

## SCIENTIFIC REPORT

## Bilateral diffuse lamellar keratitis following bilateral simultaneous versus sequential laser in situ keratomileusis

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**Aim:** To determine the difference in the incidence of bilateral diffuse lamellar keratitis (DLK) in patients undergoing simultaneous versus sequential laser in situ keratomileusis (LASIK) as an indication of intrinsic risk for inflammation.

**Methods:** A retrospective non-comparative case series of 1632 eyes that had undergone bilateral, simultaneous or sequential LASIK between April 1998 and February 2001 at a university based refractive centre by three surgeons. All cases that developed clinically evident DLK were identified and reviewed. In order to identify isolated cases and exclude those caused by environmental factors, when more than one patient in a given session developed DLK, the session was excluded. The main outcome measure was the incidence of unilateral and bilateral isolated, non-epidemic DLK.

**Results:** Of 1632 eyes, 126 eyes (7.7%) of 107 patients developed at least grade 1 DLK. In six operating sessions, DLK was observed in more than one patient per session, and on this basis 13 patients were excluded. 16 of the 94 remaining patients developed DLK in both eyes (17.0%). Six of 41 patients (14.6%) in the simultaneous group, versus 10 of 53 patients (18.9%) in the sequential group developed bilateral DLK ( $p > 0.5$ ).

**Conclusion:** In isolated, non-epidemic bilateral DLK, a similar incidence was observed regardless of whether the surgery was simultaneous or sequential, suggesting an underlying intrinsic cause for DLK.

Diffuse lamellar keratitis (DLK) is a condition described by a non-infectious aggregation of inflammatory cells in the interlamellar interface that accumulates within the first week after laser in situ keratomileusis (LASIK).<sup>1,2</sup> This pattern of cellular infiltration along the lamellar interface has been noted not only after primary LASIK procedures, but after re-treatments or associated with epithelial defects, both traumatic<sup>3</sup> and spontaneous.<sup>4</sup>

Since the initial descriptions of cases of DLK, multiple aetiologies have been hypothesised. However, it is unlikely that a single causative agent might explain all cases, as it most likely represents a non-specific inflammatory response. A potential plane that persists indefinitely is created by the microkeratome, allowing inflammatory cells to migrate along this interlamellar space in response to an inflammatory event. Potential stimulants may include debris deposited by surgical instruments including the microkeratome,<sup>5–7</sup> powder from gloves,<sup>5</sup> intralamellar haemoglobin,<sup>8</sup> particles from the drape,<sup>9</sup> endotoxins,<sup>10–12</sup> meibomian gland secretions,<sup>13</sup> epithelial defects,<sup>14,15</sup> and povidone-iodine solution.<sup>1</sup>

It was our opinion that DLK seemed to represent a non-specific response to a wide variety of potential insults. As it has been emphasised in previous descriptions and studies, clustered epidemic cases can often be attributed to identifiable environmental causes such as endotoxins released from steri-

liser biofilms.<sup>10–12</sup> However, more frequently we have observed isolated, non-epidemic cases. Although a bilateral case may still represent an environmental source for DLK, it may in fact be the result of an endogenous factor common to both eyes of the same patient—for example, lid flora, meibomian secretions or host immune system response. If this were true, we would expect isolated DLK to be bilateral in a certain number of sequential as well as simultaneous cases, even if other patients undergoing surgery at the same time were unaffected. We therefore elected to examine whether non-epidemic, isolated bilateral DLK occurred as frequently in simultaneous as in sequential cases.

## METHODS

We retrospectively reviewed the available clinical charts of all refractive surgery clinic patients who underwent bilateral, simultaneous or sequential LASIK between April 1998 and February 2001 at a university based refractive centre. Cases performed as part of an FDA study protocol were excluded, owing to variable accessibility of those records. All the surgeries were performed by three highly experienced surgeons. In order to minimise the probability of including cases in which inflammation was the result of external environmental factors, and to identify isolated cases, we excluded all patients in any operating session if more than one patient developed DLK.

