2010 Dry Eye Update

BY MALAIKA DAVID, ASSOCIATE EDITOR

This month's installment of the "Peer Review" column highlights the most recently published articles on diagnostic testing and the therapeutic management of dry eye syndrome. Although the subject matter is certainly not new, the increased use of computers, corneal-based refractive surgery, clear corneal cataract surgery, and multifocal IOLs has brought the management of symptomatic dry eyes to the forefront of discussions at major ophthalmic meetings around the world. My first-hand experience with dry eye occurred after LASIK nearly 15 years ago, and the recollection keeps me keenly aware of the need to address and manage dry eye symptoms at their onset with a stepwise systematic approach to restoring the ocular surface.

The management of dry eye syndrome requires ophthalmologists first to identify the underlying cause(s) of patients' symptoms. It is important to take a careful medical history and search for potential etiologies. They can include radiation therapy and status post refractive surgery (LASIK, astigmatic keratotomy, and cataract surgery) as well as systemic diseases such as rheumatoid arthritis, diabetes, lupus, scleroderma, Sjögren's syndrome, vitamin A deficiency, chronic recurrent herpetic keratitis, and Bell's palsy. Other potential instigators are medications, including antihistamines, decongestants, birth control pills, diuretics, angiotensin-converting enzyme inhibitors, narcotic analgesics, antidepressants, and acne medications. Finally, several environmental factors can cause dry eye. Common triggers include computer usage, reading, prolonged driving, wind, heat exposure, altitude, low humidity, smoke, and contact lens usage.

Although this review is limited to the diagnosis and management of aqueous-deficient, neurotrophic, and evaporative dry eye syndromes, I would like to bring attention to a less conventional but growing alternative therapy for the treatment of eyes that do not respond to commercially available treatment options. In 2004, the use of autologous serum eye drops was reported for the treatment of nonhealing epithelial defects and chronic severe punctate keratopathy.[1] Autologous serum contains epidermal growth factor, vitamin A, transforming growth factor, fibronectin, and other cytokines thought to be of benefit to corneal epithelial cellular proliferation.

The management of meibomian gland dysfunction (MGD) and blepharitis will be covered in an upcoming edition of the "Peer Review" column. I hope you enjoy this installment, and I encourage you to seek out and review the articles in their entirety at your convenience.

—Mitchell C. Shultz, MD, section editor

SCREENING METHODS

In order to assess the degree of concordance between common dry eye diagnostic tests, researchers evaluated the tear film and ocular surface by meibomian gland pathology, ocular surface grading, conjunctival epithelial and goblet cells, phenol red thread test, and fluorescein tear breakup time (TBUT). Statistical correlations among all tests were evaluated using a McNemar's test to compare results. Dry eye symptoms were assessed using McMonnie's dry eye questionnaire. A statistically significant difference was reported between phenol red thread results and those of all other tests ($P < .001$). The MGD pathology, McMonnie's dry eye questionnaire, and TBUT results correlated with McNemar's test results. A lack of concordance was found among all other tests ($P = .001$).[2]

A cross-sectional study of 200 patients analyzed screening methods and associated factors of MGD and dry eye. Researchers aimed to characterize patients with aqueous deficiency, evaporative dry eye, or mixed causes; analyze the relationship between symptoms and signs; and evaluate a screening test for MGD and its association with dry eye. Patients' outcomes were measured by dysfunctional tear syndrome level, MGD grade, Schirmer's test, fluorescein TBUT, corneal fluorescein staining grade, and irritative eye symptoms. Researchers

found that patients' MGD screening grades were associated with TBUT ($P = .007$). This connection was especially evident in the upper eyelid and in correlation to reading difficulty ($P = .007$) and reversibility of symptomatic blurring with lubricants ($P = .006$). Abnormal Schirmer's test scores were associated with early morning discomfort ($P < .001$), and reduced TBUT scores were linked to discomfort in windy conditions ($P < .001$). Fifty-eight percent of patients were diagnosed with evaporative dry eye, and 30.5% of patients were diagnosed with aqueous tear deficiency. Individuals with aqueous tear deficiency exhibited the most severe fluorescein staining in the central and inferior cornea.[3]

