

The Epidemiology of Diffuse Lamellar Keratitis

R. Doyle Stulting, MD, PhD,*† J. Bradley Randleman, MD,*† Jane M. Couser, BS,† and Keith P. Thompson, MD*†

Purpose: To report the incidence and outcomes of diffuse lamellar keratitis (DLK) after LASIK and to analyze potential causative factors.

Methods: Retrospective review of 15,119 cases (11,232 primary procedures and 3887 enhancements) from 7168 patients undergoing LASIK from May 1995 through October 2002, comparing preoperative data and postoperative outcomes for each case developing DLK to patients in the study population and a control series of eyes that did not develop DLK.

Results: We identified 61 eyes (0.40%) that developed DLK after LASIK. Three study groups were identified based on sterilization protocols used: (1) steam autoclave without reservoir (8348 cases), (2) cassette autoclave with reservoir (6771 cases), (3) steam autoclave without reservoir and new instrument cleaner (1758 cases). Significantly more eyes developed DLK with Protocol 2 (47 cases, 0.94%) than with Protocol 1 (11 cases; 0.1%; $P < 0.0001$) or Protocol 3 (3 cases, 0.2%; $P < 0.0005$). There was no significant difference in the incidence of DLK in Protocol 1 versus Protocol 3. DLK was significantly more common after primary procedures than with enhancement procedures only under Protocol 2. No individual developed DLK after more than 1 procedure. Treatment protocols included frequent topical steroids only (24 cases, 39.3%), frequent topical steroids and oral steroids (19 cases, 31.2%), or topical and oral steroids combined with lifting and irrigating beneath the flap (18 cases, 29.5%). Final refractions and visual acuities were not significantly different in eyes that developed DLK and those that did not.

Conclusions: DLK is a nonspecific inflammatory response to multiple stimuli that cannot be attributed solely to individual variation in the inflammatory response, the microkeratome, or material deposited by the microkeratome. Sterilizers with reservoirs may cause some cases of DLK. With appropriate diagnosis and treatment, DLK should resolve without sequelae, yielding visual outcomes comparable to cases with uneventful postoperative courses.

Key Words: diffuse lamellar keratitis, epidemiology, LASIK, sterilizers (*Cornea* 2004;23:680–688)

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From the *Emory University Department of Ophthalmology, Atlanta, Georgia; and †InView Refractive Surgery Center, Atlanta, GA.

Reprints: R. Doyle Stulting, MD, PhD, Emory Laser Vision, 875 Johnson Ferry Road, Suite 100, Atlanta, GA 30342.

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Diffuse lamellar keratitis (DLK) is a white blood cell infiltrate between the flap and stromal bed that appears within a few days after laser in-situ keratomileusis (LASIK), typically associated with moderate foreign body sensation and decreased visual acuity.¹ With appropriate treatment, DLK usually resolves without sequelae.

Since Smith and Maloney² described DLK in 1998, additional cases have been reported.^{1,3–18} Causes of DLK have been thought to include povidone-iodine solution,² meibomian gland secretions,³ microkeratome blade debris,⁴ carboxymethylcellulose drops,⁵ interface hemoglobin,⁶ bacterial endotoxins,^{7–9} and epithelial defects at the time of surgery.^{10–13} Both sporadic and epidemic cases of DLK have been reported.¹⁸

We first diagnosed DLK in 1995 and found the incidence to be 0.18% (2/1062 cases).¹⁹ After February 1999, we did not systematically monitor the incidence of DLK, which seemed to remain low and relatively constant until December 2000, when the incidence appeared to increase. This prompted a retrospective review of operating room procedures and prospective monitoring for DLK.

The purpose of this investigation was to identify factors that may contribute to the development of DLK, to review methods of treatment, and to report visual outcomes.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients who underwent LASIK at Emory Vision (Atlanta, GA) from May 1995 through October 2002. The earliest subset of data was from patients who had LASIK from May 1995 through February 1999. Some of these data have previously been published.¹⁹ The remainder of the data were derived from patients who underwent LASIK from December 2000 through October 2002.

All patients were prepared for surgery with povidone iodine 10% solution (Iodophor PVP Swabstick, Aplicare Inc, Branford, CT) and draped with an adhesive drape. Proparacaine hydrochloride 0.5% (Bausch & Lomb, Tampa, FL), naphazoline hydrochloride 0.025% (Naphcon A, Alcon Laboratories, Fort Worth, TX), and ketorolac tromethamine 0.5% (Acular, Allergan, Irvine, CA) drops were instilled. A wire eyelid speculum was then inserted. A radial keratotomy marker coated with methylene blue (Porex Surgical Inc., College Park,

