Topical Cyclosporine A Treatment in Corneal Refractive Surgery and Patients With Dry Eye

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ABSTRACT

PURPOSE: To evaluate preoperative and postoperative dry eye and the effect of cyclosporine A treatment in patients screened for corneal refractive surgery and treated with photorefractive keratectomy (PRK) or LASIK.

METHODS: A consecutive case series of 1,056 patients screened for corneal refractive surgery from 2007 to 2012 was retrospectively analyzed. The level of preoperative and postoperative dry eye and the responsiveness to topical cyclosporine A treatment were assessed.

RESULTS: One eye of each patient was randomly selected. A total of 642 eyes progressed to surgery: 524 (81.6%) and 118 (18.4%) underwent LASIK and PRK, respectively. Of 81 (7.7%) diagnosed as having dry eye, 55 were deemed potential candidates and optimized for refractive surgery. Thirty-seven patients with moderate dry eye were treated with topical cyclosporine A prior to surgery (mean duration: 3.2 ± 2.1 months; range: 1 to 12 months). After cyclosporine A treatment, 28 (75.7%) eyes underwent LASIK, 4 (10.8%) eyes underwent PRK, and 5 (13.5%) eyes were not operated on due to failed treatment of dry eye. Postoperative refractive surgery-induced neurotrophic epitheliopathy (LINE in LASIK) was noted in 132 (27.3%) and 12 (11.1%) eyes that underwent LASIK and PRK, respectively. Topical cyclosporine A was prescribed in 79 LASIK-induced and 3 PRK-induced dry eyes. After 12 months or more of cyclosporine A treatment, 5 (6.1%) eyes continued to have dry eye symptoms or signs.

CONCLUSIONS: Topical cyclosporine A treatment is effective therapy for optimizing patients for refractive surgery and treatment of new onset or worsened dry eye after surgery.

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Dry eye disease is a multifactorial disease of the lacrimal glands, tears, and ocular surface that results in symptoms of discomfort, visual disturbance, and tear-film instability; there is also the potential of damaging the ocular surface that is commonly associated with inflammation of the lacrimal glands and subconjunctival tissues.[1] In the general population, the prevalence of dry eye disease has been reported to range from 5% to more than 30%, depending on the group under study and the criteria for diagnosis.[2] Refractive surgery candidates commonly present with dry eye conditions and most patients who previously underwent LASIK have some level of LASIK-induced dry eye for at least a few months postoperatively.[3]

The management of dry eye disease and associated ocular surface conditions includes pharmacological and non-pharmacological approaches before and after surgery (eg, eyelid hygiene, punctal occlusion, topical tear substitutes, and topical cyclosporine A). Artificial tears are the most common topical medications used in treatment and are essentially palliative. Thus, they reduce symptoms without addressing the underlying cause of the disease.[4] During the past decade, studies have confirmed an underlying inflammatory component to the pathophysiology of dry eye disease in most patients[5,6] and the introduction of topical 0.05% cyclosporine A (an anti-inflammatory immune-modulatory agent) has had a major impact on the overall approach to prophylaxis and

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treatment of dry eye. The neurotrophic epitheliopathy induced by the transection or ablation of corneal afferent sensory nerve fibers during the refractive procedure also appears to be influenced by topical cyclosporine A treatment.[7]

Several previous studies have demonstrated the benefits of topical cyclosporine A to treat dry eye disease.[8-11] However, few studies have addressed the role of topical 0.05% cyclosporine A treatment in patients with dry eye before and after corneal refractive surgery.[7,12] The current study evaluates dry eye incidence and risk factors and characterizes the use of cyclosporine A in a refractive surgery practice.

PATIENTS AND METHODS

Study Population

Approval was obtained from the Institutional Review Board at the Cleveland Clinic and the tenets of the Declaration of Helsinki were followed. A retrospective review was performed on all patients who underwent screening for refractive surgery by one surgeon (SEW) from 2007 to 2012 and who did not have a prior history of eye surgery, including refractive surgery, ocular allergies, active ocular infections, or corneal abnormalities such as stromal scars or dystrophies.

