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Incidence of Diffuse Lamellar Keratitis After LASIK with 15 KHz, 30 KHz and 60 KHz IntraLase Femtosecond Laser Flap Creation

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Abstract

Purpose—To compare the incidence of diffuse lamellar keratitis (DLK) after laser in situ keratomileusis (LASIK) with flap creation using the IntraLase® 15 kHz (FS15), 30 kHz (FS30), or 60 kHz (FS60) femtosecond laser.

Setting—University-based academic practice, Ann Arbor, Michigan, USA

Methods—We retrospectively reviewed 520 consecutive myopic LASIK surgeries performed using the IntraLase FS15, FS30, or FS60 femtosecond laser for flap creation from January 1, 2005 to June 1, 2007. Preoperative clinical characteristics, treatment parameters, intraoperative and postoperative complications were recorded. Statistical comparisons were made using repeated measures analysis, analysis of variance, chi-square, and Fisher's exact tests.

Results—Five hundred twenty eyes of 274 patients were included in the study. One hundred seventy-six eyes (93 patients) were treated using the FS15 laser, 180 eyes (93 patients) with the FS30 laser, and 164 eyes (89 patients) with the FS60 laser. Seventeen eyes (10%) in the FS15 laser group, 24 eyes (13%) in the FS30 laser group, and 23 eyes (14%) in the FS60 laser group developed DLK. There was no statistically significant difference in the incidence of DLK among the three groups ($p=0.68$).

Conclusion—This study found no significant difference in the incidence of DLK among the FS15, FS30, and FS60 groups.

BACKGROUND AND SIGNIFICANCE

Diffuse lamellar keratitis (DLK) is a non-infectious corneal inflammation sometimes encountered after laser assisted in-situ keratomileusis (LASIK). It was first described by Smith

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Although decreased energy settings used with higher frequency femtosecond lasers are hypothesized to decrease DLK, this study of DLK after LASIK with 3 femtosecond laser frequencies showed no statistically significant differences.

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and Maloney in 1998¹ as a granular, white cell infiltrate within the LASIK flap interface. It may be associated with redness, tearing, pain, photophobia and decline in central vision. It is usually noted within the first 5 days after LASIK surgery, although delayed cases of DLK have been reported.^{2–5}

The natural course of DLK is variable. Some cases resolve spontaneously while others progress to severe inflammation, flap necrosis and a hyperopic refractive shift.⁶ Given the potential for devastating consequences, vigilance and prompt treatment are required. Corticosteroids, either topical or oral, are the mainstay of treatment; in more severe cases, flap lifting and irrigation is required. Fortunately, progression to advanced stages of DLK is rare.^{7–8} Nevertheless, DLK increases the risk of future LASIK enhancement⁹ and may result in decreased contrast sensitivity.¹⁰

The etiology of DLK is poorly understood. Cases of DLK have been attributed to bacterial endotoxins,^{11–14} chemicals or debris produced during autoclaving,¹⁵ surgical gloves,¹⁶ surgical drapes,¹⁷ marking pens,^{18–19} meibomian gland secretions,^{20–21} atopy,²² iatrogenic epithelial defects,^{23–25} lower average endothelial cell density,²⁶ and wider palpebral fissure height.²⁶ Ultimately, DLK is thought to be related to how endogenous factors modulate a patient's response to exogenous exposures.^{27–28}

With the advent of femtosecond LASIK flap creation, the rate of DLK has been noted to increase. The rate of DLK after microkeratome LASIK flap creation is estimated to be 0.4–7.7%.^{7,23–24,26–29} In comparison, the rate of DLK after femtosecond LASIK flap creation ranges from 0.4–19.4%.^{29–32} When comparing the 15 kHz femtosecond laser to the Moria microkeratome, studies by both Javaloy and Gil-Cazorla found the incidence of post-LASIK DLK to be significantly higher when the femtosecond laser was used.^{29,32} However, femtosecond lasers are associated with advantages such as more accurate flap dimensions, fewer flap complications,^{31–32} stronger flaps,³³ and the ability to make thinner and customized flaps. Thus, interest in femtosecond lasers for LASIK flap creation has not been dampened by the increased incidence of DLK.

