear film.

More dry eye: Addressing ocular surface toxicity in glaucoma patients

OSD results when the LFU system is overburdened and compensatory mechanisms fail to maintain homeostasis. This loss of homeostatic control and loss of compensatory mechanisms results in hyperosmolarity and desiccating stress, the two known aberrant activators of the native immunity of the eye[3]—this is the root cause of OSD.

The aberrant activation of toll like receptors (TLR) results in an unleashing of molecular inflammatory mediators. A chronic, self-perpetuating cycle of increasing inflammation ensues unless interventions are deployed, such as pharmacologic interventions, and identification of the root sources of hyperosmolarity and desiccating stress. Interventions that normalize osmolarity within the tears may result in resolution of the signs and symptoms.[15]

Related: A tearscope made of paper?

Thus, hyperosmolarity can be understood to be a cause and consequence of inflammation, a relevant marker of disease activity, and a source of epithelial hyperplasia/refractive errors.

OSD in the surgical patient: Impact of inflammation

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Mounting evidence suggests that ocular surface health is critically important in patients undergoing cataract surgery, as it is a significant cause of IOL calculation errors and post-surgical refractive surprises.

It is also an underappreciated entity: Although only about 22% of preoperative cataract patients come in with the diagnosis of DED, as many as 80% will have evidence on pre-operative examination of ITF level 1, 2, or 3 DED.[16]

Post-surgical wound healing, namely proliferation, differentiation, and apoptosis, are mediated by cytokines and receptors. The risk of postoperative complications is lowered when steps are taken to optimize wound healing and expedite corneal epithelium renewal.[17]

Related: Exploring balance of controlling inflammation, IOP in uveitis

Fortunately for patients, the increased understanding of OSD and its importance dovetails with the market availability of sophisticated diagnostics and newer therapeutic modalities. Validated questionnaires, including the OSDI and SPEED,[18] are quick and easy to use to identify cases needing follow up and track response to therapy over time.

Tear osmolarity testing (TearLab)[19] is an efficient method of screening for OSD and monitoring progress. Examination techniques such as light manual meibomian gland expression on the lids may reveal non-obvious MGD contributing to the evaporative load, while Lissamine Green and fluorescein staining can be used to unmask corneal and conjunctival consequences of OSD.

Meanwhile, a point of care test (InflammaDry, RPS) to detect MMP-9 activity in the tear film (a marker for Th17 driven inflammation),[20,21] and LipiView to assess the meibomian glands may be added as indicated to build a more complete understanding of each patient's unique presentation and disease features.

Another modality, interferometry, can be used to identify thinning of the lipid layer.[22-25] Topography, aberrometry, and other objective measures of assessing the visual performance and integrity of the tear film may be employed.

Recent: Fibrin adhesives another approach to epithelial ingrowth post-LASIK

Preoperative identification of OSD is important for IOL calculations, optimal visual performance outcomes, and healthy postoperative wound healing. If significant inflammation is identified, steroid-sparing immunomodulators, such as 0.05% cyclosporine emulsion (Restasis, Allergan), have been shown to improve goblet cell density and immunoregulatory cytokines such as TGF-*B*2 within 6 weeks of initiation of therapy.[26]

Improvements in the health of the LFU optimize the pre-operative keratometric measurements and IOL calculations, the postoperative wound healing response, and postoperative visual performance.

More: Postop keratometry not associated with night-vision problems

During surgery, use of femtosecond cataract surgery may reduce the potential to incite inflammation. Use of clear corneal incisions may help prevent inducing postoperative symptoms in eyes with DED.[27,28] Notably, corneal keratocyte apoptosis can be detected as early as 4 hours after scrape injury and continue for a week in a murine PRK wound healing model.[29]

Postoperative period

In the postoperative period, complex cytokine-mediated wound healing events occur, including: keratocyte apoptosis; lacrimal gland growth factor response; myofibroblast differentiation and cytokine production; activated inflammatory cell infiltration; metalloproteinase upregulation; stromal remodeling; epithelial hyperplasia; myofibroblast and inflammatory cell apoptosis; and, finally, return to normal state.[29]

Further, the lacrimal gland produces growth factors in response to epithelial injury that modulate a healthy wound healing response.[29] It stands to reason that starting with a healthy LFU improves the wound healing response.