Factors recorded included whether an eye had dry eye prior to refractive surgery, whether treatment for dry eye was prescribed prior to refractive surgery, whether treatment for dry eye was deemed adequate to proceed with refractive surgery, how long the eyes were pretreated with 0.05% cyclosporine A prior to refractive surgery, whether the procedure choice was affected by preoperative dry eye, and how long eyes that had preoperative dry eye were treated postoperatively with topical 0.05% cyclosporine A. Also noted were eyes that developed dry eye symptoms and signs only after refractive surgery, the response of such eyes to cyclosporine A, and the duration of treatment of these eyes with cyclosporine A after refractive surgery.

Other risk factors that could influence dry eye disease were also addressed, such as age, sex, procedure (LASIK or photorefractive keratectomy [PRK]), and myopic or hyperopic correction.

Assessment of Dry Eye Disease

For diagnosis of dry eye disease prior to refractive surgery, a history of contact lens intolerance and dry eye symptoms (ie, scratchiness, burning, foreign body sensation, or fluctuating vision) and punctate epithelial erosion (PEE) of the cornea or conjunctiva detected with lissamine green staining are usually present. The severity of corneal PEE was graded as follows: 1 to 5 PEE = mild; 6 to 30 PEE = moderate; and greater than 30 PEE = severe.

Refractive Surgery

Stromal tissue ablation was performed with the VISX S4 IR (Abbott Medical Optics, Inc., Irvine, CA) in both LASIK and PRK. Flaps for LASIK were created with either a 30- or 60-kHz IntraLase laser (Abbott Medical Optics). Femtosecond laser settings were flap diameters of 9.0 to 9.3 mm (largest diameter in this range possible without cutting into the limbal vasculature) with a standard 55° superior hinge and 55° side-cut angle. The lamellar cut and side cut were performed with an energy of 1.2 µJ with the 30-kHz laser and 1.0 µJ with the 60-kHz laser, respectively. The attempted flap thickness was 100 to 110 µm. When mitomycin C was used in PRK (it always was for myopia corrections greater than 5 diopters [D] or astigmatism corrections greater than 1.5 D), a sponge wetted with mitomycin C 0.02% was applied for 30 seconds and the cornea was subsequently irrigated with balanced salt solution.

All eyes were treated with 0.5% moxifloxacin hydrochloride ophthalmic solution or 0.5% gatifloxacin ophthalmic solution and prednisolone acetate 1% ophthalmic suspension four times daily for 1 week after PRK or LASIK. In addition, nonpreserved artificial tears were used four to eight times per day as needed after surgery. Patients who underwent PRK wore bandage contact lenses for 5 to 7 days postoperatively.

Postoperative follow-up was scheduled as follows: 1 day, 1 week, and 1, 3, 6, and 12 months, with additional visits scheduled if re-treatment was needed.

Statistical Analysis

Statistical analysis was performed with SPSS version 20.0 software (SPSS, Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed in proportions and analyzed by Pearson's chi-square test. Linear regression models were adjusted for age and sex to determine the independent association between preoperative and postoperative dry eye and refractive surgery parameters. For all statistical tests, a P value of less than .05 was considered statistically significant.

RESULTS

One eye of each patient was randomly selected for the study. A total of 1,056 eyes of 1,056 patients were included. Five hundred fourteen (48.7%) were male and 542 (51.3%) were female, with a mean age of 39.2 years (range: 18 to 76 years). A total of 642 eyes (642 patients) underwent refractive surgery. Thus, 414 eyes (414 patients) evaluated at refractive screening did not have subsequent surgery. Many patients who had a normal screening did not proceed with the surgery due to various reasons (eg, cost of surgery, anxiety about surgery,

