

Laser in situ keratomileusis in patients with a history of ocular herpes

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PURPOSE: To report the outcomes of laser in situ keratomileusis (LASIK) in patients with a history of ocular herpes simplex virus (HSV) or herpes zoster ophthalmicus (HZO).

SETTING: Clínica Baviera, Instituto Oftalmológico Europeo, Madrid, Spain.

METHODS: In this retrospective case series, the records of eyes with a history of ocular herpes that had LASIK from 2003 through 2005 were reviewed. The main outcome measure was postoperative recurrence of ocular herpes.

RESULTS: Forty-nine eyes (48 patients) with a history of ocular herpes (HSV keratitis, 28 eyes; HSV eyelid lesions, 17 eyes; HZO, 4 eyes) were identified. All LASIK procedures were uneventful. Herpetic disease was inactive at the time of surgery in all eyes and for more than 1 year in 31 eyes. Perioperative antiviral systemic prophylaxis was used in 13 patients with a history of HSV keratitis. No eye developed reactivation of herpetic keratitis during the follow-up (range 1 to 28 months).

CONCLUSIONS: Laser in situ keratomileusis was safe in patients with a history of ocular herpes; no recurrences occurred during the follow-up period. However, candidates should be selected with caution and surgery performed only in eyes in which the herpes has been inactive for 1 year before surgery, without stromal disease, and with regular topography and pachymetry maps and normal corneal sensitivity. The most reasonable clinical strategy is perioperative systemic antiviral prophylaxis.

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Whether laser in situ keratomileusis (LASIK) should be performed in patients with a history of ocular herpes is a matter of concern and controversy because of the risk for reactivation of herpetic disease after surgery. In a survey mailed to faculty and course participants at the refractive surgery symposium of the

American Academy of Ophthalmology, most respondents (57%) did not recommend surgery in patients with herpes simplex virus (HSV); however, 29% said they would perform LASIK in such cases (A.G. Yashar, "LASIK Preferred Procedure, but PRK Still Has a Place," *Ophthalmology Times*, April 1, 2000, pages 14–15).

Although inactive herpetic eye disease is not considered an absolute contraindication to refractive procedures, a U.S. Food and Drug Administration (FDA) publication states, "The safety and effectiveness of refractive procedures has not been determined in patients with some diseases. Discuss with your doctor if you have a history of any of the following: Herpes simplex or herpes zoster (shingles) involving the eye area" (U.S. FDA, "When Is LASIK Not for Me?" [online]. Available at: www.fda.gov/cdrh/LASIK/when.htm. Accessed August 18, 2007). However, when considering LASIK in patients with inactive herpetic keratitis, surgeons will find little information in the literature, particularly on the selection of appropriate candidates and need for antiviral prophylaxis.

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Laser in situ keratomileusis has been shown to reactivate HSV-1 in rabbits,¹ and a few anecdotal reports²⁻⁶ suggest that LASIK could trigger ocular HSV reactivation in humans. However, based on the same model⁷ and 2 short series in humans,^{8,9} it has been suggested that prophylactic perioperative antiviral therapy can protect the cornea from HSV reactivation after LASIK. There is even less information on the history of herpes zoster ophthalmicus (HZO) and LASIK.¹⁰ Thus, little information is available in the literature on the proper approach to LASIK in a patient with inactive herpetic keratitis.

The aim of this pilot study was to report the outcomes of LASIK in patients with a history of ocular herpes.

PATIENTS AND METHODS

This retrospective case-series review comprised eyes that had LASIK at Clínica Baviera between 2003 and 2005. More than 40 000 refractive procedures are performed per year at the clinic, a private ophthalmologic institution with 22 centers throughout Spain. Patients with a history of ocular herpes were identified by an electronic search of medical histories using the key word *herpes*. The electronic charts of the identified patients were analyzed, and the following data were collected: age, sex, involved eye, last episode of ocular herpes, preoperative and postoperative spherical equivalent (SE), preoperative and postoperative uncorrected visual acuity (UCVA) and best corrected visual acuity, presence of leucoma, follow-up, use of systemic antiviral prophylaxis and topical postoperative corticosteroids, and recurrences of ocular herpes.

