Cyclosporine 0.05% Ophthalmic Preparation to Aid Recovery From Loss of Corneal Sensitivity After LASIK

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ABSTRACT

PURPOSE: To determine whether cyclosporine (0.05%) can safely and effectively accelerate corneal nerve regeneration after LASIK, thereby facilitating faster recovery of corneal sensitivity.

METHODS: This prospective, randomized, single-center clinical study comprised 44 eyes of 22 patients scheduled to undergo bilateral LASIK. One eye was randomly assigned to receive cyclosporine drops twice daily for 3 months in addition to standard postoperative LASIK medication. Corneal sensitivity was measured using the Cochet-Bonnet esthesiometer in four areas outside and five areas inside the LASIK flap preoperatively and at 1 day, 1 week, 1 month, and 3 months postoperatively. Safety parameters of best spectacle-corrected visual acuity and the incidence of adverse events were also collected.

RESULTS: For all four points outside the LASIK flap, normal corneal sensitivity was maintained throughout the study. In addition, no significant difference was found between the cyclosporine-treated eyes and the control eyes at these points. All points within the LASIK flap except the point closest to the hinge demonstrated profound corneal hypoesthesia at 1 day, 1 week, and 1 month postoperatively with no differences noted between the control and cyclosporine-treated eyes. These same points had statistically significantly greater corneal sensitivity in the cyclosporine group relative to the control group ($P \leq .011$) at 3 months postoperatively.

CONCLUSIONS: Cyclosporine was shown to significantly improve corneal sensitivity at 3 months after LASIK, which suggests that topical cyclosporine promotes enhanced corneal nerve regeneration. [*J Refract Surg*. 2008;24:337-343.]

Laser in situ keratomileusis (LASIK) involves mechanical section of the corneal nerves during the creation of the flap to expose the stromal bed for laser ablation. The corneal nerve destruction caused by LASIK is known to dramatically reduce corneal sensation and thus cause dry eye symptoms. Studies show an increase in prevalence of dry eye symptoms from 38% preoperatively to 69% to 85% during the first few weeks after LASIK.[1] After LASIK, the corneal nerve fibers gradually reinnervate the cornea, and corneal sensation is slowly restored.[2]

Touching the cornea triggers one of the most sensitive protective reflexes of the human body. The threshold of sensitivity, especially in the center of the cornea, is exceedingly low, so pathologic changes can be diagnosed early and precisely and can be used for diagnosis, follow-up, and even prognosis of various corneal disorders. Loss of normal corneal sensation may compromise the protective blink reflex, delay epithelial wound healing, decrease tear flow, and be associated with neurotrophic keratitis, sterile corneal melts, and infectious keratides.[3-5]

Several studies have found that systemic administration of macrolides or macrolide analogs can also promote myelinated nerve growth. One such macrolide, cyclosporine, is currently available as a commercial ophthalmic preparation (Restasis, 0.05%; Allergan Pharmaceuticals, Irvine, Calif) indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

This study was performed with the objective of determining whether cyclosporine can accelerate regeneration of non-

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Dr Peyman has a patent pending neuronal regeneration. The remaining authors have no financial or proprietary interest in the materials presented herein.

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myelinated corneal nerves after LASIK, thereby facilitating faster recovery of corneal sensitivity.

PATIENTS AND METHODS

This prospective, randomized, single-center study comprised 44 eyes of 22 patients. The study duration was 3 months after LASIK surgery, with scheduled follow-up at 1 day, 1 week, and 1 and 3 months postoperatively. Informed patient consent was obtained prior to the performance of any surgical procedures.

Inclusion criteria were patients scheduled to undergo bilateral LASIK who were at least 21 years old, who had a difference in the refractive correction of both eyes of no greater than 2.00 diopters (D) sphere and 1.00 D cylinder, and who were willing to comply with follow-up. Exclusion criteria included, but were not limited to, patients with an active ocular infection, corneal abnormalities, and any other ocular pathologies; patients with signs or symptoms of dry eye or any condition that decreased their corneal sensitivity/tear flow; patients with previous ocular/refractive surgery; patients with unstable myopia, a history of neurological pathologies, or a history of diabetes; and patients with known or suspected hypersensitivity to any of the ingredients in the cyclosporine formulation.

All patients had prior informed consent and were recruited from the investigator's current patient population. Patients were enrolled in the study in a sequential manner only after it was determined they qualified according to the study inclusion and exclusion criteria.