EVAPORATIVE DRY EYE

Researchers evaluated 5 µL of nonstimulated tears of 30 patients suffering from evaporative dry eye and 30 healthy control subjects. The patients with evaporative dry eye had a TBUT of less than 10 seconds, and the healthy subjects had a TBUT of more than 10 seconds. Tear proteins were separated by mono- and bidimensional sodium dodecyl sulfate and polyacrylamide gel electrophoresis. Samples were characterized by immunoblotting and enzymatic digestion. Digested peptides were analyzed by liquid chromatography and electrospray ionization quadrupole time-of-flight mass spectrometry. For protein identification, investigators conducted a comparative data analysis using the Mascot (Matrix Science, London, England) and the Swiss-Prot human protein database. Statistical analyses were performed by applying a *t*-test for independent data and a Mann-Whitney test for unpaired data ($P < .05$). Compared to healthy patients, individuals with evaporative dry eye had decreased levels of lactoferrin ($P = .001$), lipocalin-1 ($P = .0001$), and lipophilin A through C ($P = .006$). Alternatively, the last group of patients had a significant increase in serum albumin ($P = .0001$). No changes were revealed for lysozyme ($P = .07$) and zinc a-2 glycoprotein ($P = .7$). Proteomic analysis showed a downregulation of lipophilin A and C and lipocalin-1 in patients, which investigators noted may be associated with post-translational modifications.[4]

THE EFFECT OF MECHANICAL MICROKERATOME VERSUS FEMTOSECOND LASER ON DRY EYE'S DEVELOPMENT

In a randomized study, 183 patients (183 eyes) underwent LASIK surgery with a flap created by either a mechanical microkeratome or a femtosecond laser. No patients had signs, symptoms, or treatment of dry eye before the surgery. The need for postoperative dry eye treatment was assessed, and a slit-lamp assessment of the cornea was conducted preoperatively and 1 month postoperatively. By the 1-month postoperative visit, 8% of eyes in the femtosecond laser group had at least trace punctate epithelial keratopathy compared to 46% in the microkeratome group ($P < .0001$). Twenty-four percent of patients in the microkeratome group required cyclosporine A treatment compared to 7% in the femtosecond laser group ($P < .0001$). Eyes in the femtosecond laser group had statistically significantly lower punctate epithelial erosion scores than eyes in the microkeratome group ($P = .0005$) 1 month after surgery. Thirteen percent of eyes in the femtosecond laser group and 41% in the microkeratome group were symptomatic 1 month postoperatively ($P < .0001$). The mean flap thickness was 111 ±14 µm in the femtosecond laser group and 131 ±25 µm in the microkeratome group ($P < .0001$). Investigators found no correlation between the flap's thickness and a higher incidence of LASIK-induced dry eye.[5]

ARTIFICIAL TEARS

In a prospective, randomized, parallel-group, comparative study, 30 patients with dry eye were randomly assigned to two treatment groups. Patients in the first group were treated with artificial tears containing carbomer-based lipid-containing gel, and patients in the second group were treated with artificial tears containing hydroxypropyl gel. Schirmer's test values, TBUT, and patients' subjective assessment of symptoms were measured at baseline and at 2 and 4 weeks after baseline. At baseline, the mean Schirmer's test value for both eyes was 4.83 mm in the carbomer-based lipid-containing gel group and 4.30 mm in the hydroxypropyl gel group. Patients in both treatment groups experienced an improvement from baseline in symptoms and signs, Schirmer's test value, and TBUT at 2 and 4 weeks after treatment. In the carbomer-based lipid-containing group, the Schirmer's test scores increased to a mean of 8.20 mm in the right eye and 9.33 mm in the left eye after 2 weeks and rose to 10.07 mm in the right eye and 10.86 mm in the left eye after 4 weeks. In the hydroxypropyl gel group, the Schirmer's test scores increased to 5.13 mm in the right eye and 5.60 mm in the left eye after 2 weeks and rose to 6.93 mm in the right eye and 6.53 mm in the left eye after 4 weeks. The increase in Schirmer's test values in both eyes was significantly greater at 2 and 4 weeks in the carbomer-based lipid-containing gel group than in the hydroxypropyl gel group ($P < .05$). In the carbomer-based lipid-containing gel group, the subjective assessment was reported as excellent in 26.6% of eyes and as good in 73.4% of eyes versus 13.4% excellent and 33.4% good in the hydroxypropyl gel group at 4 weeks ($P = .004$).[6]