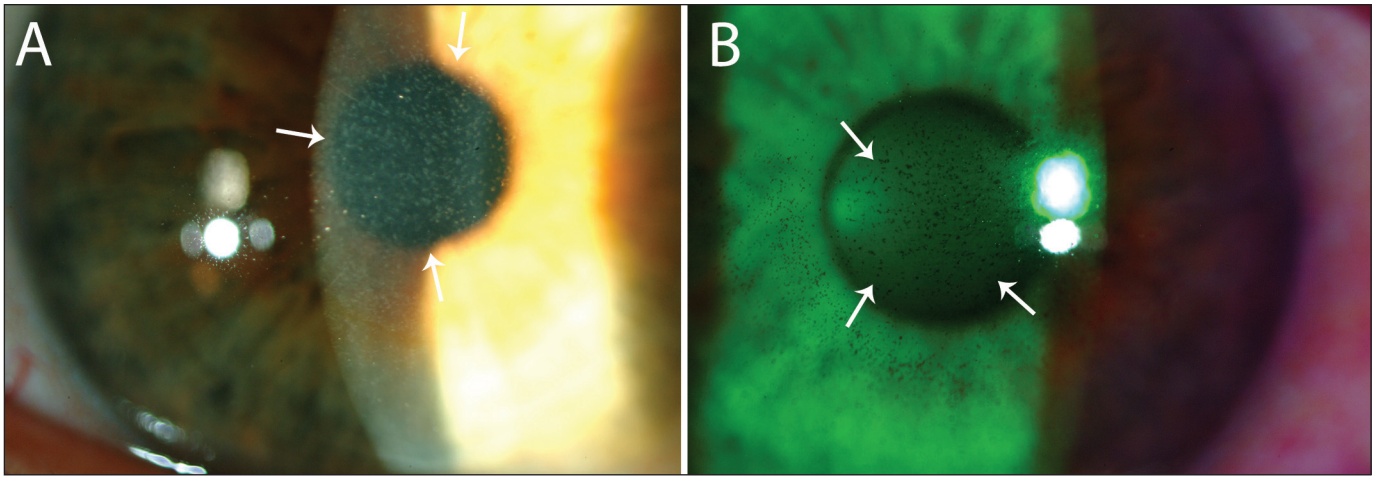

Figure 1. Slit-lamp photographs of corneas with punctate epithelial erosions present at the refractive surgery screening examination (original magnification x40). (A) A cornea with 2+ punctate epithelial erosions (arrows) seen in the slit beam on the anterior cornea surface. (B) Cornea with 2+ lissamine green staining (arrows) before surgery.

TABLE 1
Dry Eye Profile of Patients (n = 81) Screened for Laser Refractive Surgery

Variable	Patients
Contact lens intolerance	12 (14.8%)
Punctate epithelial erosions	
Absent	19 (24.5%)
Mild	16 (19.6%)
Moderate	46 (56.8%)
Dry eye symptoms	57 (70.4%)

and decision to go elsewhere for surgery). Other patients had at least one clinical factor that was deemed a contraindication to refractive surgery. The most common exclusion factors were abnormal corneal topography and low or insufficient central corneal thickness. Other common factors were high myopia, cataract or insipient cataract, high hyperopia, patients not willing to accept monovision, and unstable refraction.

LASIK was performed in 524 (81.6%) and PRK in 118 (18.4%) eyes. Mean spherical equivalent was -4.4 ± 2.3 D (range: -0.5 to -12.00 D) and +1.9 ± 1.2 D (range: +0.5 to +5.0 D) for myopia and hyperopia, respectively. Mean astigmatism was 1.0 ± 0.7 D, with a range of 0.25 to 5.25 D.

Preoperative Dry Eye and Pretreatment With Topical Cyclosporine A

At the initial screening for refractive surgery, 81 (7.7%) of the 1,056 patients were diagnosed as having dry eye disease (**Figure 1** and **Table 1**). A higher dry eye incidence was found in women than men (9.9% vs 5.2%, $P = .004$). Age was not associated with dry eye incidence in the screened patients ($P = .479$).