Surgical Procedure and Postoperative Cyclosporine Treatment

Before bilateral LASIK, one eye was randomly assigned as the study eye, and the fellow eye as the control eye using a computer-generated randomization schedule. The surgeon ensured that the hinge position of the LASIK flap was the same for both eyes of the patient (approximately 11 o'clock in right and left eyes). The LASIK flap was performed in all cases with a Moria CB microkeratome (Moria, Antony, France) with a 130-µm head and the ablation was performed with a VISX excimer laser (Advanced Medical Optics, Santa Ana, Calif).

At the completion of the LASIK procedure, the surgeon administered one drop of the cyclosporine (Restasis 0.05%) onto the corneal surface of the study eye. For each day thereafter, until 3-month follow-up, the study eye was administered one drop of cyclosporine twice per day, approximately 12 hours apart. The control eye did not receive cyclosporine or a placebo drop. Both eyes received the standard postoperative medication of prednisolone acetate 1% (Econopred; Alcon Laboratories Inc, Ft Worth, Tex) and moxifloxacin hydrochloride (Vigamox; Alcon Laboratories Inc)—one drop hourly while awake starting on the day of surgery, 1 drop four times daily administered until 1-week follow-up, one drop administered twice daily for 2 days, and one drop administered four times daily for 2 days. Artificial tears (Systane; Alcon Laboratories Inc) were administered hourly on the surgery day and then as needed for dry eye sensation.

Outcome Measures

Postoperative outcomes of the study eye were compared to those of the control eye. The primary safety parameters were best spectacle-corrected visual acuity (BSCVA) and the incidence of adverse events. The key efficacy parameter in this study was corneal sensitivity.

Distance visual acuity (uncorrected and best corrected) was measured with standardized Snellen distance visual acuity charts in accordance with the manufacturer's recommendations for use. The same charts were used for all distance acuity measurements on a given patient throughout the clinical study. The illumination level was kept constant throughout the clinical study.

Corneal sensitivity was measured preoperatively, 1 week, and 1 and 3 months postoperatively using the Cochet-Bonnet esthesiometer in accordance with the manufacturer's instructions. The instrument consists of a nylon filament 6.0 cm long and 0.12 mm in diameter. The force exerted by the filament when it touches the cornea is inversely proportional to its length. Results are presented as centimeters of length of the nylon filament, with 6.0 cm being maximum sensitivity of the cornea and 0 cm being corneal anesthesia at that point tested. To minimize bias, all measurements were taken by the same experienced examiner who was masked with regard to which eye of each patient received the cyclosporine drops.

Measurements were taken at nine different areas in each cornea: the four quadrants of the untreated cornea (areas 1, 2, 8, and 9), the peripheral quadrants of the flap (areas 3, 4, 6, and 7), and the center of the flap (area 5) (Fig 1). Patients lay in a supine position looking straight ahead and were asked to indicate when the stimulus was felt. The filament was moved towards the cornea smoothly at a perpendicular angle. Contact was detected by a slight bending in the filament. If there was no patient response to the first contact, the length of the filament was decreased by 0.5 cm to increase its rigidity, and the procedure was repeated until the patient reported feeling corneal contact. The longest filament length at which a minimum of three stimulus applications produced a positive response from the patient was recorded. This was considered to be the corneal touch threshold.

Statistical Analysis

The Wilcoxon sum rank test was used to determine the statistical significance between the study and control eyes for the measures of corneal sensitivity and BSCVA. The paired samples *t* test was used for manifest refraction spherical equivalent (MRSE) to determine the statistical significance between the study and control eye of each patient.

RESULTS

At 3 months postoperative, complete follow-up data were obtained for 38 (86%) eyes (19 patients). Two patients dropped out early in the study and were replaced; one additional patient missed 1- and 3-month follow-up. Average patient age was 36.8 years (range: 22 to 49 years); 50% were male, 50% were Hispanic, 45.5% were Caucasian, and 4.5% were Black.

Manifest Refraction Spherical Equivalent

Preoperatively, the study group had a mean MRSE of -2.06 ± 2.79 D compared to -2.45 ± 2.99 D in the control group; the mean MRSE was slightly more myopic in the control group (P=.034). The mean preoperative intended correction (MRSE) was -2.07 ± 2.91 D in the study group and -2.27 ± 3.03 D in the control group; no significant difference was evident (P=.259).