GA) was used to make fiducial lines on the cornea. The suction ring was applied to the surface of the conjunctiva and activated. A Barraquer applanation tonometer verified that the intraocular pressure was greater than 65 mm Hg. The corneal surface was moistened with proparacaine. The Chiron Automated Corneal Shaper (ACS, Chiron Vision Corp., Irvine, CA) or the Hansatome (Bausch and Lomb, Irvine, CA) microkeratome was used with a 160- or 180- μ m plate. The Chiron ACS was in use from 1995 through 1999, whereas the Hansatome was used from December 2000 through October 2002. Simultaneous bilateral surgery was performed in most cases. The same blade was used for the second eye unless there was a thin flap or flap complication in the first eye. Summit (Summit Technology, Waltham, MA), Nidek (Nidek Technologies, Pasadena, CA), and Autonomous (Alcon Laboratories, Inc, Fort Worth, TX) excimer lasers were used for the ablations. For enhancement procedures, the original flap was lifted using a Sinsky hook and a cyclodialysis spatula, when possible, and the remainder of the case proceeded in the same way as a primary treatment. In rare cases when blunt dissection of the flap was not possible, a new flap was cut. Postoperatively, all patients routinely used topical antibiotics QID, topical steroids (prednisolone acetate 1%) QID, and nonpreserved artificial tears as needed. Each patient was seen within 24 hours after surgery.

Preoperative factors that were analyzed included patient age, gender, the outcome of previous LASIK procedures in the same eye, uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), and manifest refraction.

Surgical data included the date of surgery, procedure type (primary surgery or enhancement), type of microkeratome used for flap creation, laser used for ablation, surgeon, and instrument-cleaning protocol used for each case.

Three different instrument sterilization protocols were used during the study period. From May 1995 through February 1999, a steam autoclave without a reservoir was used (Tuttnauer Autoclave steam sterilizer, model 2340 EK, Tuttnauer Co, Ltd, Jerusalem, Israel) and the standard instrument cleaner recommended by the microkeratome manufac-

turer (Palmolive Original Dishwashing Liquid, Colgate-Palmolive Co, New York, NY) was used for all instrument cleaning. Beginning in April 2000, a cassette sterilizer with a reservoir was used (Statim Cassette Autoclave, SciCan Inc, Pittsburgh, PA) with the standard instrument cleaner. Routine cleaning of the sterilizer unit included following the standard manufacturer recommendations for maintenance in addition to draining and drying the reservoir daily, refilling the reservoir with steam-processed distilled water each morning, and weekly cleaning, which included running a cycle with autoclave cleaner followed by a cycle with distilled water, followed by draining and drying the reservoir. Then, in response to an outbreak of cases developing DLK in December 2000 and a persistent increase in the number of cases of DLK, the sterilization protocol was again changed in July 2001. The cassette sterilizer was replaced with a steam sterilizer (Steris Amsco Renaissance 3013 Prevac steam sterilizer, Steris Corp, Mentor, OH), and a new instrument cleaner was used (Universal Instrument Cleaner and Lubricant, B. Graczyk, Inc, Glendale Heights, IL). Thus, 3 distinct populations with different sterilization protocols were available for analysis (groups 1–3, Table 1).

Postoperative data included the occurrence and severity of DLK, the treatment protocol, and the degree of residual corneal scarring that was present. The severity of DLK was classified according to the system described by Linebarger and colleagues.²⁰ Stage 1 DLK was defined by white cells under the periphery of the flap; Stage 2 by white cells centrally; Stage 3 by a denser aggregation of white cells centrally, usually with an associated reduction in visual acuity; and Stage 4 by stromal melting and permanent scarring. We also documented the course of the fellow eye in bilateral LASIK cases, the course of subsequent LASIK procedures in affected eyes, and final postoperative outcomes, including UCVA, BSCVA, and final manifest refraction.

We defined DLK as interface inflammation out of proportion to inflammation associated with any epithelial defect or interface blood that might have been present, with negative cultures, if obtained. Thus, cases were excluded from analysis

TABLE 1. Rate of DLK Stratified by Date of Surgery and Sterilization Protocol

Group*	Date of Surgery	Number of Patients	Total Procedures	Primary Procedures	Enhancements	DLK Cases (%)
1	05/95–02/99	3379	8348	6426	1922	11 (0.13%)
2	12/00–07/01	2804	5013	3500	1513	47 (0.94%)
3	07/01–10/02	985	1758	1306	452	3 (0.17%)
Totals		7168	15119	11232	3887	61 (0.40%)

*Group 1, steam autoclave without reservoir, standard instrument cleaner; group 2, cassette autoclave with reservoir, standard instrument cleaner; group 3, steam autoclave without reservoir, new instrument cleaner.

if they had interface inflammation that could be readily explained by the presence of a large intraoperative epithelial defect or red blood cells under the flap.