Recently, it has been reported that reducing femtosecond energy settings, especially side-cut energy, decreases the incidence of DLK.^{31,33,34} It has been theorized that higher frequency femtosecond lasers may cause less DLK because they allow for lower energy settings. The purpose of this study was to compare the incidence of DLK with different femtosecond laser frequencies: specifically the IntraLase® 15 kHz (FS15), 30 kHz (FS30), or 60 kHz (FS60) femtosecond lasers (Abbott Medical Optics, Irvine, CA).

METHODS

This study was approved by the University of Michigan Institutional Review Board. We retrospectively reviewed on the records of 520 eyes of 274 consecutive patients who underwent myopic LASIK using the FS15, FS30, or FS60 laser for flap creation from January 1, 2005 to June 1, 2007. Surgeries before February 1, 2006 were performed with the FS15 laser. The FS30 laser was used from February 1, 2006 to October 9, 2006, and subsequent cases were performed with the FS60 laser. The Technolas 217 excimer laser (Bausch & Lomb, Rochester, NY) was used in all cases for stromal ablation.

Clinical data collected included: date of LASIK surgery, age, gender, preoperative presence of meibomian gland dysfunction (MGD), history of atopy based on self report of seasonal allergies, eczema or asthma, preoperative Schirmer values after topical anesthetic, preoperative intraocular pressure (IOP), and preoperative use of ocular medications. Recorded treatment data included: femtosecond laser frequency, corneal thickness, optical zone, raster energy, raster spot separation, side cut energy, intended flap thickness, flap diameter, ablation depth,

and treated refractive error. Residual bed thickness was calculated by subtracting ablation depth and flap thickness from preoperative corneal thickness. Postoperative uncorrected and best-corrected distance visual acuities (UDVA and CDVA) were recorded at 1 day and 1 week after LASIK.

Intraoperative and postoperative complications were recorded. For patients who developed DLK, the day of onset, grade, treatment instituted, and day of resolution were recorded. DLK was graded clinically as previously described by Linebarger et al.³⁵ Stage 1: white granular cells located in flap periphery; Stage 2: white cells migrate toward flap center; Stage 3: white cells more densely clumped, often with relative peripheral clearing; Stage 4: stromal melting, scarring, bullae formation, and stromal volume loss.

The standard postoperative treatment protocol was either prednisolone acetate 1% and a fourth generation fluoroquinolone eye drop or a combination corticosteroid and antibiotic eye drop every 2 hours for the first 24 hours. This was then decreased to four times a day for the first postoperative week and subsequently tapered. If DLK was detected, more intense corticosteroids were started as indicated by the clinical course.

Comparisons between the femtosecond laser frequencies were made using analysis of variance for continuous subject-based variables and linear mixed regression models (to adjust for inter-eye dependency) for continuous eye-based variables; categorical comparisons were made using chi-square and Fisher's exact tests. Univariable repeated measures logistic regression models, using generalized estimating equations to correct for inter-eye correlation, were used to assess differences in rates of DLK among clinical and treatment variables. P-values less than 0.05 were considered statistically significant. All analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

RESULTS

Five hundred twenty eyes of 274 patients were included. Two-hundred forty six patients underwent binocular and 28 monocular LASIK. One hundred seventy-six eyes (93 patients) were treated using the FS15, 180 eyes (93 patients) with the FS30, and 164 eyes (89 patients) with the FS60. One patient had their left eye initially treated in 2005 using the FS15 then subsequently had the right eye treated in 2007 with the FS60. The mean patient age was 38.4 years (range: 21–67). One hundred fifty-seven (57%) were women and 117 (43%) were men. There was significantly greater preoperative corneal thickness in the FS60 group (563 μ m in the FS60 group versus 553 μ m in both the FS15 and FS30 groups; $p=0.05$). There were no other statistically significant preoperative differences among the three groups (Table 1).

The overall incidence of DLK in this cohort was 12% (64/520). Seventeen (10%) of the 176 eyes in the FS15 group, 24 (13%) of the 180 eyes in the FS30 group, and 23 (14%) of the 164 eyes in the FS60 group developed DLK. There was no statistically significant difference in the incidence of DLK among the three groups ($p=0.68$).