After refractive evaluation, 55 (67.9%) of the patients with dry eyes were deemed to be potential candidates for refractive surgery based on the mild to moderate dry eye severity, a level of refractive error within the correctable range, normal corneal thickness, normal corneal topography, and otherwise normal eye examinations, and proceeded with optimization for surgery. Eighteen patients (22.2%) with mild dry eye were treated with nonpreserved artificial tears only. Thirty-seven (45.7%) eyes with moderate dry eye were treated with topical 0.05% cyclosporine A twice per day before reevaluation (at 1- to 2-month intervals) and approval for surgery when the patients had no further dry eye symptoms, no corneal lissamine green staining was present, and Schirmer's test with anesthesia was greater than 5-mm wetting in 5 minutes (**Figure 1**). Schirmer's test was not routinely used in screening for dry eye due to its variability, but was used in patients diagnosed as having dry eye after treatment because a Schirmer's test with anesthesia greater than 5 mm of wetting after 5 minutes was one criterion used to proceed with surgery. Patients with severe preoperative dry eye were not considered candidates for LASIK or PRK. The duration of preoperative cyclosporine A treatment was 3.2 ± 2.1 months (range: 1 to 12 months) between screening and proceeding with refractive surgery.

Ocular rosacea with meibomian gland inspissation and anterior blepharitis were noted in 11% and 8% of the candidates screened for corneal refractive surgery, respectively. In the group of patients diagnosed as having dry eye based on contact lens intolerance, dry eye symptoms, or punctate epithelial erosions, 13% had ocular

TABLE 2

Demographics and Clinical Data of Patients Who Underwent Refractive Surgery With Preoperative Dry Eye or Developed Dry Eye Postoperatively

Variable	Preoperative Dry Eye (n = 32)	Postoperative Dry Eye (n = 144)
Age (y)	39 ± 11.8	40.6 ± 12.5
Male/female	12/20	53/91
LASIK/photorefractive keratectomy	28/4	132/12
Myopia (spherical equivalent in diopters)	-4.3 ± 1.7	-3.9 ± 2.1
Hyperopia (spherical equivalent in diopters)	1.7 ± 0.6	2.2 ± 1.3
Cyclosporine use (months after surgery)		
0 to 6	14 (51.9%)	43 (52.5%)
7 to 12	5 (18.5%)	14 (17.1%)
> 12	8 (29.6%)	25 (30.4%)