To compare postoperative outcomes, we analyzed a population of 100 consecutive eyes with uneventful postoperative courses after LASIK performed from January to March 2002 using sterilization Protocol 3. We compared final manifest refraction, UCVA, BSCVA, and lines gained or lost after surgery to outcomes for the cases that developed DLK. Final outcomes were measured between 3 and 6 months postoperatively when eyes had achieved stable postoperative refractions.

For statistical analysis, we used Fisher exact test and Student *t* test.

RESULTS

A total of 15,119 LASIK cases from 7168 patients with adequate follow-up were included for analysis, including 11,232 primary cases and 3887 enhancements. There were 8348 cases from May 1995 through February 1999 (group 1), and 6771 cases from December 2000 through October 2002, including 5013 cases in group 2 and 1758 cases in group 3 (Table 1). For group 1 and group 3, no more than 1 case occurred on a single day. In group 2, however, multiple cases of DLK occurred on the same day; 36 cases occurred on days when more than 1 eye developed DLK (15 separate days with 5 being the maximum number of cases occurring on a single day) (Table 2). Eleven cases occurred as isolated events on days when no other cases occurred.

We identified 61 (0.40%) eyes that developed DLK after LASIK, including 40 cases with Stage 1 DLK, 18 cases with Stage 2 DLK, and 3 cases with Stage 3 DLK. Gram stains, bacterial cultures, and fungal cultures were performed on 4 of the first 11 cases that occurred from 1995 through 1999, and all were negative. Thereafter, neither Gram stains nor cultures were obtained when DLK was diagnosed.

Cases were evenly distributed between men and women (Table 3). Significantly more eyes developed DLK after primary LASIK and in cases in which the Nidek laser was used (Table 3). There were 28 cases of bilateral LASIK that developed DLK unilaterally, with 15 cases of first eye involvement and 13 cases of second eye involvement (Table 3). Seven cases developed DLK after enhancements in eyes with previous LASIK, but none of these cases had developed DLK after their primary procedure. Thirteen cases that developed DLK had subsequent LASIK enhancement, and none of these cases developed DLK after enhancement.

The incidence of DLK varied significantly by sterilization protocol (Fig. 1). The difference between Protocol 1 and Protocol 3 was not significant ($P = 0.72$); however, both Protocol 1 ($P < 0.0001$) and Protocol 3 ($P = 0.0005$) had significantly lower rates of DLK than Protocol 2.

TABLE 2. Occurrence of DLK by Day From December 2000 to July 2001 (Group 2)

Day*	Total LASIK Cases Performed	DLK Cases (%)
1	64	1 (1.6%)
8	56	5 (8.9%)
9	66	3 (4.5%)
13	27	2 (7.4%)
20	49	1 (2.0%)
22	63	1 (1.6%)
23	93	2 (2.2%)
24	35	2 (5.7%)
30	70	2 (2.9%)
36	60	2 (3.3%)
37	90	2 (2.2%)
43	66	1 (1.5%)
51	46	2 (4.3%)
58	68	4 (5.9%)
72	45	2 (4.4%)
76	48	1 (2.1%)
78	55	1 (1.8%)
82	19	1 (5.3%)
86	69	2 (2.9%)
90	49	2 (4.1%)
104	66	2 (3.0%)
114	33	1 (3.0%)
115	35	1 (2.9%)
118	37	1 (2.7%)
141	37	1 (2.7%)
156	46	2 (4.3%)

*Day, days on which DLK occurred from December 2000 through July 2001, numbered consecutively with the first day with a case developing DLK reported as day 1.

When each study group was analyzed separately, there was no significant correlation between the development of DLK and gender, laser used, or eye involvement (Table 3). Significantly more cases developed DLK after primary procedures in group 2; however, DLK occurred as frequently among primary procedures as it did among enhancements in groups 1 and 3 (Table 4).

All 61 cases of DLK resolved without permanent corneal scarring. Treatment included frequent topical steroids only (24 cases, 39.3%), frequent topical steroids and oral steroids (19 cases, 31.2%), or topical and oral steroids combined with lifting and irrigating beneath the flap (18 cases, 29.5%). Most (91%) of the cases from May 1995 through February 1999 were managed by lifting and irrigating beneath the flap, whereas most (84%) of the cases after December 2000 were managed with topical steroids only (Fig. 2). Additionally, all

TABLE 3. Overall DLK Rates by Demographics

Demographics	DLK Cases (%)	P
Gender		
Male	35/7092 (0.49%)	0.122
Female	26/8027 (0.32%)	
Procedure		
Primary	54/11232 (0.48%)	0.008
Enhancement	7/3887 (0.18%)	
Laser		
Nidek	48/9831 (0.49%)	0.03
Summit/autonomous	13/5288 (0.25%)	
Involved eye in bilateral cases*		
First eye	15 (53.6%)	0.79
Second eye	13 (46.4%)	

*Bilateral LASIK cases with unilateral development of DLK.

of the cases presenting through 1999 were initially managed with fortified topical antibiotics with broad-spectrum coverage until the noninfectious mechanisms for DLK were better understood; thereafter, only routine postoperative topical antibiotics were used for DLK cases.

