Published in final edited form as:
J Cataract Refract Surg. 2009 October ; 35(10): 1756–1760. doi:10.1016/j.jcrs.2009.05.032.

Dry eye associated with laser in situ keratomileusis: Mechanical microkeratome versus femtosecond laser

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Abstract

Purpose—To compare the incidence of laser in situ keratomileusis (LASIK)–associated dry eye and the need for postoperative cyclosporine A treatment after flap creation with a femtosecond laser or a mechanical microkeratome.

Setting—Cole Eye Institute, Cleveland, Ohio, USA.

Methods—Eyes were randomized to flap creation with an IntraLase femtosecond laser (30 or 60 kHz) or a Hansatome microkeratome. No patient had signs, symptoms, or treatment of dry eye preoperatively. Flap thickness was determined by intraoperative ultrasonic pachymetry. Slitlamp assessments of the cornea and need for postoperative dry-eye treatment were evaluated preoperatively and 1 month postoperatively.

Results—The flap was created with the femtosecond laser in 113 eyes and with the microkeratome in 70 eyes. The difference in mean central flap thickness between the femtosecond group (111 μm ± 14 [SD]) and the microkeratome group (131 ± 25 μm) was statistically significant (*P*<.001). The incidence of LASIK-associated dry eye was statistically significantly higher in the microkeratome group (46%) than in the femtosecond group (8%) (*P*<.0001), as was the need for postoperative cyclosporine A treatment (24% and 7%, respectively) (*P*<.01). In the microkeratome group, there was no correlation between thick flaps and a higher incidence of LASIK-induced dry eye.

Conclusions—Eyes with femtosecond flaps had a lower incidence of LASIK-associated dry eye and required less treatment for the disorder. In addition to neurotrophic effects from corneal nerve cutting, other factors may be important because no correlation was found between flap thickness (or ablation depth) and the incidence of LASIK-induced dry eye.

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Dr. Wilson is a consultant to Allergan, Irvine, California, USA. No author has a financial or proprietary interest in any material or method mentioned.

Laser in situ keratomileusis (LASIK) remains the most commonly performed refractive surgical procedure.[1] Advances in techniques and instruments have reduced the incidence and severity of flap abnormalities and other potentially severe complications of LASIK. One of the most common problems after surgery is LASIK-associated dry eye.[2–4] One condition that is thought to play an important role in dry eye after LASIK is LASIK-induced neurotrophic epitheliopathy (LINE), a term suggested by Wilson[2] and Ambrósio et al.[3] to describe the neurotrophic component of LASIK dry eye and that results from damage to the nerves during flap formation and stromal ablation.[2–4]

Corneal innervation is an integral component of the lacrimal gland–ocular surface functional unit,[5] which coordinates basal and stimulated tear production, lid blinking, tear spreading, and tear clearance.[2–9] In addition, neurotrophic factors released from corneal nerves are important in the normal physiology of corneal epithelial cells.[10] Denervation of the central cornea after LASIK is the result of surgical amputation of the nerve fibers produced by flap cutting and stromal ablation.[2–4,6–9] The significant decrease in sensation in the area of the flap after LASIK normally recovers in a progressive manner from 3 to 9 months after LASIK.[3,8,11–13] This nerve recovery is best seen on confocal microscopy[3] and generally correlates with resolution of, or at least marked improvement in, LASIK-induced dry eye.[3]

Frequently, LINE is seen in LASIK patients who do not have underlying chronic dry-eye disease before surgery. In other LASIK patients,[4] a combination of chronic dry eye, albeit mild, and superimposed neurotropic epitheliopathy contribute to the symptoms and signs of the postoperative disorder. In either case, the typical presentation involves corneal punctate epithelial erosions that are best seen using lissamine green or rose bengal staining as well as well as symptoms such as fluctuating vision, blurred vision, stinging, pain, photophobia, and visual fatigue.[2,3,11,14–16] Many patients with LINE have no symptoms or only mild fluctuations in vision.[2,3]

The lamellar cut to fashion the flap for LASIK can be performed using a mechanical microkeratome or a femtosecond laser. Our clinical experience with the IntraLase femtosecond laser (Abbott Medical Optics, Inc.) over the past few years has given us the clinical impression that the incidence and severity of LASIK-associated dry eye is less with that mode of flap creation than with the Hansatome microkeratome (Bausch & Lomb). Thus, we performed a retrospective study to compare the incidence of LASIK-associated dry eye and the need for postoperative cyclosporine A treatment between femtosecond laser flap creation and mechanical microkeratome flap creation.