The main outcome measure of the study was the recurrence of herpes after surgery.

RESULTS

Forty-nine eyes of 48 patients (35 women, 13 men) with a history of ocular herpes were identified. The mean age of the patients was 37.06 years \pm 8.14 (SD). Herpes simplex virus keratitis was present in 28 eyes of 27 patients, including 1 case of LASIK over penetrating keratoplasty (PKP) for herpetic keratitis; HSV eyelid lesions in 17 eyes of 17 patients; and HZO in 4 eyes of 4 patients. The time from last ocular episode to surgery (range 10 months to 20 years) was known in 36 patients. Herpetic disease was inactive at the time of surgery in all cases and had been inactive for more than 1 year in 31 cases. Subepithelial leucoma was present before surgery in 16 eyes (15 with a history of HSV keratitis, 1 with a history of HZO keratitis). No eye had stromal disease. Topography and pachymetry maps were regular and within normal limits in all cases, excluding cases with focal thinning or irregular astigmatism that could have been caused by herpetic disease. The mean central corneal thickness measured by ultrasound pachymetry (DGH Technology, Inc) was 557.46 \pm 30.49 μ m (range 505 to 637 μ m).

Laser in situ keratomileusis was performed using the Moria One microkeratome (Microtech) and was uneventful in all eyes. The Technolas 217C excimer laser with PlanoScan software (Bausch & Lomb) was used in 40 eyes, the Technolas 217z with Zyoptix software in 4 eyes, the Technolas 217z100 with the Tissue Saving software in 2 eyes, and the Mel 80 excimer laser (Carl Zeiss Meditec) in 3 eyes. A topical combination of tobramycin 3 mg/mL and dexamethasone 1 mg/mL (TobraDex) was given 4 times a day for 1 week except in 2 cases in which the use of postoperative topical corticosteroids was intentionally avoided. All patients were instructed to use preservative-free artificial tears for 2 months.

Perioperative antiviral systemic prophylaxis was used in 13 patients with a history of HSV keratitis (8 eyes with and 5 eyes without preoperative leucoma) and in 1 case of LASIK over PKP for herpetic eye disease. Antiviral prophylaxis was performed preoperatively and postoperatively in 10 cases. The time of onset of antiviral therapy before surgery ranged from 2 days to 2 weeks, and time of discontinuation after surgery ranged from 5 days to 5 months. Valacyclovir was used in 6 cases, acyclovir in 7 cases, and famciclovir in 1 case. Topical acyclovir ointment was added to the systemic prophylaxis regimen for 1 week after surgery in 1 case. No recurrences of herpetic disease occurred during a mean follow-up of 6.71 months (range 1 to 28 months).

Visual and refractive outcome data were as follows: mean preoperative SE, -2.46 diopters (D) (range -11 to +6.25 D); mean postoperative SE, -0.12 (range -1.25 to +1.25 D); and UCVA, 20/25 or better in 85.7% of eyes. The efficacy was 83.6%, and the safety index was 1.02.

DISCUSSION

An area of concern for patients having excimer laser photoablative procedures and for ophthalmologists performing it is whether latent herpes will reactivate and cause postoperative keratitis. Although anecdotal recurrences of HSV-1 have been reported after LASIK,²⁻⁶ 2 short case series^{8,9} found successful outcomes with no recurrences when perioperative systemic antiviral therapy was administered. However, the authors note the limited number of cases (3 in the first series⁸ and 5 in the second⁹) and suggest that larger case series with longer follow-ups be performed. We believe the study presented here is the largest series reported to date and offers further evidence that LASIK can be performed safely in patients with inactive herpetic disease.

