Staying Local with Blepharitis Treatment

Ways to diagnose and categorize the disease, and thoughts on the best way to treat it when it occurs.

Mark B. Abelsohn, MD, CM, FRCSI, FARVO, Aron Shapiro and Caroline Tobey, Andover, Mass.

Blepharitis is a condition that involves the eyelids and associated structures, so why do we treat a blepharitis-affected lid by putting a topical steroid or antibiotic drops in the eye along with some lid scrubbing? We see the eye as our patient, and we don’t want to waste our therapeutic efforts by sending drugs to far-off places such as the liver or the kidneys; instead, it makes much more sense to deliver an effective treatment straight to the source of discomfort, which in this case is the lid.

This month we’ll go over the basics of blepharitis, explore the ins and outs of drug delivery, and consider how current delivery methods may be falling short when it comes to this common ocular disorder. What should become clear is that the eyelids and conjunctiva, while geographically close, may require very different treatment applications, and the course of therapy for blepharitis should be administered accordingly.

The ABCs of Blepharitis

Blepharitis is a multifactorial ocular surface disorder that can consist of an inflammation of the eyelid margin, including the lid and its dermis; the eyelashes, the tarsal conjunctiva, the mucocutaneous junction; and the meibomian glands. The condition is typically chronic and characterized by intermittent, acute flare-ups. Blepharitis can also be associated with a variety of systemic diseases like dermatitis, as well as ocular surface diseases such as dry eye, conjunctivitis or keratitis.1 Signs and symptoms of blepharitis include swelling, thickening, scaling and/or crusts of the eyelids, redness of the lid margins, bulbar and palpebral hyperemia, gritty eyes and itchy eyelids. Staphylococcal blepharitis patients frequently exhibit mild adhesion of the lids, thickened lid margins, and missing and misdirected eyelashes; seborrheic blepharitis appears as greasy flakes or scales around the base of the eyelashes and a mild redness of the eyelids.2

We, too, have gotten involved in the classification of blepharitis, and in 2006 we created a classification system known as the Ora Calibra Blepharitis Scales, which consist of standardized, photo-validated scales for blepharitis and meibomitis based on anatomical descriptors. These validated scales have been used in previous clinical trials in order to accurately assess factors such as:

- lid margin redness;
- palpebral conjunctival redness;
- lid-edge shape;
- keratinization;
- lash folliculitis and debris;
- meibomian gland alignment, secretion viscosity and secretion color;
- perigland redness, and
- lash loss.

To construct the scales, a panel of clinicians ranked digital images from least severe to most severe, and they selected representative images to generate a scale of 0 to 3 (normal to severe). A lid margin evaluation was also performed, analyzing regional lid edge redness (temporal, medial and nasal) as well as lash folliculitis, lid hyperkeratinization, lash madarosis, cross-sectional posterior lid edge shape and lash debris. Additionally, Ora’s direct meibomian gland tracking technology system is able to track and observe meibomian gland secretion’s viscosity, color and thickness over time.

These scales have been used in

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multiple studies conducted for the treatment of blepharitis, and have become a standard for blepharitis disease classification. One such study (supported by Allergan in collaboration with Schepens Eye Research Institute) compared testosterone 0.03% ophthalmic with a placebo, and showed that testosterone was effective in relieving symptoms of blepharitis as measured by the Ora Calibra scales. This result was anticipated based upon the known role of androgens in regulation of the meibomian glands and formation of the tear film's lipid layer.

The scales were also used in a multicenter, randomized, investigator-masked, and active-controlled, 15-day study evaluating the clinical efficacy and safety of tobramycin 0.3%/dexamethasone 0.05% (TobraDex ST) ophthalmic suspension compared to azithromycin 1% (Azasite) ophthalmic solution in the treatment of moderate to severe blepharitis or blepharoconjunctivitis. This study demonstrated a statistically significant improvement (decrease, $p=0.0002$ in mean global score in subjects treated with tobramycin/dexamethasone compared to subjects treated with azithromycin.

The standard treatment regimen for blepharitis has historically consisted of localized lid hygiene, including the use of warm compresses and eyelid scrubs. These treatment modalities may have limited efficacy for many patients, however, especially those with more severe cases of the disease. Topical antibiotics are recommended to decrease the bacterial load, and topical corticosteroids may help in cases of severe inflammation. However, a bacterial etiology for blepharitis and the efficacy of treating it with an antibiotic have yet to be fully proven, and the only recent placebo-controlled study failed to show efficacy. There isn’t one approved yet, but a localized, prescription-grade anti-inflammatory formula applied directly to the lid would be an improved approach for blepharitis treatment.