As expected, treatment parameters were significantly different among the 3 femtosecond laser groups (Table 2). The higher frequency femtosecond lasers had decreased raster energy, raster spot separation, and side cut energy. The average raster energy was 3.1 ± 0.3 μ J for the FS15, 2.0 ± 0.1 μ J for the FS30, and 1.7 ± 0.1 μ J for the FS60 ($p<0.01$), and raster spot separation decreased progressively from 10 μ m to 8 μ m. The average side cut energy was 4.0 ± 0.2 μ J for the FS15, 3.0 ± 0.1 μ J for the FS30, and 2.2 ± 0.1 μ J for the FS60 ($p<0.01$). In addition, throughout the study period there was a statistically significant trend toward using thinner flaps ($p<0.01$) and larger optical zones ($p=0.03$). Due to the thicker average preoperative corneal thickness and thinner average flaps created, the FS60 group had significantly greater residual bed thickness ($p<0.01$). Flap diameter also differed significantly among the 3 groups (FS15: 8.7

$\pm 0.3\text{mm}$, FS30: $8.8\pm 0.3\text{mm}$, and FS60: $8.6\pm 0.3\text{mm}$; $p<0.01$). There were no statistically significant differences in spherical equivalent treated or ablation depth.

When evaluating all cases regardless of femtosecond laser frequency, we found no statistically significant differences in the incidence of DLK based on preoperative characteristics or treatment parameters (Table 3). Cases that developed DLK on average had thinner flaps created ($118.13\pm 8.52\mu\text{m}$) compared to cases that did not develop DLK ($120.75\pm 7.58\mu\text{m}$) ($p=0.09$).

All patients were started on postoperative eye drops on the day of surgery. They used corticosteroid and antibiotic eye drops, either separately ($n=152$) or as a combined eye drop ($n=250$). There was no significant difference in incidence of DLK between these treatment regimens ($p=0.50$).

DLK Cases

Overall, 39 of the 274 patients in this cohort developed DLK. Twenty-five patients (64%) developed bilateral and 14 patients (36%) unilateral DLK. Ten patients had LASIK performed in both eyes but developed DLK in only 1 eye.

Of the 64 eyes that developed DLK, 50 (78%) were Stage I, 11 (17%) Stage II, and 3 (5%) Stage III (Table 4). There were no cases of Stage IV DLK in this patient cohort. Fourteen eyes (22%) were maintained on the standard four times a day topical corticosteroid eye drop treatment regimen while fifty eyes (78%) were treated with more frequent corticosteroid eye drops every 1–3 hours as deemed clinically necessary. Two patients (3 eyes with DLK) were treated with oral prednisone 60mg daily. Only 2 cases (3%), required flap lift and irrigation. Fifty cases (78%) resolved within 2 weeks after LASIK surgery, but 3 cases (5%) required over a month before DLK resolved.

One week post-LASIK visual acuity information was available for 494 eyes (Table 5). At one week post-LASIK, UDVA was 20/20 or better in 26 eyes (47%) and 20/40 or better in 53 eyes (96%) that developed DLK. In contrast, among those that did not develop DLK, UDVA was 20/20 or better in 282 eyes (65%) and 20/40 or better in 423 eyes (97%) ($p=0.40$) at 1 week post-LASIK. At 1 week, CDVA was 20/20 or better in 35 eyes (64%) and 20/40 or better in 54 eyes (98%) that developed DLK. In eyes that did not develop DLK, CDVA was 20/20 or better in 380 eyes (87%) and 20/40 or better in 437 eyes (100%).

Since preliminary data suggested that thinner flaps may increase the risk of DLK, we performed further analysis to explore this possibility (Table 6). Using 120 μm flap thickness as a standard, 20.6% (20/97) of eyes with thinner flaps developed DLK compared to 10.4% (44/423) of eyes with thicker flaps. The odds of DLK is 2.13 times higher (95% CI, 1.10 to 4.12) when the flap is $<120\mu\text{m}$ vs. $120\mu\text{m}$ ($p=0.02$). However, when this was broken down by laser frequency group, the FS30 laser was the only group within which this finding was significant.

DISCUSSION

Femtosecond-assisted LASIK flap creation has been associated with an increased risk of DLK compared to microkeratome flap creation.³² Confocal and histologic studies of human and rabbit corneas have demonstrated that femtosecond LASIK flap creation results in greater stromal cell apoptosis, monocyte influx, and a higher wound healing index when compared to flaps created using a microkeratome.^{32,36,37} Netto et al found that higher frequency femtosecond lasers caused less corneal inflammation, and that a 60 kHz femtosecond laser induced a similar amount of inflammation as a microkeratome.³⁷ This suggests that higher femtosecond laser frequency should decrease DLK rates due to the decreased energy settings that are used in creating LASIK flaps.

