

# Diffuse lamellar keratitis after laser in situ keratomileusis associated with surgical marker pens

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**PURPOSE:** To describe a series of cases of diffuse lamellar keratitis (DLK) after laser in situ keratomileusis (LASIK) associated with intraoperative use of a surgical marker pen.

**SETTING:** Singapore National Eye Centre, Singapore, Singapore.

**METHODS:** A review of all 115 patients (125 eyes) who had myopic LASIK from July 23 to July 26, 2007, was performed to determine whether eyes in which the Codman surgical marker pen (Johnson & Johnson Medical) was used intraoperatively developed postoperative DLK.

**RESULTS:** Nine of 12 eyes that had LASIK or flap relifting with a Codman surgical marker pen developed grade 1 to grade 3 DLK on the first postoperative day. The 113 other eyes that had LASIK in the same week with another brand of surgical marker pen (Securline, Precision Dynamics Corp.) did not develop DLK. All eyes with DLK were treated with intensive topical steroid therapy. The DLK resolved in 2 eyes after the steroid treatment; 7 eyes required flap relifting with interface irrigation. One month postoperatively, 6 eyes with DLK had an uncorrected visual acuity of 6/7.5 or better. Two eyes developed central corneal scarring with consecutive hyperopia with a best corrected visual acuity of 6/12 after 1 month.

**CONCLUSIONS:** There was a strong association between the occurrence of DLK after LASIK with the use of the Codman surgical marker pen. One or more constituents of the ink in the Codman pen may have been responsible for this series of cases.

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Diffuse lamellar keratitis (DLK), also known as sands of Sahara syndrome, is an uncommon complication after laser in situ keratomileusis (LASIK). This noninfectious complication, which is characterized by diffuse, granular, culture-negative inflammation in the flap interface, is most commonly seen on the first postoperative day. The etiology of DLK is believed to be

contaminants in the interface that trigger an inflammatory process, which draws polymorphonuclear leukocytes and neutrophils into the anterior cornea.<sup>1–3</sup>

Since Smith and Maloney<sup>3</sup> first described DLK in 1998, many causative agents have been proposed. They include meibomian gland secretions, silicates, microkeratome oil, hemoglobin, povidone-iodine solution, bacterial endotoxin, metallic fragments, cleaning solutions, toxic chemicals, and silicone oil on surgical gloves.<sup>4–15</sup>

In this paper, we report a cluster of DLK cases that was associated with a particular brand and batch of surgical markers used during the LASIK procedure. At the Singapore National Eye Centre (SNEC), there are strict protocols for the introduction of new equipment and consumables (including new batches of consumables) for all LASIK procedures performed.

On July 24, 2007, a new batch of surgical marker pens, Codman surgical marker pens (Johnson &

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Johnson Medical, lot 06F1159), was introduced and used to mark the cornea. Eleven eyes of 9 patients had uneventful LASIK surgery by 5 different surgeons, and 1 eye had flap repositioning (due to macrostriae) using this batch of surgical marker pens. On the first postoperative day, varying grades of DLK were noted in 8 of the 11 eyes. Diffuse lamellar keratitis was also noted in the eye that had flap repositioning.

## PATIENTS AND METHODS

A review of all patients (115 patients, 125 eyes) who had myopic LASIK at SNEC from July 23 to July 26, 2007, was performed.

### Sterilizing and Cleaning Procedure

At SNEC, all surgical instruments used for LASIK are cleaned using a standard protocol and sterilized with a steam autoclave (Vacuklav, Labo-Medica Pte Ltd). After each patient had surgery, the microkeratome (XP, Bausch & Lomb) was disassembled. The blade was removed and discarded, and the microkeratome head, suction ring, lid speculum, corneal flipper, and corneal marker were cleaned with diluted enzymatic cleaner (Cidezyme, Johnson & Johnson). The instruments were gently scrubbed with a toothbrush and rinsed with distilled water. The instruments were then dried and steam sterilized in an autoclave. All instruments were double wrapped for full-cycle sterilization. No flash cycles were used.

### Surgical Technique

**Laser in Situ Keratomileusis** After 1 drop of tetracaine hydrochloride 0.5% (Tetracaine Minims) was applied, the eyelashes of the upper and lower lids were isolated from the surgical field using a surgical drape (Steril Medical Pte Ltd.). A lid speculum was used to retract the eyelids, and PVA surgical spears (Ivalon) were used to dry the conjunctival fornices. The cornea was then marked with a Hoffman or Bansal corneal marker that was coated with ink from a surgical marker. A superiorly hinged 120  $\mu$ m or 140  $\mu$ m thick flap was created with an XP microkeratome. Excimer laser ablation was then performed with a Technolas 217z100 excimer laser (Bausch & Lomb). After ablation, the flap was repositioned on the stromal bed and the interface irrigated with balanced salt solution (BSS) in 15 cc unit dose containers. A wet PVA surgical spear was used to gently wipe the flap and dry the edges of the lamellar keratectomy. One drop of ketorolac tromethamine 0.5% (Acular) and 1 drop of gatifloxacin (Zymar) were applied before the lid speculum and drape were removed. Postoperative medications were topical gatifloxacin and topical prednisolone acetate 0.12% (Pred Mild) and artificial tears (Refresh Plus).