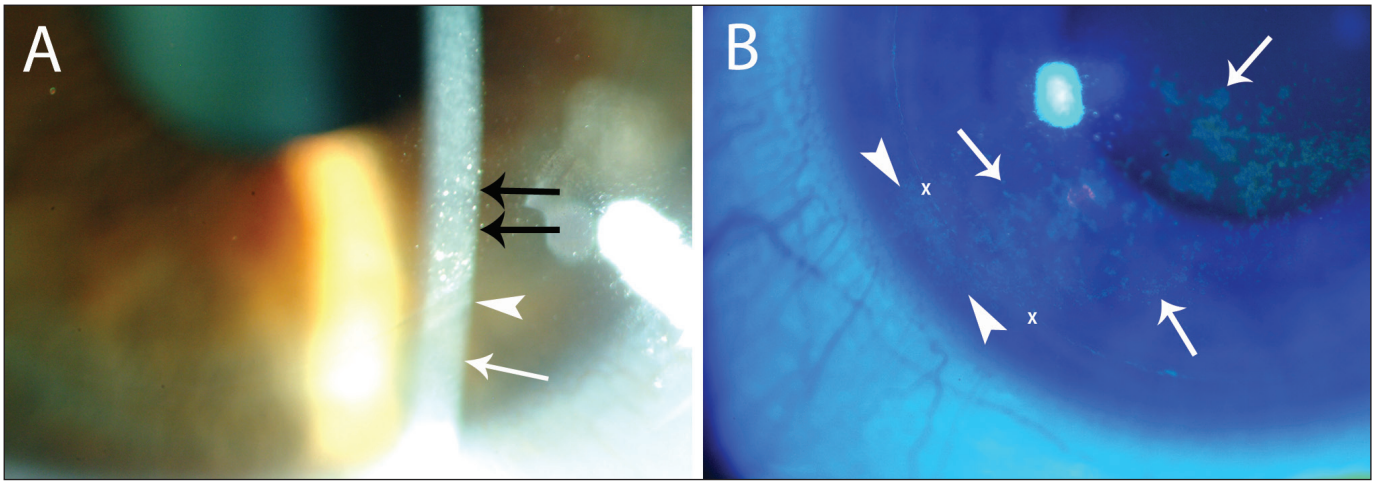

Figure 2. Slit-lamp photographs of corneas with refractive surgery-induced dry eye at 1 month after LASIK (original magnification x40). (A) Corneal epitheliopathy (black arrows) limited to the flap area. Note that beyond the flap edge (white arrowhead), there are no punctate epithelial erosions of the epithelium outside of the flap (white arrow). (B) Another cornea with 3+ punctate epithelial erosions with fluorescein staining (arrows). Note the presence of punctate epithelial erosion in the peripheral cornea (arrowheads) crossing the flap edges (X).

rosacea and 7% had anterior blepharitis. Rosacea was treated in all patients with frequent warm manual compression of the eyelids and in some patients with doxycycline 50 or 100 mg twice per day. Anterior blepharitis was treated in all patients with eyelid hygiene scrubs with baby shampoo and frequently with topical antibiotic applied to the eyelashes twice per day for 10 days.

After successful dry eye treatment, the decision for choosing LASIK or PRK surgery was based on corneal thickness and corneal topography (**Table 2**). Five (13.5%) eyes did not improve sufficiently after receiving topical cyclosporine A and were not deemed good candidates for surgery.

After refractive surgery, 24 eyes of patients who underwent LASIK continued topical cyclosporine A treatment (12 for 6 months; 5 for 4 months; and 7 for more than 1 year). Of the eyes that underwent PRK, 3 continued topical cyclosporine A treatment (2 for 6 months and 1 for more than 1 year).

When the 32 patients with moderate preoperative dry eye were compared to the 18 patients with mild preoperative dry eye at 1 month postoperatively, there was a higher incidence of PEE in the cyclosporine A group (47% vs 5.6%, P = .003). However, at 3 or 6 months, there were no statistically significant differences between both groups in corneal PEE (18.7% vs 12.5%, P = .584 and 12.5% vs 6.7%, P = .545, respectively).

At the end of follow-up, all 32 patients with moderate preoperative dry eye who had previous refractive surgery achieved good refractive surgery outcomes, although 7 eyes (7 patients) continued to be treated with topical cyclosporine A for persistent dry eye. There was no evidence that LASIK or PRK worsened dry eye beyond 9 months postoperatively.

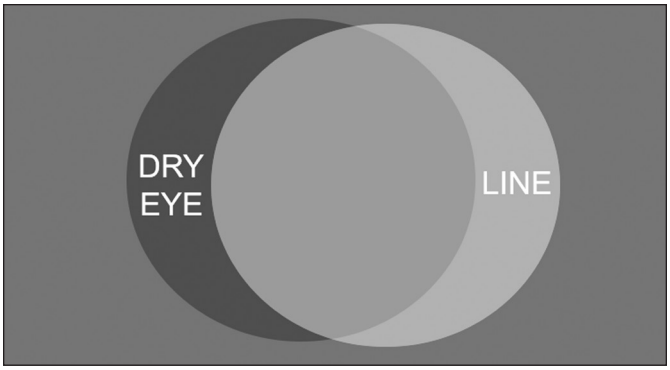

Figure 3. Schematic representation of hypothesized overlap between dry eye and LASIK-induced neurotrophic epitheliopathy (LINE). After LASIK, most patients with symptoms and signs of dry eye likely have a combination of inflammatory aqueous deficient dry eye and LINE.

Postoperative Dry Eye and Topical Cyclosporine A

At the screening examination for refractive surgery, 975 patients did not have dry eye symptoms or signs and 592 of these patients proceeded with refractive surgery. LASIK was performed in 484 (81.8%) patients and PRK was performed in 108 (18.2%) patients who proceeded to surgery.