This hypothesis was not supported by the results of our retrospective study. We found that there was no statistically significant difference in DLK development between the FS15, FS30, and FS60 ($p=0.68$). In our study, the overall incidence of DLK after IntraLase laser flap creation for LASIK was 12%. Ten percent of eyes in the FS15 group, 13% in the FS30 group, and 14% in the FS60 group developed DLK. Our rate of DLK is less than that found by Binder (19.4%) and Javaloy (17%),^{31,32} but greater than that found by Gil-Cazorla (0.5%) and Haft (0.42%)^{29,30} (Table 7). The low incidence of DLK found by Gil-Cazorla et al may be due to their standard postoperative regimen of 8x daily corticosteroid eye drops. The study by Haft et al included eyes treated by the 15 kHz and 30 kHz femtosecond lasers but did not specify how many were in each treatment group. Thus, no conclusions can be made on how femtosecond frequency affected the incidence of DLK.

As expected, we found significant differences in energy parameters when the three femtosecond lasers were compared. In addition, we found statistically significant differences in corneal thickness, flap thickness, flap diameter, residual bed thickness, and optical zone. These differences reflect changes in patient selection and treatment parameters that took place over the 2.5 year study period. As our understanding of risk factors for post-LASIK ectasia and refractive aberrations increased, a trend toward selecting patients with thicker preoperative corneas, creating thinner LASIK flaps, and treating larger optical zones was seen.

Most cases of DLK in our study were Stage I or II and resolved within 2 weeks with minimal sequelae. The majority (96%) achieved better than 20/40 uncorrected visual acuity despite developing DLK. However, patients who developed DLK were less likely to achieve 20/20 uncorrected acuity at one week post-LASIK than those who did not ($p=0.03$). A closer look at DLK severity by femtosecond laser frequency (Table 4) suggests that the FS30 laser was associated with more severe DLK requiring more intensive treatment and taking longer to resolve. However, given the small number of these cases, it is difficult to draw definitive conclusions.

Eyes that developed DLK showed a trend toward thinner average LASIK flaps ($p=0.09$). This trend toward increased DLK in thinner flaps had been previously suggested by a prospective study performed by Javaloy et al, which found that flaps $<120\mu\text{m}$ in thickness had a higher wound healing opacity index as measured by confocal microscopy.³² This was attributed to activation of the greater number of keratocytes found in the anterior stroma. We compared eyes with flaps $<120\mu\text{m}$ to flap $\geq 120\mu\text{m}$ and found there was an increased incidence of DLK in eyes with flaps $<120\mu\text{m}$ ($p=0.02$) (Table 6).

One of the complicating factors in our analysis is that there was a range of energy parameters used in our patient cohort, with overlap in the settings used in each laser frequency group. For example, the average side cut energy for the FS15 was 4.0 μJ (range: 2.9–4.2 μJ), FS30 was 3.0 μJ (range: 2.1–3.2 μJ), and FS60 was 2.2 μJ (range: 2.0–2.3 μJ) (Table 7). This was the case as well with the raster energy and raster spot separation. The lack of standardization in treatment parameters makes it difficult to assess these potentially confounding factors.

Our study otherwise found no preoperative or treatment variable that was associated with an increased risk of developing DLK. This includes no significant association with preoperative MGD ($p=0.85$) or patient atopy ($p=0.25$), both of which have been found in prior studies to be associated with an increased risk of DLK.^{20–22}

Although our study is limited by its retrospective observational design, this is the only study to our knowledge that evaluates the effect of IntraLase femtosecond laser frequency on the incidence of DLK. Our study findings do not support the hypothesis that higher frequency femtosecond laser frequencies necessarily decrease the incidence of DLK. While higher frequency femtosecond lasers have been shown in laboratory models to cause less corneal

inflammation, our findings reinforce the postulate that DLK is caused by multiple intrinsic and extrinsic factors. Higher frequency femtosecond lasers have many advantages, but they do not guarantee decreased rates of DLK.