Of the 61 affected eyes, 59 (96.7%) had sufficient long-term follow up to determine final visual outcomes (Table 5).

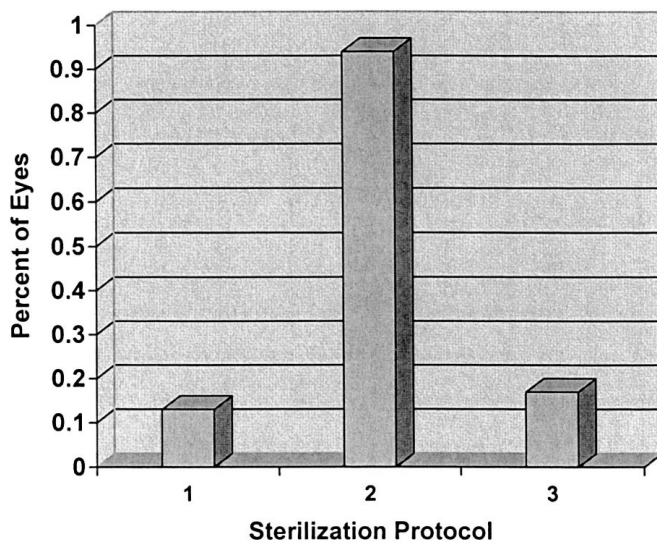


FIGURE 1. Incidence of DLK from May 1995 through February 1999 (Protocol 1: steam autoclave without reservoir and standard instrument cleaner), December 2000 through July 2001 (Protocol 2: cassette autoclave with reservoir and standard instrument cleaner), and from July 2001 through October 2002 (Protocol 3: steam autoclave without reservoir, new instrument cleaner). The difference between Protocols 1 and 3 was not significant ($P = 0.72$); however, both Protocol 1 ($P < 0.0001$) and Protocol 3 ($P = 0.0005$) had significantly lower rates of DLK than Protocol 2.

Fifty-four (91.5%) of these eyes had a final spherical equivalent refraction within 0.5 D of emmetropia compared with 89 (89%) of the controls ($P = 0.79$), 33 (55.9%) achieved 20/20 or better final UCVA compared with 69 (69%) of controls ($P = 0.12$) (Fig. 3), and 48 (81.4%) achieved 20/20 or better final BSCVA compared with 95 (95%) of controls ($P = 0.012$) (Fig. 4). Ten eyes (16.9%) lost 1 line of BSCVA compared with 1 (1%) of controls ($P = 0.0002$), while most (83.1%) maintained or gained 1 or more line of BSCVA postoperatively (Fig. 5).

DISCUSSION

Numerous cases of diffuse lamellar keratitis (DLK) have previously been reported in the literature.¹⁻¹⁹ Here, we present an additional 61 cases of DLK among a total of 15,119 eyes that underwent LASIK over a 7-year period.

Typically appearing within 48 hours after LASIK, DLK is a diffuse inflammatory cellular infiltrate in the flap interface that is out of proportion to inflammation that might be associated with any coexisting epithelial defect or blood in the interface. Cultures, when obtained, are negative. Confocal microscopy of eyes with diffuse lamellar keratitis has shown aggregations of polymorphonuclear leukocytes, mononuclear cells, and abnormal linear structures in the interface.²¹⁻²³

DLK has been classified into 4 stages based on severity.²⁰ Most of our cases (65.6%) did not progress beyond Stage 1, which typically responds well to topical steroids and carries a favorable prognosis.²⁰

A variety of etiologies for DLK have been proposed, including energy from the excimer laser, povidone-iodine solution,² meibomian gland secretions,³ debris introduced on the microkeratome blades,⁴ the use of carboxymethylcellulose drops,⁵ and bacterial endotoxins.⁷⁻⁹ Previous studies¹⁰⁻¹⁴ demonstrated a strong relationship between epithelial defects and the presence of interface inflammation. We agree that epithelial defects are a definite risk factor for interface inflammation; however, we recommend reserving the term DLK to describe interface inflammation without an obvious cause, such as interface blood⁶ or a significant overlying epithelial defect. Thus, patients with these causes of inflammation were excluded from our analysis.

As expected, we found no difference in the incidence of DLK by gender (Table 3). Seven eyes that developed DLK after enhancements had uneventful postoperative courses after their primary procedures. Thirteen other eyes that developed DLK during primary LASIK had uneventful postoperative courses after subsequent enhancements. Therefore, DLK cannot be attributed solely to a hypersensitivity reaction to materials used during LASIK surgery.