At all postoperative time points no significant difference in MRSE was noted between the study and control eyes. At 1 month postoperative, mean MRSE in the study group was 0.05 ± 0.36 D versus 0.16 ± 0.30 D in the control group (P=.156). At 3 months postoperative, mean MRSE in the study group was 0.27 ± 0.43 D versus 0.21 ± 0.37 D in the control group (P=.671).

Best Spectacle-corrected Visual Acuity

Preoperatively, all patients had 20/40 or better BSCVA and no statistically significant difference was noted between the study and control eyes (P=1.0). At 1 week postoperative, 95.5% of the study eyes and 95.5% of the control eyes had 20/25 or better BSCVA with no case worse than 20/40; no statistically significant difference was found between the two groups (P=.705). One month postoperative, all eyes had 20/20 or better BSCVA with no significant difference between study and control eyes (P=.317). At 3 months postoperative, all eyes had 20/20 or better BSCVA, with the exception of one study eye and one control eye achieving a BSCVA of 20/25. No significant difference was found between the study and control eyes at 3-month follow-up (P=1.0).

Additionally, no adverse events were reported throughout the duration of this study.

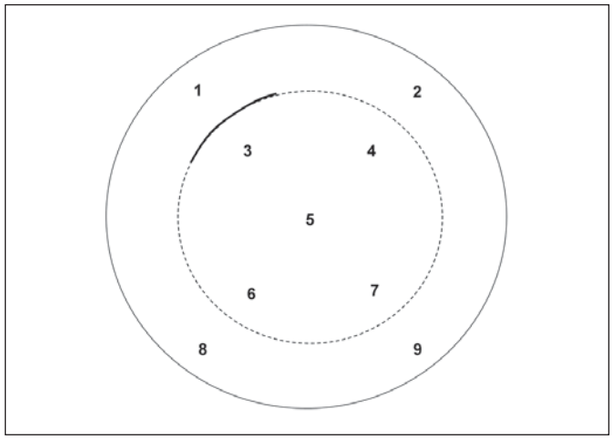

Figure 1. Diagram of an eye after LASIK shows the different areas tested for corneal sensitivity. The dotted line represents the corneal flap; the bold line represents the hinge (between area 1 and 3).

Corneal Sensitivity

Corneal sensitivity was measured at areas outside of the LASIK flap (points 1, 2, 8, and 9) and within the flap (points 3 through 7) preoperatively and up to 3 months postoperatively. Results showed that for all points outside the LASIK flap, normal corneal sensitivity was maintained. In addition, no significant difference was found between the cyclosporine-treated eyes and control eyes. Table 1 provides a comparison of median values of corneal sensitivity between the two groups at all time periods tested whereas Table 2 compares the proportion of cases in which the corneal sensitivity in the cyclosporine-treated eye was better, worse, or the same as in the control eyes at 3 months postoperatively.

At corneal point 1, there was no difference between the study and control groups, and the median postoperative corneal sensitivity remained the same as preoperative levels. At 3 months postoperative, in more than half the cases the corneal sensitivity was the same (58%); and there was a comparable incidence (P=.272) of the cyclosporine-treated eye or the control eye showing a better corneal sensitivity (16% vs 26%, respectively). A similar outcome for the other areas (points 2, 8, and 9) outside the LASIK flap area was found.

All points within the LASIK flap (points 3-7) demonstrated no difference in corneal sensitivity between the study and control eyes at 1 day, 1 week, and 1 month postoperatively and, except for the point closest to the hinge (point 3), all of the other points at all of these postoperative time points demonstrated profound loss of corneal sensitivity (median values of 0.25 cm or less). Point 3, while demonstrating a decrease from baseline, never decreased below a median value of 3.5 cm. At 3 months postoperatively, all points within the LASIK

TABLE 1

Median Corneal Sensitivity Measurements Using the Cochet-Bonnet Esthesiometer (mm)