Postoperative dry eye was more frequent after LASIK compared to PRK (27% vs 11%, $P < .0001$), after LASIK for hyperopia compared to LASIK for myopia (55% vs 25%, $P < .002$, regardless of age), in females than males (36% vs 21%, $P < .0001$), and in patients older than 60 years ($P = .024$) (**Figure 2** and **Table 2**). The use (n = 93) or not (n = 25) of mitomycin C in PRK had no influence on postoperative dry eye development (17% vs 20%, $P = .432$).

Fluctuating vision and punctate epithelial erosions were observed at 1 week postoperatively in 98% of eyes that were diagnosed as having dry eye after refractive surgery. Moderate to severe dry eyes were treated with topical cyclosporine A, which included 79 patients with LASIK-induced dry eye (41 for 3 to 6 months, 14 for 6 to 12 months, and 24 for more than 1 year postoperatively) and 3 patients with PRK-induced dry eye (2 for 6 months and 1 for more than 1 year postoperatively). Only 5 (6.1%) patients treated with cyclosporine A continued to have dry eye symptoms or signs after a minimum of 12 months of treatment.

Comparing the 79 patients with moderate LASIK-induced dry eye to the 53 patients with mild LASIK-induced dry eye at 1 or 3 months after surgery showed no statistically significant difference in PEE incidence (77.7% vs 66.7%, $P = .53$ and 44.9% vs 32.1%, $P = .142$, respectively). Similarly, comparing the 3 patients with moderate PRK-induced dry eye to the 9 patients with mild PRK-induced dry eye at 1 or 3 months after surgery showed no significant difference in PEE scores (67.7% vs 22.2%, $P = .157$ and 33.3% vs 44.4%, $P = .735$, respectively).

DISCUSSION

Careful diagnosis and optimal management of dry eye before and after corneal refractive surgery improves visual outcomes and patient satisfaction. In this study of more than 1,000 consecutive candidates screened for LASIK or PRK, preoperative and postoperative dry eye and the response to the treatment of dry eye were studied retrospectively.

Of the 1,056 eyes included, 7.7% were found to have dry eye symptoms and signs at the preoperative screening examination; this percentage would likely be higher in drier and warmer climates. The primary sign used to detect dry eye in these patients was lissamine green staining because the Schirmer's test tends to be highly variable and (in our opinion) only reliable when consistently low. Many of these patients with mild to moderate dry eye were successfully optimized for refractive surgery with a combination of topical cyclosporine A and nonpreserved artificial tears and ointments. In addition, most of the patients were able to proceed with LASIK. Patients with moderate dry eye were found to have outcomes that were similar to patients with mild dry eye after surgery if topical cyclosporine A treatment was continued for 6 to 9 months, although some patients required longer treatment (especially if they had dry eye signs and symptoms prior to surgery).

More patients developed symptoms and signs of dry eye after refractive surgery. The risk factors found in the current study are in agreement with prior studies, which have observed higher refractive surgery-induced dry eye in females,[1] older patients,[13] LASIK,[14] or correction of hyperopia.[15] In this study, 27% of eyes that had LASIK and 11% of eyes that had PRK developed dry eye at least temporarily after surgery even if they had no symptoms or signs of dry eye preoperatively. The primary mechanism of development of dry eye after refractive surgery in eyes that had no prior symptoms or signs is thought to be LASIK-induced neurotrophic epitheliopathy (LINE), attributable to injury to the corneal nerves.[3] LASIK is known to transiently exacerbate preexisting dry eye and trigger transient dry eye in patients who previously had no complaints.[16-19] Many patients who developed moderate dry eye after refractive surgery had resolution of symptoms and corneal lissamine green stain when treated with topical cyclosporine A. We hypothesize that dry eye in postoperative patients actually represents an overlap syndrome of aqueous deficient dry eye and LINE, and that treatment of the underlying inflammatory dry eye disease with topical cyclosporine A decreases corneal epitheliopathy and the associated symptoms (**Figure 3**). Many patients likely have a subclinical dry eye that is not detected during preoperative screening and the

added stressor of damage to the corneal nerves leads to manifest disease. The relatively low rate of preoperative dry eye noted in the current study could be due to such undetected subclinical dry eye combined with the retrospective nature of the study. In many of these patients, treatment of the underlying dry eye disorder with topical cyclosporine A effectively suppresses the epitheliopathy associated with LINE. However, other patients may develop pure LINE without underlying inflammatory dry eye and may not respond to cyclosporine A treatment but have symptoms and signs that resolve after regeneration of the corneal nerves.