Overall, significantly more cases occurred after primary LASIK than after enhancements (0.48% vs 0.18%, $P = 0.008$); however, this difference existed only in group 2, when the sterilizer with reservoir was in use. There was no significant difference in the rate of occurrence of DLK in primary procedures

TABLE 4. Epidemiologic Comparisons for Each Study Group

Group	Gender		Procedure		Laser		Eye	
	Male	Female	Primary	Enhancement	Nidek	Summit/Autonomous*	First Eye	Second Eye
1	0.22%	0.04%	0.16%	0.05%	0.19%	0.05%	40%	60%
2	1.0%	0.82%	1.23%	0.26%	0.97%	0.84%	56%	43%
3	0.12%	0.21%	0.08%	0.44%	0.14%	0.29%	N/A	

*The Summit laser was in use from 1995 through 1999 (group 1), and the Autonomous was in use from 2000 through 2002 (groups 2 and 3).

and enhancements between groups 1 and 3. For bilateral LASIK cases with unilateral DLK, we found an equal distribution of first and second eye involvement overall (Table 3) and for each study population (Table 4). The fact that DLK occurred after enhancements, and the equal occurrence of DLK in the first and second eyes of bilateral cases treated with the same blade, indicate that debris introduced from the microkeratome cannot be the sole stimulus for DLK in this cohort of patients.

Even though there was a weak overall association of DLK with the Nidek laser (Table 3), within each group there were no differences in the development of DLK based on the laser used for ablation (Table 4). Thus, we believe that DLK is not an excimer laser-specific phenomenon.¹

During the study period, three separate sterilization protocols were employed (Table 1). Initially, a steam autoclave without reservoir and the standard instrument cleaner recommended by the microkeratome manufacturer (Palmolive) was used for all instrument cleaning.

In April 2000, the facility converted to a cassette autoclave with reservoir system. Immediately after introduction of the new sterilization system, there was no noticeable increase in the low rate of occurrence of DLK. By December 2000, surgeons became aware of an apparent increase in the frequency of DLK. This led to formal analysis of the incidence of DLK, which was found to be 1.87% (17/909 cases) during December 2000, compared with 0.13% (11/8348 cases) from May 1995, through February 1999.

At the time of our original analysis, published literature suggested that bacterial endotoxins might be responsible for some cases of DLK.⁷⁻⁹ Peters and colleagues⁸ reported that

bacterial endotoxins could incite a potentially severe interface inflammatory response in rabbits. Peters and colleagues⁸ and Holland and colleagues⁷ both found significant bacterial colonization in the reservoirs of cassette sterilizers. These studies,^{7,8} as well as a report by Yuhan and colleagues,⁹ implicated biofilms in these reservoirs as potential sources of bacterial endotoxins causing DLK. The timing of our outbreak of DLK cases, approximately 8 months after we began to use sterilizers with reservoirs, is consistent with biofilm developing in the reservoirs that could release sufficient endotoxin to cause DLK.

In an effort to reduce the rate of DLK, our institution began to use a steam autoclave without a reservoir system for sterilizing our microkeratomes, and the transition to this system was completed in July 2001 (group 3). Afterward, the incidence of DLK returned to the level that we observed before sterilizers with a reservoir were used (0.17%) (Fig. 1).

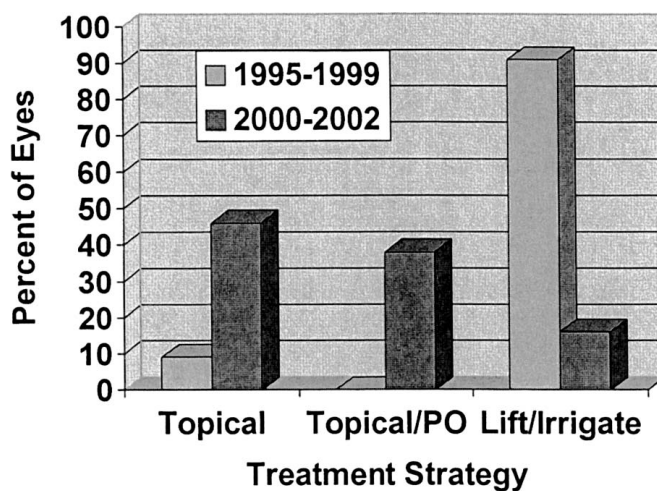


FIGURE 2. Treatment strategies for DLK cases. Topical, topical steroids only; Topical/PO, topical and oral steroids; Lift/Irrigate, lifting and irrigation under flap with concurrent topical steroid use.