		Corneal Sensitivity Measurements (mm)					
	Eye	Preop	*P* Value	1 Day	*P* Value	1 Week	*P* Value
Point 1	Study	6.00	.334	6.00	.522	6.00	.297
	Control	6.00		6.00		6.00	
Point 2	Study	6.00	.169	6.00	.811	6.00	1.000
	Control	6.00		6.00		6.00	
Point 3	Study	6.00	.068	4.25	.732	3.50	.147
	Control	6.00		3.50		4.25	
Point 4	Study	6.00	.191	0.25	.258	0.00	.890
	Control	6.00		0.00		0.00	
Point 5	Study	6.00	.083	0.00	.526	0.00	.493
	Control	6.00		0.00		0.00	
Point 6	Study	6.00	.527	0.00	.632	0.00	.166
	Control	6.00		0.00		0.00	
Point 7	Study	6.00	.739	0.00	.658	0.00	.317
	Control	6.00		0.00		0.00	
Point 8	Study	6.00	.405	5.75	.111	6.00	.379
	Control	6.00		5.50		6.00	
Point 9	Study	6.00	.785	5.50	.478	5.75	.213
	Control	6.00		5.50		5.50	

flap, except the point closest to the hinge (point 3), had significantly better corneal sensitivity in the cyclosporine eye than in the control eye (Fig 2, Table 1).

At corneal point 3, there was no difference between the study and control groups with regard to median value (5 cm in both groups); however, 53% of cases had better corneal sensitivity in the cyclosporine-treated eye, compared to 32%, which had the same corneal sensitivity in both eyes, and 16% reported better corneal sensitivity in the control eye. Although these results were not statistically significant, a strong trend favoring the cyclosporine-treated eye was apparent (*P*=.058).

At corneal point 4, the median corneal sensitivity was better in the cyclosporine-treated group at 3 months postoperatively (5 vs 3 cm). Individual comparison between the study and control eye confirmed this finding, with 84% of cases reporting a better corneal sensitivity in the cyclosporine-treated eye, compared to 11% favoring the control eye, and 5% reporting the same corneal sensitivity in both eyes. Statistical analysis showed a significant difference between the study and control eyes (*P*=.011).

Corneal point 5 in the center of the LASIK flap demonstrated the greatest difference between the cyclosporine-treated eyes and control eyes. The median corneal sensitivity was much greater in the study eye than the control eye at 3 months postoperative (5 vs 1 cm). Eighty-four percent of cases had better corneal sensitivity in the cyclosporine eye than in their control eye (*P*=.002).

Corneal point 6 demonstrated a greater corneal sensitivity in the cyclosporine-treated eyes than the control eyes (median: 4.5 vs 1 cm), and a statistically significant difference was evident between the two groups (*P*=.003), with 79% of cases showing a better corneal sensitivity in their cyclosporine-treated eye than their fellow control eye.

Corneal point 7 demonstrated a greater corneal sensitivity in the cyclosporine-treated eyes than the control eyes (median: 4.5 vs 1 cm), and a statistically significant difference was evident between the two groups (*P*=.002), with 74% of cases showing a better corneal sensitivity in their cyclosporine-treated eye than their fellow control eye.

DISCUSSION

It is well understood that LASIK flap creation requires the mechanical dissection of corneal nerves, resulting in corneal nerve destruction and conse-

Corneal Sensitivity Measurements (mm)			
1 Month	*P* Value	3 Months	*P* Value
6.00 6.00	.221	6.00 6.00	.272
6.00 6.00	.660	5.50 6.00	.968
5.00 5.00	.861	5.00 5.00	.058
0.00 0.00	.674	5.00 3.00	.011
0.00 0.00	.259	5.00 1.00	.002
0.00 0.00	.379	4.50 1.00	.003
0.00 0.00	.227	4.50 1.00	.002
6.00 6.00	.319	5.50 5.50	.754
6.00 6.00	.203	5.80 5.50	.151

quently reduced corneal sensitivity within the LASIK flap area.

Perez-Santonja et al[6] showed that after LASIK, 6 months were necessary for full recovery of corneal sensitivity, which was also confirmed by Nassaralla et al,[3] although for higher degrees of myopia (>7.75 D) 9 months were required. Erie et al[7] showed that following LASIK, subbasal nerve density is reduced by 51%, 35%, and 34% at 1, 2, and 3 years, respectively ($P<.001$), compared to preoperative levels, with full recovery at 5 years postoperative. Calvillo et al[8] also showed that both subbasal and stromal corneal nerves in LASIK flaps recover slowly and do not return to preoperative densities by 3 years after LASIK.