Patients and Methods

Clinical data of normal patients who had LASIK to correct low to moderate myopia by the same surgeon (S.E.W.) from 2005 to 2007 at Cole Eye Institute were reviewed. One eye of each patient was randomly chosen for inclusion in the study. The patients in the study had surgery during an interval when both the microkeratome and femtosecond laser were being used for LASIK. Inclusion criteria were no symptoms or signs of dry eye before LASIK, no previous eye surgery, no topical ocular medications before surgery, and no other ocular conditions, such as ocular rosacea or chronic blepharitis. In addition, no eye in the study had

LASIK flap complications or postoperative enhancement during the first 9 months postoperatively.

Patients were stratified according to the device used to create the flap; that is, the femtosecond laser or the microkeratome. Flaps were created with a 30 kHz or 60 kHz IntraLase femtosecond laser or with a Hansatome microkeratome with a standard-compression 180 μm depth and 9.5 mm diameter suction head. Femtosecond flap settings were a diameter of 9.0 to 9.3 mm and a standard 55-degree hinge and 55-degree side-cut angle. The lamellar cut and side cuts were performed with an energy of 1.2 μJ with the 30 kHz laser and 1.0 μJ with the 60 kHz laser. The attempted flap thickness was 100 to 110 μm in eyes treated with the femtosecond laser. The hinges in all eyes were superior. In the microkeratome group, the same blade was used in both eyes of each patient and the right eye was always treated first. Stromal tissue ablation was performed with the Visx Star S4 IR (Abbott Medical Optics, Inc.) or LADARWave 600 (Alcon, Inc.) excimer laser under topical anesthesia in all cases.

The preoperative evaluation consisted of a complete ophthalmic examination comprising uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest and cycloplegic refractions, topographic analysis, wavefront analysis, fundus examination, Goldman applanation tonometry, ultrasound pachymetry, and slitlamp biomicroscopy. As part of the preoperative routine, patients were advised not to wear soft contact lenses for at least 4 days or rigid lenses for at least 3 weeks before the screening evaluation.

Eyes were treated with moxifloxacin hydrochloride ophthalmic solution 0.5% and prednisolone acetate 1% ophthalmic suspension USP 4 times daily for 1 week. In addition, nonpreserved artificial tears (Systane or Refresh Plus) were used 4 to 8 times a day for 1 week as needed.

Scheduled at postoperative follow-up visits were at 1 day, 1 week, and 1, 3, and 9 months. At each examination, UDVA, CDVA, manifest refraction, corneal topography, Goldman applanation tonometry, and slitlamp biomicroscopy were evaluated.

All eyes were assessed preoperatively and 1 month postoperatively by the same observer (S.E.W.). The presence or absence of LINE in each eye was determined from the slitlamp drawing of corneal punctate epithelial keratopathy at the slitlamp examination at the 1 month follow-up visit before any treatment with cyclosporine A. The severity of LINE was also recorded for each eye at the 1-month visit. Severity was graded trace (a few punctate epithelial erosions), 1+ (more than a few but less than 12 punctate epithelial erosions), 2+ (12 or more, but not nearly confluent punctate epithelial erosions), 3+ (nearly confluent punctate epithelial erosions), or 4+ (confluent punctate epithelial erosions) on the LASIK flap in each eye. Symptoms of LASIK dry eye, such as photophobia, grittiness, soreness, visual fluctuation, and burning, were also noted. Finally, patients who had a LINE grade of 1+ or greater were treated with topical cyclosporine A 0.05% (Restasis) beginning at the 1-month visit. The number of eyes in each group that required treatment was determined.

Statistical comparisons between groups were performed with the Student *t* test, Pearson chi-square test, Fisher exact test, and Wilcoxon rank-sum test using JMP statistical software (version 7, SAS Institute Inc.). Multivariant analysis was performed to determine whether flap thickness, manifest spherical equivalent (SE), or the method used to create the flap was a significant variable in the development of LINE. A *P* value less than 0.05 was considered statistically significant.