The mechanism by which excimer laser corneal surgery might trigger reactivation of herpes simplex is

unclear. In animal models, reactivation of latent HSV after LASIK has been shown¹; however, only 6 cases have been reported after LASIK in humans.²⁻⁶ Between 60% and 90% of the adult population is HSV-1-positive.¹¹ If we take into account that each year an estimated 48 000 cases¹² of active HSV eye disease present in the United States and hundreds of thousands of LASIK procedures are performed annually, a larger number of cases of recurrent HSV disease after LASIK could be expected to occur. Therefore, reactivation of ocular HSV disease after LASIK is underreported or the risk for reactivation in humans is lower than expected.

Of the 6 cases of reactivation reported in humans, 2 had a history of ocular disease,^{2,5} 2 had a history of recurrent herpes labialis,^{4,5} and 1 occurred after LASIK over PKP for herpetic disease³; 1 study⁶ did not report previous clinical herpetic disease. Thus, herpetic reactivation after LASIK may occur not only in patients with a history of ocular herpes but also in patients with a history of herpes labialis, even in the absence of previous herpetic clinical disease. Recurrences in previous reports were unilateral in 4 cases^{2,4,5} and bilateral in 1 case.⁶ Time from surgery to reactivation was 1 day in 2 cases,^{2,4} 1 month in 1 case,⁶ 6 weeks in 1 case,⁵ and 2 years in 1 case.⁵ Two cases had stromal involvement and 3 to 4 recurrent episodes.⁵ Preoperative antiviral prophylaxis was not used in any case, and famciclovir was prescribed on the same day of surgery in only 1 case.² All eyes responded well to antiviral therapy. An additional case of reactivation was reported in an eye with polymicrobial keratitis after LASIK that required PKP.¹³

Based on the results in an experimental model⁷ and 2 short case series in humans,^{8,9} it has been suggested that patients with a history of recurrent ocular herpes may safely have LASIK with a lower risk for recurrent herpes while on antiviral prophylaxis with valacyclovir. However, whether systemic prophylaxis is necessary in all cases and the optimum treatment regimen remain unknown. In the present study, only patients with a history of herpetic keratitis received prophylaxis, although none had reactivation of the disease. Perhaps not all patients have the same risk for reactivation or the history of herpetic disease is false in some cases, explaining the absence of reactivation when prophylaxis was not administered. In our study, however, 15 eyes had subepithelial leucoma before surgery and only 8 received prophylaxis. Although the presence of subepithelial leucoma does not confirm the history of herpes, it makes the history less likely to be false. In our study, 7 patients with a history of herpetic keratitis and subepithelial leucoma did not receive prophylaxis. This was because ours was a retrospective study, so patients did not follow

a treatment protocol; thus, it was the surgeon's decision whether to prescribe antiviral prophylaxis and there are no clear guidelines in the literature on the indications for prophylaxis. According to the results in previous studies^{8,9} and given the rare side effects of antiviral treatment, the most reasonable clinical strategy is to use perioperative antiviral prophylaxis. Prophylaxis should be systemic because topical therapy does not prevent reactivation in sensory ganglia.¹⁴ The times of onset and discontinuation are not known. Nevertheless, in a previous report,² although prophylactic oral famciclovir was started 1 day after LASIK, herpes recurred the following day. In an experimental model,⁷ prophylaxis was started 2 days before LASIK. In 2 previous short case series in humans,^{8,9} treatment was started 1 week before LASIK and discontinued 2 weeks after; this was the regimen used in most cases in our study. No prophylaxis was used in cases with previous eyelid lesions, and none had reactivation of the herpes.

The drugs and doses used in our study were consistent with those recommended in previous reports. The success of antiviral prophylaxis with acyclovir requires adequate oral doses to achieve the necessary therapeutic serum levels. In the New Zealand White rabbit latency model,⁷ the acyclovir serum levels that significantly reduced HSV-1 ocular shedding were similar to those in patients after a single 500 or 1000 mg dose. Systemic acyclovir 800 mg 3 times a day⁸ or systemic valacyclovir 500 mg twice a day⁹ has been used in previous studies of humans.