Laser in situ keratomileusis was performed sequentially in each eye on separate days or simultaneously on the same day according to patient and surgeon preference.

**Flap Repositioning** For flap repositioning, the eye was anesthetized and draped in the same manner as for LASIK. The cornea was marked with a corneal marker coated with surgical marker. The flap edge was identified and then lifted with a Maloney flap flipper. The flap was smoothed and repositioned on the stromal bed and the interface irrigated

with BSS. A wet PVA surgical spear was used to gently smooth the flap and dry the keratectomy edges. A bandage contact lens (Acuvue, Johnson & Johnson) was then applied. Postoperative eyedrops were similar to those for LASIK.

### Surgical Marker Pens Used

On the morning of July 24, 2007, a new batch of Codman surgical marker pens was introduced into the SNEC LASIK operating theater. The surgical marker pens were used to ink the corneal markers. Before this, another brand, the Securline surgical marker pen (Precision Dynamics Corp.), was used. All marker pens were single use; that is, 1 marker pen was used for each patient and disposed of after the procedure.

According to the manufacturers, the Securline surgical marker pen contains gentian violet dye in a water-based dispersion agent that includes a proprietary amount of ethylene glycol in excess of 1% and the Codman surgical marker pen contains gentian violet dye in an alcohol-based carrier that includes a proprietary amount of propylene glycol.

### Staging of Diffuse Lamellar Keratitis

Stage 1 DLK is defined by the presence of white granular cells in the periphery of the lamellar flap, outside the visual axis. Stage 2 is defined by the presence of white granular cells in the center of the flap, involving the visual axis; in the periphery; or in both. Stage 3 is the aggregation of more dense, white, and clumped cells in the central visual axis, with relative clearing in the periphery. Stage 4 is characterized by the presence of stromal melting, permanent scarring, and associated visual morbidity.<sup>16</sup>

### Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 11.5, SPSS, Inc.). The differences between the 2 marker pen groups in categorical clinical outcomes were assessed using chi-square tests. Statistical significance was set at  $P < .05$ .

## RESULTS

One hundred twenty-five eyes of 115 patients had LASIK at SNEC from July 23 to July 27, 2007. On July 24, 2007, 11 eyes of 9 patients had LASIK and 1 eye had flap repositioning with intraoperative use of a Codman surgical marker pen (Table 1). There were no extraordinary circumstances (eg, changes in operating theater conditions, staff, or protocol or instruments) associated with the period from July 23 to 27, 2007, other than the introduction of Codman surgical marker pens on July 24, 2007. In all other eyes that had LASIK at SNEC that week, including 17 eyes (17 patients) that had LASIK on July 24, 2007, a Securline surgical marker pen was used.

Nine of the 12 eyes that had LASIK or a flap relifting with intraoperative use of a Codman surgical marker pen developed from grade 1 to grade 3 DLK on the first postoperative day (Table 2). No other abnormalities, including corneal flap or epithelial problems, were noted postoperatively. One patient (#4) who

**Table 1.** Association between surgical marker pen use and DLK after LASIK.

Outcome	Number of Eyes (Patients)	
	LASIK with Codman Marker	LASIK with Securline Marker
DLK present	9* (8)	0
DLK not present	3 (2)	113 (105)

DLK = diffuse lamellar keratitis; LASIK = laser in situ keratomileusis  
 \*One eye had flap repositioning for macrostriae using the Codman surgical marker

had LASIK in the left eye with intraoperative use of a Securline surgical marker pen on July 23, 2007, developed macrostriae of the flap on the first postoperative day. No signs of DLK were noted at that time. Patient 4 subsequently had flap relifting and repositioning in the left eye and LASIK in the right eye on July 24, 2007; the Codman surgical marker pen was used for both procedures. Diffuse lamellar keratitis was noted in both eyes on July 25, 2007. All other eyes that had LASIK with intraoperative use of a Securline surgical marker pen had an uneventful postoperative course.

Three patients (#3, 5, and 8) who had DLK in 1 eye had LASIK in the contralateral eye with intraoperative use of a Securline surgical marker pen before July 24, 2007. No contralateral eye developed DLK. One patient (#1) had LASIK using a Securline surgical marker pen in the contralateral eye 2 days later also had an uneventful postoperative recovery. The remaining

unused Codman surgical marker pens were examined. No abnormalities were detected in the packaging. Statistical analysis of eyes that had LASIK on July 24, 2007, revealed a strong association between DLK and the use of the Codman surgical marker ( $P < .001$ ).