Many factors may actually contribute to the pathology of dry eye disease in individual patients. Several studies have demonstrated the importance of inflammatory components, including altered balance of cytokines and growth factors, increased concentrations of inflammatory markers, and increased tear osmolarity.[5,12,20-22] The transection of a large number of afferent sensory nerve fibers during the corneal flap creation leads to LINE and contributes to the appearance of dry eye.[3,23] Even eyes that underwent PRK can develop postoperative dry eye. In these cases, the neurotropic component is likely attributable to excimer laser ablation of the corneal nerve endings.

Topical cyclosporine A has been shown to be effective in patients with dry eye who undergo excimer laser refractive surgery. Salib et al.[12] observed that patients treated with cyclosporine A before and after LASIK have greater refractive visual acuity predictability than patients treated only with artificial tears. Ursea et al.[24] also reported a faster recovery of the visual acuity in patients treated with topical cyclosporine A for 12 months postoperatively. In patients who develop dry eye symptoms and signs only after surgery, topical cyclosporine A is similarly effective in reducing symptoms such as fluctuating vision and signs such as corneal staining with lissamine green, likely through immune-modulatory and anti-inflammatory effects and resulting increased tear production and normalization of tear composition.[10,25] A recent study[26] found that topical cyclosporine A treatment for 3 months after PRK or LASIK did not improve visual outcomes or patient symptoms and did not alter the inflammatory mediators present in the tear film. However, it is important to note that most patients enrolled in that study were young males with low myopic spherical equivalent corrections; patients with that profile are already less prone to develop dry eye after refractive surgery regardless of dry eye treatment, meaning the cyclosporine A effect might be less pronounced than it would be in middle-aged females or patients who had higher corrections for myopia or hyperopia.

The current study also revealed that more than half of the patients who developed dry eye after refractive surgery could successfully stop treatment with topical cyclosporine A without recurrence of symptoms and signs after 6 months of treatment (**Table 2**). More than two-thirds of these patients stopped treatment at approximately 1 year after refractive surgery. Sub-basal and stromal corneal nerves recover slowly after refractive surgery (especially after LASIK) and it can take years to return to preoperative densities, depending on the attempted correction.[27,28] Some patients choose to continue topical cyclosporine A indefinitely, many because of a recurrence of symptoms of dry eye within a few weeks to months of cessation of topical cyclosporine A. Many of these patients likely had underlying chronic dry eye that responded to topical cyclosporine A treatment.

It is important to note that all patients who underwent LASIK included in this study had flap creation with a femtosecond laser. The incidence of postoperative dry eye would likely have been much higher if patients who had LASIK flaps with microkeratomes were included.[29]

The results of this study demonstrate that topical cyclosporine A is a useful adjuvant for patients who have refractive surgery. Many patients who present for screening for surgery can be effectively optimized for surgery to improve important measures such as aberrometry used in custom excimer laser ablation and to decrease the incidence and severity of dry eye symptoms and signs after surgery. Similarly, topical cyclosporine A is effective in treating postoperative dry eye/LINE that develops in many patients who did not have preoperative symptoms or signs of dry eye. In both groups, topical 0.05% cyclosporine A improved patient satisfaction by reducing visual fluctuations that are a hallmark of dry eye disease.

AUTHOR CONTRIBUTIONS

Study concept and design (AAMT, MRS, SEW); data collection (AAMT); analysis and interpretation of data (AAMT, MRS, SEW); drafting of the manuscript (AAMT, MRS, SEW); critical revision of the manuscript (AAMT, SEW); statistical expertise (AAMT); supervision (SEW)

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