¹We did not strictly control for the type of laser, but (1) it is theoretically difficult to understand why the type of laser would have anything to do with DLK—the type of radiation is the same and the amount of tissue removed is basically the same. (2) The case mix with the lasers was about the same before, during, and after the outbreak, so there was no reason to suspect the lasers.

TABLE 5. Visual Outcomes After Resolution of DLK

Patient	DLK Stage	Preop BSCVA (20/x)	Final BSCVA (20/x)	Final UCVA (20/x)	Final MR	Lines Gained/Lost	Follow-Up (months)
1A	1	25	25	30	-0.75 + 0.25 × 51	0	3
1B	1	20	20	25	-0.5 + 1.25 × 173	0	3
2A	1	20	16	20	-0.5 sphere	1	1
2B	1	20	20	60	-1.5 + 0.25 × 005	0	1
3	2	16	20	20	Plano	-1	6
4	2	12	16	16	-0.5 sphere	-1	4
5	2	25	30	30	-0.25 + 1.00 × 67	-1	6
6	2	20	25	30	+ 0.5 + 0.50 × 125	-1	12
7	2	12	12	12	-0.25 + 0.25 × 140	0	12
8	2	30	25	25	Plano	1	3
9	2	20	25	80	-2.5 + 0.75 × 162	-1	5
10	2	40	40	40	-0.25 + 0.50 × 103	0	7
11	2	20	25	25	-0.5 sphere	-1	3
12	1	20	20	20	-0.25 sphere	0	1
13	1	30	25	40	-1.75 + 2.75 × 150	1	1
14A	3	16	10	16	-0.5 sphere	1	3
14B	3	16	10	16	-0.25 sphere	1	3
15A	1	20	16	20	-0.25 sphere	1	6
15B	1	20	16	30	-1 sphere	1	6
16	1	25	25	30	-0.75 + 0.50 × 90	0	2
17	1	20	12	16	-0.5 sphere	2	6
18	1	20	25	30	Plano	-1	3
19	1	20	16	20	Plano	1	8
20	1	20	20	20	-0.25 sphere	0	10
21A	3	16	16	16	Plano	0	3
21B	2	16	16	16	-0.25 sphere	0	3
22	1	20	16	20	0.25 + 0.50 × 76	1	16
23	2	20	20	40	-0.5 + 0.25 × 128	0	10
24A	2	16	16	16	-0.25 sphere	0	3
24B	2	16	16	16	Plano	0	3
25	1	20	20	20	-0.25 sphere	0	15
26	1	20	20	20	Plano	0	1
27	1	20	16	16	-0.25 + 0.25 × 156	1	12
28	2	16	12	16	-0.25 sphere	1	1
29	3	20	20	30	-0.75 sphere	0	12
30	1	16	12	16	-0.25 + 0.50 × 15	1	12
31	1	16	20	20	-0.25 sphere	-1	1
32	1	30	25	25	0.5 + 0.25 × 128	2	19
33	2	20	20	30	-0.5 + 1.00 × 115	0	18
34A	1	25	20	25	-0.5 sphere	1	6
34B	1	25	20	25	-0.5 sphere	1	6
35A	1	20	20	25	-0.75 + 0.75 × 25	0	10
35B	1	20	20	20	-0.25 + 0.25 × 105	0	10
36	1	20	20	40	-1 + 0.50 × 74	0	1
37	1	20	20	20	Plano	0	1
38	1	20	16	20	Plano	1	12
39A	1	16	12	12	Plano	1	14
39B	1	16	12	12	Plano	1	14

TABLE 5. (continued) Visual Outcomes After Resolution of DLK

Patient	DLK Stage	Preop BSCVA (20/x)	Final BSCVA (20/x)	Final UCVA (20/x)	Final MR	Lines Gained/Lost	Follow-Up (months)
40A	1	20	16	16	-0.25 sphere	1	9
40B	1	20	16	16	-0.25 sphere	1	9
41A	2	25	20	20	-0.25 sphere	1	12
41B	1	25	20	20	-0.25 sphere	1	12
42	1	16	20	30	Plano + 1.00 × 121	-1	12
43	1	20	16	20	-0.75 + 0.50 × 90	1	7
44	1	20	20	25	-0.75 + 0.75 × 74	0	5
45	1	16	20	25	0.25 + 0.25 × 4	-1	6
46	1	16	16	20	-0.25 + 0.25 × 39	0	2
47	2	20	20	50	-0.5 + 1.00 × 145	0	7
48	1	20	20	25	-0.5 sphere	0	6

One study²⁴ has disputed the possibility that endotoxins from sterilizer reservoirs can incite a clinically significant inflammatory response under normal conditions. This study found that, in an experimental model with regular changing of the reservoir water, the amount of endotoxin never reached a level felt to be clinically significant or capable of causing an inflammatory reaction in the cornea. In our practice, however, we adhered strictly to the cleaning regimen recommended by

the manufacturer. Nevertheless, we saw a dramatic increase in the number of DLK cases that occurred while this sterilizer was in use. In fact, the data from our study combined with those from previous publications⁷⁻⁹ strongly suggest that the use of cassette sterilizers with reservoirs can significantly increase the rate of DLK after LASIK in clinical practice.