Limited studies have been performed to investigate a topical treatment to promote corneal nerve regeneration. These studies have investigated ocular treatments to encourage the sensory nerves to regenerate and reinnervate the cornea using neurotrophin/nerve growth factors. Lambiase et al[9] showed that application of nerve growth factor (NGF) restored corneal integrity and improved corneal sensitivity in patients with corneal neutrophic ulcers. Animal and clinical studies[10,11] also demonstrated the efficacy of substance P and insulin-like growth factor (IGF-1) to stimulate corneal sensory nerves for neurotrophic keratopathy. Also, substance P-derived peptide-phenylalanine-glycine-leucine-methionine amide (FGLM-NH_2) and IGF-1 exhibited a beneficial effect on superficial punctate keratitis in individuals with neurotrophic keratopathy.[12]

Several studies have found that macrolides or macrolide analogs can also promote nerve growth. Cyclosporine A, and more recently FK-506 (tacrolimus), are used systemically as immunosuppressant drugs on highly antigenic nerve allografts. However, neurotoxic complications have been noted in the central and peripheral nervous system but an increased rate of axonal regeneration has also been shown.[13]

Steiner et al[14] showed that the nonimmunosuppressive analogs of the immunosuppressive drugs FK-506, rapamycin, and cyclosporine A (CsA) promote neurite outgrowth both in PC12 cells and sensory neuronal cultures of dorsal root ganglia with potencies resembling their immunosuppressive homologs. Immunophilin ligands used systemically were neurotrophic in intact animals. FK-506 and L-685,818 (the C18-hydroxy, C21-ethyl derivative of FK-506) treatment of rats with crushed sciatic nerves enhanced both functional and morphologic recovery.

Katsube et al[15] investigated the effect of a limited course of systemic immunosuppression using CsA in rat peripheral nerve allotransplants. Phenotypes of Schwann cells in groups without, with continuing, and with limited (12 weeks) CsA treatment were examined immunohistochemically in allogeneically and syngeneically transplanted animals from 4 to 36 weeks after transplantation. Results showed that in the group receiving no CsA, little nerve regeneration was obtained; donor Schwann cells were rejected and replaced by recipient cells. In continuing and limited-course CsA groups, successful nerve regeneration was achieved at postoperative week 36, as was also observed in the syngeneic group. Schwann cells in the continuing CsA group remained donor-derived. In the limited-course CsA group, graft rejection and loss of function occurred after the withdrawal of CsA.

Carreau et al[16] studied the neurotrophic effects of FK-506, rapamycin, and CsA on in vitro dorsal root ganglia taken from different segmental levels (cervical, thoracic, and lumbar/sacral), and on rat embryonic septal cholinergic neurons in culture. At a low concentration (1 nM), FK-506 significantly increased (+83%) the number of neurites of thoracic dorsal root ganglia explants. At a higher concentration (100 nM), it also enhanced the neuritogenesis of thoracic (+100%) and lumbar/sacral (+57%) dorsal root ganglia, but not cervical dorsal root ganglia explants. Rapamycin dis-

TABLE 2

Corneal Sensitivity Comparison Between Cyclosporine-treated Eyes and Control Eyes at 3 Months Postoperative

	Percentage			
	Cyclosporine-treated Eye Better	Same	Control Eye Better	*P* Value
Point 1	16	58	26	.272
Point 2	32	37	32	.968
Point 3	53	32	16	.058
Point 4	84	5	11	.011
Point 5	84	0	16	.002
Point 6	79	5	16	.003
Point 7	74	11	16	.002
Point 8	21	47	32	.754
Point 9	32	58	11	.151