For the treatment of blepharitis, the American Academy of Ophthalmology also recommends the use of lid scrubs, as they serve as a maintenance regimen for chronic circumstances. Lid scrubs are also recommended as a background standard of care in investigative clinical trials. Traditionally, however, patients’ compliance with lid scrubs is limited due to the labor-intensive and messy nature of the treatment. Additionally, while foaming lid cleansers and premoistened pads are available, there is no universally accepted regimen for lid hygiene and lid scrubs.

Blepharitis also has an inflammatory component and, if left untreated, it can result in significant lid notching and scarring. This is very uncomfortable for the patient and can also lead to reduced effectiveness of the lid in performing its natural function of spreading the tears across the ocular surface to keep the surface hydrated.

**The Problem with Drops**

When a drop hits the eye, three parts of the anterior segment—the cornea, conjunctiva, and sclera—act as routes for the drug’s absorption, though the cornea is the primary route for ocular penetration. There is a reason that topical drops have become the delivery method of choice for eye-care practitioners. For one, drops have significant advantages over other methods, including the minimization of adverse systemic effects as well as the avoidance of first-pass metabolism, which restricts the concentration of drug that ultimately reaches its target tissue.

However, drops do have a few shortcomings, as well. First, they can be particularly difficult to physically manage for some patients, especially the elderly. Additionally, there is an array of physical and physiological barriers that protect the eye and significantly diminish the amount of drug being delivered. The cornea acts as a powerful protective wall, due to its relatively small surface area and low permeability. These natural ocular barriers, like the blinking reflex and tear turnover, equip the eye with an effective removal system for foreign bodies, including eye drops. Epithelial tight junctions also avert the diffusion of larger molecules and act as a barrier for smaller molecules.

The eye’s rapid turnover of tears creates quite a problem for an ocular drop. The tear film is typically only about 7 µL in volume, whereas one
eye drop is about 30 to 50 μL, depending on the surface tension characteristics of the drug. Thus, approximately only 1 to 3 percent of a topical drop penetrates to the intended target tissues in the eye. The remainder of the drop drains from the tear film by way of the nasolacrimal system and is then either deposited on the eyelids or metabolized by enzymes in the tears and surface tissues. As a result, at least 50 percent of the applied topical solution disappears due to drainage and does not enter the eye. The subsequent reflex blinking that occurs when a drop hits the eye also decreases bioavailability. Additionally, the contact time of a drug with the ocular tissues it’s trying to access is only around one minute, due to the constant production of lacrimal fluid (0.5 to 2.2 μL/min). In addition to the physical and physiological roadblocks the eye inherently creates for a drop, tear flow is also very different from person to person, making an appropriate treatment course all the more difficult. For example, one study showed that dry-eye patients, who already have a compromised tear film, may undergo enhanced drug absorption because the barrier functions mentioned above aren’t working adequately.

Certain factors in a drug’s formulation can modify its ability to penetrate these delicate yet robustly protective ocular tissues. These factors include the drug’s general physiological mechanism of action, as well as the tissue concentrations of the active ingredient over time. However, there are methods that increase a drug’s dwell time on the affected eye. For example, various compounds like high-viscosity solutions can be added to topically administered ophthalmic drugs in order to enhance corneal absorption, either by increasing corneal residence time or corneal penetration. These types of solutions yield an increased dwell time on the ocular surface, which allows for longer absorption time. One such example of a drug with an added absorption component is the ocular steroid Tribradex, which was reformulated as Tribradex ST to reflect a decrease in the amount of steroid (from 0.1% to 0.05%) as well as the addition of an inactive agent (xanthan gum), to stabilize the combination and increase contact time. Despite a reduced drug concentration, pharmacokinetic bioequivalence studies showed equivalent anterior chamber concentrations of dexamethasone following dosing of Tribradex and Tribradex ST.

An Optimal Vehicle

Ideally, treating the lid directly may circumvent problems of topical drug delivery. An optimal vehicle would provide a means for prolonging residence time at the site of application and improving tissue penetration. Surprisingly, despite the number of eye drop uses to treat ocular surface disease, no products have been developed for local delivery to the lid for blepharitis, although we have found time to develop topical products for the cosmetic treatment of our eyelashes. Latisse (Allergan), bimatoprost 0.03% solution, is approved for increasing eyelash length, thickness and darkness in patients with hypotrichosis of the eyelashes. Latisse was repurposed from the glaucoma medication Lumigan, after the medication was found to cause patients’ eyelashes to grow thicker. Latisse is applied topically, directly to the lashes with a sterile brush, rather than in Lumigan’s original form of an eye drop.

And perhaps there’s something we can learn from the success of a product such as Latisse: When you want to treat a local condition, the more locale the delivery, the better the result will be. What better example of this need is there than the delivery of therapeutic benefits directly to the affected lids?

By now, it should be clear that we feel improvements in blepharitis therapies are needed, and that these ought to include enhancements in the localized delivery of drugs such as topical steroids. By zeroing in on the local nature of this condition, it’s reasonable to presume that treatment success can also be brought into sharper focus.