In a prospective, interventional, single-center study, 48 patients (48 eyes) with age-related cataracts were randomized to receive either tobramycin and dexamethasone eye drops (Tobradex; Alcon Laboratories, Inc.) or the same treatment in addition to preservative-free artificial tears containing hydroxypropyl gel after phacoemulsification. Patients were evaluated with corneal and conjunctival staining using fluorescein and lissamine green, TBUT, the Schirmer's I test with anesthesia, tear clearance, and the ocular surface disease index (OSDI) preoperatively and 1 month postoperatively. Conjunctival impression cytology was performed to analyze CD3, CD11b, and HLA-DR inflammatory markers. The patients who were treated with the addition of preservative-free artificial tears containing hydroxypropyl gel showed statistically significantly better results in TBUT ($P = .0004$), OSDI ($P = .0002$), ocular symptoms subscale ($P = .0004$), vision-related function subscale ($P = .0002$), CD3 markers ($P = .011$), and HLA-DR markers ($P = .0002$) compared with patients who received tobramycin and dexamethasone eye drops without preservative-free artificial tears containing hydroxypropyl gel.[7]

In a multicenter, prospective, open-label study, 418 patients with bilateral dry eye syndrome and a history of using artificial tears or a desire to use them participated in a 4-week patient registry to evaluate the ease of use, acceptability, and efficacy of hydroxypropyl cellulose ophthalmic inserts. Patients participated in two office visits and a follow-up telephone evaluation over a 4-week period. On the first visit, patients underwent a clinical evaluation and completed a quality-of-life questionnaire. They were also trained to insert the hydroxypropyl cellulose ophthalmic inserts into the inferior cul-de-sac of each eye. After the first visit, patients used the inserts once daily as monotherapy or with existing therapy. On the second visit, another clinical evaluation was conducted, and patients completed a questionnaire on signs, symptoms, activities of daily life, and quality of life associated with dry eye syndrome. Investigators reported statistically significant improvements in discomfort, burning, dryness, grittiness, stinging, light sensitivity, the clinical signs of keratitis, conjunctival staining, and tear volume ($P < .05$). Mean OSDI scores improved by 21.3% ($P < .05$). More than 80% of patients completed the second visit. Blurred vision, which affected 8.7% of patients, was the most common adverse event leading to discontinuation of use. Fifty-three percent of participants reported in their evaluation that the inserts improved the effectiveness of their existing therapy, including artificial tears, punctal plugs, and cyclosporine emulsion.[8]

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ESSENTIAL FATTY ACIDS

In an overview of the literature regarding essential fatty acids and their role in dry eye syndrome, Rosenberg and Asbell analyzed eight studies found in the National Library of Medicine database. Six were randomized, placebo-controlled trials in humans. A separate study investigated supplementation in rodents, and another was an epidemiological study. The investigators noted that all of the human dry eye syndrome studies reviewed either omega-6 or combination therapy rather than omega-3 supplementation alone. They found this odd, considering that omega-3 fatty acids have been proven to have anti-inflammatory benefits in other fields. The six studies performed in humans evaluated most of the same parameters to determine the effects of supplementation and reported different results. Rosenberg and Asbell concluded that the studies preliminarily confirmed a relationship between essential fatty acids and dry eye syndrome, but they stated that the efficacy of essential fatty acids in the treatment of dry eye syndrome would benefit from a large, multicenter, randomized clinical trial.[9]

He and Bazan reviewed research regarding the effect of omega-3 fatty acids on dry eye syndrome. The research was conducted in their laboratory at Louisiana State University Health Science Center in New Orleans. The investigators stated that derivatives of omega-3s—such as resolvins—decrease inflammation and increase tear production. They stated that a combination of nerve growth factor and pigment epithelial-derived factor with docosahexaenoic acid may improve corneal nerves' regeneration after a corneal injury. They also noted that docosahexaenoic acid can synthesize neuroprotectin D1 when combined with pigment epithelial-derived factor, which may have therapeutic value in preventing serious consequences of nerve damage such as dry eye, epithelial erosion, and corneal ulcerations.[10]