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Biography

TABLE 1

Preoperative characteristics

	FS15	FS30	FS60	TOTAL	P-value*
Total patients	93	93	89	274**	-
Total Eyes	176	180	164	520	-
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P-value*
Age (years)	39.2 (9.6)	38.6 (10.6)	37.6 (10.3)	38.4 (10.1)	0.567
IOP (mmHg)	14.3 (1.8)	14.0 (2.6)	13.8 (2.9)	14.0 (2.5)	0.409
K Thickness (μm)	553.1 (26.6)	552.5 (28.3)	562.9 (37.0)	552.7 (61.8)	0.051
	Total (%)	Total (%)	Total (%)	Total (%)	P-value*
Gender					
Female	51 (55.4)	49 (52.7)	57 (64.0)	157 (57.3)	0.229
Male	42 (45.2)	44 (47.3)	32 (36.0)	117 (42.7)	
Schirmer's					
≤5 mm	10 (10.9)	7 (7.6)	4 (4.7)	21 (7.7)	0.650
6–10 mm	20 (21.7)	19 (20.7)	18 (20.9)	57 (20.8)	
≥10 mm	62 (67.4)	66 (71.7)	64 (74.4)	192 (70.1)	

Abbreviations: FS15= IntraLase 15kHz femtosecond laser; FS30= IntraLase 30kHz femtosecond laser; FS60= IntraLase 60kHz femtosecond laser; IOP=intraocular pressure; MGD=meibomian gland dysfunction; K=corneal

* P values from ANOVA for continuous patient-based variables, linear mixed regression models for continuous eye-based variables, and Chi-square or Fisher's exact tests for categorical variables.

** One subject had one eye treated by the FS15 and one eye by the FS60

TABLE 2

Treatment parameters

	FS15 mean (SD)	FS30 mean (SD)	FS60 mean (SD)	P-value *
Flap Thickness (μm)	121.8 (8.5)	120.4 (7.7)	118.9 (6.6)	0.001
Flap Diameter (mm)	8.7 (0.3)	8.8 (0.3)	8.6 (0.3)	<0.001
Side Cut Energy (μJ)	4.0 (0.2)	3.0 (0.1)	2.2 (0.1)	<0.001
Raster Energy (μJ)	3.1 (0.3)	2.0 (0.1)	1.7 (0.1)	<0.001
Optical Zone (mm)	6.3 (0.5)	6.4 (0.5)	6.5 (0.5)	0.028
Ablation Depth (μm)	88.6 (36.6)	87.0 (35.8)	83.5 (34.2)	0.472
Residual Bed (μm)	342.7 (38.2)	345.0 (38.8)	360.4 (43.3)	0.002
Spherical Equivalent	−4.2 (2.0)	−4.1 (2.0)	−3.7 (1.7)	0.112
Raster Spot Separation	Total (Percent)	Total (Percent)	Total (Percent)	
8	0 (0.0)	0 (0.0)	116 (70.7)	<0.001
9	3 (1.7)	180 (100.0)	48 (29.3)	
10	173 (98.3)	0 (0.0)	0 (0.0)	

Abbreviations: FS15= IntraLase 15kHz femtosecond laser; FS30= IntraLase 30kHz femtosecond laser; FS60= IntraLase 60kHz femtosecond laser; SD=standard deviation

* P values from ANOVA for continuous patient-based variables, linear mixed regression models for continuous eye-based variables

TABLE 3

DLK risk by preoperative and treatment variables

	DLK (n=64)	No DLK (n=456)	
	Number (%)	Number (%)	P-Value*
MGD	7 (10.9)	52 (11.4)	0.848
Atopy	22 (34.4)	108 (23.7)	0.247
Schirmer's			
<5	4 (6.3)	27 (5.9)	0.797
6–10	10 (15.6)	79 (17.3)	
≥10	50 (78.1)	344 (75.4)	
Raster spot separation			
8	21 (18.0)	96 (82.1)	0.296
9	28 (12.2)	202 (87.8)	
10	15 (8.7)	158 (91.3)	
	Mean (SD)	Mean (SD)	P-value*
K Thickness (μm)	550.66 (34.3)	556.47 (30.2)	0.665
Flap Thickness (μm)	118.13 (8.5)	120.79 (7.6)	0.088
Flap Diameter (μm)	8.75 (0.3)	8.71 (0.3)	0.538
Raster Energy (μJ)	2.15 (0.6)	2.30 (0.6)	0.164
Side Cut Energy (μJ)	2.92 (0.7)	3.08 (0.7)	0.260
Optical Zone (mm)	6.39 (0.4)	6.39 (0.5)	0.937
Ablation Depth (μm)	93.23 (37.2)	85.45 (35.2)	0.160
Residual Bed (μm)	339.30 (43.8)	350.24 (39.9)	0.232