All eyes with DLK were treated with intensive topical steroids (prednisolone acetate 1% (Pred Forte) hourly and topical gatifloxacin 4 times a day. The DLK in 2 eyes resolved with the steroid therapy. Seven eyes developed grade 3 to 4 DLK despite intensive steroid therapy and required flap relifting with interface irrigation.

One month postoperatively, 6 of the 9 eyes with DLK had an uncorrected visual acuity (UCVA) of 6/7.5 or better and clear corneas (Table 3). Two eyes (patient 2) developed central cornea scarring with consecutive hyperopia and a best corrected visual acuity (BCVA) of 6/12. This patient was seen again 4 months after surgery. The UCVA was 6/12 and 6/15 in the right eye and left eye, respectively. The manifest refraction was +1.00 sphere in the right eye and +2.50 -4.50 × 60 in the left eye. The BCVA was 6/7.5 and 6/6, respectively. Both corneas were clear.

## DISCUSSION

Although DLK is an uncommon complication after LASIK, it is potentially sight threatening. There are few reports of outbreaks of DLK,<sup>5,13</sup> and the specific causative factor is usually not known. It is generally agreed that DLK is caused by a contaminant in the

**Table 2.** Data of all patients who had LASIK on July 24, 2007.

Patient	Age (Y)	Sex	Eye	Date of LASIK	Surgical Marker Used	Presence of DLK	Irrigation Performed (Postop Day)
1	22	F	Right	7/24/07	Codman	Yes	Yes (3)
			Left	7/26/07	Securline	No	—
2	36	F	Right	7/24/07	Codman	Yes	Yes (6)
			Left	7/24/07	Codman	Yes	Yes (6)
3	26	M	Right	7/24/07	Codman	Yes	Yes (3)
			Left	7/17/07	Securline	No	—
4	28	M	Right	7/24/07	Codman	Yes	No
			Left	7/23/07*	Securline*	Yes <sup>†</sup>	Yes (2)
5	30	F	Right	7/24/07	Codman	Yes	No
			Left	7/23/07	Securline	No	—
6	42	M	Right	7/24/07	Codman	No	—
			Left	7/24/07	Codman	No	—
7	26	M	Right	7/23/07	Securline	No	—
			Left	7/24/07	Codman	Yes	Yes (2)
8	27	F	Right	7/24/07	Codman	Yes	Yes (2)
			Left	7/23/07	Securline	No	—
9	28	F	Right	7/24/07	Codman	No	—
			Left	7/23/07	Securline	No	—

DLK = diffuse lamellar keratitis; LASIK = laser in situ keratomileusis

\*Patient had flap repositioning on 7/24/07 for macrostriae using the Codman surgical marker.

<sup>†</sup>DLK was noted only on 7/25/07, 1 day after the flap was repositioned with the Codman surgical marker.

**Table 3.** One-month postoperative outcomes in eyes with DLK.

Pt	Eye	Date of LASIK	Preop BCVA	Preop Refraction	1 Mo Postop			DLK Stage Before Washout	Corneal Clarity
					UCVA	BCVA	Refraction		
1	Right	7/24/07	6/6	-4.00 -0.75 × 95	6/6	6/6	Plano	3	Clear
2	Right	7/24/07	6/6	-4.50 -2.00 × 5	6/30	6/12	+6.50 -3.50 × 90	4	Faint central scar
2	Left	7/24/07	6/6	-4.50 -1.25 × 180	6/45	6/12	+8.50 -4.50 × 80	4	Faint central scar
3	Right	7/24/07	6/6	-4.75 -0.75 × 5	6/6	6/6	Plano	3	Clear
4	Right	7/24/07	6/6	-2.50 -0.75 × 80	6/6	6/6	+0.75 -0.50 × 110	No washout	Clear
4	Left	7/23/07	6/6	-2.75 -0.50 × 110	6/6	6/6	+0.50 sphere	3	Clear
5	Right	7/24/07	6/6	-5.50 -0.50 × 120	6/6	No data*	Not done*	No washout	Clear
7	Left	7/24/07	6/6	-4.00 sphere	6/12	6/7.5	+0.75 -0.75 × 80	3	Faint paracentral scar
8	Right	7/24/07	6/6	-8.75 -2.00 × 180	6/7.5	6/6	+0.25 -0.75 × 90	3	Clear

BCVA = best corrected visual acuity; DLK = diffuse lamellar keratitis; LASIK = laser in situ keratomileusis; Pt = patient; UCVA = uncorrected visual acuity  
 \*Refraction not performed

flap interface that triggers an inflammatory response. Studies using confocal microscopy have shown that leukocytes, such as polymorphonuclear cells and mononuclear cells, appear beneath the flap in the area of DLK.<sup>1,2</sup> The inciting contaminant of DLK is varied, and myriad contaminants, including meibomian gland secretions, silicates, microkeratome oil, hemoglobin, povidone-iodine solution, bacterial endotoxin, metallic fragments, cleaning solutions, toxic chemicals, and silicone oil on surgical gloves,<sup>4-15</sup> have been shown to be associated with DLK. To our knowledge, there are no previous reports of an association between the use of surgical marker pens and DLK.