CYCLOSPORINE A

In a prospective, randomized, controlled, parallel group study, 150 patients (300 eyes) were treated for dry eye syndrome. Fifty patients were treated with

cyclosporine A 0.05% b.i.d., 50 were treated with retinyl palmitate 0.05% q.i.d., and a control group of 50 patients received neither cyclosporine nor retinyl palmitate. All patients used artificial tears q.i.d. as an adjunctive treatment. Symptom scoring, TBUT assessment, Schirmer's testing without anesthesia, corneal fluorescein staining, and conjunctival impression cytological analysis were performed before treatment began and at the first, second, and third months after treatment was initiated. Both cyclosporine A 0.05% and retinyl palmitate 0.05% significantly improved blurred vision, TBUT assessments, Schirmer's I score results, and impression cytological findings in patients with dry eye ($P < .05$) compared to the control group treated with artificial tears alone.[11]

Forty patients (40 eyes) with dry eye were treated with topical cyclosporine A 0.05% with impression cytology. Schirmer's tests, TBUT, and OSDI scores and goblet cell densities were recorded before treatment and after 6 months of treatment. Patients were classified into three grades based on clinical and biomicroscopic factors. Twelve patients with dry eye symptoms such as burning, itching, and epiphora were classified as grade 1. Eighteen patients who met the criteria for grade 1 with the addition of corneal staining, punctate keratitis, and filaments were classified as grade 2. Ten patients who met the requirements for grade 2 but also had corneal scars and neovascularization were classified as grade 3. The mean Schirmer's test value was 3.2 ±1.6 mm before treatment and 8.4 ±4.3 mm after 6 months of treatment. The mean TBUT was 4.4 ±1.8 seconds before treatment, and it increased to 11.8 ±4.8 seconds at the 6-month visit ($P = .00$). The mean clinical grade regressed from 1.9 ±0.8 before treatment to 0.8 ±1.2 after treatment ($P = .00$). The mean OSDI score was 30.0 ±11.7 before treatment and 21.3 ±11.0 after treatment ($P = .00$). The mean goblet cell density in all cases was 12.3 ±8.7 before the treatment, and it increased to 33.0 ±25.4 after treatment ($P = .04$). Investigators stated that topical cyclosporine A 0.05% treatment with impression cytology was effective in grade-1 and 2 dry eye patients, but results were poor in grade-3 dry eye patients.[12]

OPHTHALMOLOGISTS' PERCEPTIONS

In an effort to understand ophthalmologists' perceptions and treatment of patients with moderate-to-severe dry eye syndrome, Asbell and Spiegel conducted an online survey in October 2007. The survey was distributed to 7,882 ophthalmologists in the United States. The response rate was 3.1%, and those who treated four or more patients with moderate-to-severe dry eye were asked to complete the survey. The survey questions assessed participants demographics, perceptions of moderate-to-severe dry eye, the goals of dry eye treatment, dry eye therapeutic characteristics, the measure of therapeutic success, and potential gaps in the treatment of dry eye.[13]

Ninety-four percent of respondents agreed that more options are needed for the treatment of moderate-to-severe dry eye. Thirty-three percent of participants felt that current therapies were extremely or very effective for moderate-to-severe dry eye, and 5% agreed that current therapies were extremely or very effective for severe dry eye. Ninety-two percent agreed that multiple therapeutic agents are needed to manage moderate-to-severe dry eye. The respondents prescribed or recommended an average of 3.2 different treatments over the course of 1 year for patients with moderate dry eye and 4.9 different treatments for patients with severe dry eye. The most highly ranked goals for the treatment of moderate-to-severe dry eye were maintaining and protecting the ocular surface, which ranked 1 or 2 x 74%, and lubricating and hydrating the ocular surface, which ranked 1 or 2 x 67%.[13] ■

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