Regarding postoperative topical corticosteroids, although 1 study of humans⁸ recommended avoiding them, the other⁹ used fluorometholone 4 times a day for 1 week under antiviral systemic therapy without recurrences. In our study, all patients received topical corticosteroids for 1 week except 2, in whom corticosteroids were intentionally avoided at the surgeon's discretion to exclude the possibility of recurrent disease induced by corticosteroids. This was a retrospective study, and it was the surgeon's decision to modify the standard postoperative protocol as there are no clear guidelines in the literature regarding use of postoperative steroids in these cases. Although a prolonged steroid regimen after LASIK could potentiate viral replication, it seems unlikely that the usual short course of topical steroids 4 times a day for 1 week is involved in recurrent herpetic keratitis after LASIK as this was the case in the remaining patients in our study. Thus, we do not believe that the standard protocol of topical steroids for 1 week, under antiviral prophylactic therapy, should be modified.

In our study, LASIK was successfully performed without recurrences in a patient with PKP for herpetic disease. One study reports reactivation with

perforation in a graft after LASIK,³ although the patient was not under a full prophylactic dose of acyclovir and viral investigation was negative. Two recent series of LASIK after PKP^{15,16} included 2 patients with previous herpetic disease and no recurrences. No information on antiviral prophylaxis was provided, although the authors recommend surgery be avoided in cases of recent herpetic disease.¹⁷ Thus, in our opinion, under proper prophylactic antiviral coverage, LASIK seems a reasonable option for the correction of refractive errors after PKP when other noninvasive alternatives, such as contact lenses or spectacles, are not feasible.

The limited number of cases with a history of HZO in our study is illustrative, although the small sample lacks the power to provide meaningful results. None of our patients received antiviral prophylaxis. One report¹⁰ describes a "presumed reactivation of herpes zoster ophthalmicus following LASIK." It occurred 2 months after LASIK, and the authors state the recurrence was likely coincidental. Despite this, they recommend that patients with a history of HZO be given prophylactic antiviral therapy before refractive surgery.

Last, a special consideration in patients with a history of herpes simplex or zoster is corneal sensitivity. Both diseases are well-known causes of neurotrophic keratitis,¹⁴ which can be aggravated by further LASIK-induced corneal nerve damage. Data on preoperative corneal sensitivity were not available in our study, and although no cases of LASIK-induced neurotrophic epitheliopathy were identified, it seems reasonable to alert surgeons to this issue for use when they are evaluating patients for surgery.

The small sample, the wide range of refractive errors, and the lack of a control group prevent us from drawing conclusions about refractive outcomes. However, the safety index in our study was higher than 1, which illustrates the safety of the procedure.

One significant concern when performing LASIK in patients with a history of herpetic keratitis, apart from recurrences triggered by surgery, is the behavior of future recurrences in a cornea with a lamellar structure. Could recurrences after LASIK potentially have more serious visual consequences than in a virgin cornea? Could patients develop associated diffuse lamellar keratitis? Could diagnosis and management be more troublesome? Recurrences of herpetic stromal disease have been reported 2 months and 2 years after LASIK in 2 patients, respectively.⁵ The outcomes and response to treatment were similar to those in virgin corneas.

Our study had limitations. One limitation is that retrospective studies have well-known limitations in terms of misinterpretation of data and lack of data. Second, a history of herpetic keratitis may be false in

some patients, and the results will be biased as a consequence. Third, the length of follow-up was limited, although patients who presented with reactivations after surgery would be expected to visit our clinics again.

In conclusion, we think that LASIK can be considered in patients with inactive herpetic ocular disease with proper informed consent and under perioperative systemic antiviral prophylaxis. However, caution is recommended in the selection of candidates, and special attention should be paid to the following: a detailed and consistent clinical history, an inactive period of at least 1 year before surgery, absence of stromal disease, regular topography and pachymetry maps, and normal corneal sensitivity. Patients must be informed of the remote risk for reactivation. Should the surgeon decide to perform LASIK, the most reasonable clinical strategy would be to use preoperative and postoperative systemic antiviral prophylaxis. The need for perioperative systemic antiviral prophylaxis and the optimum treatment regimen remain unknown to date.

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