Intensive topical steroid therapy is the recommended treatment for grade 1 or 2 DLK, and flap relifting with interface irrigation is advocated for grade 3 or above.<sup>16</sup> In our series, only 2 of the 9 eyes responded to topical steroids alone; 7 eyes required flap relifting and interface irrigation. Eyes that had flap relifting within 3 days of surgery before developing grade 4 DLK had good 1-month postoperative outcomes compared with eyes that had flap relifting and irrigation later. Two eyes developed consecutive postoperative hyperopia similar to the cases of central toxic keratopathy described by Sonmez and Maloney.<sup>17</sup> Therefore, we recommend that DLK be monitored closely and treated intensively with topical steroids. Flap relifting with interface irrigation is indicated once grade 3 DLK is seen and should not be delayed.

In our cluster of DLK cases, there was a strong epidemiologic association between DLK and the use of Codman surgical marker pens. Seventy-five percent of all eyes that had LASIK or flap relifting with intraoperative use of a Codman surgical marker pen developed DLK; no eye that had LASIK with intraoperative use of a Securline surgical marker pen, whether before, after, or on the day of the DLK outbreak, developed DLK. Contralateral eyes of

patients with DLK that had LASIK using a Securline surgical marker pen also did not develop DLK.

Gentian violet is the ink in both the Codman and Securline surgical marker pens used at our center; however, the vehicle is different. The Codman surgical marker pen uses an alcohol-based vehicle that includes a proprietary amount of propylene glycol. The Securline surgical marker pen contains a water-based dispersion agent that includes a proprietary amount of ethylene glycol. We believe it is highly likely that 1 or more constituents of the ink in the Codman surgical marker incited the inflammatory response that led to DLK.

Although gentian violet is common to both types of marker pens, there have been no previous reports of DLK caused by gentian violet. Gentian violet is known to bind to beef corneal stroma<sup>18</sup> and nucleic acids.<sup>19</sup> Higher concentrations of gentian violet have been reported to cause corneal and conjunctival abrasions, corneal edema, keratoconjunctivitis sicca, and cytotoxicity to rabbit endothelium.<sup>20-23</sup> The absorption of dye is related to the initial dye concentration, contact time, temperature, and pH.<sup>24</sup> However, there were no clinically observable corneal changes, such as epithelial edema or erosions, to suggest that gentian violet toxicity was the cause of the DLK in our series of cases.

Propylene glycol (also called propanediol) and ethylene glycol are petroleum derivatives that act as solvents, surfactants, and wetting agents. Both are used in the production of antifreeze and de-icing solutions and are used in hydraulic brake fluid. Although there are no reports of either chemical causing eye inflammation or DLK in the literature, high concentrations of propylene glycol have been shown to cause endothelial cell loss.<sup>25</sup> Propylene glycol has also been studied in rabbit eyes as a potential component of vitrification solution for corneas.<sup>26-28</sup> The possible role of propylene glycol as a cause of DLK in our series cannot be established without extensive biochemical analysis. Other potential

causes of DLK include contaminants introduced during manufacturing or changes in the percentage concentrations of the constituents of the ink of this batch of Codman surgical marker pens.

The swift identification of the possible cause of DLK during this outbreak was attributed to the strict policy of allowing only a single change in our LASIK protocol at any one time, be it changes in instruments, equipment, surgical consumables, medications, or processes. If any complication or adverse event occurred subsequent to this change, it would allow us to isolate the possible causative factors faster. Therefore, the Codman surgical marker was identified as the most probable cause of DLK as it was the only change made to our standard LASIK protocol on the day of the outbreak.

In conclusion, this is the first reported incidence of a DLK outbreak associated with the use of Codman surgical marker pens. We believe that 1 or more constituents of the ink in the Codman surgical marker pens may have resulted in this outbreak of DLK at our center. In our series, early flap relifting and irrigation once grade 3 DLK was diagnosed resulted in better visual outcomes. Johnson & Johnson Medical was informed of this outbreak of DLK associated with their Codman surgical marker pens. They replied that they investigated and found no abnormalities with the manufacturing materials, processes, or packaging of the surgical marker pens. They also stated that the pens were intended for use in marking intact skin only, implying that the use of the surgical marker pens for LASIK was an "off-label" application.

Laser in situ keratomileusis surgeons should be aware of the possibility that Codman surgical marker pens could be a cause of DLK after LASIK.

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