Sequential surgery was defined as surgery performed on each eye on two consecutive days, while simultaneous surgery was defined as surgery performed on both eyes on the same day. In simultaneous surgery, the second eye was draped separately after completing the treatment of the first eye, and a second microkeratome and new blade used for the second eye. Before surgery, the eyelids were prepared with Betadine 5% (Purdue Frederick, Norwalk, CT, USA). The eyelashes and eyelids were isolated with a drape. A lid speculum was placed. Preoperative medication included oxybuprocaine (proparacaine) 0.5% and ofloxacin 0.3%. The surgeons and assistants wore powder-free gloves during the instrument set up and surgery. The automated corneal shaper (ACS) (Bausch and Lomb, Irvine, CA, USA) or the Moria Carriazo-Barraquer (Microtech, Doylestown, PA, USA) were used to make corneal flaps. All patients were prescribed a topical fluoroquinolone, ofloxacin 0.3% (Allergan, Irvine, CA, USA) four times a day and fluoromethalone 0.1% (FML, Allergan, Irvine, CA, USA) four times a day starting immediately postoperatively. For surgery performed sequentially, if DLK was noted in the first eye, for the second eye the frequency of topical corticosteroid application following surgery was prophylactically increased to every hour while awake until the degree of inflammation could be assessed on the first day after surgery.

For each eye in which DLK developed, we recorded the date of surgery, the grade of inflammation and whether the patient had simultaneous or sequential surgery. A  $\chi^2$  test to compare proportions in each group was performed using STATA.

## RESULTS

Of 1632 eyes that underwent bilateral surgery, 126 eyes (7.7%) of 107 patients developed DLK; 119 (94%) of these were categorised as grade 1 or 2 (mild DLK). In one surgical session, three patients developed grade 1 DLK (both eyes of a simultaneous case, and in one eye of two sequential cases). In five other surgical sessions, grade 1 DLK developed in two different patients (five simultaneous and five sequential). Since DLK appeared in more than one patient in these sessions, these patients were excluded from the analysis (13 patients). In all other cases, DLK appeared in only one patient of all patients undergoing surgery in that session (94 patients).

Of these 94 patients, 41 (43.6%) underwent simultaneous surgery and 53 (56.4%) underwent sequential surgery. Six of 41 patients (14.6%) in the simultaneous group, versus 10 of 53 patients (18.9%) in the sequential group developed bilateral DLK ( $p > 0.5$ ).

## DISCUSSION

We identified isolated, non-epidemic cases of DLK, and found that some degree of inflammation appeared in both eyes in a similar proportion of cases, whether or not surgery was performed on the same day or one day apart. This observation is consistent with the hypothesis that in a certain proportion of cases, DLK can be attributed to intrinsic rather than environmental causes. It might be expected that observed DLK in one eye might lead to more careful attention to potential causes of DLK in the second eye and, as noted, patients were advised to use topical corticosteroids more frequently on the first night following surgery in the second eye. In spite of this, inflammation in the second eye occurred at least as frequently with these measures as it did in simultaneous cases. Thus, a better understanding of the causes of DLK is necessary to effectively reduce its incidence.

In order to exclude epidemic cases of DLK that could produce multiple cases of DLK in both eyes of a number of patients over many days whether surgery was sequential or simultaneous, we excluded data from all sessions in which any degree of inflammation was noted in more than one patient. In so doing, we have characterised the incidence of bilateral inflammation specifically for sporadic and isolated cases of DLK. Our data suggest that such sporadic cases represent the majority of DLK events (88%), and the majority of such isolated cases are mild (94% grade 1 or 2). Our data specifically examining sequential surgery suggest that if inflammation develops in one eye, approximately 18% of patients will develop inflammation in the other. Inflammation in the second eye can very probably be attributed to factors intrinsic to the patient, and in a majority of cases is not caused by environmental factors that are associated with epidemic inflammation.

This study is certainly limited by its retrospective design. The data we recorded do not afford us an opportunity to reliably identify those features unique to the patient that may increase their risk for DLK, in one or both eyes. As a follow up study, we feel it would be worthwhile to prospectively examine the role that preoperative ocular symptoms, medications, meibomian gland health and function, lid margin dysfunction or conjunctival and lid flora might have in this condition. If associations were identified it would be reasonable to further investigate the role that specific intervention might have on DLK incidence.

This study might also be interpreted as suggesting that since bilateral DLK seems to occur with similar frequency whether surgery is simultaneous or sequential, with regard to

the risk of inflammation there is no advantage to be gained by sequential rather than simultaneous surgery. However, because of the relatively low degree of inflammation (grade 1 to 2) in the majority of cases, we were unable to evaluate the effectiveness of the more aggressive corticosteroid treatment that was applied to the contralateral eye when surgery was performed in a sequential fashion. If more aggressive corticosteroid treatment does indeed limit the severity of the DLK that is more likely to occur in the second eye if seen in the first, then there would indeed be an advantage to sequential rather than simultaneous surgery.

In summary, there was no difference in the incidence of non-epidemic, isolated bilateral DLK in simultaneous and sequential LASIK, suggesting an underlying intrinsic cause for isolated DLK. Further study is required to better define specific risk factors for the development of DLK following LASIK, and the effectiveness of various treatment strategies.

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