Abbreviations: DLK=diffuse lamellar keratitis; MGD=meibomian gland dysfunction; K=corneal

* P values calculated from univariable repeated measures logistic regression models using generalized estimating equations to account for inter-eye correlation

TABLE 4

DLK cases

	FS15 (n=17)	FS30 (n=24)	FS60 (n=23)	Total (n=64)
	Number (%)	Number (%)	Number (%)	Number (%)
DLK Stages				
Stage I	14 (82.4)	17 (70.8)	19 (82.6)	50 (78.1)
Stage II	2 (11.8)	6 (25.0)	3 (13.0)	11 (17.2)
Stage III	1 (5.9)	1 (4.2)	1 (4.4)	3 (4.7)
Time to resolution				
<1 week	8 (47.1)	10 (41.7)	13 (56.5)	31 (48.4)
1–2 weeks	8 (47.1)	5 (20.8)	6 (26.1)	19 (29.7)
2–4 weeks	1 (5.9)	6 (25.0)	4 (17.4)	11 (17.2)
>1 month	0 (0.0)	3 (12.5)	0 (0.0)	3 (4.7)

Abbreviations: FS15= IntraLase 15kHz femtosecond laser; FS30= IntraLase 30kHz femtosecond laser; FS60= IntraLase 60kHz femtosecond laser; DLK=Diffuse lamellar keratitis

TABLE 5

Visual acuity outcomes

	DLK (n=55)	No DLK (n=439)	
	Number (%)	Number (%)	P-value
POW1 UDVA			
≥ 20/20	26 (47.3)	282 (64.5)	0.0350 *
20/25 to 20/40	27 (49.1)	141 (32.3)	
< 20/40	2 (3.6)	14 (3.2)	
POW1 CDVA			
≥20/20	35 (63.6)	378 (86.5)	<0.001 **
20/25 to 20/40	19 (34.6)	59 (13.5)	
< 20/40	1 (1.8)	0 (0.0)	

Abbreviations: DLK=diffuse lamellar keratitis; POW1=postoperative week 1; UDVA=uncorrected distance visual acuity; CDVA= corrected distance visual acuity

* P value calculated by Fisher's exact test, two-tailed

** P value calculated by 2x2 chi-square after collapsing < 20/40 and 20/25 - 20/40 groups

TABLE 6

DLK by flap thickness

	<120 μ m	$\geq$ 120 μ m	#DLK/Total (%)	p-value *	OR (CI)	p-value **
	#DLK/Total (%)	#DLK/Total (%)				
FS15	3/26 (11.5)	14/150 (9.3)		0.721	1.17 (0.30, 4.50)	0.821
FS30	11/37 (29.7)	13/143 (9.1)		0.001	4.69 (1.38, 15.97)	0.014
FS60	6/34 (17.7)	17/130 (13.1)		0.494	1.39 (0.53, 3.67)	0.508
Total	20/97 (20.6)	44/423 (10.4)		0.006	2.13 (1.10, 4.12)	0.025

Abbreviations: FS15= IntraLase 15kHz femtosecond laser; FS30= IntraLase 30kHz femtosecond laser; FS60= IntraLase 60kHz femtosecond laser; DLK=Diffuse lamellar keratitis; OR=odds ratio; CI=confidence interval

* P values calculated by Chi-square test or Fisher'

** P values calculated by logistic regression (GEE) model

TABLE 7

Studies of DLK after femtosecond LASIK flap creation

	FS Laser(kHz)	No. eyes	Raster energy	Side cut energy	Flap thickness	Spot separation	Postop steroids	DLK incidence
Binder ³¹	15	103	4.0	6.0–8.0	110–140	10.0–14.0	-	20 (19.5%)
Javaloy ³²	15	100	1.6	2.3	120	-	QID	17 (17%)
Gil-Cazorla ²⁹	15	1000	1.7	1.9	120	-	8×daily	5 (0.5%)
Hafit ³⁰	15 30	4772	2.7 1.9	3.0 2.3	110–120 100–120	12.0 11.0	- -	15 5
Choe	15 30 60	176 180 164	1.9–3.3 1.9–2.3 1.6–1.9	2.9–4.2 2.1–3.2 2.0–2.3	100–130 100–130 100–130	9.0–11.0 9.0 8.0–9.0	QID QID QID	17 (9.7%) 24 (13.3%) 23 (14.0%)

Abbreviations: FS=femtosecond; DLK=diffuse lamellar keratitis