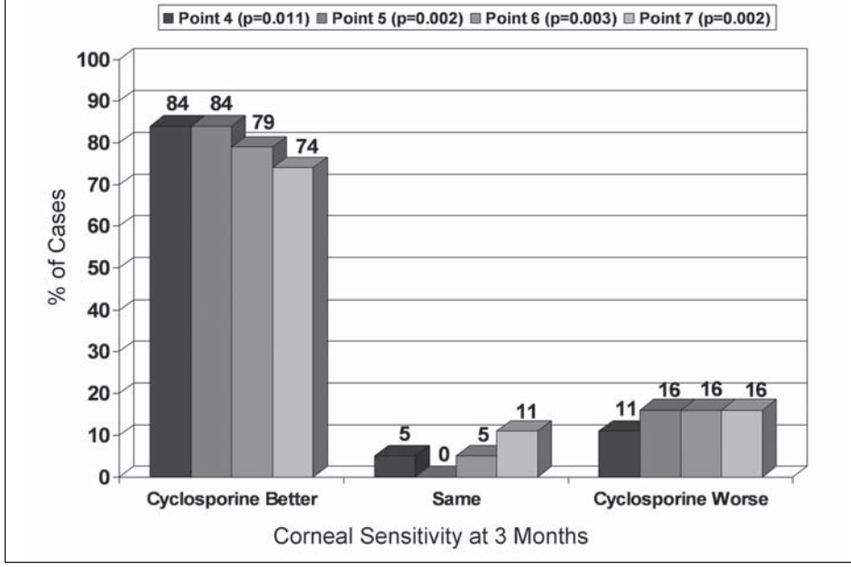

Figure 2. Comparison of corneal sensitivity between cyclosporine and control eyes at 3 months postoperatively in four areas within the corneal flap farthest from the hinge. At all of these points, 74% to 84% of cases had better corneal sensitivity in the cyclosporine-treated eye. In contrast, only 11% to 16% of cases had worse corneal sensitivity in the cyclosporine-treated eye.

played a converse effect, reducing the development of dorsal root ganglia explants from cervical and thoracic segments (−78% at 1 nM in thoracic dorsal root ganglia). Cyclosporine A (from 1 to 100 nM) was without effect on dorsal root ganglia neuritogenesis. In contrast to NGF, which increased neurite length (+116% at 3 ng/mL), neither FK-506 nor rapamycin affected this parameter. In summary, the results demonstrated that FK-506 enhances the differentiation of mammalian peripheral and central nerves in culture. Cyclosporine A did not affect development of these neurons; the differences in culture conditions as well as animal species may explain the discrepancy with previous data.[14]

In vitro and in vivo studies demonstrating the neurotrophic or no effect of macrolides and macrolide analogs on myelinated nerves prompted clinical research into its possible use for non-myelinated corneal nerve recovery after LASIK. The main efficacy variable under investigation was the extent of corneal sensitivity recovery after LASIK in the cyclosporine-treated eye compared to the fellow eye with no cyclosporine treatment.

Results showed that after 3 months of treatment with topical cyclosporine, corneal areas within the flap area had statistically significantly greater corneal sensitivity than control. The most central corneal area

(point 5) demonstrated the greatest difference in corneal sensitivity compared to control (P=.002), with 84% of cases reporting better corneal sensation in the cyclosporine-treated eye than the control eye. The center of the cornea (point 5) has the slowest and lowest relative recovery rate according to numerous studies,[3,6,17,18] thus the fact that the greatest difference was seen in the central corneal area is an impressive result.

Also, median corneal sensitivity at 3 months was much closer to preoperative levels in the cyclosporine-treated eye than that of the control eye for all points within the LASIK flap, except point 3—closest to the flap hinge. Corneal sensitivity outside the flap area was not significantly different between the study and control eyes, a finding that was expected. It was not surprising that the area within the LASIK flap closest to the hinge demonstrated reasonable corneal sensitivity throughout as it was partially innervated by corneal nerves entering the flap through the intact hinge.

Comparison of the cyclosporine-treated eyes to the control eyes showed no significant difference in postoperative BSCVA, and no adverse events were reported in either group.

Complete corneal recovery after LASIK is a slow process, and compromised corneal sensitivity can be a precarious situation. A low corneal sensitivity threshold is required to detect foreign bodies, injury, or pathologic changes early. The loss of normal corneal sensation can compromise the protective blink reflex, delay epithelial wound healing, decrease tear flow, and be associated with neurotrophic keratitis, sterile corneal melts, and infectious keratides. Studies have demonstrated that after LASIK at least 6 months is necessary for full recovery of corneal sensitivity, and even longer for higher degrees of myopia. Furthermore, complete nerve reinnervation to preoperative density levels is not complete before 5 years postoperative.

To date, no application has shown faster corneal nerve recovery (within 3 months after LASIK) than what was shown in this clinical study using an immunosuppressant agent. One explanation might be that the corneal nerves are not myelinated in contrast to other in vivo studies. This could explain the surprising effect we observed in our experiment after topical application of cyclosporine, instead of systemic administration used in previous reports. Another questionable mechanism of action rather than corneal nerve regeneration might be enhanced corneal nerve sensitivity with cyclosporine. These two mechanisms can be differentiated by the use of confocal microscopy. Unfortunately, confocal microscopy was not available at the study site but should be incorporated in future studies.

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