Although we changed both sterilizer and instrument cleaner simultaneously, we believe that the reduction in the

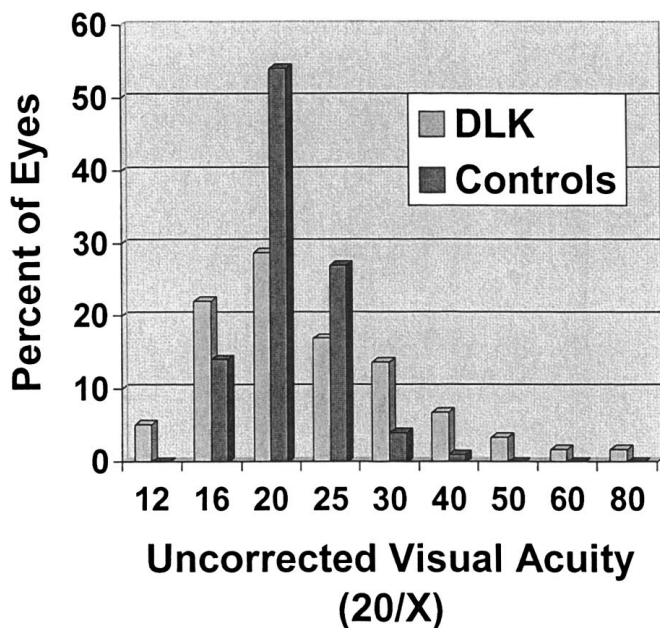


FIGURE 3. Final uncorrected visual acuity in eyes developing DLK (DLK) compared with eyes with uneventful postoperative courses (Controls). After the resolution of DLK, 33 (55.9%) eyes achieved 20/20 or better final UCVA compared with 69 (69%) control eyes ($P = 0.12$).

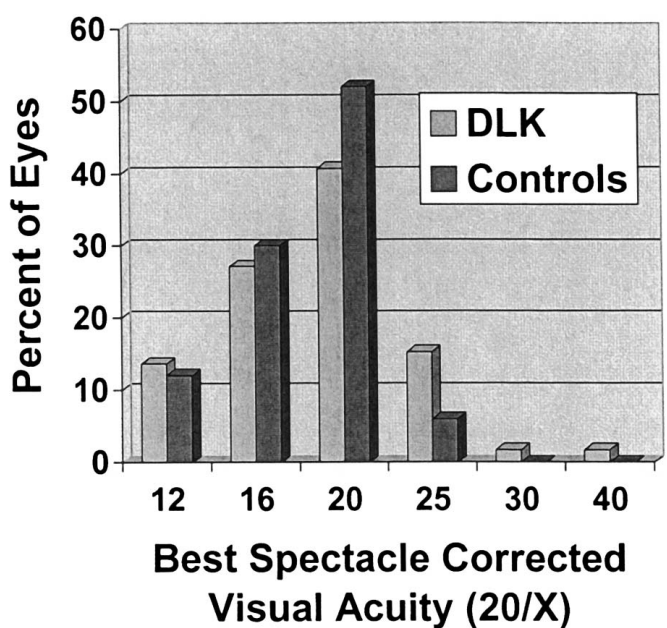


FIGURE 4. Final best spectacle-corrected visual acuity in eyes developing DLK (DLK) compared with eyes with uneventful postoperative courses (Controls). After the resolution of DLK, 48 (81.4%) eyes achieved 20/20 or better final BSCVA compared with 95 (95%) control eyes ($P = 0.012$).

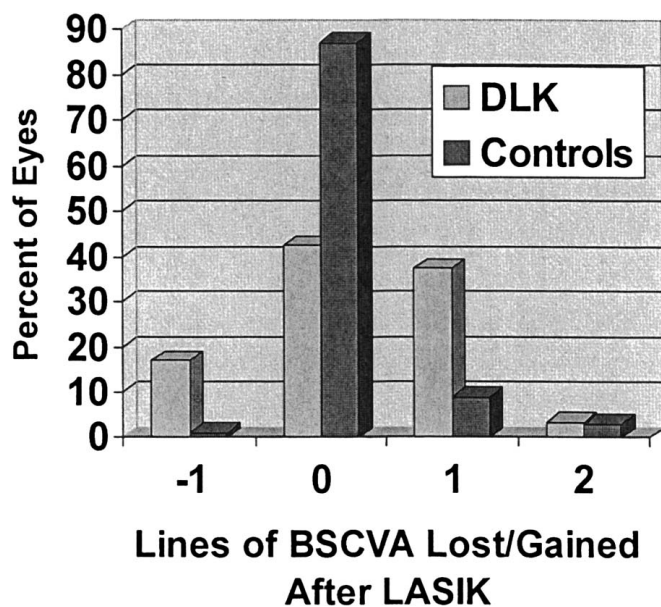


FIGURE 5. Lines of best spectacle-corrected visual acuity gained or lost after LASIK in eyes developing DLK (DLK) compared with eyes with uneventful postoperative courses (Controls).