Results

Of the 411 patients who had LASIK during the study period, 183 met the inclusion criteria. Of the 183 eyes, 133 had LASIK with the femtosecond laser and 70, with the microkeratome. In the femtosecond group, the flap diameter setting was 9.3 mm in 95% of eyes and 9.0 mm or greater all eyes; a standard 55-degree hinge and 55-degree side cut angle were used in all eyes in the group. There was no difference between the femtosecond group and the microkeratome group in the proportion of cases performed with each of the 2 excimer lasers.

Table 1 shows the patients' demographic data and preoperative characteristics. There were no statistically significant differences between the femtosecond group and the microkeratome group in age, sex distribution, or central corneal thickness. The mean attempted correction was significantly higher in the femtosecond group than in the microkeratome group (P = .0, Student *t* test).

The mean flap thickness was 111 ± 14 μm in the femtosecond laser group and 131 ± 25 μm in the microkeratome group (Figure 1). The difference between the groups was statistically significant (P<.0001, Student *t* test), indicating much greater variation in flap thickness, including more thin flaps and more thick flaps, with the microkeratome.

Figure 2 shows the incidence of LINE in each group. Nine eyes (8%) in the femtosecond group and 32 eyes (46%) in microkeratome group had at least trace punctate epithelial keratopathy on the flap 1 month after surgery. The difference between the groups was statistically significant (P<.0001, Pearson chi-square test). There was no difference between eyes in which the flap was created with the 30 kHz femtosecond laser (n = 55) and eyes in which the flap was created with the 60 kHz femtosecond laser (n = 58).

The severity of signs of LASIK dry eye was statistically significantly different between the 2 groups (Figure 2). Eyes in the femtosecond laser group had statistically significantly lower punctate epithelial erosion scores than eyes in the microkeratome group 1 month after surgery (P = .0005, Fisher exact test). There was no significant difference between eyes that had LASIK with the 30 kHz femtosecond laser and eyes that had LASIK with the 60 kHz femtosecond laser.

Fifteen patients (13%) in the femtosecond group and 29 patients (41%) in the microkeratome group were symptomatic 1 month postoperatively. The difference between the 2 groups was statistically significant (P<.0001, Pearson chi-square test). The difference between groups in the need for topical cyclosporine A treatment postoperatively was also statistically significant (P = .001, Pearson chi-square test), with 8 eyes (7%) in the

femtosecond group and 17 eyes (24%) in the microkeratome group requiring treatment. There was no difference between eyes that had LASIK with the 30 kHz femtosecond laser and eyes that had LASIK with the 60 kHz femtosecond laser.

Although flap thickness variability was significantly greater in the microkeratome group, there was no statistically significant difference in mean flap thickness between patients who had LASIK-associated dry eye after surgery and those who did not ($P = .9$, Student *t* test). There was also no difference in the mean SE correction between the 2 subgroups ($P = .8$, Student *t* test).

Although the same blade was used in both eyes of each patient in the microkeratome group, with the right eye treated first, there was no statistically significant difference in the measured dry-eye parameters between right eyes and left eyes of patients in that group.

Multivariant analysis showed that the method used to form the flap (femtosecond laser or microkeratome) was the only significant variable in the development of LINE ($P < .0001$).

Discussion

Dry eye is the most frequent complication of LASIK, with symptoms and signs occurring in up to 90% of eyes, depending on the study.[2,6,7] Symptoms after the procedure are typically variable but include fluctuating vision and ocular discomfort, especially in the first 6 to 8 months after surgery.[2–4,17] Patients often present with corneal punctate epithelial erosions that can be observed without application of dyes but are enhanced with lissamine green or rose bengal staining. In severe cases, fluorescein staining may also be noted. Surprisingly, most eyes with this disorder have little, if any, decrease in tear production compared with preoperative levels,[2–4,9,18] although some studies report small decreases.[19,20]

Several possible mechanisms contributing LASIK-induced dry eye have been proposed. The mechanisms include injury to the afferent sensory nerve fibers, a reduction in neurotrophic influences on epithelial cells, a decreased blinking rate, decreased tear production, altered tear-film stability and distribution, increased tear evaporation, and injury to limbal goblet cells.[2–4,9,21–23] The preponderance of data supports the hypothesis that the most important factor in the pathophysiology of LASIK-induced dry eye is the transection of afferent sensory nerves in the anterior third of the stroma during the lamellar cut.[2–4] The disorder tends to be more common and more severe in the context of an underlying chronic dry eye.[3] It has become evident, however, that the disorder is multifactorial.