In addition to controlling the inflammatory response to surgery with postoperative medications, choosing topical applications that minimize the epitheliotoxic and tear-destabilizing benzalkonium chloride (BAK) load may help prevent OSD exacerbations.

Related: Reverse side cut produces better self-sealing efficacy

For example, while NSAID therapy counteracts inflammation and postoperative pain, historically, certain formulations (and especially generic preparations) may be harsh to the ocular surface and may elevate the risk of corneal ulcers and melts.[30]

Corneal nerves have four types of afferent nociceptors: osmoreceptors, mechanoreceptors, thermoreceptors, and inflammation inducible nociceptors. They also produce efferent wound healing peptides such as VIP (vasoactive intestinal peptide), Substance P, IGF (insulin-like growth factor), and BMP-7 (bone morphogenic protein). Theoretically, ensuring that the LFU is restored, fully integrated and optimally functioning (including the corneal nerves) helps us to achieve a greater level of healing.

Newer bromfenac formulations, such as bromfenac ophthalmic solution 0.07% (Prolensa, Bausch + Lomb), are formulated with a lower concentration of active drug, thereby reducing the potential for complications while still delivering potent inhibition of prostaglandin synthesis.

More recently, bromfenac ophthalmic solution 0.075% (BromSite, Sun Ophthalmics), which is formulated in a proprietary drug delivery vehicle (DuraSite) that stabilizes small molecules in a polymeric mucoadhesive matrix, has become available and is approved for commercialization in the U.S. market, becoming the first and only NSAID to receive a prevention of pain after cataract surgery indication from the FDA.

Related: IV-free sedation may help anxious cataract patients

The polymer prolongs the residence time of bromfenac on the ocular surface by reducing the rate of medication loss caused by blinking, tearing, and normal tear turnover, thereby leading to increased penetration. This drug, which contains low levels of BAK, offers superior penetration, as demonstrated by higher concentration of active drug in aqueous humor in a phase II study.[31]

Yet, in a phase III study, it also exhibited very high levels of anti-inflammatory activity.[32] Additionally, since preservatives can impact the TBUT of healthy volunteers for up to 3 days after a single dose,[33] it stands to reason that minimizing the BAK exposure in postoperative medications is important for our OSD patients.

Conclusions

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Managing OSD in the perioperative period begins with a proactive approach. The mantra is to identify early and set the patient up for long term success. Intervening aggressively to optimize the LFU and ocular surface prior to surgery, use of surgical techniques that lower the potential to induce inflammation, and thoughtful use of agents pre- and postoperatively that minimize the impact on the ocular surface are good strategies.

Related: New drape speeds ophthalmic surgery

Patients with OSD represent a large population with an already compromised ocular surface and significant inflammatory load, and so while the need to reduce inflammation from ocular surgery is the primary objective, mitigating the risk of further insulting the compromised ocular surface while striving for LFU physiologic restoration is also of compelling consideration.

DED can be a frustrating entity for providers and patients. It is difficult to treat and highly variable in appearance. However, the importance of inflammation in the dry eye cascade presents an opportunity to rethink and recalibrate approaches to diagnosis and treatment.

Recent: Pearls for using dual blade to lower IOP

As eye care providers, looking beyond the surface of the cornea to understand the underlying mechanisms of OSD helps us to devise strategies to eliminate inflammation cause and effect and to achieve physiologic restoration of the LFU. The visual performance, patient satisfaction, and physician satisfaction with a job well done in optimizing health are rich rewards indeed.

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