incidence of DLK is attributable to eliminating the use of a cassette sterilizer for several reasons. First, the cleaning solution remained constant when the cassette sterilizers were implemented and the DLK incidence rose (group 1 versus group 2). Second, the DLK rates are comparable between groups 1 and 3, even though different cleaning solutions were used in these protocols. In support of this concept, Nakano and colleagues²⁵ found that cleaning solutions, including Palmolive, did not incite interface inflammatory responses in rabbit models.

From this study, we cannot exclude meibomian gland secretions, povidone-iodine solution, carboxymethylcellulose drops, microkeratome debris, contaminants on the microkeratome blades, inflammatory material that is washed under the flap from the surface of the eye, or reactions to cleaning solutions as stimuli for the development of some cases of DLK. It seems possible that any or all of these factors might stimulate mild inflammatory responses in susceptible individuals. However, there were no changes in surgical protocol during the study period that would have altered any of these factors, and elimination of the cassette autoclave with a reservoir resulted in about a 5-fold reduction in the incidence of DLK to 0.14% (14/10,106 cases, $P < 0.0001$). Thus, although any or all of these factors may rarely stimulate an interface inflammatory response in susceptible individuals, the elimination of tabletop cassette autoclaves with reservoirs may eliminate clusters of DLK and have a significant impact on the overall rate incidence of DLK.

Taking into account the variety of inflammatory responses seen after other eye surgery, it seems unlikely that the occurrence of mild interface inflammation will ever be completely eliminated; thus, effective treatment strategies become important.

In addition to topical steroid use, a variety of treatments have been proposed for DLK, including intraoperative use of intrastromal steroids,²⁶ oral corticosteroids,²⁷ and even phototherapeutic keratectomy.²⁸ Initially, we used relatively aggressive measures in the management of DLK, with early flap elevation, culture and Gram stain of interface material, and topical fortified antibiotics. Later, we became more confident that eyes with a typical appearance of DLK were not infected, and we attained good results with topical steroids alone in the majority of our cases (Fig. 2). When necessary, we also used a short course of oral steroids. From 2000 through 2002, only 8 cases (16%) failed to respond to conservative treatment and required irrigation of the flap for resolution of DLK.

We recommend topical steroids for the treatment of Stage 1 and Stage 2 DLK with frequent observation. Irrigation of the flap interface and oral steroids should be considered for Stage 3 and Stage 4.

All DLK cases resolved without serious scarring or other sequelae. Postoperative manifest refraction after the resolution of DLK was comparable to that in patients with uneventful postoperative courses, with 91.5% achieving spherical equivalent refractions within 0.5 D of emmetropia (Table 5). Final visual acuity also compared favorably to that of controls, with 55.9% of eyes achieving UCVA of 20/20 or better (Fig. 3), and 81.4% achieving BSCVA 20/20 or better (Fig. 4). Significantly more eyes with DLK, 10 (16.9%), lost 1 line of BSCVA compared with controls, 1 (1%; $P = 0.0002$); however, most (83.1%) maintained or gained 1 or more line of BSCVA postoperatively (Fig. 5).

It remains critical to differentiate DLK from infectious keratitis presenting after LASIK. Infectious keratitis presents with a more localized, irregular infiltrate, usually with a more delayed onset after surgery compared with DLK.²⁹ Although bacterial keratitis can present as early as postoperative day 1,²⁹ most cases of infectious keratitis after LASIK, especially *Mycobacterium* and fungal keratitis, have delayed presentations,²⁹⁻³¹ in contrast to DLK. During this study period, we encountered 2 cases of infectious keratitis that were readily distinguished from DLK based on onset of presentation and the appearance of the infiltrate.

In summary, diffuse lamellar keratitis is a nonspecific inflammatory response to multiple stimuli, with both sporadic and clustered occurrence. DLK cannot be attributed to an allergic response to materials to which the patient is exposed during the procedure, solely to the microkeratome or to material deposited by the microkeratome. Sterilizers with reservoirs may play a role in the development of DLK, especially clustered cases. At our institution, the elimination of these ster-

ilizers significantly reduced the incidence of DLK. With appropriate diagnosis and treatment, favorable postoperative outcomes can be achieved after the resolution of DLK.

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