It is significant that our study included only eyes with no symptoms or signs of dry eye before surgery and no previous treatment with cyclosporine A. Yet, eyes in which the flaps were created with a microkeratome had significantly more signs and symptoms of LASIK-induced dry eye than eyes in which a femtosecond laser was used for flap creation. In addition, eyes in the femtosecond group required less treatment with cyclosporine than eyes in the microkeratome group. One explanation for these findings is that the femtosecond laser generated thinner flaps, with a lower deviation in flap thickness, than the microkeratome; therefore, there was less damage to the afferent sensory nerves in the anterior stroma. If, however, the difference between the femtosecond laser and microkeratome were attributable

only to differences in flap thickness, we would expect that eyes in the microkeratome group with thick flaps would have more LASIK-induced dry eye than eyes with thin flaps; however, there was no significant difference between the 2 subgroups. Also, because patients in the femtosecond group had a significantly higher mean SE correction than patients in the microkeratome group, we would have expected more stromal nerve ablation and more LASIK-induced dry eye in the femtosecond group. However, the microkeratome group had a higher incidence and severity of LASIK-induced dry eye. These findings suggest that factors other than flap thickness are important in the pathophysiology of LASIK-induced dry eye after surgery performed with the Hansatome microkeratome. Thus, additional factors, such as damage to conjunctival goblet cells,[24] may also have played an important role in the microkeratome group. A porcine model study[25] that used a blood pressure transducer connected to the anterior chamber by direct cannulation found that intraocular pressure (IOP) reached a mean of 122.52 ± 30.40 mm Hg during the suction phase and 160.52 ± 22.73 mm Hg in the cutting phase with the Moria 2 microkeratome. The IOP levels with the IntraLase femtosecond laser were 89.24 ± 24.26 mm Hg and 119.33 ± 15.88 mm Hg, respectively. Although no comparable study is available for the Hansatome microkeratome, these results show that there can be substantial differences in IOP with different instruments. Both the IntraLase femtosecond laser and Hansatome microkeratome have suction rings; however, the differences in the design or function of different rings, along with pressure exerted at specific points on the ocular surface, could be important in the mechanism of LASIK-induced dry eye.

We also considered suction time as a possible factor affecting the incidence and severity of dry eye. The suction time was approximately 56 seconds with the 30 kHz femtosecond laser and 40 seconds with the 60 kHz laser. The microkeratome suction time was approximately 20 seconds. If suction time were an important factor, we would have expected to find a higher incidence or greater severity of dry eye in the femtosecond group.

We do not interpret the results in this study to indicate that neurotrophic factors are not important in LASIK-induced dry eye. Many studies[2–5,9] suggest that transient loss of corneal sensation has a role in LASIK-induced dry eye. However, the results in our support the view that multiple factors contribute to the disorder.

The favorable response to topical cyclosporine A treatment in a majority of patients who develop LASIK-induced dry eye after femtosecond laser or microkeratome LASIK suggests that underlying subclinical inflammatory dry-eye disease is another factor in the pathophysiology of the disorder.[2] In some patients, cutting the corneal nerves likely introduces an additional stressor to mild, chronic dry eye.[3,26]

Thus, regardless of the underlying mechanisms, our study found a lower incidence of LASIK-induced dry eye when surgery was performed with the IntraLase femtosecond laser rather than the Hansatome microkeratome. When LASIK-induced dry eye did occur, it tended to be less severe after femtosecond LASIK than after microkeratome LASIK.

Acknowledgments

Supported in part by United States Public Health Service grants EY010056 and EY015638 from the National Eye Institute, Bethesda, Maryland, and Research to Prevent Blindness, New York, New York, USA.

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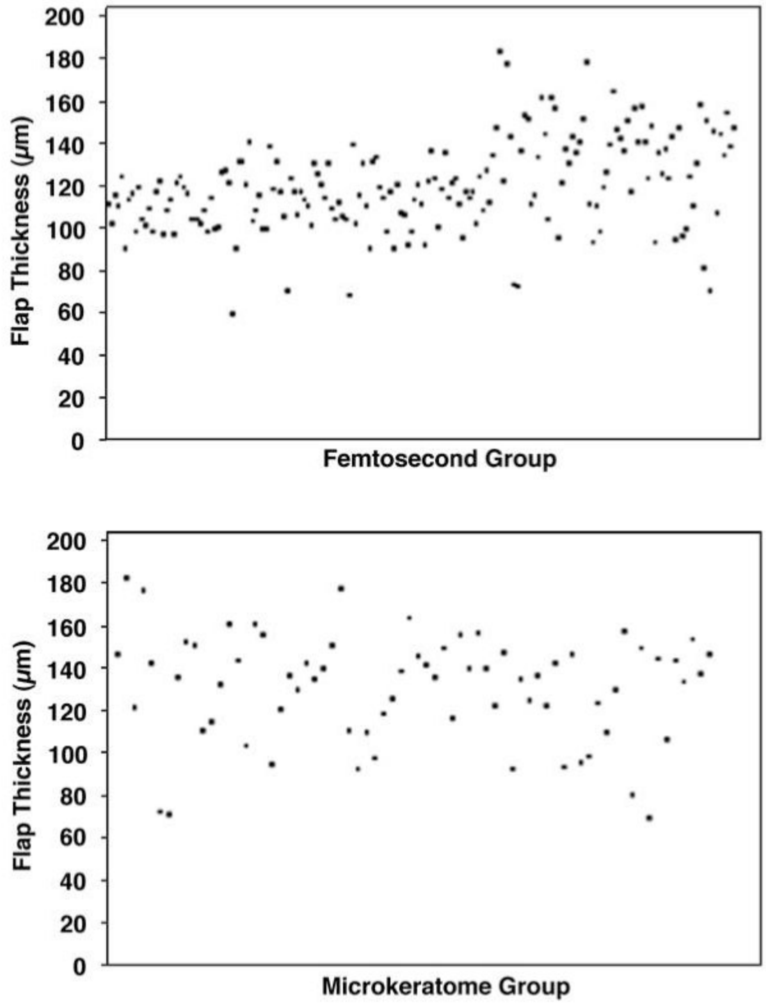

Figure 1. Distribution of flap thicknesses during LASIK

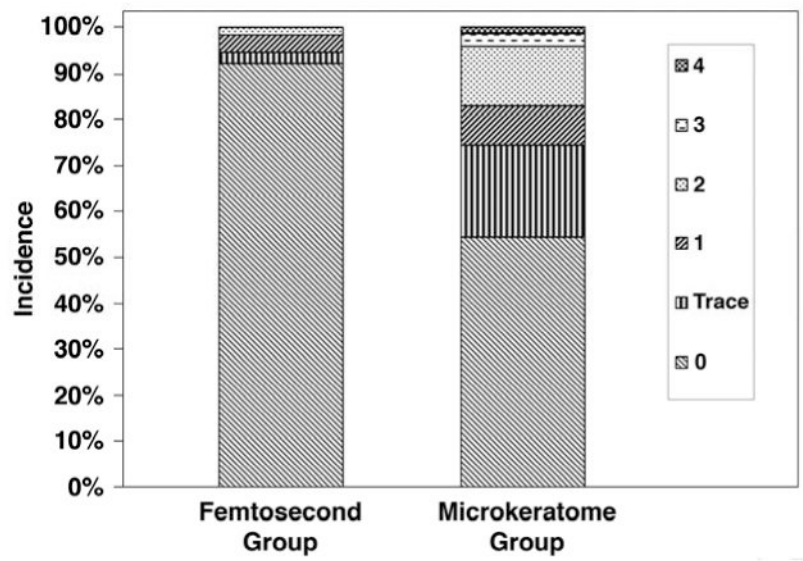

Figure 2.

Severity of corneal punctate epithelial erosions 1 month after LASIK.

Table 1

Patient demographic data and preoperative characteristics.

	Group		
Characteristic	**Femtosecond (n = 113)**	**Microkeratome (n = 70)**	***P* Value**
Age (y)			
Mean	43	45	.8
Range	20–72	20–72	
Sex, n (%)			
Female	60 (53)	38 (54)	.9
Male	53 (47)	32 (46)	
Mean CCT (μm) ± SD	558 ± 30	560 ± 34	.6
Mean SE (D) ± SD	−4.24 ± 2.3	−3.56 ± 1.9	.04

CCT = central corneal thickness; SE = spherical equivalent